NDA 19813

Reviews

AUG 7 1990

NDA 19-813

Alza Corporation
950 Page Mill Road
Palo Alto, CA 94303-0802

Attention: Virgil A. Place, M.D.
Senior Director, Medical and Regulatory Affairs

Gentlemen:

Please refer to your new drug application dated December 21, 1987 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for DURAGESIC (Fentanyl Transdermal System) 25 ug/h, 50 ug/h, 75 ug/h and 100 ug/h.

We also acknowledge your additional correspondence dated February 11, 1988, May 13, 1988, August 25, 1989, October 23, 1989, March 23, 1990, April 11, 1990, May 16, 1990, May 17, 1990 and August 7, 1990 amending the application.

Reference is also made to your submissions dated August 2 and 3, 1990 outlining various manufacturing and control changes and commitments. We remind you that additional suppliers and manufacturing sites must have approved supplementary applications prior to use.

We have completed the review of this application including the draft labeling which was submitted on August 7, 1990 and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended. Accordingly, the application is approved effective on the date of this letter.

Please submit twelve copies of the final printed version of the FPL when it is available. This submission should be designated for administrative purposes as "FPL for approved NDA 19-813". Approval of this labeling is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed. In such cases, the policy of the Center for

Drug Evaluation and Research is to proceed with approval. We expect your cooperation to help resolve expeditiously any problems that may occur with respect to validations.

As a reflection of our mutual understanding of the importance of initial promotional campaigns on physicians' use of a new drug (or a new use of a drug), we note your commitment to develop with us and with the Division of Drug Advertising and Labeling, a satisfactory introductory advertising campaign. Please submit, in duplicate, all advertising copy you intend to use in your proposed introductory promotional and/or advertising campaign. Send one copy to:

Division of Drug Advertising and Labeling
HFD-240, Room 10B-04
5600 Fishers Lane
Rockville, MD 20857

and one copy to:

Pilot Drug Evaluation Staff
HFD-007, Room 9B-23
5600 Fishers Lane
Rockville, MD 20857.

Should you have any questions please contact:

James P. Hannan, R.Ph.
Project Manager
Pilot Drug Evaluation Staff (HFD-007)
Telephone: (301) 443-4250

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

Carl C. Peck, M.D.
Director
Center for Drug Evaluation and Research

DRAFT

Division of Surgical - Dental Drug Products
Chemistry

1: Chemistry Review Number: Two

2: Dated July 17,1990

3: Type and Number of Application: NDA 19-813

4: Center's Therapeutic Classification: 2,3,B

5: Status of Application: Original

6: Name of Applicant: Alza Corporation

7: Addresses:

The drug substance is incorporated into the Reservoir Gel. The Reservoir Gel is manufactured by:

a) Alza Corporation
950 Page Mill Road
Paolo Alto, CA 94303-0802

b) Alza Corporation
700 Eubanks Drive
Vacaville, CA 95688

8: Product Names:

(a) Proprietary: Transdermal Therapeutic System (Fentanyl) TTS
(fentanyl)

(b) Established:

USAN: Fentanyl
USP: Fentanyl

(c) Code Name and Number: CAS No: 437-38-7

9: Dosage Form(s), Strength/Potency and Route of Administration:

TRANSDERMAL THERAPEUTIC SYSTEM (FENTANYL)

Nominal Delivery Rate	Drug Content	Size
25 mcg/hr	2.5 mg	10 cm^2
50 mcg/hr	5.0 mg	20 cm^2
75 mcg/hr	7.5 mg	30 cm^2
100 mcg/hr	10.0 mg	40 cm^2

10: Proposed Marketing Status: Rx

11: Pharmacological Category and Indication:

Narcotic Agonist Analgesic-Synthetic ~~Opid~~ Opiad Related to the Phenylpiperidines.

12: Structural Formula, Chemical Name, Empirical Formula Molecular Weight

a: Names

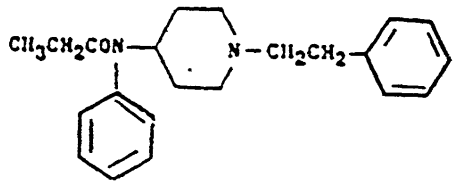
Drug Substance: Fentanyl Base

N-phenyl-N-(1-2-phenylethyl) -4-piperidinyl] propanamide

ALZA Code Number: 80285

Also Known As: Leptanal

b: Structural Formula:



Chemical Names: N-Phenyl-N-[1-2-(phenylethyl) -4-piperidinyl] propanamide

N-(1-phenethyl-4-piperidinyl) propionanilide

N-(1-phenethyl-4-piperidinyl)-N-phenyl propionamide

Chemical Abstracts Service Reg: No: 437-38-7

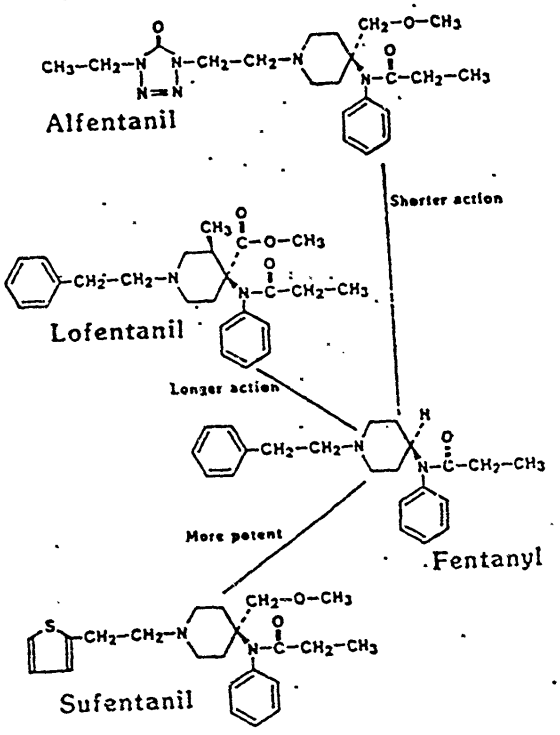
Wisswesswer Line Notation: T6NTJ AZR & DNR & V2

Molecular Formula: $C_{22}H_{28}H_2O$

Molecular Composition: C 78.53%, H 8.39%, N 8.33%, O 4.76%

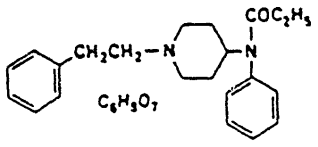
Molecular Weight: 336.46

13:(a) Fentanyl and its Derivatives

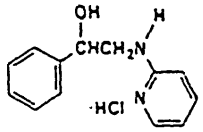


13:(b) Structural Formulas of Related Compounds:

a) FENTANYL CITRATE (Sublimaze)



b) PHENYRAMIDOL HYDROCHLORIDE (Analexin)



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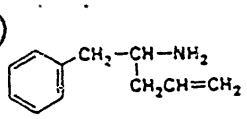
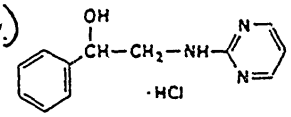


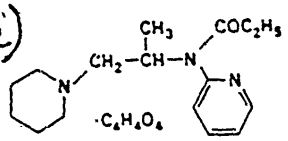
alethamine

d)



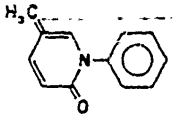
fenyripol HCl

e)



propiram fumarate

f)



pirfenidone

14: Document Date:

Dec: 21, 1987 - Form 356h (Chemistry Review #1)
Dec: 21, 1987 - Cover Letter
Amendments: Aug: 25, 1989, March 23, 1990, Jun 29, 1990 (subject of this review)

15: CDB Date: Dec: 29, 1987, Sept: 5, 1989, March 30, 1990, July 2, 1990

16: Division Date: Dec: 29, 1987, Sept: 5, 1989, Mar: 30, 1990, Jul 2, 1990

17: Assigned Date: Jan: 7, 1988, Sept: 11, 1989, April 3, 1990, Jul: 10, 1990

18: Supporting Documents:

(5)

Authorization Letter dated May 26, 1987

There is no specific description of the packaging operations for TTS (Fentanyl).

A deficiency letter was written
that they describe the packaging operations and relevant in-process controls including sampling plan acceptance specifications and test methodologies.

b)

Their authorization letter is dated April 8, 1987.

master file does not contain any information:

i) Name of suppliers/manufacturers of the

ii) The tests and specifications performed on the components.

iii) A description of the manufacturing procedure and

iv) Their statement

"The components of this structure are approved for food packaging under CFR 21, ADHESIVES, Para. 175.105, LOW DENSITY POLYETHYLENE 175.105, 177-1520 IONOMER, 175.105, 177-33a."

is a misleading because they have not given the exact chemical name of the components to relate to these regulations.

c)

Authorization Letter dated: December 21, 1987

(6)

Comment: A deficiency letter dated October 28, 1987 concerning the synthesis of fentanyl citrate has been written. In an initial submission dated August 15, 1983, they submitted a synthesis description beginning

Since the above comment, the manufacturer/supplier has submitted the following information in a letter dated March 23, 1988 and April 8, 1988:

a)

b)

HFD 120

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

JUN 14 19..

NDA#. 19-813

Applicant:
Sponsor: Alza Corporation
Address: 950 Page Mill Rd.
Palo Alto, Ca
94303-0802

Division: HFD-120
Chemist Review:
Reviewing Chemist: Wilson Brannon
Date Received: 5/18/88
Date Completed: 6/14/88
Received CDB:

Product Name:

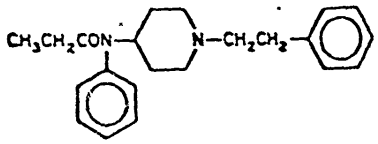
Proprietary: Transdermal Therapeutic System TTS (Fentanyl)
Non-proprietary:
Compendium: Fentanyl Citrate
USAN:
Code Name/Number: CAS No. 437-38-7
Drug Classification:
Patent Number:

Dosage Form(s) and Route(s) of Administration: Transdermal Therapeutic System

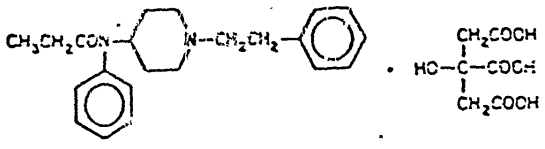
Pharmacological Category and/or Principal Indication: Narcotic Analgesic

Structural Formula & Chemical Name:

Fentanyl Citrate [*1963*] (fen' ta nil). USP. $C_{22}H_{28}N_2O.C_6H_8O_7$. 528.60. [Fentanyl is INN.] (1) Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)



Fentanyl



MEETING MINUTES
NDA 19-813

MAR 7 1989

DRUG: Transderamal Therapeutic System (Fentanyl)
SPONSOR: Alza Corporation
DATE: February 2, 1989
LOCATION: Conference Room 10B-45

ATTENDEES: P. Leber, M.D.
F. Vocci, Ph.D.
E. Nevius, Ph.D. (HFD-713)
P. Kelley, Ph.D. (HFD-713)
R. Temple (HFD-100)
P. Botstein (HFD-100)
C. Kovacs, CSO

SUBJECT: Working Meeting

Background:

The firm's application was transferred to this division in May, 1988. On June 17, 1988, the firm was informed by a teleconference that their proposed labeling claim was not supported by the type of preclinical and clinical data submitted. Instead of withdrawing the NDA and re-submitting a new package to support a revised claim, the firm amended their application with a revised indication: "...for the control of moderate to severe pain in patients requiring opioid analgesia following surgery or for palliative therapy in patients with cancer."

Dr. Leber stated that the purpose of this meeting was to discuss the difficulties in reviewing this application. The following was discussed:

1. Dr. Vocci made a presentation of the clinical studies performed by the firm in support of their post-op claim, their reported findings, and ADR's.

   There were 6 controlled studies performed in the perioperative/post-operative setting utilizing the fentanyl patch versus a placebo patch and evaluating the need for supplemental morphine and changes in pain intensity. Dr. Vocci pointed out the following:
   (1). Data from 5 of the studies demonstrates that the patch reduces but does not eliminate the need for supplemental morphine.
   (2). This reduction in need for supplemental morphine occurs over the 12-24 hour post-op period. During the first 0-12 hours post-op, the patch has sub-therapeutic effects.
   (3). Respiratory depression and nausea/vomiting increased in the fentanyl patch groups.
   (4). Instructions for the patch recommend a bolus of 100-300 micrograms of fentanyl intraoperatively.

   Dr. Kelley stated that in the Caplan study, the p value is slightly in favor of the fentanyl treatment.

   Dr. Leber agreed that over the time interval selected, the firm does demonstrate effectiveness of their product as an analgesic. However, questions and concerns regarding safety in the perioperative environment should not be made by this division. Dr. Leber recommended that a

specialist (i.e., an anesthesiologist) be responsible for making the clinical judgement.

Dr. Temple advised that a consult to HFD-160 with specific questions and concerns be sent through his office. He will also recommend that the portion of the application with the post-op claim be presented to an Anesthesiology Advisory Committee. Furthermore, he stated that the 2 claims in this application need to be reviewed separately by those with the appropriate expertise.

2. Dr. Vocci presented an overview of the data submitted in support of the Of note clinically, all utilizing the fentanyl patch were open label studies, and no study had assay sensitivity. There was one 7-day study performed in however, this study was a crossover design and may have had carryover effects since the patches were changed every 24 hours.

Dr. Leber pointed out that inappropriate clinical studies were performed in support of a (i.e., no safety data, only 1 pain model used). Dr. Temple agreed that this portion of the application should be turned down on the basis of inadequate clinical data.

3. The issue of the firm using a claim for without performing carcinogenicity studies was discussed. Dr. Temple stated that given the survival expectation he would not impose this requirement on the firm now, but perhaps post-marketing. Dr. Leber disagreed that neccessarily have a short survival span and should be performed, unless a new policy is written. Dr. Temple suggested that the oncology group be consulted in regard to

ACTION:

1. Dr. Vocci will develop a consult to HFD-160 with specific questions regarding clinical issues and concerns related to the firm's post-op claim. This consult is to be sent through Dr. Temple's office.

2. Dr. Leber has recommeded that the Anesthesiology Advisory Committee be involved in this application.

3. Dr. Kelley will perform an analysis on the 7-day study.

4. Survival rate expectation for cancer patients with pain will need to be determined.

Carol Kovacs, CSO

Division of Surgical-Dental Drug Products

Chemistry

1. Chemistry Review Number: One

2. Dated 4-11-88

3. Type and Number of Application: NDA 19-813

4. Center's Therapeutic Classification: 2,3,8

5. Status of Application: Original

6. Name of Applicant: Alza Corporation

7. Addresses:

   The drug substance is incorporated into the Reservoir Gel. The Reservoir Gel is manufactured by:

8. Product Names:

   (a) Proprietary: Transdermal Therapeutic System (Fentanyl) TTS (fentanyl)

   (b) Established:

   USAN: Fentanyl
   USP: Fentanyl

   (c) Code Name and Number: CAS No. 437-38-7

9. Dosage Form(s), Strength/Potency and Route of Administration:

TRANSDERMAL THERAPEUTIC SYSTEM (FENTANYL)

Nominal Delivery Rate	Drug Content	Size
25 mcg/hr	2.5 mg	10 cm^2
50 mcg/hr	5.0 mg	20 cm^2
75 mcg/hr	7.5 mg	30 cm^2
100 mcg/hr	10.0 mg	40 cm^2

10. Proposed Marketing Status: Rx

11. Pharmacological Category and Indication:

Narcotic Agonist Analgesic-Synthetic Opiod Related to the Phenylpiperidines.

12. Structural Formula, Chemical Name, Empirical Formula Molecular Weight

a. Names

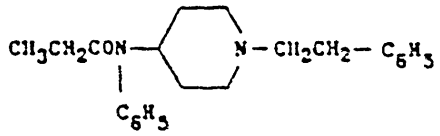
Drug Substance: Fentanyl Base

N-phenyl-N-[1-2-phenylethyl)-4-piperidinyl]propanamide

ALZA Code Number: 80285

Also Known As: Leptanal

b. Structural Formula:



Chemical Names: N-Phenyl-N-[1-2-(phenylethyl)-4-piperidinyl]propanamide

N-(1-phenethyl-4-piperidinyl) propionanilide

N-(1-phenethyl-4-piperidinyl)-N-phenyl propionamide

Chemical Abstracts Service Reg. No. 437-38-7

Wisswesser Line Notation: T6NTJ AZR& DNR&V2

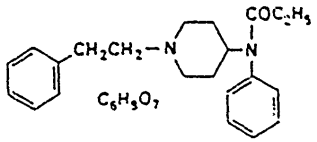
Molecular Formula: $C_{22}H_{28}N_2O$

Molecular Composition: C 78.53%, H 8.39%, N 8.33%, O 4.76%

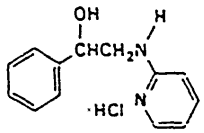
Molecular Weight: 336.46

13. Structural Formulas of Related Compounds:

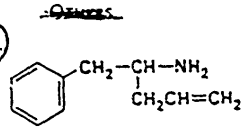
a.) FENTANYL CITRATE (Sublimaze)



b.) PHENYRAMIDOL HYDROCHLORIDE (Analexin)

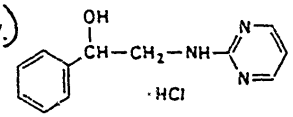


c.)



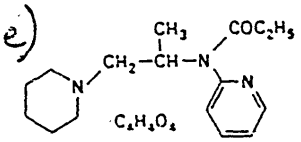
alethamine

d.)



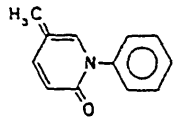
fenyripol HCl

e.)



propiram fumarate

f.)



pirfenidone

14. Document Date:

Dec. 21, 1987 - Form 356h
Dec. 21, 1987 - Cover Letter

15. CDB Date: Dec. 28, 1987

16. Division Date: Dec. 29, 1987

17. Assigned Date: Jan. 7, 1988

18. Supporting Documents:

Pages 5-8

CONTAINED
TRADE SECRET INFORMATION
301(j)

20. Remarks

a) Presently the clinical studies are under review by the medical officer.

b) The pharmacologist's review states the following conclusion:

Transdermal Therapeutic System (fentanyl) [TTS (fentanyl)] has been studied adequately in laboratory animals and has been shown to be relatively safe and efficacious. The toxicological profile which has been developed provides an adequate basis for concluding that the drug can be adequately labeled to provide assurance of its relative safe use in humans.

c) Presently, we have not consulted a microbiologist. We are requesting information of a microbial nature.

21. Conclusion and Recommendations:

The NDA application is not approvable under section 505[b](2)(3)(4)(5) and (6) of the act and 21 CFR 314.50.

See draft review of chemist letter item #24.

Juanita Ross
Juanita Ross
Reviewing Chemist

NDA 19-813
HFD-160
Doc. Rm. 160
R/D JRoss
R/D init by GPoochikian 5/6/88
F/T LSturdivant 5/19/88
Wang 1880M Disk 0087M
CSO JIM HANNON

D. Special Toxicity

ALZA Final Report TR-87-1772-026
USP XXI: Biological Testing of Film, PET/EVA; Control No. 261487, [not previously submitted].....

ALZA Final Report TR-81-1702-030
USP XX: Biological Testing of Plastic Containers - Implantation Test, Systemic Injection Test, and Intracutaneous Injection Test of Film, EVA (9% VA); 2 mil, Control No. 13628, for Raw Material Qualification and Quality Assurance; [not previously submitted].....

ALZA Final Report TR-86-1774-007
USP XX: Biological Testing of Film, FCD/Polyester, 3 mil, HT, Control No. 220586, for Quality Assurance; [not previously submitted].....

Medical Grade Pressure Sensitive Adhesive (99% solids); Lot 6250-25A (USP Class V Extractables Test); [original submission vol. 5.1/183].....

Medical Grade Pressure-Sensitive Adhesive (99% solids); Lot 6250-25A (Pyrogen Test); [original submission vol. 5.1/151].....

Medical Grade Pressure-Sensitive Adhesive (99% solids); Lot 6250-25A (Tissue Cell Culture); [original submission vol. 5.1/262].....

Medical Grade Pressure-Sensitive Adhesive (44% in Freon PCA); Lot 6250-25B (Tissue Cell Culture); [original submission vol. 5.1/283].....

Medical Grade Pressure-Sensitive Adhesive (44% in Freon PCA); Lot 6250-25B (Ninety-Day Implant Test); [original submission vol. 5.2/001].....

E. Reproduction

1963 and 1967b [not previously submitted].....

TRR-111 intravenous administration - on days 6-18 of gestation

TRR-44 subcutaneous administration for 21 days to 3 gestation

TRR-45 subcutaneous administration for 21 days

F. Mutagenicity

Genetic Evaluation of in Bacterial Reverse Mutation Assays; [original submission vol. 5.2/252].....

ALZA Final Report TR-85-1772-059
In Vitro Microbiological Mutagenicity Assays to ALZA Corporation Extracts Nos. 04330 and T074; [original submission vol. 12.1/278].....

ALZA Final Report TR-85-1772-061
Mouse Lymphoma Cell Mutagenesis Assay ($TK^{+/-}$ -> $^{-/-}$) of ALZA Corporation; Extract Nos. 04330 and T074, [original submission vol. 12.1/319].....

ALZA Final Report TR-85-1772-060
In Vitro Hepatocyte DNA Repair Assays of ALZA Corporation Extracts Nos. 04330 and T074; [original submission vol. 12.1/301].....

ALZA Final Report TR-85-1772-068
In Vitro Microbiological Mutagenicity Assays to ALZA Corporation Extracts with Fentanyl; [original submission vol. 12.1/393].....

ALZA Final Report TR-85-1772-066
In Vitro Hepatocyte DNA Repair Assay With Fentanyl for ALZA Corporation; [original submission vol. 12.1/343].....

Nonclinical Laboratories

Sponsor

GLP Statement: Adequate

Behavior

Gardocki and Yelnosky gave 5 groups of 10 male white mice analgesic doses of fentanyl (0.01-1 mg/kg, s.c.). At 0.05 mg/kg or less, mice showed slight increases in motor activity and at 0.10 mg/kg, activity increased moderately accompanied by Straub tail reaction and circling. At 0.5 mg/kg, mice showed a marked increase in activity and increased muscle tone. Near-lethal and lethal doses of fentanyl (1-300 mg/kg) produced an increased severity of the above effects with an increased responsiveness to touch and auditory stimuli, colonic convulsions, hind limb paralysis and corneal blanching leading to death (mortality ranged from 20% at 10 mg/kg to 100% at 300 mg/kg). Duration of these changes was about 1 hr with 1.0 mg/kg, ranging up to 16 hr with near-lethal doses. Deaths occurred within 24 hr.

Gardocki and Yelnosky reported that in dogs, 0.0125-1 mg/kg, i.m. fentanyl produced decreased motor activity, ataxia, decreased responsiveness to auditory stimuli, bradycardia, respiratory depression (occasionally tachypnea), salivation and defecation. Duration of effects increased with increasing dose (40 minutes to 20 hr).

study in 4 dogs (0.3 mg/kg fentanyl intra-arterially) showed decreased activity, bradycardia, loss of righting reflex and convulsion (1 dog). All dogs recovered in 24 hr. (Pharmacologist review of 7-19-57).

Respiration

Brown et al (Br. J. Anaesth. 52: 1101-1106, 1980) studied effects of single and repeated i.v. injections of fentanyl on respiration in 14 spontaneously breathing, conscious rabbits. Maximum depression occurred 5 min after injection. Fentanyl (1.25 mcg/kg) caused significant decreases in respiratory frequency and minute volume up to 10 min; significant decreases lasted up to 15 min with 2.5 and 5 mcg/kg. Following injections of 2.5 or 5 mcg/kg, PCO_2 increased significantly but returned to normal after 20 min. Concurrent decrease in serum pH showed a similar pattern.

Repeated i.v. injections (every 15 min for 1 hr) produced stepwise decreases in respiratory rate; however, tidal volume progressively increased so that changes in minute volume were not significantly different from those of saline controls. Maximum changes in PCO_2 differed significantly from saline controls, and by the third dose, PCO_2 had not returned to baseline values before the next injection.

Stephen and Cooper (Anesthesia 32: 324-327, 1977) administered fentanyl 0.025 mg/kg, i.p. to newborn rabbits 30 min. prior to inducing anoxia. Rabbits showed significant respiratory depression (dyspnea, apnea and gasping). Gardocki and Yelnosky gave dogs fentanyl (0.010-0.040 mg/kg, i.v.) which produced an immediate decrease in respiratory minute volume.

Cardiovascular Effects

Gardocki and Yelnosky gave dogs 2 doses of fentanyl (0.0025 and 0.005 mg/kg, i.v., 15 min apart). Blood pressure decreased 20%, heart rate remained unchanged in 2 dogs and decreased (140-100 bpm) in 1 dog. ECG was unaffected. In another dog study, 0.010-0.040 mg/kg, i.v. caused immediately decreased blood pressure (maximum effect in 10 min) which lasted 30 min and bradycardia within 2 min. ECG showed ventricular premature contractions at 0.010 mg/kg, i.v. and prolongation of the P-R interval (1 animal at 0.010 mg/kg and all dogs at 0.040 mg/kg). pharmacologist review, 8-7-75) reported slight hypotension and intense bradycardia in nonanesthetized dogs receiving 0.05 mg/kg, i.v. fentanyl. Atropinization predisposes the dog to a pressor response to fentanyl.

Emesis

Gardocki and Yelnosky reported no emetic activity in dogs in doses up to 10 mg/kg, i.m.

Hypotension

Gardocki and Yelnosky reported that dogs given 4 doses of fetanyl (0.01-0.04 mg/kg, i.v.) at 30 min. intervals showed that the animals rapidly develop tolerance to the hypotensive effect of the drug.

Withdrawal

reported that fentanyl suppressed the withdrawal symptoms of morphine-addicted monkeys at 1/75 the morphine dose. When Innovar was given to monkeys for 2 weeks (b.i.d., s.c.) at the highest tolerated dose and abruptly withdrawn, signs of abstinence were very mild.

Neuromuscular Transmission

Gardocki and Yelnosky reported that fentanyl (up to 0.16 mg/kg, i.v.) did not affect neuromuscular transmission in anesthetized cats.

Femoral Blood Flow

Gardocki and Yelnosky reported that intra-arterial injections of 0.050 fentanyl did not affect femoral blood flow.

Hemolysis

reported that when heparinzed dog blood (1 ml) was added to either 0.05, 0.1, 0.25, 0.5, 0.75 or 1 ml of 0.01% fentanyl solution at the highest dilution there was 7% hemolysis.

B. ACUTE TOXICITY

Respiratory deaths occur in rats from doses of fentanyl which are approximately 1/4 that of the calculated LD_{50}. Values are in terms of fentanyl base. (1963, 1964 and 1967b and Gardocki and Yelnosky 1964)

Species	Route	mg/kg LD50 (range)	Observations - Toxic signs
mouse	p.o.	120	For both i.v. and s.c. routes- initial depression was followed by stimulation, increased motor activity, circling, straub tail response, mydriasis, respiratory depression, and convulsions. Onset of signs were 1-2 minutes: all deaths in 24 hours. These signs are similar to those seen with morphine.
	i.v.	11.2 (7.4-16.8)	
	s.c.	62 (27-142)	
rat	i.v.	2.3 (1.5-3.5)	Reduced sensitivity to noise, rigidity, prostration, respiratory depression, and cyanosis.
	s.c.	9.5 (4.9-19)	
hamster	i.m.	8	
dog	i.v.	14.9	
	i.m.	30-40	
	s.c.	1.2	
guinea pig	i.v.	3 (100% death)	
	i.m.	65	
monkey	i.v.	0.03	

MULTIDOSE TOXICITY STUDIES

Species	Group	Mode of Administration	Doses mg/kg/day	Duration (wks)	Laboratory	Report No.
Rat	2M, 2F	Diet	5,10,20,40, 80,160,320	2	Janssen Labs	BRR-130
	20M, 20F	Intramuscular	0			
	15M, 15F	Intramuscular	0.1, 0.4	4	Janssen Labs McNeil Labs	TRR-9
	10M, 10F	Intravenous	0,0.01,0.02, 0.05,0.075, 0.1	4	Janssen Labs McNeil Labs	TRR-126
Rabbit	6F	topical	0, 0.7	4	ALZA	TR-85-1772-025
	6M, 6F	topical	0, 0.7	13	ALZA	TR-85-1772-026
Dog	4M, 4F	Intramuscular	0	4	Janssen, McNeil	TRR-9
	3M, 3F	Intramuscular	0.1, 0.4			
	3M, 3F	Intravenous	0,0.1,0.3, 1.0	4	Janssen, McNeil	TRR-108

SUBCHRONIC TOXICITY

RAT

BRR-130-14 day study: in diet (August 1963 and July 1967b submission

No. of animals/level	2M and 2F
Dosage levels (mg/kg)	5, 10, 20, 40, 80, 160, and 320 per day
Duration and route	14 days; in the diet
Growth effect	Weight loss with doses of 20 mg/kg and greater in spite of increased food consumption. Weight gain on the 5 and 10 mg/kg levels.
Mortality	No deaths at 5 mg/kg; 2 deaths at 10, 20, and 40 mg/kg; 4 deaths at 80 and 320 mg/kg; 1 death at 160 mg/kg.
Signs	The surviving animals on the 40 and 160 mg/kg doses had blood around the mouth and lower abdomen, bloody urine, and diarrhea during the first week.

TRR-9 -30 day study: intramuscular injection (August 1963 and July 1967b

No. of animals/level	20 M and 20 F on control; 15 M and 15 F on test levels
Dosages levels (mg/kg)	0, 0.1 and 0.4 (per day)
Duration and route	4 weeks, i.m.
Growth effect	Reduced weight gain on low dose, slight weight loss on the high dose
Mortality	4 deaths at 0.1 mg/kg, 8 deaths at 0.4 mg/kg
Food consumption	Not measured
Hematology	Normal values
Clinical chemistry	Not done
Organ weights	Normal

SUBCHRONIC TOXICITY

RAT

Gross pathology	Hemorrhage at site of injection in several animals in both control and test groups.
Histopathology	None related to drug administration.
Other comments	Muscle sites not examined or not submitted for examination.

TRR-126 - 30 day study; intravenous injection July 1967b

No. animals/level	20
Dosage levels (mg/kg)	0, 0.01, 0.02, 0.03, 0.05, 0.075, and 0.1 (per day)
Duration and route	30 days; i.v.
Mortality (%)	0, 0, 10, 45, 71, 67, and 83 (100% of males at 0.1 mg/kg).
Signs	No gross abnormalities among survivors. Cardiac lesions noted were not dose related but due to cardiac puncture. Some increase in SGOT levels were noted.

RABBIT

TR-85-1772-025; 28 day repeated application study - ALZA

No. animals/level	6 female
Dosage levels (mg/kg)	0 and 0.7 (per day)
Duration and route	Daily for 28 days; transcutaneous
Mortality	None
Growth effects	None
Signs	No treatment related signs observed
Organ weights	At $p < 0.05$, no statistically significant differences for organ wt, organ wt/kg body wt, or organ wt/gram brain wt.

SUBCHRONIC TOXICITY

RABBIT

Gross necropsy	Normal
Histopathology	Skin sites treated with gauze pads, TTS Placebo and TTS (fentanyl) had reversible subtle microscopic changes. Organs were normal.

TR-85-1772-026; 90 day repeated application - ALZA

No. animals/level	6 male and 6 female
Dosage level (mg/kg)	0 and 0.66 (per day)
Duration and route	Daily for 90 days; transcutaneous
Mortality	One TTS (fentanyl) treated male died on day 78, cause unrelated to drug administration; probable cause aerogenous bacterial infection
Growth effects	None
Signs	None
Hematology	Normal values, consistent among the 3 groups
Clinical Chemicals	No drug related differences
Gross Pathology	None related to drug administration
Skin histopathology	Reversible subtle microscopic changes to sham, TTS Placebo, and TTS (fentanyl) treated site
Systemic pathology	None related to drug administration
Histopathology	None related to drug administration

SUBCHRONIC TOXICITY

DOG

TRR-9-30 day study; intramuscular injection (July 1967b

No. of animals/level	4 M and 4 F on control; 3 M and 3 F on each dose level.
Dosage level (mg/kg)	0, 0.1, and 0.4 (per day)
Duration and route	4 weeks; i.m.
Growth effects	Test dogs did not gain weight, one at each test level lost more than one kg during the study.
Mortality	No deaths
Food consumption	Not measured
Hematology	Slight increase in hemoglobin concentration in test males, some decreased WBC in both test males and females (in low normal range).
Clinical chemistry	Not done
Gross pathology	None, normal organ wts and organ wt/body wt ratios.

TRR-108 - 30 day study; intravenous injection (May 12, 1967 and July 1967b

No. animals/level	3 male and 3 female
Dosage levels (mg/kg)	0, 0.1, 0.3, and 1.0 (per day)
Duration and route	30 day; i.v.
Mortality	None
Growth effects	Decreased body weight at 1 mg/kg
Signs	Sedation and dose related convulsions were observed.
Organ weights	Dose related decrease in spleen and gonads.
Gross necropsy	Normal
Histopathology	Possible mild cholestasis at high dose.

SPECIAL STUDIES

Material	STUDY TYPE	Laboratory	Report No.
Film,	USP Class VI-Plastic Container	ALZA	TR-87-1772-026
Film,	mouse systemic injection	ALZA	TR-81-1702-030
Film,	rabbit intracutaneous injection	ALZA	TR-86-1774-007
	rabbit intramuscular implant		
Silicone Adhesive	USP, Class V	Dow Corning	M8412-U
	pyrogen test	Dow Corning	M8412-P
	tissue cell culture	Dow Corning	M8412-C
		Dow Corning	M8413-C
	90 day subdermal implantation	Dow Corning	M8413-N
	implantation, rabbits	Dow Corning	M8413-S
	sensitization, guinea pigs		
Fentanyl	cytotoxicity assay	ALZA	TR-86-1772-023
TTS (fentanyl)	sensitization, guinea pig	ALZA	TR-85-1772-024
	primary skin irritation	ALZA	TR-84-1772-015
TTS (fentanyl)	7 day skin irritation	ALZA	TR-84-1772-015
	primary skin irritation	ALZA	TR-83-1723-010
Drug reservoir	primary skin irritation	ALZA	TR-84-1722-022
	primary skin irritation	ALZA	TR-79-7830-004
	primary skin irritation	ALZA	TR-84-1744-019

SPECIAL STUDIES

USP Biological Tests - Plastic

The materials in the following studies met the requirements of Class VI - 50°C Plastics.

TR-87-1772-026 - film

TR-81-1702-030 - film,

TR-86-1774-007 - film,

amine resistant silicone adhesive
as evaluated for safety by

USP Class V - 121°C plastics
The material met the test requirements.

pyrogen test
The material met the requirements for absence of pyrogens.

tissue cell culture

No cytopathic effects were produced by 2 lots of the adhesive or their extracts.

90 day subdermal implantation in rabbits

Tissue responses to were essentially equivalent to the USP polyethylene control over all exposure intervals; 3, 10, 30, and 90 days.

guinea pig sensitization - adhesive

No sensitization response was observed. Therefore, under the condition of this test method has a minimal skin sensitization potential.

Muscle irritation study with fentanyl

A single 0.5 ml i.m. dose (0.1 mg base/ml) showed a slight tissue response compared to a severe response to tetracycline (125 mg/ml)

SPECIAL STUDIES

TR-86-1772-023: cytotoxicity of fentanyl - ALZA

Fentanyl was compared to compounds showing severe to no cytotoxicity and appears not to be strongly cytotoxic. There was no cytotoxicity below 0.3 mg/ml.

TR-85-1772-024: guinea pig sensitization TTS (fentanyl) - ALZA

The results of this test, utilizing a modified Buehler technique for topical induction, indicate TTS (fentanyl) is a weak sensitizer in guinea pigs.

TR-84-1772-015: primary skin irritation and 7 day repeated application - ALZA

Single 24 hour exposure and 7 day repeated applications of TTS (fentanyl) to clipped skin of 6 rabbits resulted in mild topical irritation.

TR-83-1723-010: primary skin irritation of - ALZA

Mild irritant

TR-84-1772-022: primary skin irritation of drug reservoir - ALZA,

Mild irritant

TR-79-7830-004: primary skin irritation of film, - ALZA

Mild irritant

TR-84-1772-019: primary skin irritation of film ALZA

Mild irritant

NDA 19-813

Applicant: Alza Corporation
Palo Alto, CA 94303-0802

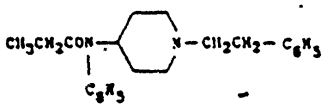
Review #1

Date of Review: March 11, 1988

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary
Date of Receipt - December 28, 1987

Drug: Transdermal Therapeutic System (fentanyl) [TTS (fentanyl)]

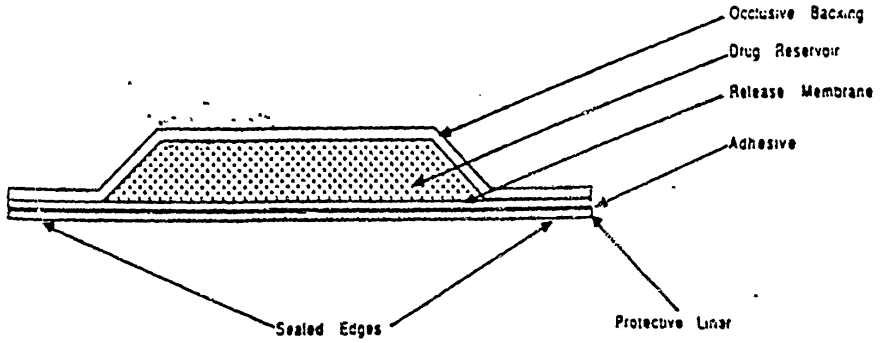
Fentanyl Base (Leptanal)
Alza Code Number: 80285
Molecular Weight: 336.46
Molecular Formula: $C_{22}H_{28}N_2O$



N-(1-phenyethyl-4-piperidyl) propionanilide

TTS (fentanyl) is a transdermal system providing continuous controlled systemic delivery of fentanyl, a narcotic agonist analgesic, for 72 hours. Four system sizes are available: 10, 20, 30 and 40 cm^2. Each system contains 2.5 mg fentanyl and 0.1 ml of alcohol USP per 10 cm^2. The amount of fentanyl released from each system, 25 mcg/hr/10 cm^2, is directly proportional to the area. The composition per unit area of all four system sizes is identical.

TTS (fentanyl) is a rectangular, transparent unit comprising a peel strip and four functional layers proceeding from the outer surface toward the surface adhering to the skin: 1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP 3) an membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a silicone adhesive.



Formulation:

Component Weight per Dosage Form (mg)

Nominal Delivery Rate Delivery Area (Size)	25 mcg/hr (10 cm^2)	50 mcg/hr (20 cm^2)	75 mcg/hr (30 cm^2)	100 mcg/hr (40 cm^2)
Component				
Occlusive Backing				
Film,				
Drug Reservoir				
Fentanyl Base (Active Component)	2.5	5	7.5	10
Purified Water, USP				
Ethanol, 95%, USP				
Release Membrane				
Film,				
Contact Adhesive				
Silicone Adhesive (amine resistant)	--	--	--	--
Protective Liner				
Film,				
Total Weight:				mg

is a processing aid and is not a component of the final system

Category: Narcotic Agonist Analgesic - Synthetic Opioid Related to the Phenylpiperidines

Related IND: - Transdermal Therapeutic System (TTS) - Fentanyl
NDAs:

Marketing Indication: Prolonged control of moderate to severe pain requiring narcotic analgesia.

Each TTS (fentanyl) should be applied to non-irritated skin on the upper torso and may be worn continuously for 72 hours before applying a new system on a different skin site. For surgical use, a dose of 50-100 mcg/hr TTS (fentanyl) is applied 1 - 2 hours prior surgery. For chronic use, a recommended dosage increment is 25 mcg/hr every 72 hours. TTS (fentanyl) - 100 is approximately equivalent in analgesic activity to 60 mg morphine IM (10 mg every 4 hours) administered over a 24-hour period. Analgesia may persist 6-12 hours after TTS (fentanyl) removal.

New Preclinical Studies and Testing Laboratories

A. Pharmacology - Literature Review

B. Acute Toxicity

C. Multidose Toxicity

1. Rat

a. 2-week diet
b. 4-week i.m.
c. 4-week i.v.

2. Rabbit

a. 4-week topical
b. 13-week topical

3. Dog

a. 4-week i.m.
b. 4-week i.v.

REPRODUCTION STUDIES

Species	Group	Mode of Administration	Doses mg/kg/day	Duration days	Laboratory	Report No.
Rat	25F	intravenous	0,0.01,0.03	Day 6-18		TRR-111
	G_1=100, 11,11, 12, 6	subcutaneous	0,0.16,0.32, 0.64,1.25,	Day 0-21 gestation, all groups		TRR-44
	G_2=50, 6,6,3		0,0.16,0.32,			
	G_3=200,3		0,0.16			
	100,5, 5,6	subcutaneous	0,0.04,0.08, 0.16	Day 0-21		TRR-44-G2
	200,20, 20,20,20	subcutaneous	0,0.16,0.32, 0.64,1.25	Day 0-21		TRR-45
	43,28, 28,28,28	subcutaneous infusion	0,0.01,0.1, 0.5	Day 14-21		1986

REPRODUCTION STUDIES

RAT

TRR-111; i.v. administration (May 12, 1967 and July 1967b

No. of animals/level	25 bred females
Dosage levels (mg/kg)	0, 0.01 and 0.03 (per day)
Duration and route	Day 6-18 of gestation; i.v.
Evaluations	Half the dams were killed on Day 20, 1/2 were allowed to live until pups were 30 days old.
Abnormalities	No abnormalities in 417 offspring
Resorptions	31 resorptions at high dose and 6 in control group.
Mortality	For those permitted to deliver, more offspring of high-dose females died than offspring of controls
Litter	No differences in litter size or weight of pups.

TRR-44; subcutaneous - 21 days times 3 generations (May 1967 Appendix to Pharmacologist Review p. 12 and July 1967b

No. of animals/level	G_1 = 100, 11, 11, 12, 6 G_2 = 50, 6, 6, 3 G_3 = 200, 3
Dosage levels	G_1 = 0, 0.16, 0.32, 0.64, 1.25 mg/kg G_2 = 0, 0.16, 0.32, 0.64 mg/kg G_3 = 0, 0.16 mg/kg
Duration and route	For first 21 days of pregnancy for three generations; s.c.
Results	A significant decrease in pregnancies in treated group. An increase in number of still born but no change in litter size. No significant malformations.

REPRODUCTION STUDIES

RAT

TRR44-G2; subcutaneous administration (May 12, 1967 and July 1967b

No. of animals/level	100 in control, 5-6 per test dose
Dosage levels (mg/rat)	0, 0.04, 0.08, and 0.16 (per day)
Duration and route	During gestation, s.c.
Mortality	One or two died at each test dose.
Results	80 litters were born at control level. 4 litters at low dose, and 1 litter each at the higher doses. No fetal abnormalities. No decrease in litter size of successful pregnancies. Decreased birth weights and an increase in resorptions were noted at higher doses.

TRR45; subcutaneous - 21 days (May 12, 1967 and July 1967b

No. of animals/level	200 controls; 20 per treatment level
Dosage levels (mg/kg)	0, 0.16, 0.32, 0.64, 1.25 (per day)
Duration and route	21 days, s.c.
Results	A decrease in pregnancies and average weight of pups occurred due to drug. No change in litter size. The number of resorptions increased with dose.

Subcutaneous administration .; 1966

No. of animals/level	32 in control, 25, 15, 13 per test dose
Dosage levels (mcg/kg)	0, 10,100,500 (per day)
Duration and route	Prebreeding 2 weeks, during breeding and day 1-21 of gestation (about 45 days); subcutaneous continuous infusion.

REPRODUCTION STUDIES

RAT

Evaluation	All dams were killed on day 21 and uteri were examined.
Mortality	4 of 28 dams at high dose died during prebreeding period; there were no other deaths.
Results	34 dams were evaluated in control, 25, 15, and 13 dams were evaluated in the respective low, mid, and high test doses. No differences in reproductive indices and no fetal abnormalities were observed.

MUTAGENICITY STUDIES

Material	Study	Dose Exposure	Laboratory	Report No.
Silicone adhesive	Ames Assay OECD Draft, Protocols 419, 420	highest soluble concentration		TR-85-0110-04
Placebo extract	Ames Assay	Placebo extract in 5% ethanol 5-200 ul/plate		TR-85-1772-059
	MLA	2% and 10% of extract		TR-85-1772-061
	UDS	1% and 10% of extract		TR-85-1772-060
Fentanyl	Ames Assay	8-2100 mcg/plate		TR-85-1772-068
	UDS	0.4-84 mcg/ml		TR-85-1772-066
	MLA	13-126 mcg/ml		TR-85-1772-067
	transformation assay	2.5-250 mcg/ml		TR-86-1735-014
	chromosome aberration	0.6-2500 mcg/ml		TR-87-1772-015
	chromosome aberration	0.37 2.5 mcg/ml		literature

Summary Results of Mutagenicity Assays on Fentanyl

Assay	Report Number	Without S9		With S9	
		Conc. Range*	Result	Conc. Range*	Result
Ames Salmonella mutagenicity	TR-85-1772-068	8.4-2100 mcg/plate	Negative	8.4-2100 mcg/ml	Negative
Primary rat hepatocyte/UDS	TR-85-1772-066	0.4-84 mcg/ml (0.001-0.25 mM)	Negative	Not applicable	
Mouse lymphoma mutagenicity	TR-85-1772-067	13-126 mcg/ml (0.039-0.39 mM)	Negative	13-126 mcg/ml (0.039-0.39 mM)	Positive
BALB/c-3T3 transformation	TR-86-1772-014	2.5-50 mcg/ml (0.007-0.15 mM)	Negative	10-250 mcg/ml (0.03-0.74 mM)	Negative
Chinese hamster ovary cells aberrations	TR-85-1772-015	0.62-650 mcg/ml (0.002-1.95 mM)	Negative	0.62-2500 mcg/ml (0.002-7.50 mM)	Negative
Human lymphocyte chromosome aberrations	Wagner, 1971	0.37-2.52 mcg/ml (0.001-0.007 mM)	Negative	Not done	

*Concentration range in which results were obtained.

MUTAGENICITY STUDIES

85-0110-04

Assay	Salmonella typhinurium and Reverse Mutation Assays OECD Draft Protocol Nos. 419 and 420
Dosage	Highest soluble concentration
Result	No evidence of genetic activity

TR-85-1772-059; placebo extract - Ames assay - ALZA

Assay	Placebos were extracted in 5% ethanol for 72 hr at 50° C. This extract was evaluated in five tester strains of S. typhinurium
Dosage	5-200 mcl per plate
Result	No evidence of genetic activity

TR-85-1772-061; placebo extract - mouse lymphoma assay - ALZA

Assay	Evaluation for mutagenic activity at the thymidine kinase locus in LE178Y mouse lymphoma cells in the absence and presence of metabolic activation
Dosage	2% and 10% of extract
Result	No evidence of genetic activity

TR-85-1772-060; placebo extract - unscheduled DNA synthesis

Assay	Primary culture of rat hepatocytes
Dosage	1% and 10% of extract
Result	No evidence of genetic activity

TR-85-1772-068; Ames Salmonella assay - ALZA

Assay	Strains TA-1535, TA-1537, TA-1538, TA98 and TA100, with and without metabolic activation
Dosage	8-2100 mcg per plate fentanyl
Result	No evidence of mutagenicity

TR-85-1772-066; unscheduled DNA synthesis assay - ALZA

Assay	Primary culture of rat hepatocytes
Dosage	0.4 to 84 mcg/ml fentanyl
Result	No evidence of genotoxicity

TR-85-1772-067; mouse lymphoma assay - ALZA

Assay	Evaluation for mutagenic activity at the thymidine rivase locus in L51784 mouse lymphoma cells in the absence and presence of metabolic activation
Dosage	13 to 126 mcg/ml fentanyl
Result	Without activation there was no evidence of mutagenicity. With activation the mutation frequencies of the cultures treated with 37 and 62 mcg/ml were significantly increased over control and the results were considered positive.

TR-86-1772-014; cell transformation assay - ALZA

Assay	BALB/C-3T3 transformation assay with and without metabolic activation
Dosage	25-250 mcg/ml
Result	Fentanyl did not induce cell transformation

TR-87-1772-015: chromosomal aberration assay in CHO cells - ALZA

Assay	In vitro chromosomal aberration assay in Chinese hamster ovary (CHO) cells with and without metabolic activation.
Dosage	0.62 to 2050 mcg/ml
Result	Compound was toxic in non-activated assay above 615 mcg/ml and nontoxic in the activated assay at 2050 mcg/ml. The results indicated that fentanyl did not cause chromosomal aberrations in vitro in CHO cells.

Chromosome Abberration - Wagner (1971)

Assay	Human lymphocyte chromosomes
Dosage	0 - 3.7×10^{-6} mol/l fentanyl
Result	No evidence of cytogenic activity

G. ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

Fentanyl was not metabolized *in vitro* by human keratinocytes, or skin homogenates.

Primary metabolic pathway for fentanyl involves oxidative dealkylation in the liver to phenylacetic acid and norfentanyl, and small amounts of hydroxy(phenethyl) fentanyl. Chronic drug exposure had no impact on metabolic pathways or distribution of metabolites. Renal elimination of metabolites predominates.

ALZA Research Report; June - December 1986.

Witham *et al*. (1986) - Pharmaceutical Research 3(5):54S, 1986

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Eur. J. Clin. Pharmacol. 4:137-141, 1972

Lehmann and associates (1981, 1982, and 1983)
- Anaesthesist 30:461-466, 1981
- Anaesthesist 31:221-227, 1982
- Anaesthesist 32:165-173, 1983

Evaluation

Transdermal Therapeutic System (fentanyl), also known as [TTS (fentanyl)], is a transdermal system providing continuous controlled systemic delivery of fentanyl, a Schedule II controlled substance and potent narcotic analgesic, for 72 hours. TTS (fentanyl) is a narcotic agonist analgesic, a synthetic opioid related to the phenylpiperidines, approximately 100 times more potent than morphine, which is indicated for prolonged control of moderate to severe pain. Each TTS (fentanyl) should be applied to non-irritated skin on the upper torso and may be worn continuously for 72 hours before applying a new system on a different skin site. For surgical use, a dose of 50-100 mcg/hr TTS (fentanyl) is applied 1 to 2 hours prior to surgery. A 40 cm^2 system would provide 2.4 mg fentanyl per 24 hr, corresponding to 0.048 mg/kg/50 kg subject. For chronic use, a recommended dosage increment is 25 mcg/hr every 72 hours. TTS (fentanyl) - 100 is approximately equivalent in analgesic activity to 60 mg morphine IM (10 mg every 4 hours) administered over a 24-hour period. Analgesia may persist 6-12 hours after TTS (fentanyl) removal.

Fentanyl is the active ingredient in two approved drugs: Innovar (fentanyl citrate+droperidol) Injection (NDA 16-049) and Sublimaze (fentanyl citrate) Injection (NDA 16-619). Fentanyl (0.05 to 0.1 mg, i.v.) produces immediate onset and lasts from 30-60 minutes. The therapeutic dose ranges from 0.05 to 0.10 mg repeated every 1-2 hours. Following intramuscular administration, onset is 7-8 minutes; duration is 1 to 2 hours and t 1/2 is 1.5-6 hours.

Fentanyl, administered acutely, in mice, rats, guinea pigs, dogs and monkeys causes death by respiratory depression, similar to morphine, and has shown the following LD_{50} values (mg/kg):

	i.v.	s.c.
mouse	11.2	62
rat	2.3	9.5
guinea pig	3	--
dog	14.9	1.2
monkey	0.03	

Subchronic toxicity studies of fentanyl have been conducted in rats (2-week diet, 4-week i.v and i.m.), rabbits (4 and 13-week topical) and dogs (4-week i.v. and i.m.).

In rats, 2-week diet studies of fentanyl (5-320 mg/kg/day) showed mortalities at 10 mg/kg and above. Four week i.v. studies in rats (0.01-0.1 mg/kg/day) showed dose-related mortalities beginning at 0.02 mg/kg with increased SGOT levels. Four week i.m. studies in rats (0.1-0.4 mg/kg/day) showed mortality at both levels. The NOEL in rats was 5 mg/kg orally and 0.01 mg/kg intravenously. These data were obtained from by the applicant..

In New Zealand White rabbits, 28-day and 90-day repeated applications of TTS-Fentanyl-25 (10 cm^2 systems with nominal delivery of 0.6 mg/24 hr, equivalent to 0.2 mg/kg, which is approximately 4 times the maximum daily human transdermal dose of fentanyl), produced mild irritation which was comparable to that in placebo and sham controls. No apparent drug-related toxicity was observed. Measurements of residual drug content of the applied systems resulted in an inferred dose of 0.7 mg/kg.

In dogs, 4-week i.v. studies of fentanyl (0.1-1.0 mg/kg/day) showed decreased body weight at 1.0 mg/kg, dose-related decreases in spleen and gonad weights and possible mild cholestasis at 1.0 mg/kg. Four week i.m. studies (0.1 and 0.4 mg/kg/day) also showed decreased body weight at both levels. These data were also obtained from by the applicant.

Special toxicity studies were conducted on raw material films and amine-resistant silicone adhesive) employed in the TTS (fentanyl).

Based upon USP Biological Tests - Plastic Containers (single dose systemic injections in mice, intracutaneous injections in rabbits and implantation of films into the paravertebral muscle of rabbits), requirements of Class VI-50 degree C Plastics were met by Film, Film, and Film

Extracts of Medical Grade Pressure-Sensitive Adhesives passed the USP Class V-121 degree C Plastics test in mice and rabbits, demonstrated no pyrogenicity in rabbits, showed no cytopathic effects in a minimal essential media tissue cell culture test, passed 90-day subdermal implantaton tests in rabbits (responses were comparable to USP polyethylene control) and showed minimal skin-sensitizing potential in guinea pigs.

Fentanyl citrate (single 0.5 ml i.m.) in rabbits showed slight irritation at 72 hours compared to pyralgin (moderate to severe) and tetracycline (severe). Fentanyl in human keratinocytes tissue culture showed no cytotoxicity at concentrations below 1 mM (0.3 mg/ml) and was not strongly cytotoxic.

A guinea pig skin senstization test, using a modified Buehler technique for topical induction, indicated that TTS (fentanyl) is a weak sensitizer in this species.

Rabbit primary skin irritation tests on intact and abraded skin of rabbits showed that TTS (fentanyl) is a moderate irritant (2.2) and the placebo is a mild irritant (2.0). The drug reservoir materials (fentanyl, hydroxyethyl cellulose, and 30% ethanol in water) without surrounding membranes were categorized as mild irritants; Film, and Film were mild irritants.

A 7-day repeated application study in rabbits placed both the TTS (fentanyl) and placebo in the mild irritant category.

Applicant refers to reproduction studies of fentanyl, reported by their submission to . In a study in which rats received fentanyl (0.01 and 0.03 mg/kg, i.v.) from day 6-18 of gestation, there was an increase in the 24-hour pup death rate and an increase in the number of resorptions among high dose rats permitted to deliver. When fentanyl was given subcutaneously (0.04-0.31 mg/kg - 1st generation; 0.04-0.16 mg/kg - 2nd generation; 0.04 mg/kg - 3rd generation) to female rats during the first 21 days of pregnancy for 3 generations, there was a significantly decreased pregnancy rate in treated rats; litter size was unaffected and there were no drug-related malformations. In rats which received fentanyl (0.04-0.31 mg/kg, s.c.) for the first 21 days of pregnancy, there was a dose-related decrease in the number of pregnancies, a dose-related decrease in the birthweight of offspring and an increased number of resorptions. Results of these studies are reflected in the Pregnancy - Category C labeling for Sublimaze.

Fujinaga et al (Anesth Analg 65:51-S170, 1986) infused 4 groups of rats (28/group) for 30 days before and during pregnancy with fentanyl (0, 10, 100 or 500 mcg/kg/day) delivered from rate-controlled osmotic pumps. Plasma levels of fentanyl were approximately 0.25, 1.3 and 8.5 ng/ml. (Plasma levels of fentanyl during human surgery have been reported to be between 0.5 and 10 ng/ml.) Groups showed no differences in reproductive indices and fetal morphological examinations revealed no adverse treatment effects. Similar results were reported by Mazze et al (Teratology 34:51-57, 1986).

Mutagenicity assays of fentanyl (Ames: 8-2100 mcg/plate; mouse lymphoma: 13-126 mcg/ml; unscheduled DNA synthesis: 0.4-84 mcg/ml; mammalian cell transformation: 2.5-250 mcg/ml; chromosomal aberration (0.37-2500 mcg/ml), silicone adhesive (Ames) and placebo extract (Ames, mouse lymphoma and unscheduled DNA synthesis) showed no evidence of genetic activity. Results from the mouse lymphoma assay with metabolic activation indicate a mutagenic potential associated with fentanyl at concentrations of 37 mcg/ml (2,000 times the therapeutic plasma level for fentanyl).

Keratinocytes, a predominate cell type of the epidermis, possess enzymes associated with the metabolism of drugs and other xenobiotics. When human keratinocytes were exposed to growth medium containing ^{14}C-fenantyl for 6 days, no metabolites of fentanyl were found in either the medium or the cell extracts. Witham et al (Pharmaceutical Research 3(5):54S, 1986) also reported that fentanyl was not metabolized by skin homogenates, hairless mouse skin or human epidermal homogenates. In vitro studies of tritiated fentanyl with adult Wistar rat liver homogenates, in vivo studies of tritiated fentanyl in NMRI mice and Wistar rats and studies of equimolar mixtures of fentanyl and deuterium-labeled fentanyl in male Wistar rat and male Hartley guinea pig hepatocytes have shown that the primary metabolic pathway involves oxidative dealkylation in the liver into phenylacetic acid and norfentanyl, and small amounts of hydroxy (phenethyl) fentanyl and 4-(N-propionylanilino) piperidine.

Studies in rabbits with ^{3}H-fentanyl (20 mcg/kg) have shown that the fall in plasma concentration and urinary excretion were more rapid in rabbits than in man, signifying a slower metabolism and longer biological half-life of fentanyl in humans than in rabbits.

The proposed labeling is acceptable from the standpoint of pharmacology.

Conclusion

Transdermal Therapeutic System (fentanyl) [TTS (fentanyl)] has been studied adequately in laboratory animals and has been shown to be relatively safe and efficacious. The toxicological profile which has been developed provides an adequate basis for concluding that the drug can be adequately labeled to provide assurance of its relative safe use in humans.

Clyde G Oberlander
Pharmacologist

cc: NDA 19-813
HFN-160, Doc. Rm. 160
R/D:C. Oberlander:3/11/88
R/D init. by:Dr. Inscoe:3/14/88

NDA 19-813

Alza Corporation
Palo Alto, CA 94303-0802

Type of Submission: Original NDA
Date of Submission: December 21, 1987
Date of Receipt: March 8, 1990
Date of Review: July 18, 1990

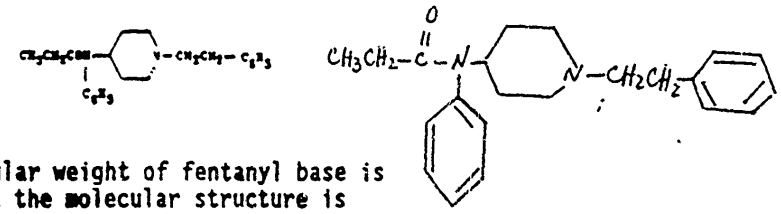
Review #2

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
ADDENDUM TO PHARMACOLOGY REVIEW OF March 11, 1988

Drug: Duragesic

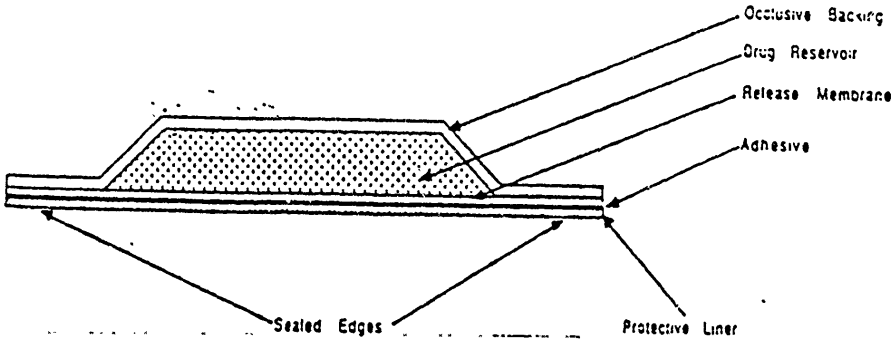
Transdermal Therapeutic System (fentanyl)

DURAGESIC is a transdermal system providing continuous controlled systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours.[1] The chemical name is N-(1-phenylethyl-4-piperidyl) propionanilide. The structural formula is



The molecular weight of fentanyl base is 336.5, and the molecular structure is $C_{22}H_{28}N_2O$. The n-octanol:water partition coefficient is 860:1.

TTS (fentanyl) is a rectangular, transparent unit comprising a peel strip and four functional layers proceeding from the outer surface toward the surface adhering to the skin: 1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP gelled with [redacted] 3) an [redacted] membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a silicone adhesive.



System Components and Structure

The amount of fentanyl released from each system (25 µg/h per 10 cm^2) is directly proportional to the surface area. The composition per unit area of all four system sizes is identical.[2] Each system also contains 0.1 mL of alcohol USP per 10 cm^2.

Dose (µg/h)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.5
50	20	5
75	30	7.5
100	40	10

[3]

The NDA was previously reviewed by Reviewing Pharmacologist (Clyde Oberlander) on March 11, 1988. All preclinical studies and data were listed and evaluated and no new preclinical study has been submitted since March 11, 1988. This review serves as addendum to that review.

Summary and Evaluation:

The application is for Transdermal Therapeutic System (fentanyl), which according to the applicant delivers the potent narcotic agent fentanyl continousouly at a controlled rate with a single application for 72 hrs.

Fentanyl, N-(1-Phenethyl-4-piperidinyl) propionanilide, is a synthetic narcotic analgesic of phenylpiperidine group. It is the active ingredient of two approved products: Innovar Injection and Sublimaze Injection (marketed since 1968).

The TTS system and the proposed four systems to be marketed are described on page 1 and 2 of this review.

Duragesic is indicated for the control of moderate to severe pain in patients requiring opioid analgesia following surgery or for palliative therapy in patients with cancer.

The efficacy and safety of parenteral fentanyl citrate as an analgesic have been established in the laboratory animals and through long marketing experience. No new pharmacology study was conducted. The summaries of literature survey on preclinical pharmcology data were submitted by the applicant and can be found in the Pharmacology Review of March 11, 1988 on pages 8-10.

The studies conducted by the applicant and mostly related to safety were (1) two subchronic (28-day and 90-day) topical toxicity studies in rabbits, (2) several studies on the TTS fentanyl and/or its components to evaluate the toxicity (according to USP Biological Tests), irritation potential and mutagenic potential, and (3) one in vitro study to evaluate the extent of metabolism of fentanyl by human keratinocytes. In addition, one published reproduction study in rats was submitted.

No efficacy or pharmacokinetic data on the TTS fentanyl (an approved drug in a new delivery system) were generated from the laboratory animals. These data, critical for application review, should be obtained from clinical studies. Previously the efficacy and pharmacokinetic of the active ingredient-fentanyl citrate-have been adequately studied in the laboratory animals.

In the 28-day and 90-day topical application studies in rabbits, TTS fentanyl at 0.7 mg/kg did not show systemic adverse effects. No significant local irritation was observed for both placebo and TTS fentanly. The results from three rat and two dog studies were previously obtained by Janssen and described in the Pharmacology Review of March 11, 1988. No target organ toxicity was established in either species following 4 weeks of intramuscular or intravenous administrations. Mortalities were observed in rats from 20 mcg/kg (i.v.), but not in dogs up to 1 mg/kg (i.v.).

Special studies were conducted according to the USP Biological Tests on the occlusive backing, release membrane, contact adhesive and protective liner. The results showed that these components met USP requirements.

Using guinea pig skin sensitization test, TTS fentanyl was shown to be a weak sensitizer.

From the results of rabbit primary skin irritation tests, the following categorizations can be made: TTS fentanyl was moderate irritant whereas all other components including TTS placebo, the drug reservoir materials (fentanyl, and 30% ethanol in water) without surrounding membrane, Film, and Film, were all mild irritants. A seven-day repeated topical application in rabbits showed that both TTS fentanyl and TTS placebo were mild irritants. Previously intramuscular injections of fentanyl citrate revealed slight tissue responses in rats, dogs and rabbits. Furthermore, fentanyl at concentration of 0.3 mg/ml or below was not cytotoxic in human keratinocytes. Taking the data together, TTS fentanyl may cause mild irritation, however, significant local irritation is not anticipated in human use.

Reproduction studies showed no teratogenic effect in rabbits and rats. Fentanyl was embryotoxic (increased resorptions) to rats at 30 mcg/kg (i.v.) and at 310 mcg/kg (s.c.). In rats, dose-related decreases of pregnancy rate and birth weight of pups were observed at 40-310 mcg/kg (s.c.). The results were described under Pregnancy Category C in the package insert. Published reports revealed no adverse reproductive effects (no teratogenic or embryocidal) in rats following continuous mini-osmotic pump infusion up to 500 mcg/kg/day (s.c.) from 14 days prior to mating, continuing through mating and 21 days of gestation.

Mutagenicity studies on fentanyl (Ames Test, mouse lymphoma forward mutation assay, unscheduled DNA synthsis, mammalian cell transformation and chromosomal aberration assays in human lymphocytes and Chinese hamster ovary cells) were negative except the mouse lymphoma assay which showed positive for fentanyl from 37 mcg/ml (2,000 times therapeutic plasma level from TTS fentanyl) in the presence of metabolic acitvation. Mutagenicity studies on silicone adhesive (Ames test) and the TTS placebo extract (Ames test, mouse lymphoma and unscheduled DNA synthesis) were negative.

In vitro study using ^{3}H-fentanyl did not reveal significant metabolism by human keratinocytes.

Typographic errors and addendum to the preclinical studies were amended (see New Correspondence of 7/7/90).

Conclusions:

From the preclinical studies in the laboratory animals and in vitro studies, it can be concluded that:

(1) TTS fentanyl is relatively safe.
(2) TTS fentanyl can be a mild irritant and a weak sensitizer.
(3) TTS fentanyl does not appear to be mutagenic potential.
(4) TTS fentanyl does not appear to be significantly metabolized by human keratinocytes.
(5) The occlusive backing (Film, , drug reservoir components (fentanyl, , ethatnol), release membrane (Film and contact adhesive (silicone adhesive, amine resistant) all met USP Biological Tests requirements and are considered safe.
(6) The efficacy and pharmacokinetic data on TTS fentanyl (an approved drug in a new delivery system) are critical for application review and should be generated from clinical studies. No such data are available from preclinical studies.

The active ingredient of the TTS fentanyl-fentanyl as a citrate salt-has been previously shown to be efficacious and relatively safe in the laboratory animals. In addition, long marketing experience has documented its efficacy and safety in human use. Fentanyl has not been shown to be teratogenic in rodents. Adverse reproductive effects, however, included decreased pregnancy rate and embryocidal effects from 40-310 mcg/kg in rats.

Recommendations:

Based on the conclusions (1)-(5), the toxicological profile which has been developed provides an adequate basis for concluding that the product can be adequately labled to provide assurance of its relative safe use in humans. Therefore, from the standpoint of pharmacology, the application is approvable.

Recommendations to reviewing Medical Officer:
The efficacy and pharmacokinetic data on TTS fentanyl, critical for application review, should be generated from clinical studies.

Pharmacology Portion of Letter to Applicant:

None.

Dou Huey Jean

Dou Huey Jean, Ph.D.
Pharmacologist

cc:
NDA 19-813
HFD-007/Div. File
HFD-007/DHJean
HFD-007/JPHannan
HFD-007/Shekitka
HFD-340
R/D Init by CHChen 7/19/90
F/T by DHJean, 7/18/90, 8/2/90, (page 4)
Wang #0508P

alza

NDA 19,813

August 7, 1990

Food and Drug Administration
Pilot Drug Evaluation
Division (HFD-007)
Room 9B-45
5600 Fishers Lane
Rockville, MD 20857

Attention: John Harter, MD, Director
Pilot Drug Evaluation Division

Subject: Submission of final draft package insert

Dear Dr. Harter:

At the request of Dr. Wright, we are providing the enclosed copy of the final draft package insert for DURAGESIC.

If you require additional information, please contact Janne Wissel at (415) 494-5059 or me at (415) 404-5543.

Sincerely,

Mary Southam

Mary A. Southam, Ph.D.
Product Registration Manager

ALZA CORPORATION, 950 PAGE MILL ROAD, P.O. BOX 10950, PALO ALTO, CA 94303-0802 (415) 494-5000 TELEX 345526

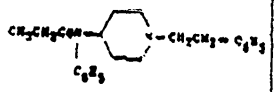
August 7, 1990 8:52am

DURAGESIC® - CII
Fentanyl Transdermal System

WARNING: May be habit forming.

DESCRIPTION

DURAGESIC is a transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-Phenyl-N-(1-2-phenylethyl-4-piperidyl) propanamide. The structural formula is



The molecular weight of fentanyl base is 336.5, and the empirical formula is $C_{22}H_{28}N_2O$. The n-octanol:water partition coefficient is 860:1. The pKa is 8.4.

System Components and Structure

The amount of fentanyl released from each system per hour is proportional to the surface area (25 µg/h per 10 cm^2) . The composition per unit area of all system sizes is identical. Each system also contains 0.1 mL of alcohol USP per 10 cm^2.

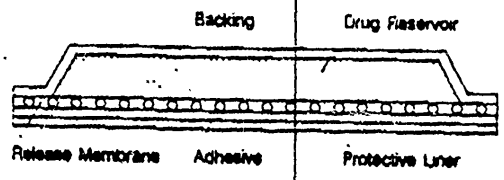
Dose* (µg/h)	Size (cm^2)	Fentanyl Content (mg)
25	10	2.5
50**	20	5
75**	30	7.5
100**	40	10

*Nominal delivery rate per hour
**FOR USE IN OPIOID TOLERANT PATIENTS

DURAGESIC is a rectangular transparent unit comprising a protective liner and four

functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) a backing layer of polyester film; 2) a drug reservoir of fentanyl and alcohol USP gelled with hydroxyethyl cellulose; 3) an ethylene-vinyl acetate copolymer membrane that controls the rate of fentanyl delivery to the skin surface; and 4) a fentanyl containing silicone adhesive. Before use, a protective liner covering the adhesive layer is removed and discarded.



(not to scale)

The active component of the system is fentanyl. The remaining components are pharmacologically inactive. Less than 0.2 mL of alcohol is also released from the system during use.

CLINICAL PHARMACOLOGY

Pharmacology

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid μ-receptor. These μ-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.

In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized.

In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly

occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood levels of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

At therapeutic dosages, fentanyl usually does not exert major effects on the cardiovascular system. However, some patients may exhibit orthostatic hypotension and fainting.

Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in man show no clinically significant histamine release in dosages up to 50 µg/kg.

Pharmacokinetics (see table and graph)

DURAGESIC releases fentanyl from the reservoir at a nearly constant amount per unit time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin

varies over the 72 hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (25, 50, 75, and 100 µg of fentanyl per hour) are sufficiently accurate as to allow individual titration of dosage for a given patient. The small amount of alcohol which has been incorporated into the system enhances the rate of drug flux through the rate-limiting copolymer membrane and increases the permeability of the skin to fentanyl.

Following initial DURAGESIC application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following DURAGESIC application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72 hour application period. Peak serum levels of fentanyl generally occurred between 24 and 72 hours after a single application. Serum fentanyl concentrations achieved are proportional to the DURAGESIC delivery rate. After several sequential 72-hour applications, patients reach a steady state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl (see graph and Table A).

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 17 (range 13-22) hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life ranges from 3-12 hours.

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Serum Fentanyl Concentrations Following Multiple Applications of DURAGESIC 100 µg/h

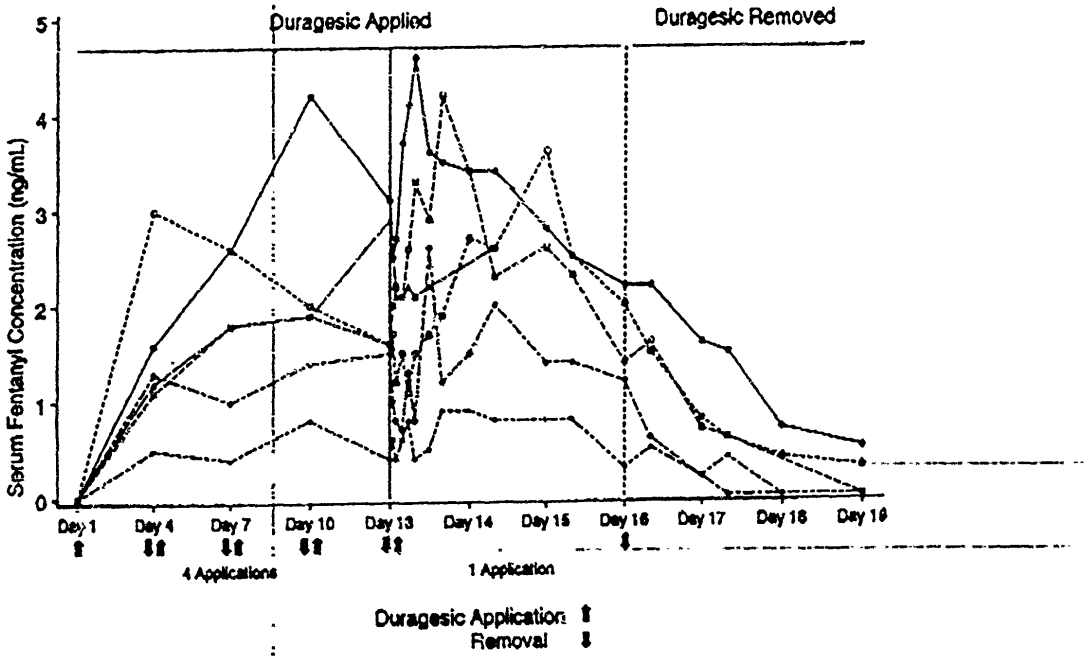

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TABLE A

Range of Pharmacokinetic Parameters of Fentanyl in Patients

	Clearance (L/h) Range (70 kg)	Volume of Distribution V_{ss} (L/kg) Range	Half Life $t_{1/2}$ (h) Range	Maximal Concentration C_{max} (ng/mL) Range	Time to Maximal Concentration (h) Range
IV Fentanyl					
Surgical Patients	27 - 75	3 - 8	3 - 12		
Hepatically Impaired Patients	3 - 80+	0.8 - 8+	4 - 12+		
Renally Impaired Patients	30 - 78				
DURAGESIC 25 µg/h			*	0.3 - 1.2	26 - 78
DURAGESIC 50 µg/h			*	0.6 - 1.3+	24 - 72+
DURAGESIC 75 µg/h			*	1.1 - 2.6	24 - 48
DURAGESIC 100 µg/h			*	1.9 - 3.8	25 - 72

+ Estimated

* After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in 17 hours

Fentanyl plasma protein binding capacity increases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood.

The average volume of distribution for fentanyl is 6 L/kg (range 3-8, N=8). The average clearance in patients undergoing various surgical procedures is 46 L/h (range 27-75, N=8). The kinetics of fentanyl in geriatric patients has not been well studied, but in geriatric patients the clearance of IV fentanyl may be reduced and the terminal half-life greatly prolonged (see PRECAUTIONS).

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Fentanyl is metabolized primarily in the liver. In humans the drug appears to be metabolized primarily by N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Pharmacodynamics

Analgesia

DURAGESIC is a strong opioid analgesic. The approximate analgesic potency of transdermally administered fentanyl to parenteral morphine ranges from 1:20 to 1:30 in non opioid-tolerant patients in acute pain.

Minimum effective analgesic serum concentrations of fentanyl in opioid naive patients range from 0.2 to 1.2 ng/mL; side effects increase in frequency at serum levels above 2 ng/mL. Both the minimum effective concentration and the concentration at which toxicity occurs rise with increasing tolerance. The rate of development of tolerance varies widely among individuals.

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Respiratory Effects

At equivalent analgesic serum concentrations, fentanyl and morphine produce a similar degree of hypoventilation. A small number of patients have experienced clinically significant hypoventilation with DURAGESIC. Hypoventilation was manifest by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In clinical trials of 357 nontolerant patients using DURAGESIC, 13 patients experienced hypoventilation. As a consequence, 10 of 13 nontolerant patients received naloxone, two patients had their dose reduced and one patient required no treatment beyond verbal stimulation. Of the 13 events, seven were associated with DURAGESIC 100 µg/h and six were associated with DURAGESIC 75 µg/h. The incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in patients weighing less than 63 kg (9 of 13). Although patients with impaired respiration were not common in the trials, they had higher rates of hypoventilation.

While most patients using DURAGESIC chronically develop tolerance to fentanyl induced hypoventilation, episodes of slowed respirations may occur at any time during therapy; medical intervention generally was not required in these instances.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations. However, the risk of hypoventilation increases at serum fentanyl concentrations greater than 2 ng/mL in non opioid-tolerant patients, especially for patients who have an underlying pulmonary condition or who receive usual doses of opioids or other CNS drugs associated with hypoventilation in addition to DURAGESIC. The use of DURAGESIC should be monitored by clinical evaluation. As with other drug level measurements, serum fentanyl

concentrations may be useful clinically, although they do not reflect patient sensitivity to fentanyl and should not be used by physicians as a sole indicator of effectiveness or toxicity.

See WARNINGS, PRECAUTIONS, and OVERDOSAGE for additional information on hypoventilation.

Cardiovascular Effects

Intravenous fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with DURAGESIC was less than 1%.

CNS Effects

In opioid naive patients, central nervous system effects increase when serum fentanyl concentrations are greater than 3 ng/mL.

CLINICAL TRIALS

DURAGESIC was studied in patients with acute and chronic pain (postoperative and cancer pain models).

The analgesic efficacy of DURAGESIC was demonstrated in an acute pain model with surgical procedures expected to produce various intensities of pain (eg hysterectomy, major orthopedic surgery). Clinical use and safety was evaluated in patients experiencing chronic pain due to malignancy. Based on the results of these trials, DURAGESIC was determined to be effective in both populations, but safe only for use in opioid-tolerant patients. Because the risk of hypoventilation (4% incidence) in non opioid-tolerant patients, DURAGESIC should not be used for postoperative analgesia (see PRECAUTIONS).

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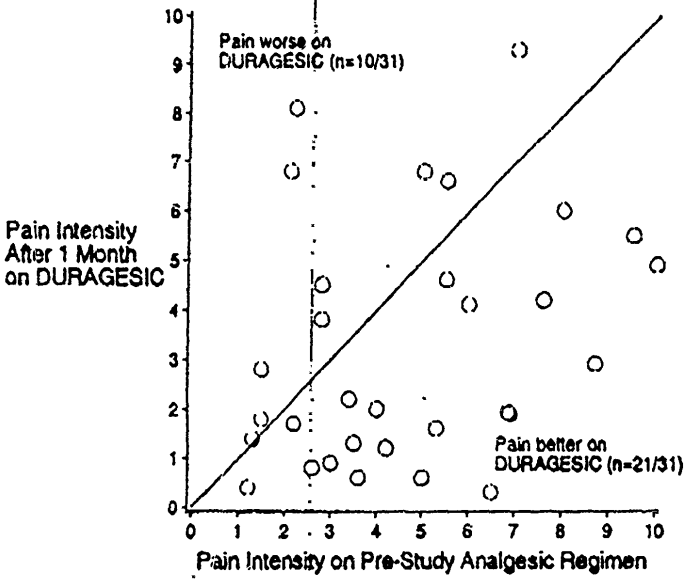
DURAGESIC as therapy for pain due to cancer has been studied in 153 patients. In this patient population, DURAGESIC has been administered in doses of 25 µg/h to 600 µg/h. Individual patients have used DURAGESIC continuously for up to 866 days. At one month after initiation of DURAGESIC therapy, patients generally reported lower pain intensity scores as compared to a prestudy analgesic regimen of oral morphine (see graph).

Visual Analogue Score of Pain Intensity Ratings at Entry in the Study and After One Month of DURAGESIC Use



INDICATIONS AND USAGE

DURAGESIC is indicated in the management of chronic pain in patients requiring opioid analgesia.

DURAGESIC is not recommended in the management of postoperative pain because it has not been adequately studied in these patients and because of the interpatient variability in absorption and disposition of fentanyl seen in the controlled clinical trials. Based on the information available, it is not possible to identify factors to be used to select a dose which will be safe and effective in individual postoperative patients.

In patients with chronic pain, it is possible to individually titrate the dose of the transdermal system to minimize the risk of adverse effects while providing analgesia. For the majority of these patients DURAGESIC is a safe and effective alternative to other opioid regimens (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

DURAGESIC is contraindicated in patients with known hypersensitivity to fentanyl or adhesives.

WARNINGS

PATIENTS WHO HAVE EXPERIENCED ADVERSE EVENTS SHOULD BE MONITORED FOR AT LEAST 12 HOURS AFTER DURAGESIC REMOVAL SINCE SERUM FENTANYL CONCENTRATIONS DECLINE GRADUALLY AND REACH AN APPROXIMATE 50% REDUCTION IN SERUM CONCENTRATIONS 17 HOURS AFTER SYSTEM REMOVAL.

DURAGESIC SHOULD BE PRESCRIBED ONLY BY PERSONS KNOWLEDGEABLE IN THE CONTINUOUS ADMINISTRATION OF POTENT OPIOIDS, IN THE MANAGEMENT OF PATIENTS RECEIVING POTENT OPIOIDS FOR TREATMENT OF PAIN, AND IN THE DETECTION AND MANAGEMENT OF HYPOVENTILATION INCLUDING THE USE OF OPIOID ANTAGONISTS.

THE CONCOMITANT USE OF OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS, INCLUDING OTHER OPIOIDS, SEDATIVES OR HYPNOTICS, GENERAL ANESTHETICS, PHENOTHIAZINES, TRANQUILIZERS, SKELETAL MUSCLE RELAXANTS, SEDATING ANTIHISTAMINES, AND ALCOHOLIC BEVERAGES MAY PRODUCE ADDITIVE DEPRESSANT EFFECTS. HYPOVENTILATION, HYPOTENSION AND PROFOUND SEDATION OR COMA MAY OCCUR. WHEN SUCH COMBINED THERAPY IS CONTEMPLATED, THE DOSE OF ONE OR BOTH AGENTS SHOULD BE REDUCED BY AT LEAST 50%.

PRECAUTIONS

General

DURAGESIC doses greater than 25 µg/h are too high for initiation of therapy in non opioid-tolerant patients and should not be used to begin DURAGESIC therapy in these patients.

DURAGESIC may impair mental and/or physical ability required for the performance of potentially hazardous tasks (eg driving, operating machinery). Patients who have been given DURAGESIC should not drive or operate dangerous machinery unless they are tolerant to the side effects of the drug.

Patients should be instructed to keep both used and unused systems out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself and flushed down the toilet immediately upon removal. Patients should be advised to dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet.

Hypoventilation (Respiratory Depression)

Hypoventilation may occur at any time during the use of DURAGESIC.

Because significant amounts of fentanyl are absorbed from the skin for 17 hours or more after the system is removed, hypoventilation may persist beyond the removal of DURAGESIC. Consequently, patients with hypoventilation should be carefully observed for degree of sedation and their respiratory rate monitored until respiration has stabilized.

The use of concomitant CNS active drugs requires special patient care and observation. See WARNINGS.

Chronic Pulmonary Disease

Because potent opioids can cause hypoventilation, DURAGESIC should be administered with caution to patients with preexisting medical conditions predisposing them to hypoventilation. In such patients, normal analgesic doses of

opioids may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

DURAGESIC should not be used in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. DURAGESIC should be used with caution in patients with brain tumors.

Cardiac Disease

Intravenous fentanyl may produce bradycardia. Fentanyl should be administered with caution to patients with bradyarrhythmias.

Hepatic or Renal Disease

At the present time insufficient information exists to make recommendations regarding the use of DURAGESIC in patients with impaired renal or hepatic function. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

Patients with Fever

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one third for patients with a body temperature of 40°C (102°F) due to temperature-dependent increases in fentanyl release from the system and increased skin permeability. Therefore, patients wearing DURAGESIC systems who develop fever should be monitored for

opioid side effects and the DURAGESIC dose should be adjusted if necessary.

Central Nervous System Depressants

When patients are receiving DURAGESIC, the dose of additional opioids or other CNS depressant drugs (including benzodiazepines) should be reduced by at least 50%. With the concomitant use of CNS depressants, hypotension may occur.

Drug or Alcohol Dependence

Use of DURAGESIC in combination with alcoholic beverages and/or other CNS depressants can result in increased risk to the patient. DURAGESIC should be used with caution in individuals who have a history of drug or alcohol abuse, especially if they are outside a medically controlled environment.

Ambulatory Patients

Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients who have been given DURAGESIC should not drive or operate dangerous machinery unless they are tolerant to the effects of the drug.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Because long-term animal studies have not been conducted, the potential carcinogenic effects of DURAGESIC are unknown. There was no evidence of mutagenicity in the Ames Salmonella mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c-3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration in-vitro assays.

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In the mouse lymphoma assay, fentanyl concentrations 2000 times greater than those seen with chronic DURAGESIC use were only mutagenic in the presence of metabolic activation.

Pregnancy -- Pregnancy Category C

Fentanyl has been shown to impair fertility and to have an embryocidal effect in rats when given in intravenous doses 0.3 times the human dose for a period of 12 days. No evidence of teratogenic effects has been observed after administration of fentanyl to rats. There are no adequate and well-controlled studies in pregnant women. DURAGESIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

DURAGESIC is not recommended for analgesia during labor and delivery.

Nursing Mothers

Fentanyl is excreted in human milk; therefore DURAGESIC is not recommended for use in nursing women because of the possibility of effects in their infants.

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Pediatric Use

The safety and efficacy of DURAGESIC in children has not been established.

Geriatric Use

Information from a pilot study of the pharmacokinetics of IV fentanyl in geriatric patients indicates that the clearance of fentanyl may be greatly decreased in the population above the age of 60. The relevance of these findings to transdermal fentanyl is unknown at this time.

Since elderly, cachectic, or debilitated patients may have altered pharmacokinetics due to poor fat stores, muscle wasting, or altered clearance, they should not be started on DURAGESIC doses higher than 25 μg/h unless they are already taking more than 135 mg of oral morphine a day or an equivalent dose of another opioid (see DOSAGE and ADMINISTRATION).

Information for Patients

Instructions for the application, removal, and disposal of DURAGESIC are provided in each carton.

Disposal of DURAGESIC

DURAGESIC should be kept out of the reach of children. DURAGESIC systems should be folded so that the adhesive side of the system adheres to itself, then the system should be flushed down the toilet immediately upon removal. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet.

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If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with clear water.

ADVERSE REACTIONS

The safety of DURAGESIC has been evaluated in 357 postoperative patients and 153 cancer patients for a total of 510 patients. Patients with acute pain used DURAGESIC for 1 to 3 days. The duration of DURAGESIC use varied in cancer patients; 56% of patients used DURAGESIC for over 30 days, 28% continued treatment for more than 4 months, and 10% used DURAGESIC for more than 1 year.

Hypoventilation was the most serious adverse reaction observed in 13 (4%) postoperative patients and in 3 (2%) of the cancer patients. Hypotension and hypertension were observed in 11 (3%) and 4 (1%) of the opioid-naive patients.

Various adverse events were reported; a causal relationship to DURAGESIC was not always determined. The frequencies presented here reflect the actual frequency of each adverse effect in patients who received DURAGESIC. There has been no attempt to correct for a placebo effect, concomitant use of other opioids, or to subtract the frequencies reported by placebo-treated patients in controlled trials.

The following adverse reactions were reported in 153 cancer patients at a frequency of 1% or greater; similar reactions were seen in the 357 postoperative patients studied.

Body as a Whole: abdominal pain*, headache*

Cardiovascular: arrhythmia, chest pain

Digestive: nausea**, vomiting**, constipation**, dry mouth**, anorexia*, diarrhea*, dyspepsia*, flatulence

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Nervous: somnolence**, confusion**, asthenia**, dizziness*, nervousness*, hallucinations*, anxiety*, depression*, euphoria*, tremor, abnormal coordination, speech disorder, abnormal thinking, abnormal gait, abnormal dreams, agitation, paresthesia, amnesia, syncope, paranoid reaction

Respiratory: dyspnea*, hypoventilation*, apnea*, hemoptysis, pharyngitis, hiccups

Skin and Appendages: sweating**, pruritus*, rash, application site reaction - erythema, papules, itching, edema

Urogenital: urinary retention*

* Reactions occurring in 3% - 10% of DURAGESIC patients

** Reactions occurring in 10% or more of DURAGESIC patients

The following adverse effects have been reported in less than 1% of the 510 postoperative and cancer patients studied; the association between these events and DURAGESIC administration is unknown. This information is listed to serve as alerting information for the physician.

Digestive: abdominal distention

Nervous: aphasia, hypertonia, vertigo, stupor, hypotonia, depersonalization, hostility

Respiratory: stertorous breathing, asthma, respiratory disorder

Skin and Appendages, General: exfoliative dermatitis, pustules

Special Senses: amblyopia.

Urogenital: bladder pain, oliguria, urinary frequency

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DRUG ABUSE AND DEPENDENCE

Fentanyl is a Schedule II controlled substance and can produce drug dependence similar to that produced by morphine. DURAGESIC therefore has the potential for abuse. Tolerance, physical and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is relatively rare. Physicians should not let concerns of physical dependence deter them from using adequate amounts of opioids in the management of severe pain when such use is indicated.

OVERDOSAGE

Clinical Presentation

The manifestations of fentanyl overdosage are an extension of its pharmacologic actions with the most serious significant effect being hypoventilation.

Treatment

For the management of hypoventilation immediate countermeasures include removing the DURAGESIC system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific narcotic antagonist such as naloxone. The duration of hypoventilation following an overdose may be longer than the effects of the narcotic antagonist's action (the half-life of naloxone ranges from 30 to 81 minutes). The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after system removal; repeated administration of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and the release of catecholamines.

If the clinical situation warrants, ensure a patent airway is established and maintained, administer oxygen and assist or control respiration as indicated and use an oropharyngeal airway or endotracheal tube if necessary. Adequate body temperature and fluid intake should be maintained.

If severe or persistent hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy.

DOSAGE AND ADMINISTRATION

As with all opioids, dosage should be individualized. The most important factor to be considered in determining the appropriate dose is the extent of preexisting opioid tolerance. Initial doses should be reduced in elderly or debilitated patients (see PRECAUTIONS).

DURAGESIC should be applied to non-irritated and non-irradiated skin on a flat surface of the upper torso. Hair at the application site should be clipped (not shaved) prior to system application. If the site of DURAGESIC application must be cleansed prior to application of the system, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to system application.

DURAGESIC should be applied immediately upon removal from the sealed package. The transdermal system should be pressed firmly in place with the palm of the hand for 10-20 seconds, making sure the contact is complete, especially around the edges.

Each DURAGESIC may be worn continuously for 72 hours. If analgesia for more than 72 hours is required, a new system should be applied to a different skin site after

removal of the previous transdermal system.

DURAGESIC should be kept out of the reach of children. Used systems should be folded so that the adhesive side of the system adheres to itself, then the system should be flushed down the toilet immediately upon removal. Patients should dispose of any systems remaining from a prescription as soon as they are no longer needed. Unused systems should be removed from their pouch and flushed down the toilet.

Dose Selection

DOSES MUST BE INDIVIDUALIZED BASED UPON THE STATUS OF EACH PATIENT AND SHOULD BE ASSESSED AT REGULAR INTERVALS AFTER DURAGESIC APPLICATION. REDUCED DOSES OF DURAGESIC ARE SUGGESTED FOR THE ELDERLY AND OTHER GROUPS DISCUSSED IN PRECAUTIONS.

In selecting an initial DURAGESIC dose, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (eg whether it is a pure agonist or mixed agonist-antagonist), 2) the reliability of the relative potency estimates used to calculate the DURAGESIC dose needed (potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient. Each patient should be maintained at the lowest dose providing acceptable pain control.

Initial DURAGESIC Dose Selection

There has been no systematic evaluation of DURAGESIC as an initial opioid analgesic in the management of chronic pain, since most patients in the clinical trials were converted to DURAGESIC from other narcotics. Therefore, unless the patient has pre-existing opioid tolerance, the

lowest DURAGESIC dose, 25 μg/h, should be used as the initial dose.

To convert patients from oral or parenteral opioids to DURAGESIC use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.

2. Convert this amount to the equianalgesic oral morphine dose using Table B.

3. Table C displays the range of 24-hour oral and IM morphine doses that are approximately equivalent to each DURAGESIC dose. Use this table to find the calculated 24-hour morphine dose and the corresponding DURAGESIC dose. Initiate DURAGESIC treatment using the recommended dose and titrate patients upwards (no more frequently than every 3 days after the initial dose or than every 6 days thereafter) until analgesic efficacy is attained. For delivery rates in excess of 100 μg/h, multiple systems may be used.

Table 8

EQUIANALGESIC POTENCY CONVERSION

Name	Equianalgesic Dose (mg) IM[a]	PO
morphine	10	60
hydromorphone (Dilaudid®)	1.5	7.5
methadone (Dolophine®)	10	20
oxycodone (Percocet®)	15	30
levorphanol (Levo-Dromoran®)	2	4
oxymorphone (Numorphan®)	1	10 (PR)
heroin	5	60
meperidine (Demerol®)	75	---
codeine	130	200

Note: All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.

[a] Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route.

Reference: Foley, K.M. (1985) The treatment of cancer pain. NEJM 313(2): 84-95.

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Table C
DURAGESIC DOSE PRESCRIPTION BASED UPON
DAILY MORPHINE EQUIVALENCE DOSE

Oral 24-hour Morphine (mg/day)	IM 24-hour Morphine (mg/day)	DURAGESIC Dose (µg/hr)
45-134	8-22	25
135-224	23-37	50
225-314	38-52	75
315-404	53-67	100
405-494	68-82	125
495-584	83-97	150
585-674	98-112	175
675-764	113-127	200
765-854	128-142	225
855-944	143-157	250
945-1034	158-172	275
1035-1124	173-187	300

NOTE: The analgesic activity ratio of 60 mg morphine to 100 µg IV fentanyl was used to derive the equivalence of morphine to DURAGESIC. Thus, a 60 mg oral dose of morphine every 4 hours for 24 hours (total of 360 mg/day) was considered approximately equivalent to DURAGESIC 100 µg/hr.

The majority of patients are adequately maintained with DURAGESIC administered every 72 hours. A small number of patients may require systems to be applied every 48 hours.

Because of the increase in serum fentanyl concentration over the first 24 hours following initial system application, the initial evaluation of the maximum analgesic effect of DURAGESIC cannot be made before 24 hours of wearing. The initial DURAGESIC dosage may be increased after 3 days (see Dose Titration).

During the initial application of DURAGESIC, patients should use short acting analgesics for the first 24 hours as needed until analgesic efficacy with DURAGESIC is attained. Thereafter, some patients still may require periodic supplemental doses of other short-acting analgesics for 'breakthrough' pain.

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Dose Titration

The conversion ratio from oral morphine to DURAGESIC is conservative, and 50% of patients are likely to require a dose increase after initial application of DURAGESIC. The initial DURAGESIC dosage may be increased after 3 days, based on the daily dose of supplemental analgesics required by the patient in the second or third day of the initial application.

Physicians are advised that it may take up to 6 days after increasing the dose of DURAGESIC for the for the patient to reach equilibrium on the new dose (see graph in CLINICAL PHARMACOLOGY). Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic.

Appropriate dosage increments should be based on the daily dose of supplementary opioids, using the ratio of 90 mg/24 hours of oral morphine to a 25 µg/h increase in DURAGESIC dose.

Discontinuation of DURAGESIC

Some patients will require a change to other methods of opioid administration when the DURAGESIC dose exceeds 300 µg/h. To convert patients to another opioid, remove DURAGESIC and initiate treatment with half the equianalgesic dose of the new opioid 12 to 18 hours later (it takes 17 hours or more for the fentanyl serum concentration to fall by 50% after system removal). Titrate the dose of the new analgesic based upon the patient's report of pain until adequate analgesia has been attained. For patients requiring discontinuation of opioids, a gradual downward titration is recommended since it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

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HOW SUPPLIED

DURAGESIC® is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

DURAGESIC Dose (µg/h)	System Size (cm^2)	Fentanyl Content (mg)	NDC Number
DURAGESIC®-25	10	2.5	50458-033-25
DURAGESIC®-50*	20	5	50458-033-50
DURAGESIC®-75*	30	7.5	50458-033-75
DURAGESIC®-100*	40	10	50458-033-100

*For use only in opioid tolerant patients.

Safety and Handling

DURAGESIC is supplied in sealed transdermal systems which pose little risk of exposure to health care workers. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with copious amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may enhance the drug's ability to penetrate the skin.

Do not store above 86°F (30°C). Apply immediately after removal from individually sealed package. Do not use if the seal is broken. For transdermal use only.

CAUTION: Federal law prohibits dispensing without prescription

DEA order form required. A schedule CII narcotic.

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Manufactured for ALZA Corporation, Palo Alto, CA by Ivers Lee, West Caldwell, NJ

Distributed by Janssen Pharmaceutica, Piscataway, NJ

Edition Date of Package Insert

ALZA Package Control Number

August 1990

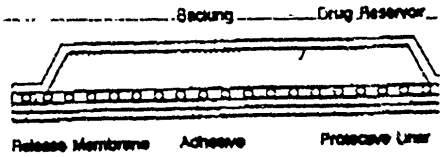
DURAGESIC™ (fentanyl transdermal system)
Instructions for Use

YOUR DOCTOR HAS PRESCRIBED DURAGESIC FOR YOUR USE ONLY. DO NOT LET ANYONE ELSE USE IT. KEEP THIS AND ALL OTHER DRUGS OUT OF THE REACH OF CHILDREN. WHEN YOU REMOVE A DURAGESIC YOU HAVE WORN, FOLD IT WITH THE STICKY SIDE INSIDE AND FLUSH IT DOWN THE TOILET IMMEDIATELY. DISPOSE OF ANY DURAGESIC SYSTEMS REMAINING FROM A PRESCRIPTION AS SOON AS THEY ARE NO LONGER NEEDED.

This leaflet will provide you with specific information about how to use DURAGESIC. Please read it carefully before you use DURAGESIC. If you have any questions or want more information, ask your doctor.

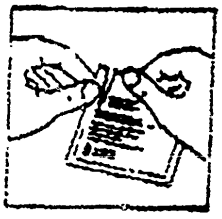
What is DURAGESIC?

DURAGESIC is a thin, adhesive, rectangular system (patch) that is placed on your skin. DURAGESIC delivers a drug called fentanyl, continuously through the skin and into the bloodstream to control your pain around-the-clock. Opioid analgesics (including fentanyl) are used to manage chronic pain.



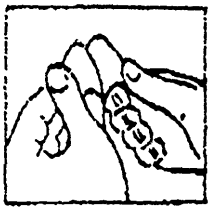
How and Where to Apply DURAGESIC

In the hospital your doctor or another qualified medical person will apply DURAGESIC for you. At home, you or a member of your family may apply DURAGESIC to your skin.

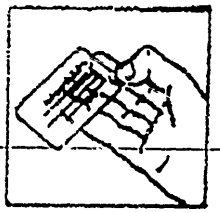


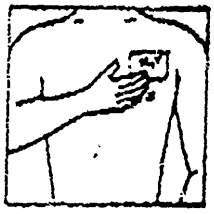
Step 1. Each DURAGESIC is sealed in its own protective pouch. Until you are ready to use DURAGESIC, do not remove it from the pouch. When you are ready to put on DURAGESIC, tear open the pouch at the small slit on the edge of the pouch.

Step 2. A stiff protective liner covers the sticky side of the DURAGESIC--the side that will be put on your skin. With the oversized, stiff, clear liner facing you, pull the liner from DURAGESIC by holding the system at the tab that sticks out from the system (try to touch the sticky side as little as possible). Throw away the liner.



Step 3. Immediately after you have taken DURAGESIC from the pouch, apply the sticky side of the DURAGESIC to a non-hairy, dry area of your front or back above the waist. If the area you select has body hair, clip (do not shave) the hair close to the skin with scissors. Do not put DURAGESIC on skin that is excessively oily, burned, broken out, cut, irritated or damaged in any way. If you need to clean the skin where the system will be applied, use only clear water. Do not use soaps, oils, lotions, alcohol or other products that might irritate the skin under the system. Make sure that the skin is completely dry. Press the DURAGESIC firmly on your skin with the palm of your hand for about 10 to 20 seconds. Make sure it sticks well to your skin, especially around the edges of the system.





Step 4. Wash your hands when you have finished applying DURAGESIC.

Step 5. After wearing DURAGESIC for 3 days, remove it (see Disposing of DURAGESIC). Then choose a <u>different</u> place on your skin to apply a new DURAGESIC and repeat steps 1 to 4, in order.

When to Apply DURAGESIC

If you need continued pain control, wear DURAGESIC continuously for three days (approximately 72 hours), or as directed by your doctor and then remove the system and replace it as directed by your doctor. Do not apply the new DURAGESIC to the same place where you removed the last DURAGESIC.

Your doctor may increase your DURAGESIC dose if your pain is not adequately controlled. IF YOU CONTINUE TO HAVE PAIN CALL YOUR DOCTOR.

Water and DURAGESIC

You can bathe, swim, or shower while you are wearing DURAGESIC. If the system does fall off, put a new DURAGESIC on your skin. Before putting on a new DURAGESIC, make sure the new skin area you have selected is dry.

Disposing of DURAGESIC

Before putting on a new DURAGESIC, remove the system you have been wearing. Fold the used DURAGESIC in half so the sticky side sticks to itself. Flush the used DURAGESIC down the toilet immediately.

Throw away any DURAGESIC systems that are left over from your prescription as soon as they are no longer needed. Remove the left over systems from their protective pouch and remove the protective liner. Fold the systems in half and flush the system down the toilet. Do not flush the pouch or the protective liner.

Safety and Handling

DURAGESIC is supplied in sealed systems which will keep the gel from getting on your hands or body. If the gel from the drug reservoir accidentally contacts the skin, the area should be washed with large amounts of water. Do not use soap, alcohol, or other solvents to remove the gel because they may increase the drug's ability to go through the skin.

Storage Instructions

Keep DURAGESIC in its protective pouch until you are ready to use it.

KEEP DURAGESIC OUT OF THE REACH OF CHILDREN.

Do not store DURAGESIC above 86°F (30°C)(room temperature). Remember, the inside of your car can reach temperatures much higher than this in the summer.

Human

NDA 19-813

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: APR 10 [illegible]

FROM: Mathematical Statistician, HFD-713

THRU: Satya D. Dubey, Ph.D.
Acting Director, HFD-710 SD

SUBJECT: NDA ~~19-813~~, Adjusting the placebo to Fentanyl supplementary Morphine comparison to a Common Pain Intensity Rating.

TO: Curtis Wright, M.D., HFD-007

1. Introduction

In the appendix are two graphs you provided. One graph is for cumulative morphine usage in a protocol where the patient can regulate his/her supplementary morphine use to control excess pain. The second graph shows the pain levels each treatment group attained. The issue is to estimate what the cumulative morphine graph would have been if the patients in the placebo and the Fentanyl groups had dosed themselves to attain the same pain intensity curves.

What follows is a "one try" recommendation which is intended to focus on robustness with possibly some loss of precision.

The following are implicit assumptions:

a. As a first approximation, there exists for each patient a linear relationship between pain intensity difference and the dose of rescue morphine. This relationship provides for zero pain relief when zero morphine has been delivered to the patient.

b. Pain scores for each patient can be considered to be pain intensity difference scores because, according to Dr. Wright, these patients suffer no preoperative pain.

c. At time T, the expectation of each patient's morphine dose-pain relief regression is the same as at any other time during the trial. Deviations from this straight

line are considered to be due to chance.

2. Procedure

This method adjusts only the placebo patient's supplementary morphine usage. This morphine dose adjustment is an attempt to bring placebo patients mathematically to the same observed level of pain experienced by the Fentanyl patients. Let i represent a patient identification number for patients in the placebo group.

A. For each patient i in the placebo group, obtain the observed morphine rescue dose and pain intensity difference (= pain intensity score) pairs at each observation time t. Call these pairs of values [P(t,i), D(t,i)]. If, at any time point, one or both of these values is not recorded, the data pair is dropped at that particular time.

B. For each patient i, compute across all times t, the median pain intensity difference P*(i) and the median supplementary morphine dose D*(i).

C. Compute across patients, the median pain intensity difference P** and the median morphine dose D**.

D. At each time point t, the increment dD by which the placebo patients morphine dose is adjusted upward is computed from the observed difference in pain intensity dP at time t by the equation

$$dD = D^{**} (dP/P^{**})$$

E. The adjusted cumulative morphine dose for the placebo patients is then recomputed.

3. Concluding Comments

The procedure just proposed is to be considered purely exploratory. I have not examined or evaluated the data in question and have no understanding of the appropriateness of the implicit assumptions a, b, or c described in this memo.

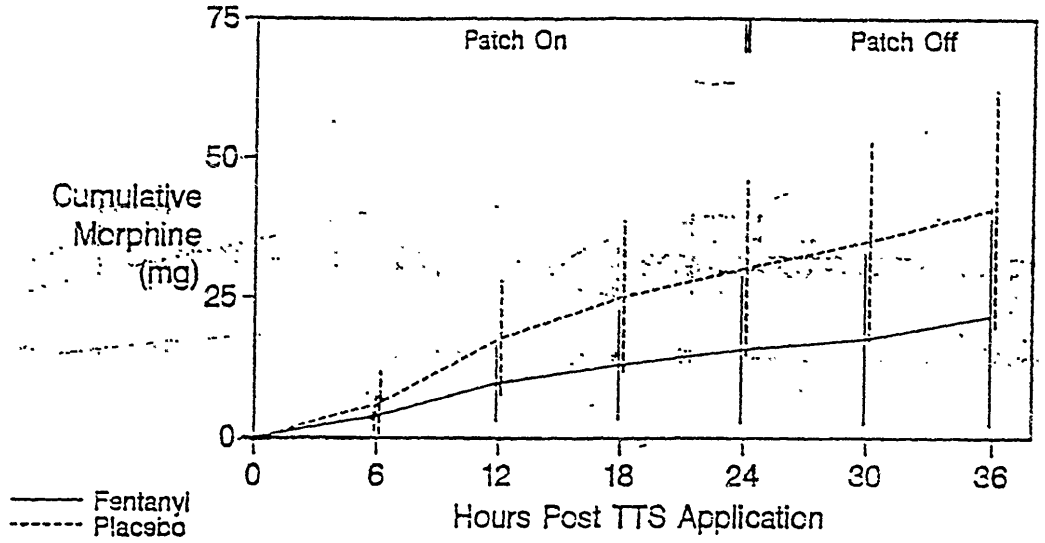
Richard A.Stein, Ph.D.
Mathematical Statistician

This memo contains 3 pages of text and 2 appended graphs.

Concur: Dr. Leung

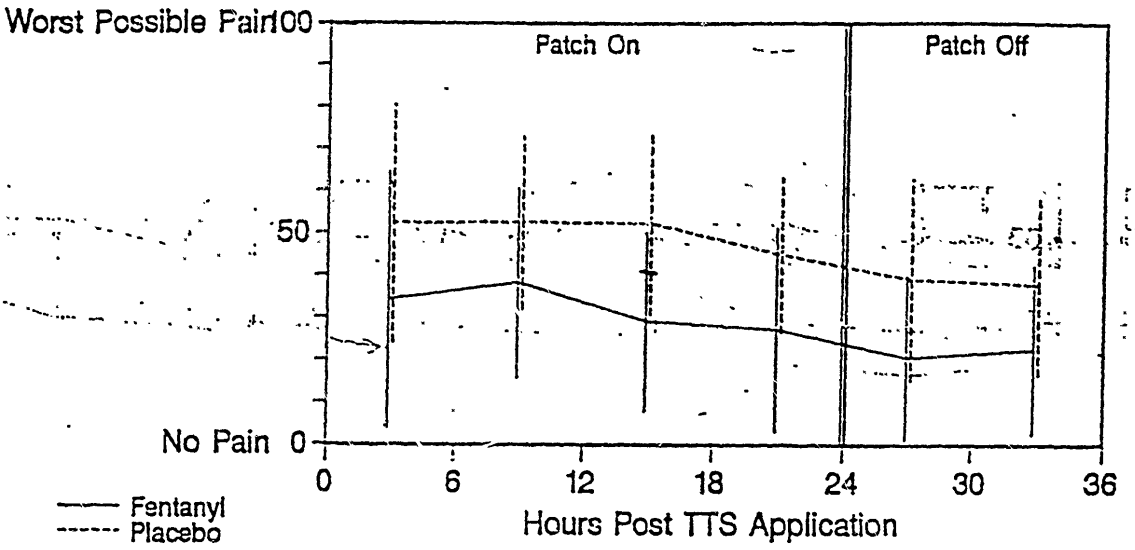
cc: Orig. NDA 19-819
HFD-007/
HFD-007/Dr. Harter
HFD-713/Dr.Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Stein
Chron.
R.A. Stein/x4594/SERB:ras:4/5/90:d=FEN01.WPF

BENEFICIAL EFFECTS
CUMULATIVE USE OF RESCUE MEDICATION
Study: CAPLAN



FENTANYL							
Mean	0.0	3.7	9.7	13.0	15.7	17.5	21.7
SD	0.0	3.6	6.8	9.8	13.1	15.2	19.5
N	20	20	20	20	20	20	20
PLACEBO							
Mean	0.0	6.1	17.8	25.1	30.3	35.0	41.0
SD	0.0	5.6	10.2	13.4	15.6	17.7	21.2
N	20	20	20	20	20	20	20
TOTAL							
Mean	0.0	4.9	13.7	19.0	23.0	26.3	31.3
SD	0.0	4.8	9.5	13.1	16.0	18.5	22.4
N	40	40	40	40	40	40	40

BENEFICIAL EFFECTS
PAIN INTENSITY RATINGS
Study: CAPLAN



FENTANYL						
Mean	34.2	38.2	29.0	27.2	20.4	22.3
SD	30.3	22.5	21.2	24.3	19.4	19.9
N	17	20	20	20	20	20
PLACEBO						
Mean	52.3	52.5	52.2	44.8	38.9	37.6
SD	28.3	20.5	21.7	18.5	24.0	21.3
N	19	20	20	20	20	20
TOTAL						
Mean	43.2	45.3	40.6	36.0	29.7	30.0
SD	30.1	22.4	24.2	23.1	23.5	21.8
N	37	40	40	40	40	40

Statistical Review and Evaluation

Date: 7/18/90

The results reported here are based on different data than used by the reviewing medical officer. His results are based on a data set I believe I received on 7/18/90 which is the FDA review deadline date. In my opinion, my views do not conflict with the medical reviewer Richard A Steeni

NDA#: 19-813/ Drug Class 2C

Applicant: Alza Corp.

Name of Drug: TTS Fentanyl

Indication: Prolonged control of moderate to severe pain.

Documents Reviewed: Vol 1.1, 1.12, 1.25-1.31, 1.37, 1.49, 2.1, 7/19/90
2.2, 5.1-5.4, 8.1, 14.2-14.4, 24.1

The reviewing medical officer for this submission is Curtis Wright, M.D., HFD-007.

1. Background

TTS Fentanyl is designed to deliver the narcotic agent fentanyl through a transdermal patch at a controlled rate for 72 hours. Patch sizes are 10, 20, 30, 40 cm square which are designed to deliver respectively 25, 50, 75, 100 mcg/hr of fentanyl.

2. Study Characteristics

A total of 280 patients scheduled for surgeries expected to produce moderate to severe pain were randomized in double blind fashion to fentanyl or placebo. The characteristics of the 6 studies reviewed are summarized in Table 1. Before surgery, the fentanyl patch was applied to the patient's skin and the patients also received bolus fentanyl as a component of their analgesic treatment. At 24 hours after surgery, the fentanyl patch was removed. Patients were evaluated for efficacy from the time of surgery to a minimum of 36 hours post surgery. For more detail, the reader is referred to the medical officer's review.

There were essentially 2 clinical outcome efficacy variables in these studies; the amount of supplemental morphine requested by the patient and pain experienced by the patient. The applicant defined the primary efficacy variable to be the amount of supplemental morphine requested by patients in the active and placebo study arms. However, for supplemental morphine to be a direct treatment comparator, it must be assumed that patients in each arm will request enough supplemental morphine so that the expected levels of pain in each treatment arm will be the same. In these studies, the expected did not happen. In the four studies where the applicant showed fentanyl to be statistically more effective than

placebo, the applicant also showed that placebo patients had significantly higher pain.

3. Applicant's Statistical Analyses and Results:

Efficacy was evaluated for 5 discrete time intervals, i.e.,

a. The postanesthesia recovery room (PAR) period.
b. Ward - 12 hours after fentanyl patch application.
c. 12 - 24 " " " " "
d. 24 - 30 " " " " "
e. 30 - 36 " " " " "

using a Wilcoxon Rank Sum Test which was applied to patients selected as follows:

A. Only patients who wore the patch the full 24 hours
B. Early removals were included if they wore the patch for the duration of the time interval defined above.
C. Using Gould's method of rank assignment.
D. Early removals were assigned the mean of the 3 highest values of morphine use in their treatment group for each study interval.

Independently of the patient selection/analysis chosen, the applicant's statistical results, based on supplemental morphine taken in isolation, for the studies of Hotchkiss, McLeskey, and Nimmo showed the effectiveness of fentanyl/placebo for the full period of time the patch was worn and 6 hours beyond when the patch was removed (i.e. 0 to 30 hours). With the exception of the PAR period, the Caplan study showed the same outcome. The studies of Plezia and Stanski did not show the effectiveness of fentanyl; however, mean morphine consumption for all time intervals up to 30 hours inclusive was always higher for the placebo patients. The statistical effectiveness of fentanyl beyond 30 hours was only shown directly for the Hotchkiss study.

There is a second interesting feature of the applicant's results. We would imagine a-priori that placebo and fentanyl patients would use enough supplemental morphine to bring themselves to comparable pain levels. This is not the case (Vol 1.1, pages 168-197). The studies of Caplan, Hotchkiss, McLeskey, and Nimmo show pain experienced by placebo patients to be significantly higher than the fentanyl patients. This does not detract from efficacy conclusions based on supplemental morphine usage since to bring placebo patients to the same level of pain as the fentanyl patients, it seems reasonable to assume that placebo patients would have to widen still further the morphine consumption gap.

4. Reviewer's Comments:

In the sense that fentanyl patients required less supplemental morphine than placebo patients, the conclusion that fentanyl is effective remains intact despite the fact that the pain levels of placebo patients were statistically higher than for fentanyl. This difference in pain level does create a dilemma at the next stage of review. What size patch should be used? It will be seen that the 50 mcg/hr patch patients don't seem to need more supplementary morphine than the 100 mcg/hr patients, despite the fact that according to Dr. Wright, the 100 mcg/hr patch shows clearly more toxicity.

A. Patch size determinations based on the studies reviewed are compounded, if not created by study design flaws. This does not mean that mathematical techniques to adjust for these flaws can not be attempted. It does mean that we should be prepared to be skeptical, and let toxicity considerations guide the choice of fentanyl patch size. These flaws are:

1. Each investigator used only one size active fentanyl patch. Therefore, an extra degree of uncertainty about the dose response relationship that is being sought is induced by heterogeneity in investigator measures of differential morphine use and pain scores.

2. Some investigators performed only one kind of surgery. Therefore, extra uncertainty about dose effects is introduced through differences in the inherent painfulness of a given type of surgical procedure.

3. To further complicate the use of these studies for making dose comparisons, some types of surgery involved patiencs of only one sex. This creates some speculation about differences in treatment effect being induced by differences in pain tolerance between the sexes.

4. It appears to be wrong, given present day analgesic practices, to believe that placebo patients can request supplementary morphine in amounts large enough to reduce their pain to the level of patients receiving transdermal fentanyl.

B. A graphical and mathematical analysis follows. If one looks at raw morphine sulfate use in the group of patients receiving fentanyl, it appears that as the fentanyl patch gets larger, the demand for morphine gets larger too (Figure 1). This idiosyncracy might be partially explained from Figure 1 by noting a second idiosyncracy, i.e. in

similar fashion, as the placebo patch size gets larger, the demand for morphine gets larger.

Figure 2 is a refinement of Figure 1 designed to see how well the explanation suggested in the previous paragraph eliminates the first impression that patients with a larger patch needing more supplemental morphine. Figure 2 is an improvement, but it is still not sufficient. Figure 2 does not make the 100 mcg/hr patch appear any more effective than the 50 mcg/hr patch.

The next refinement is to ask what role might adjustments for unequal levels of pain play in clarifying Figure 2. Unfortunately, I believe pain score adjustments will have little effect in suggesting that the larger the fentanyl patch, the less the patient needs supplementary morphine.

Figure 3 is a basic display of mean pain score over the 36 hour test period, and is relatively uninformative. Figure 4 shows the difference in pain score between placebo and fentanyl patients. The pattern of points labeled by investigator in Figure 4 is remarkably the same as the pattern in Figure 2. If the pattern in Figure 4 had clearly shown that the pain differential between fentanyl and placebo got larger as the patch got larger, then the effect would have been to adjust the placebo patient's supplemental morphine requirements upwards for patients wearing larger patches. This is what we would want to see happen for an effective fentanyl patch. Seeing the same pattern for Figures 2 and 4 indicates that adjusting supplemental morphine for dose, will not change the position of the 50 mcg/hr patch relative to the 75 and the 100 mcg/hr patches.

C. An alternate approach is to note that based on Figure 2, the McLeskey study has too great a morphine sparing effect relative to the other studies. The McLeskey study was the only one to use the 50 mcg/hr patch, and it studied only gynecological surgery. It is reasonable to ask how did the McLeskey patients compare to the gynecology patients in other studies. Unfortunately, only Hotchkiss and Plezia recruited patients having the same kind of surgery as McLeskey; and they recruited a total of 1 and 6 patients having gynecological surgery. With so few directly comparable patients, this approach is not to be recommended.

5. Comments which may be Conveyed to the Applicant:

(i) The applicant has provided satisfactory statistical evidence of the effectiveness of fentanyl.

(ii) There is an apparent lack of a morphine use fentanyl patch size dose response relationship. This would appear to be created by what this statistical reviewer considers to be design flaws. These are that each investigator used only one patch size, and the only investigator to use the 50 mcg/hr patch did only gynecological surgery. These facts make it difficult to decide how the drug should be labeled.

Richard A. Stein, Ph.D.
Mathematical Statistician

This review contains 5 pages of text and 5 appended pages.

Peer Reviewer: Dr. Leung

cc:
Orig. NDA 19-813
HFD-007
HFD-007/Dr. Wright
HFD-007/Dr. Stein
HFD-007/Mr. Hannan
HFD-713/Dr. Dubey [File: DRU 1.3.2]
R.A. Stein/x4594:ras:7/18/90:fileid=FEN02

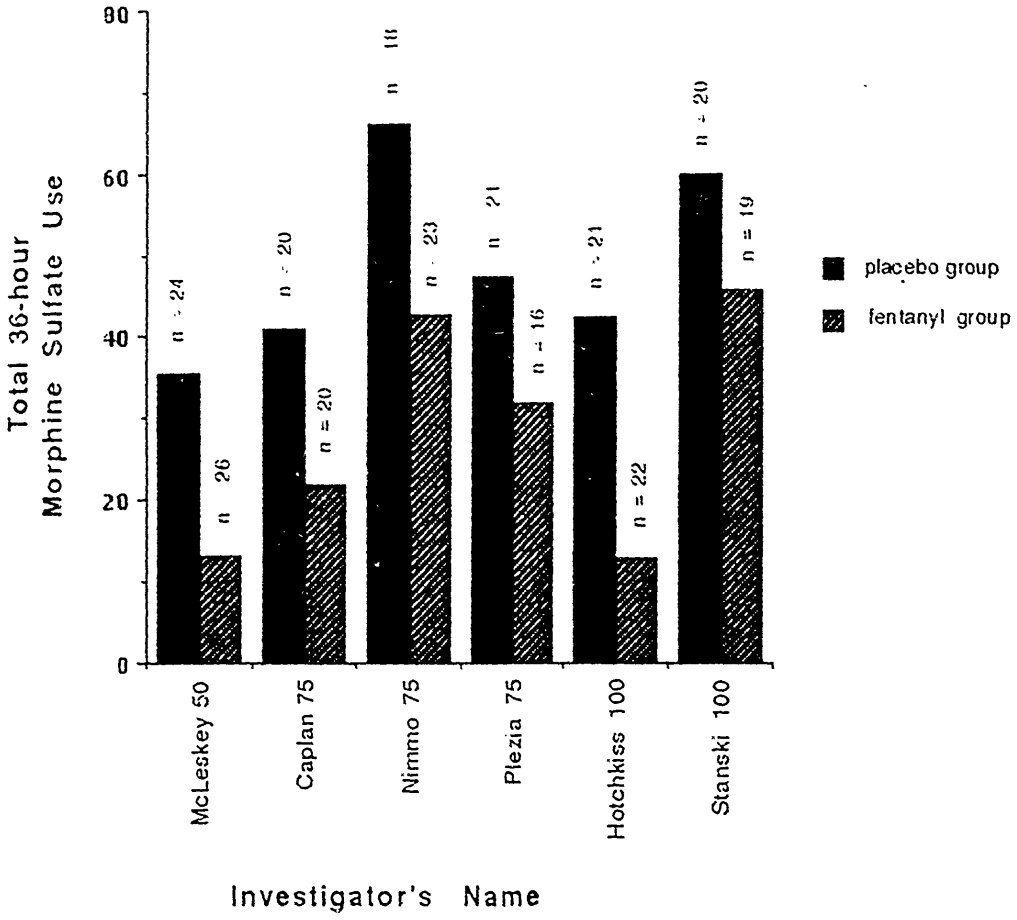
Table 1: Randomized Controlled Clinical Study Characteristics

Investigator	fentanyl (mcg/hr)	— No. of Patients — Recruited	Evaluable	2-tail p-value [1]
McLeskey	50	(28, 26)	(26, 24) [2]	0.05
Caplan	75	(22, 20)	(20, 20)	0.06
Nimmo	75	(23, 23)	(23, 18)	0.03
Plezia	75	(22, 21)	(16, 21)	0.30
Hotchkiss	100	(25, 24)	(22, 21)	0.04
Stanski	100	(23, 23)	(19, 20)	0.60
	Total:	(143,137)	(126,124)	

[1] FDA assigned p-value based on applicant's Wilcoxon Rank Sum Tests up through 30 hours inclusive post-op.

[2] Counts are respectively (fentanyl, placebo)

Figure 1: Total 36-hour Morphine Sulfate Use
Omitting "Non-Evaluable Patients



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Omitting "Non-Evaluable Patients

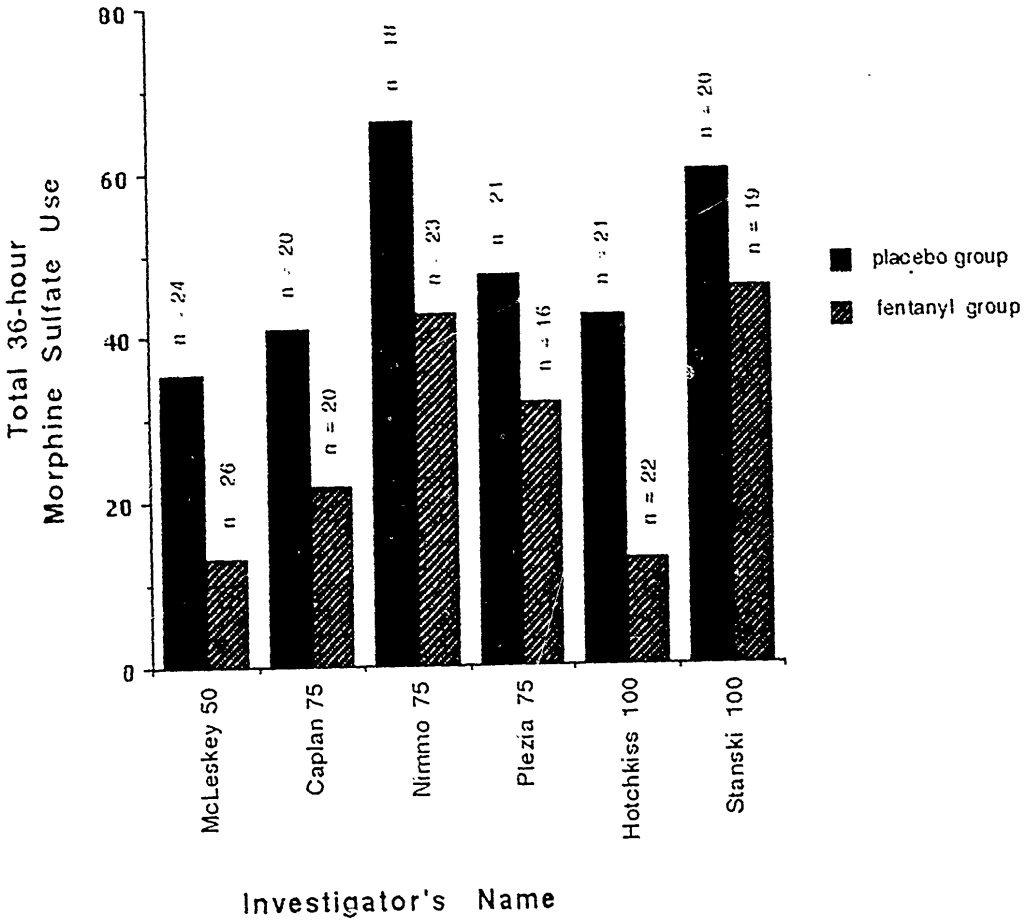

Figure 2: Differential Morphine Use over 36 Hours
Omitting Non-Evaluable Patients
(placebo minus fentanyl)

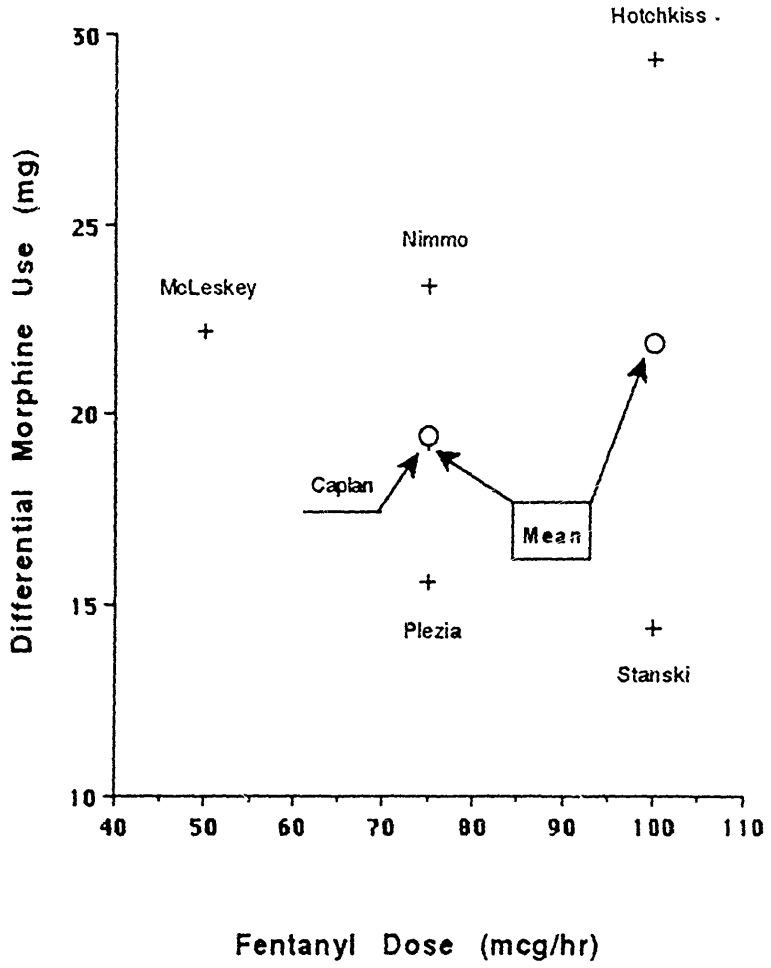

Figure 3: Mean Pain Score over36-hour Period
Omitting "non-Evaluable" Patients

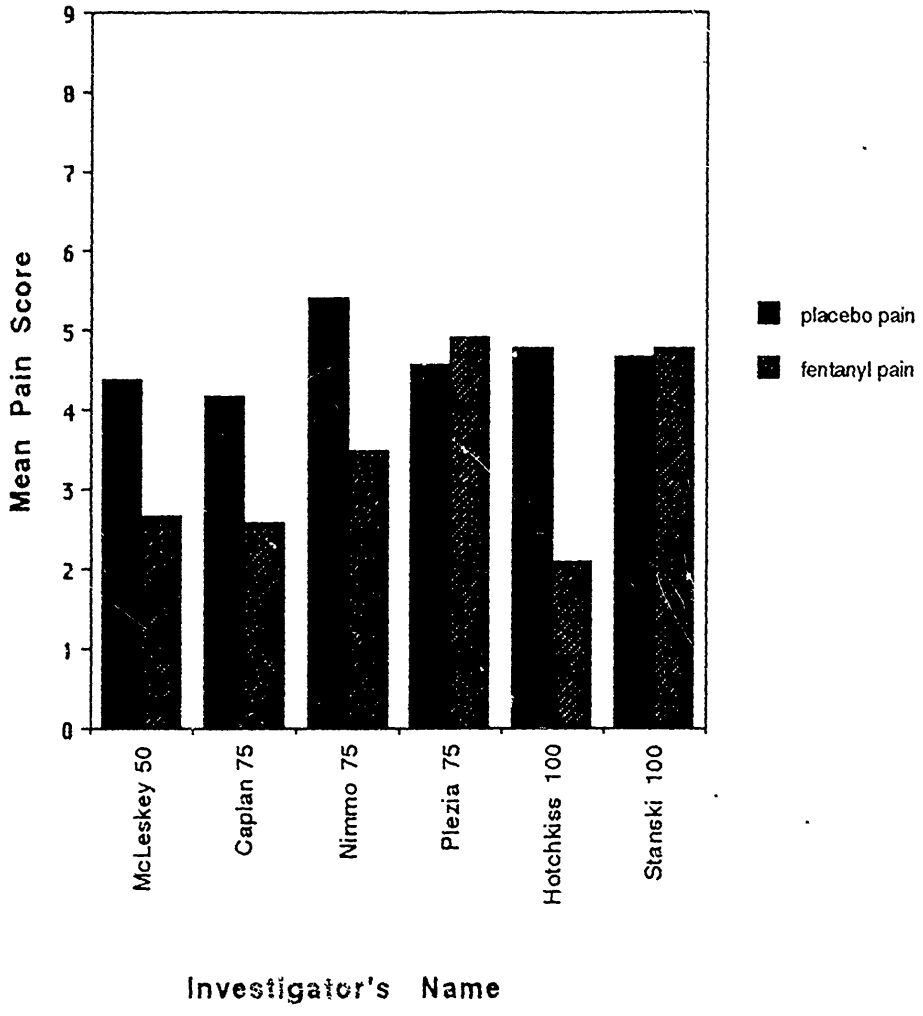

Figure 3: Mean Pain Score over36-hour Period
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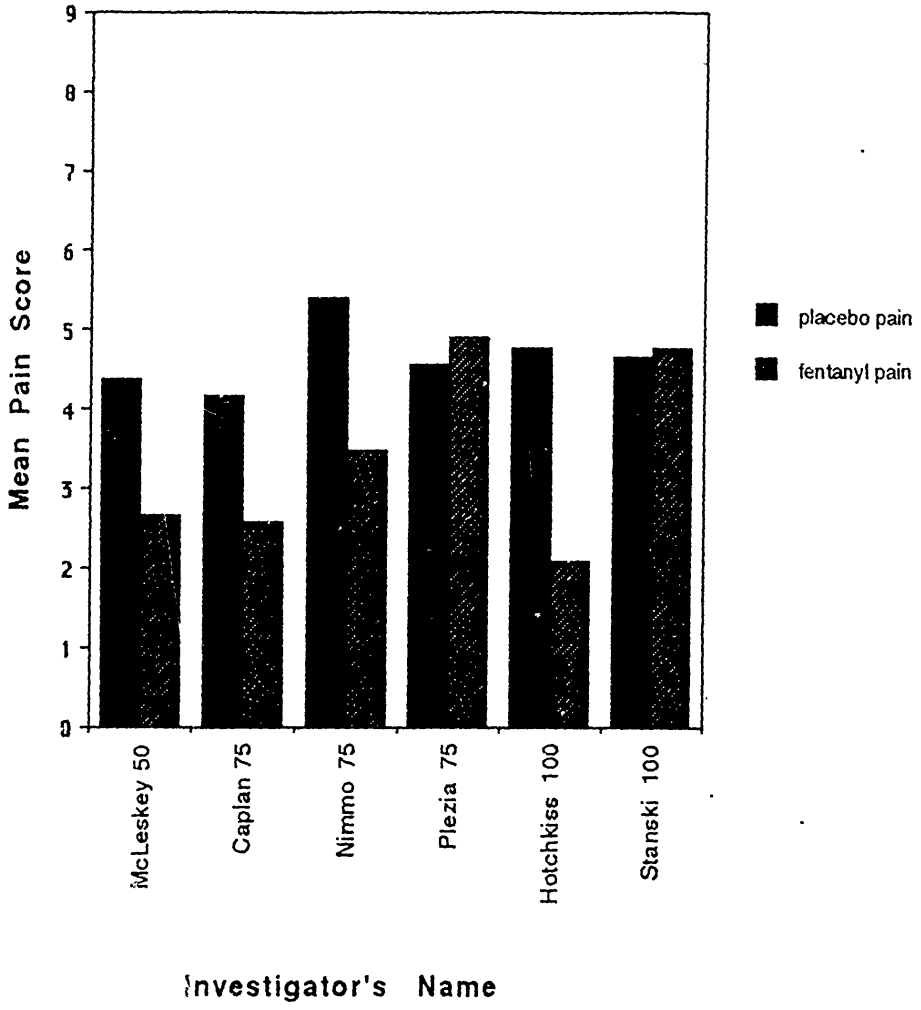


Figure 4: Pain Score Differential
Omitting "Non-Evaluable" Patients
(placebo minus fentanyl)

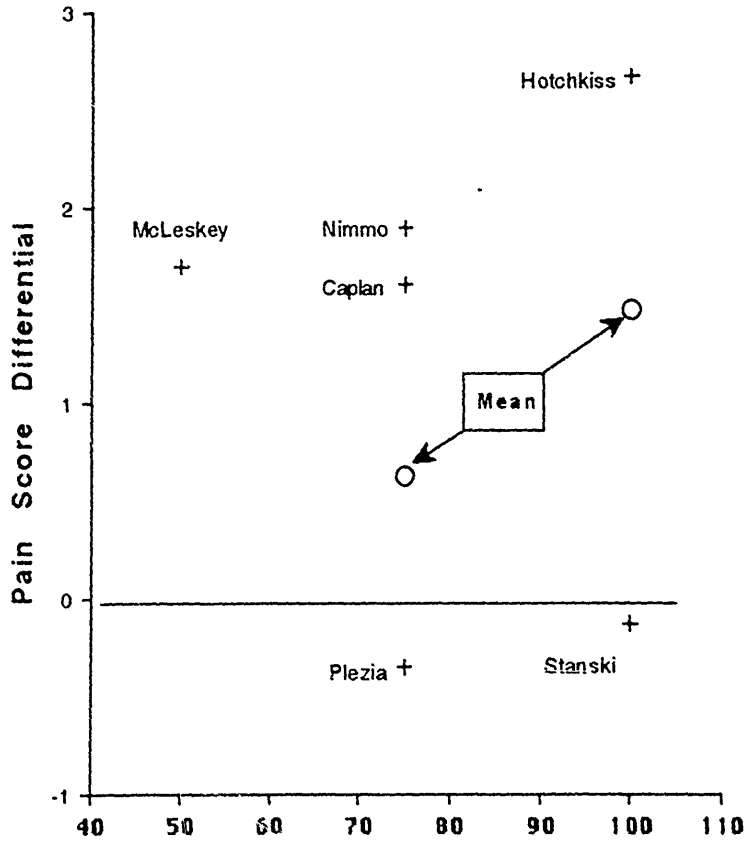
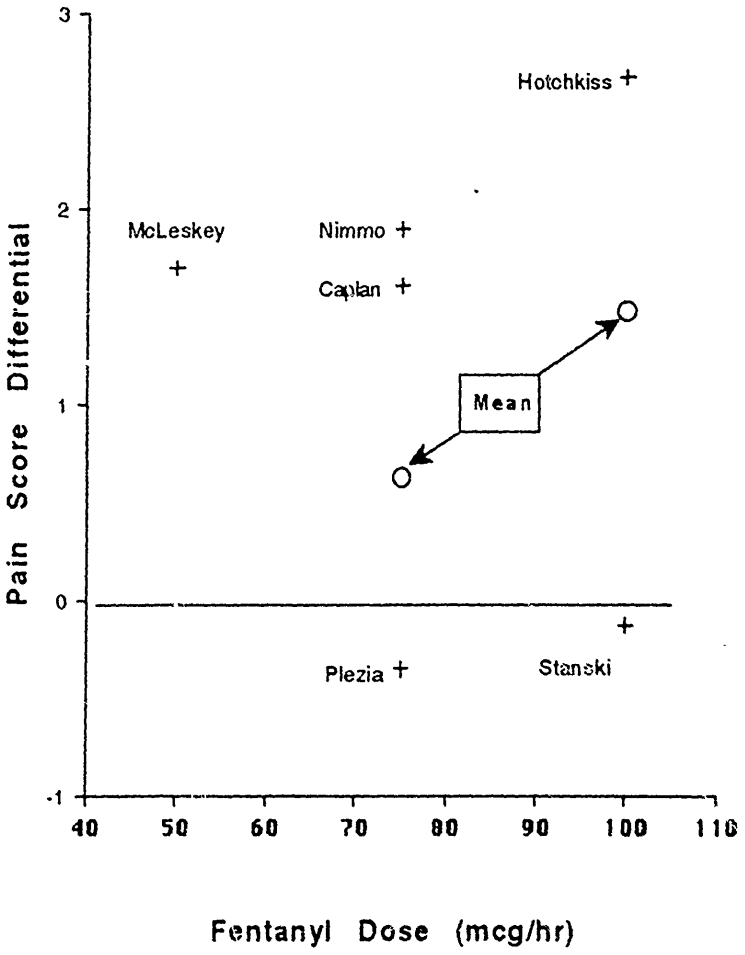


Figure 4: Pain Score Differential
Omitting "Non-Evaluable" Patients
(placebo minus fentanyl)



Medical Officer Review
NDA #: 19,813
Alza Corporation

TTS Fentanyl

(Transdermal Therapeutic System)

Volume 1- Clinical Efficacy Studies

Submitted: 12/31/87
Reviewed: 10/2/89 to 3/23/90
Curtis Wright MD,MPH

WRITTEN CWIV 4/1/90
REVIEWED MS (ALZA) 4/20/90
PEER REVIEWED RL 5/12/90
REWRITTEN CWIV 5/22/90

Table of Contents

Author'sPreface

The clinical review of the Fentanyl Patch has been divided into several parts and is not complete in this volume, which is confined to a discussion of the pivotal and supporting efficacy studies. This is partly due to the intrinsic novelty of the patch as the first transdermal opioid delivery system (Vol. II), and partly to historical accidents in the handling of the NDA. If the reader wishes a complete discussion of the TTS Fentanyl Patch and its properties he or she is directed to the following companion documents.

TTS Fentanyl Clinical Review Volume II- Pharmacokinetics and Pharmacodynamics
TTS Fentanyl Clinical Review Volume III- Integrated Analysis of Efficacy Data
TTS Fentanyl Clinical Review Volume IV- Integrated Summary of Clinical Safety
TTS Fentanyl Clinical Review Volume V- Abuse, Addiction and Diversion Potential

The reader is also advised that certain aspects of the pharmacology of the patches are not discussed at length to spare the reader the tedium of reviewing a great deal of negative material. Suffice it to say that the fentanyl patch has all of the pharmacodynamic properties of fentanyl and of the mu opioids in general. In consequence, a detailed analysis of the expected opioid side effects have not been performed in this volume (see Vol IV), and only the serious adverse events such as respiratory depression have been discussed on a study by study basis. The only pharmacologic effect of fentanyl which has not been observed with the patch are the myoclonic effects on skeletal and respiratory musculature seen in high-dose anesthetic practice.

The following report is organized around the four pivotal postoperative studies and the two clinical utility studies in cancer pain. Each study is presented as an abstract followed by a discussion in detail and finally by copies of summaries of the most significant data. No attempt has been made in this submission to integrate the studies across dose levels or to discuss the relative analgesic strength of the patch (Vol. III). In a similar fashion the abuse potential, addictiveness, and diversion risk of the patch are sufficiently complex to deserve separate discussion (Vol. V).

History of the Submission

The IND for TTS Fentanyl was submitted in 1985, and followed by an NDA for the same product in December of 1987. The IND and NDA have been under review by both HFD-120 and HFD-150 at different periods in the development of the drug, but primary responsibility for the NDA was shifted to HFD-007 in July of 1989. The drug is proposed for an NDA Day in mid-1990.

Therapeutic and scientific background for the drug

Fentanyl TTS (Transdermal Therapeutic System) is a extended release transdermal system which was developed to deliver a narcotic analgesic at a nearly constant rate for use as a supplemental analgesic in post-operative and cancer pain. It was not intended for non-cancer chronic pain, or as a single analgesic agent for all patients, and has been tested in trials where another analgesic agent (rescue medication) was available on demand to patients requiring additional analgesia beyond that provided by the transdermal system.

The parent drug substance, fentanyl, is a stable, highly lipophilic opioid analgesic (octanol/water coefficient 860:1) which is modestly bound to plasma protein (80%) , and has a 2:1 muscle/plasma, 5:1 brain/plasma, and 35:1 fat/plasma distribution ratio in animal studies. In consequence, the pharmacokinetics of the drug are dominated by redistribution to body fat in a fashion quite similar to thiopental or other lipophilic anesthetic drugs. Most clinical experience with the drug has taken place intra-operatively with doses of 50-150 μg at 30-60 minute intervals in balanced anesthesia or at higher doses in so-called "high dose fentanyl " techniques. This type of dosing gives an apparent half-life of 4 hours, clearance of 0.75 l/kg-h and an apparent volume of distribution (Vss) of 4 liters/kg in clinical studies.

Fentanyl is an effective analgesic in opioid naive individuals at blood levels between 0.6-3.0 ng/ml, single dose surgical analgesia is usually achieved at blood levels of 15-25 ng/ml, and intubation or median sternotomy is possible in opioid-naive patients who receive bolus doses which give levels of 40 ng/ml and above. The drug has been in clinical use for about 20 years, but has always been restricted to intravenous administration in the operating room, ICU, and recovery room environments because of a poor oral bioavailability due to a high first-pass metabolism.

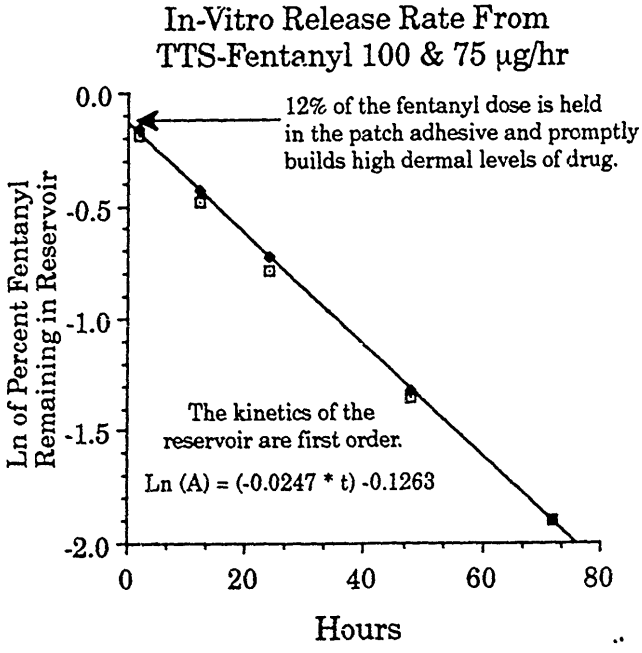
TTS fentanyl is the first dosage form of this drug substance which could be used for chronic administration without injections.

Basic Anatomy and Pharmacology of the Transdermal System

The transdermal system consists of a drug reservoir consisting of a gelled ethanolic solution containing 2.5, 5, 7.5 or 10 mg of fentanyl base and bounded on its skinward surface by a rate limiting semi-permeable membrane. The systems are labeled as delivering 25, 50, 75, and 100 μg of fentanyl base per hour, rather than by the actual amount of fentanyl

they contain. The sponsor was asked to justify labeling the systems as delivering a fixed rate of drug, when this was clearly improbable based on the thermodynamics of the system. The sponsor replied that they had considered labeling the systems by weight of fentanyl contained, but had opted for identifying them by nominal delivery rate instead, citing experience with nitrate systems where different products containing the same amount of drug delivered at different rates had created a safety problem. This argument is sound and suggests that the slight inaccuracy caused by the reference to a fixed rate of delivery is acceptable in order to avoid potential toxicity caused by substitution among transdermal systems.

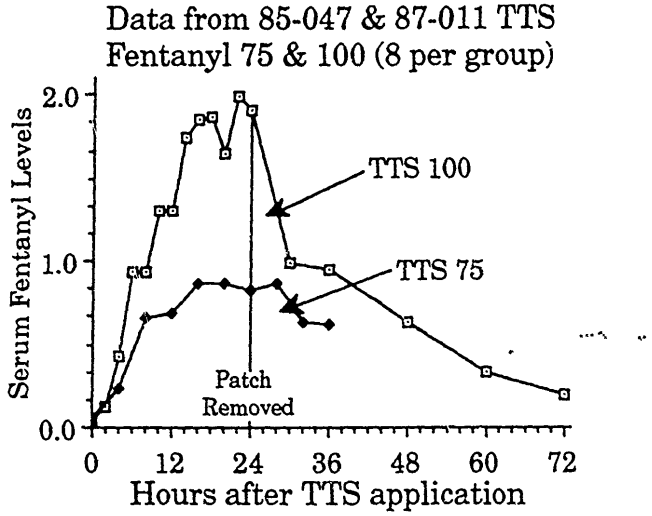
The thermodynamic drive for the delivery system is the concentration difference between the reservoir side and the adhesive covered skinward side of the membrane. The in-vitro delivery rates for the reservoir-membrane system are reported in the later volumes of the NDA and represent the maximal rates of delivery of drug through the membrane into an infinite sink. When these data are transformed and replotted in a semi-logarithmic plot:



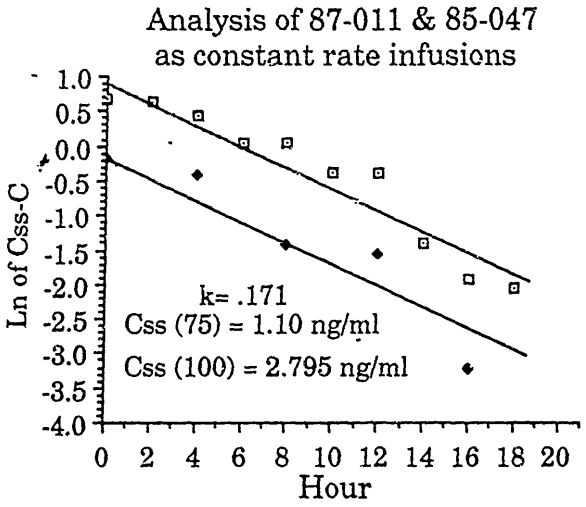
The release from the reservoir of the 75 and 100 µg/hr dosage forms (in-vitro) is first-order with a half-life of about 28 hours, and can deliver drug at rates ranging from a maximum of 200 µg per hour to a minimum of 50 µg/hr (at 72 hours) for a 10 mg system. The upper limit of drug delivery at 72 hours for the transdermal system is about 85% of the dose in the reservoir. These in-vitro studies are the basis for the sponsor's assertion that the TTS system membrane provides about half of the

resistance to the delivery of the drug, with the stratum corneum providing the other half, an assertion which was tested in human studies. Despite the high lipid solubility of fentanyl, pilot work by the sponsor showed that the presence of ethanol in the reservoir was required to provide a high concentration gradient and to alter the permeability of the stratum corneum under the TTS system. If ethanol is not present in the reservoir, or the reservoir contents are applied directly to the skin the rate of absorption is reduced below levels that are clinically useful (1/5-1/10 the enhanced rate).

The sponsor performed two studies without bolus administration of fentanyl, # 85-047 & # 87-011. The data from these studies are plotted below and show that the blood levels resulting from TTS system application are still rising up until system removal at 24 hours. Details of these studies suggest that about 10% of the drug in the system is in the adhesive layer and rapidly builds a skin "depot" under the TTS system. About 25-50 % of the dose in the reservoir is delivered at a nearly constant rate in the first 24 hours of TTS system application, and the 0.5-1.5 mg in the skin depot is slowly absorbed after the system is removed, extending the apparent half-life of the fentanyl due to continued absorption from the skin site.



These data were used to estimate the pharmacokinetic parameters for fentanyl given by the TTS system, assuming nominal rates of 100 & 75 µg/hr (based on actual delivery from TTS system content analysis). The blood levels at 24 hours suggested that the minimum effective TTS system size was likely to be the 75 µg TTS system, based on a minimum pharmacodynamically effective blood level of 1 ng/ml.

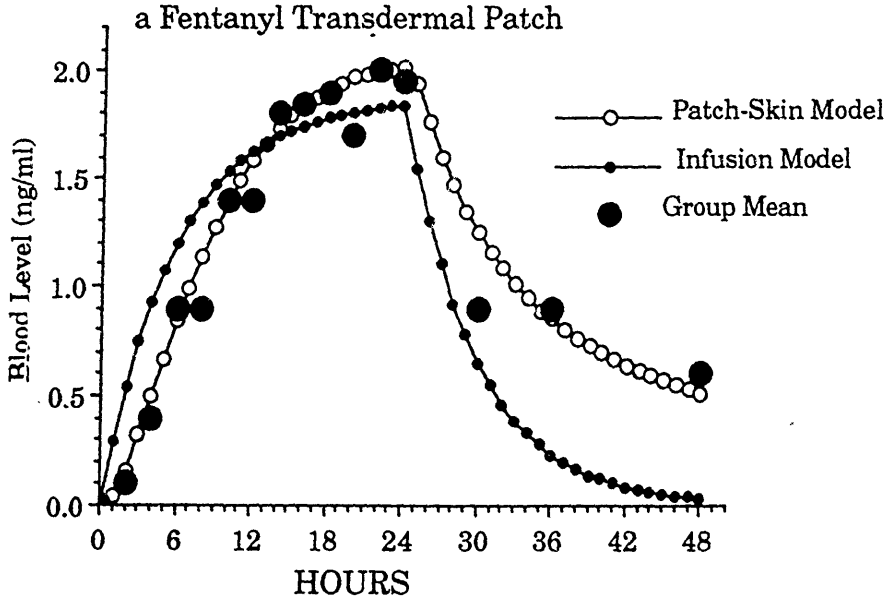


Using the nominal rates of 100 & 75 μg/hr for the TTS system the estimated clearances for 75 and 100 μg TTS systems are 75*1000/1.10 = 68 l/hr and 100*1000/2.795=35 l/hr , giving a volume of distribution between 204 and 397 liters (3-5 l/kg). The half life of the drug calculated from the administration phase of these studies is 0.693/.171 = 4 hours. These results are consistent with the reported findings of intravenous studies of fentanyl kinetics and suggest that the TTS system kinetics can be approximated by a one compartment open model assuming constant rate intravenous infusion during the period of TTS system application. These studies demonstrated that bolus fentanyl must be given if analgesic (0.5-1.0 ng/ml) concentrations of fentanyl were to be achieved within several hours of TTS system application.

Neither a one compartment open model nor the more complex tri-exponential model of fentanyl kinetics can explain all of the features of TTS system performance. Data from the pharmacokinetic studies show that there is a substantial "skin depot" built up (presumably above the stratum corneum). After TTS removal the skin depot is slowly absorbed resulting in a longer apparent half-life for fentanyl than expected following TTS system removal, based on parameters established in IV kinetic studies.

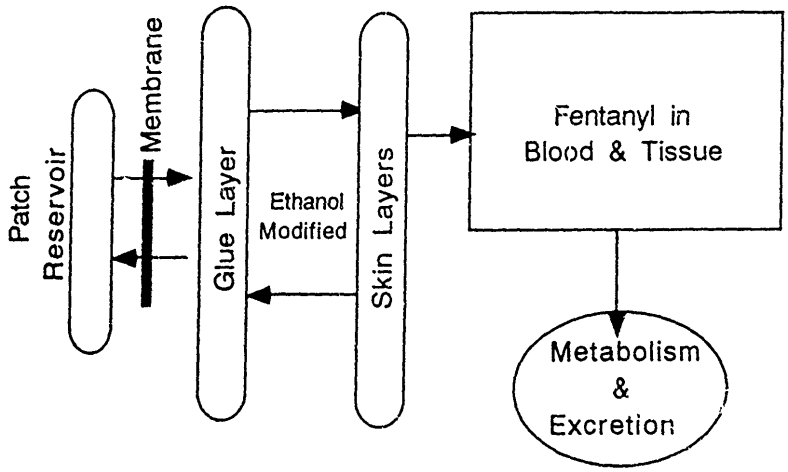
Meetings between the sponsor, HFD-007 and Biopharmaceutics resulted in a consensus that the TTS system could adequately be modeled using a system-skin-body model, using the established single compartment kinetic parameters for the apparent volume of distribution and clearance of fentanyl, a first-order permeability constant for the TTS system membrane, and estimated first-order permeability constants for the adhesive layer and the skin (assumed to be related to the characteristics of the stratum corneum, dermal blood flow, local concentration of the ethanolic enhancer, and the closeness of the coupling across the adhesive layer). This model was tested using the data from an 8 patient pharmacokinetic study available in the NDA (Vol 18.1), and a satisfactory fit of the data was accomplished .

Comparison of Actual Data and
Two Pharmacokinetic Models for
a Fentanyl Transdermal Patch



A computer model of this system was developed and was evaluated in HFD-007. It showed that application of the TTS system caused a rapid flux of fentanyl held in the adhesive layer into the epidermis, rapidly establishing a skin depot, but with no systemic delivery of drug until a substantial skin depot (0.5-0.75 mg) was established. Once the skin site was "full" of fentanyl and fully modified by ethanol, the flux to the body increased until it began to be limited by the loss of both fentanyl and ethanol from the reservoir. The interplay between these two fluxes account for the shape of the fentanyl blood level curve during TTS system application and removal.

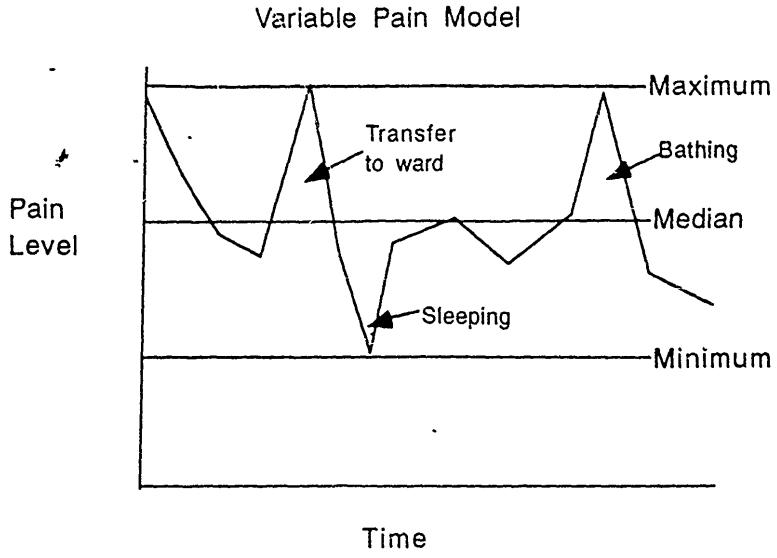
TTS Fentanyl Patch-Glue-Skin Model



Appropriate constants for the TTS system are Vss=398 liters, Cl=46 l/h, and MRT = 9.78 hours.

History of the Clinical Investigations

The intended labeling for this product was for a method of delivering high levels of opioid analgesia to cancer patients without having to use an injectable dosage form. Fentanyl was chosen as the opioid on the basis of its physical characteristics and the TTS system technology available to the sponsor. The pain model for TTS fentanyl were conditions in which doses of 10-15 mg of IM morphine are required at variable intervals to control a nociceptive stimulus with exacerbations due to emotional state, movement, or other transient conditions. The sponsor has labeled the drug for usage in peri-operative and post-operative analgesia and chronic cancer pain. The model of pain in either case is sketched below:



If the dose of an analgesic drug is adequate to control the most intense pain in a day it may be too great for the minimum pain periods. In the best clinical practice this is usually managed by allowing a patient to take a reduced dose or to skip a dose at times of low analgesic demand and to time medication administration so that there will be adequate analgesia for meals, bathing, and transfers. Controlling drug delivery is thought to be important, since current analgesic theories suggest that analgesic medication levels ought not to be allowed to drop too low, in that restoring analgesia may be more difficult than maintaining it.

The sponsor's stated goal for the TTS system was to provide a convenient method for delivering a constant amount of opioid, resulting in stable blood levels of analgesic drug capable of relieving a patient's median pain. TTS fentanyl was not intended to be given in doses which abolish all pain in all patients, but rather as a baseline analgetic with supplementation as needed by short-lived opioids to cover peak pain periods. In post-operative pain the goal was to provide long acting analgesia over the first 1-3 post-operative days, while in cancer pain the goal was to provide convenient stable analgesia with little peak to trough variation in baseline opioid levels.

These goals resulted in the clinical hypothesis that TTS fentanyl would reduce concomitant analgesic demand while providing satisfactory pain relief scores in both cancer pain and post-operative pain.

Clinical studies

Owing to the technical difficulties of analgesic studies in chronic cancer pain, the company solicited the advice of the FDA's drug abuse staff prior to development of the investigational plan. Studies were proposed

using continuous IV fentanyl infusions in ICU settings to determine the expected fentanyl requirements and kinetics of the drug, followed by efficacy studies in postoperative analgesia, and Phase III trials in chronic cancer patients. An inventory of the studies performed is supplied in the next section, showing the pivotal clinical efficacy studies in italics.

The conduct of the clinical studies of the drug was uneventful, but it was soon learned that the onset of meaningful analgesia in the postoperative efficacy studies lagged TTS system application by at least six and as long as twelve hours. In consequence, the majority of the post-operative studies utilized a bolus dose of fentanyl given at operation, and provided prn rescue medication . As will be seen later, the slow onset, extended duration of action (72 h +), and use of a bolus dose of fentanyl did not allow the usual methods of single-dose analgesic trial analysis to be used in these studies. Instead, the cumulative and interval use of rescue medication and global efficacy ratings were the primary clinical outcome variables and pain relief scores reflected the combined analgesic effects of the TTS system and the rescue medication used by the patient.

The same TTS system-PRN rescue combination was used in later cancer analgesia trials, but without any bolus doses of fentanyl. In those trials the patients were usually stabilized on morphine, converted to TTS fentanyl systems in a theoretically equianalgesic dose, then followed for pain relief and use of rescue analgesics. As in the postoperative trials, there was a high rate of use of rescue narcotics resulting in a combination of effects being measured for not only pain relief, but adverse effects as well.

Inventory of Studies

Significant Chemical Studies

Report 6.1	6.1:030	Basic Kinetics of the system membrane.

Significant Pre-Clinical Studies

McNeil	1.4: 64	LD-50 Monkey=30μg/kg IV
85-1772-025	1.4:68	28 day rabbit repeated application study
85-1772-026	1.4:127	90 day rabbit repeated application study
85-1772-004-067	1.6:001-196	Mutagenicity/chromosome studies
TRR-111,44,&45	1.6:226-246	Teratogenicity studies
NONE		No appropriate withdrawal studies in animals
NONE		No carcinogenicity studies in animals

Pharmacokinetic studies of Fentanyl Drip Analgesia

83-008-00	Stanski 1.22	45	ICU Fentanyl Drip
84-015-00	Nimmo 1.26	45	Drip efficacy
84-011-01	Miser 1.33	23	Drip doses
	Gourlay 5.9:023	30	Fentanyl Dose-Effect Levels

Pharmacokinetic Studies of TTS Fentanyl in Patients

87-011-01	Stanski 5.8	8	TTS Bioavailability
85-018-01	Niland 1.34	10	Conversion to TTS
85-042-00	Hotchkiss 1.20	6	Pilot 100
85-030-01 a&b	Nimmo 1.17-18	21	Pilot 100
85-046-01	Caplan 1.21	10	Pilot 75
85-047-00	Plezia 1.23	8	Pilot 75
85-038-00	Jackson 1.19	8	Pilot 50
85-051-00	McLeskey 1.24	8	Pilot 50
85-005-02	Stanski 1.13	10	TTS 50
85-052-01	Larijani 1.14-15	20	TTS 75
85-046-01	Caplan 1.32	21	Ventilatory Response 75
85-032-01 I	Mather 5.1	14	25-100 New TTS Daily x2

Pilot Studies of TTS Fentanyl in Post-operative analgesia

85-038-00	Jackson 1.27	5	TTS 50
85-032-01 II	Mather 5.2	40	New TTS Daily X2

Pivotal Studies of TTS Fentanyl in Post-operative analgesia

85-042-00	***Hotchkiss 1.28***	***49***	***TTS 100***
85-030-01	***Nimmo 1.26***	***46***	***TTS 100***
85-046-01	***Caplan 1.29***	***43***	***TTS 75***
85-051-00	***Mcleskey 1.31***	***54***	***TTS 50***

Supportive Studies of TTS Fentanyl in Post-operative analgesia

85-047-00	*Plezia 1.30*	*43*	*TTS 75*
85-005-02	*Stanski 1.25*	*46*	*TTS100*
85-053-00	*Muller 14.3*	*43*	*TTS 75*
87-004	*Latasch 14.4*	*60*	*TTS 75*

Utility/Efficacy Studies of TTS Fentanyl in Cancer Analgesia

87-010-01	*Payne 14.2*	*54*	*Open label 0-27 months*
86-003-01 II	*Levy 5.4*	*46*	*Controlled Trial 2 wk. x-over*

Individual Study Reports

Pivotal Studies in Postoperative Pain

85-042-00 Hotchkiss 100 μg/h TTS Fentanyl

Abstract

This was a 49-patient, randomized, double-blind, placebo-controlled, parallel -group trial of TTS fentanyl 100 in post-operative pain after head & neck, upper abdominal or thoracic surgery. TTS systems were applied 2 hours before surgery and supplemented in both experimental and control groups by a 300 μg intra-operative fentanyl bolus. Significantly better pain control was observed in 18 fentanyl patients over 21 placebo patients as measured by lower pain intensity ratings, less supplemental morphine use, and better global pain control in the fentanyl group. Mean blood levels of fentanyl ranged from 1.0-2.0 in this study and three fentanyl patients with blood levels between 2.0 and 3.0 who had undergone chest surgery were withdrawn from the study for respiratory depression.

This study was a 49-patient, randomized, double-blind, placebo-controlled, parallel-group efficacy study of TTS-100 vrs placebo-TTS system. It was carried out by Richard Hotchkiss at Emory University between Apr-Nov 1986 on a group of 31 men and 18 women who were mostly ASA class III patients. The study hypothesis was that patients who had a TTS-100 system applied 2 hours before induction of anesthesia with 300 μg fentanyl & 2-3 mg/kg thiopental (subsequent technique was nitrous-enflurane) would have better analgesia and require less supplemental morphine in the 24 hours following system application than a placebo-system group. The measures used were:

Efficacy	*Safety*
	Respiratory rate
Supplemental morphine use	*Blood levels of fentanyl*
Pain intensity scores	*Adverse effect counts*
Global pain control scores	*Withdrawals for cause*
	Episodes of respiratory depression
	Sedation scores

Outcome variables were assessed hourly for 24 hours of TTS application and for 12 hours after removal. Serum levels of fentanyl were taken at 0,4,8,12, 16, 20 & 24 hours after system application and 6,16,24,& 30 hours after removal. Global pain ratings were done for 0-24, 24-36, and 36-48 hours after TTS application. The TTS skin site was examined at 1,6,& 24 hours after application.

Patients who dropped out pre or intra-operatively due to disqualifying alterations in anesthetic technique or in the proposed surgery were excluded from efficacy analysis but included in the safety data.

49 patients were randomized to two groups of 25 fentanyl and 24 placebo, with 3 fentanyl patients and 3 placebo patients withdrawing from the study immediately for procedural reasons. Four additional patients in the fentanyl group (all thoracotomy patients) developed respiratory depression and withdrew for medication related adverse effects. This left 18 fentanyl and 21 placebo patients who completed the study.

Selection , Withdrawals, and Mistakes

Review of the demographic data on both groups revealed a 28-70 year old group of 53-99 kg men and women undergoing thoracotomy (27), upper abdominal (15) or HEENT (7) procedures. Most of the group was ASA class III, and of average height, weight, and body mass index. Review of the case summaries showed an unremarkable group of past medical histories and an average number with heavy alcohol and analgesic use. The group was typical for a large private or university CHEST or ENT clinic, and there were no clinically or statistically meaningful differences between the two groups.

Four TTS Fentanyl patients had the system removed at 6-12 hours after application due to respiratory rates less than 8 breath per minute (blood levels 2-3 ng/ml). Data were collected on these four patients at all time points, but data collected after the removal of the system were not included in the summary statistics.

It is likely that the withdrawal of these patients had the effect of modestly reducing the observed differenced between the treatment groups.

The investigators had the expected number of deviations from protocol. Five patients were re-classified as ASA class IV and not Class III, 18% of the fentanyl and 33% of the placebo patients received IV morphine instead of IM on at least one occasion, and one placebo and one fentanyl patient received an additional bolus of sufentanil in the OR. At best, these violations would be expected to modestly reduce the differences between the two groups by providing the placebo group higher levels of morphine analgesia.

Results and Analysis

The TTS system-bolus technique was effective in providing analgetic blood fentanyl levels, with the mean blood level for the experimental group ranging from 1 ng/ml at 4 hours to 2.0 ng/ml at 24 hours. This degree of drug delivery resulted in a four-fold reduction in the use of supplemental morphine by the fentanyl group. As may be seen, the active TTS system reduced pain intensity ratings, improved global pain control, and markedly increased the number of adverse experiences (28 v 16). Review of the pattern of side effects reported in the study shows no

obvious pattern other than a higher incidence of CNS complaints (11 fentanyl v 5 placebo).

There were four patients in the study who had episodes of significant respiratory depression. SCN 213, SCN 243, SCN 249, and SCN 255 were all post-thoracotomy patients who developed adverse respiratory events, chiefly slowed respirations (<8 BPM) and hypercapnea (>50 mm hg see safety summary for details). These events all occurred at a mean fentanyl level of > 2.0 ng/ml. All of these reactions must be considered to be a fentanyl-disease interaction, but must not be considered to be unusual post-thoracotomy. Of critical interest is that removal of the system did not result in an immediate fall in fentanyl levels, and that naloxone was given in addition to system removal.

Review of the blood gas data for both fentanyl and placebo groups revealed that both groups had significant hypercarbia, which was related more to the type of surgery than to system application or morphine administration.

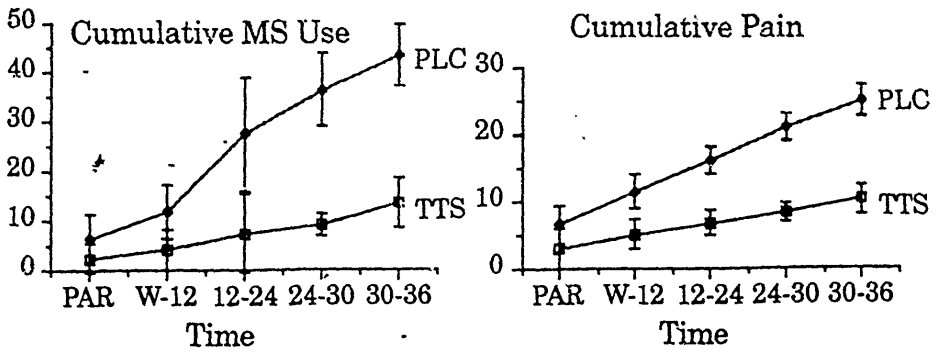
Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal.

Pharmacologic Performance

There was considerable variation in peak blood level, Tmax, and 24 hour dose among the fentanyl group. Case reports for two of the individuals with the lowest blood levels and two with the highest blood levels were reviewed to see if a ready explanation for the variation could be found. Subjects 233 & 242 had the lowest blood levels, and were a 69 kg, 67 y.o. male who had a rib resection and a 59 kg, 57 y.o. female who had a bronchoscopy. Both had exceptionally good pain relief from the TTS systems . Cases 226 & 237 had the highest fentanyl levels, and were a 53 year old 88 kg man who had gastric surgery and a 175 cm 56 kilo 28 year old female with a thoracotomy. The male in this case had few signs of opioid effects but good analgesia, while the female had pronounced opioid effects and still had poor pain control. In only one of these cases (237) was the fentanyl level obviously related to body habitus.

Additional Analyses

The sponsor provided a plot of cumulative supplemental morphine use which is an effective method of visually interpreting this kind of data, and is analogous to the plot of pain intensity differences in more usual analgesic trials. As an experiment, the data from the pain intensity ratings were plotted as cumulated pain scores in a effort to show the data in an analogous fashion. These plots clearly show the differences between the two groups and are reproduced below:



Conclusion

This study shows that post-operative pain in patients who have had a TTS 100 fentanyl system applied is lower than that experienced by controls, both by self-report and by the measurement of morphine demand. Fentanyl is clearly absorbed in amounts adequate to cause both intended and adverse effects, and it is also clear that this increased analgesia was accomplished by an increased total narcotic dose which was too great for four patients with impaired respiration. TTS fentanyl is not a first-line choice for post-pulmonary resection.

Study Type: Postoperative
C-85-042, II: TTS (fentanyl)-100 (40 cm^2)

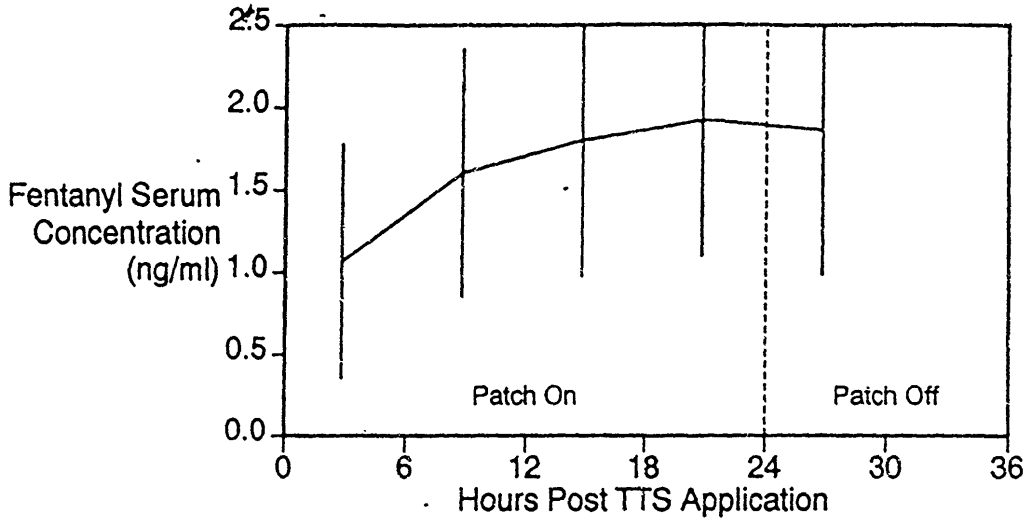
HOTCHKISS

This was a 49-patient, randomized, double-blind, parallel-group trial of a single dose level of TTS fentanyl (100 μg/hr) vs placebo in post-operative pain after upper abdominal or thoracic surgery. Patches were applied two hours before surgery and supplemented in both experimental and control groups by a 300 μg intra-operative fentanyl bolus. Significantly better pain control was observed in 18 fentanyl patients over 21 placebo patients as measured by lower pain intensity ratings (fentanyl 2.1/placebo 4.8), less supplemental morphine use (fentanyl 14.1 mg/placebo 42.3 mg), and better global pain control (fentanyl 1.7/placebo 3.5). Mean blood levels of fentanyl ranged from 1.0-2.0 with a peak mean level of 2.0 ± 0.9 ng/ml. The fentanyl group had an increased incidence of opioid side effects, and three fentanyl patients with blood levels between 2.0 and 3.0 who had undergone chest surgery were withdrawn from the study due to respiratory depression.

	FENTANYL n=25	PLACEBO n=24	TOTAL n=49
SEX			
MALES	15	16	31
FEMALES	10	8	18
SURGERY			
THORACIC	17	10	27
MAJOR ABDOMINAL	6	9	15
HEAD-NECK	2	5	7
ANESTHETIC			
NITROUS/NARCOTIC	24	24	48
TIME (MEAN HOURS)			
TTS APPLICATION TO INDUCTION	1.5	3.5	
SURGICAL PROCEDURE	4.3	3.8	
CONCOMITANT MEDICATIONS			
PREMEDICATIONS - DIAZEPAM	11	10	21
- OTHER	10	10	20
INTRAOPERATIVE NARCOTIC - FENTANYL 300 μg	24	24	48
ADJUNCTIVE MEDS - ANTI-EMETIC	3	7	10
- SEDATIVE/TRANQUILIZER	2	2	4
USE OF RESCUE ANALGESIC - MORPHINE	15	20	35
DROPOUTS			
PRE-SURGERY	1	0	1
DURING SURGERY	0	0	0
PROTOCOL VIOLATION	2	3	5
LACK OF EFFICACY	0	0	0
ADVERSE EVENTS	4	0	4
TOTAL	7	3	10
ADVERSE EVENTS REQUIRING MEDICAL EVALUATION	7	1	8

3/21/90

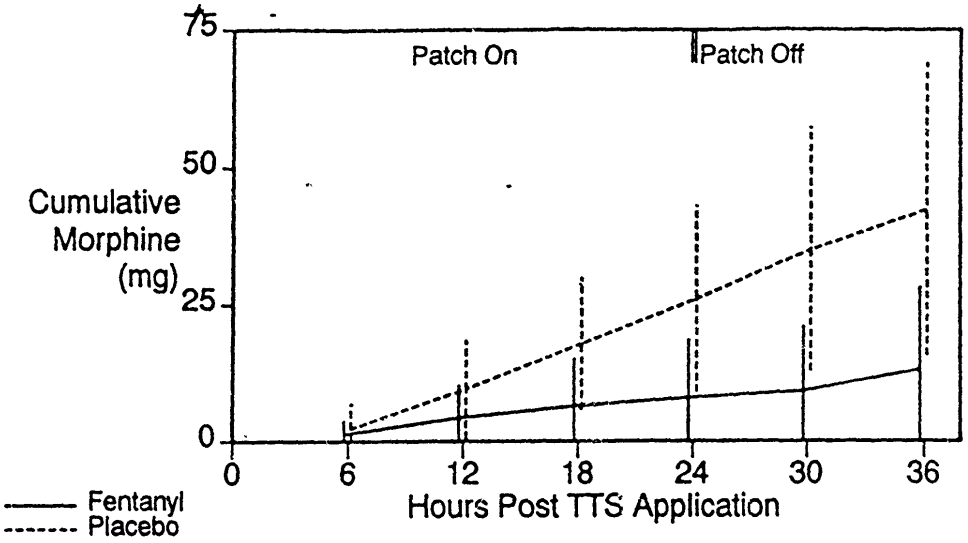
BENEFICIAL EFFECTS
FENTANYL SERUM LEVEL
Study: HOTCHKISS



FENTANYL					
Mean	1.1	1.6	1.8	1.9	1.9
SD	0.7	0.8	0.8	0.8	0.9
N	22	22	22	22	19

3/21/90

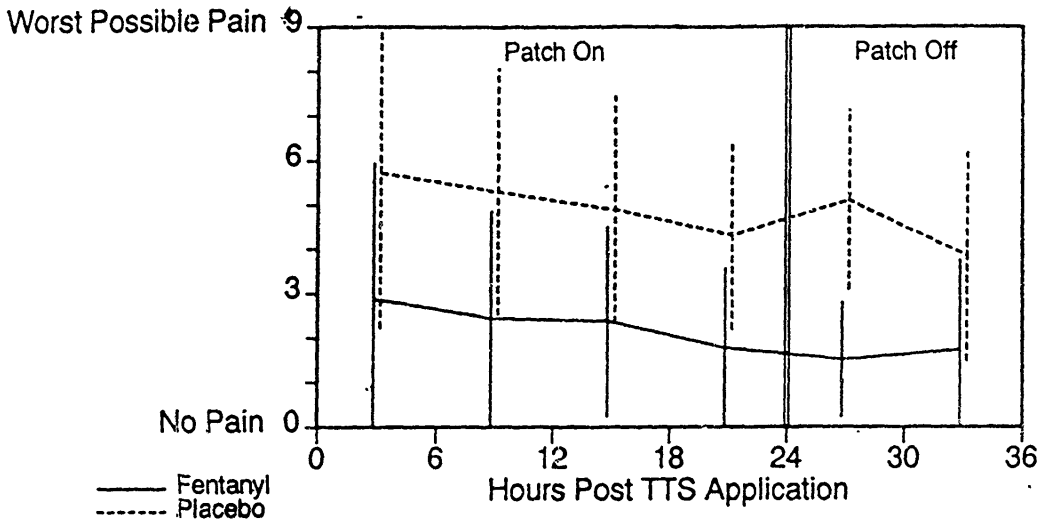
BENEFICIAL EFFECTS
CUMULATIVE USE OF RESCUE MEDICATION
Study: HOTCHKISS



FENTANYL						
Mean	1.2	4.2	6.4	7.8	9.0	12.9
SD	2.6	6.1	8.7	10.8	11.9	15.3
N	22	22	22	22	22	22
PLACEBO						
Mean	2.3	9.4	17.8	25.9	34.9	42.3
SD	4.6	9.1	12.0	17.0	22.2	26.7
N	21	21	21	21	21	21
DIFFERENCE						
Mean	1.1	5.2	11.4	18.1	25.8	29.3
SE	1.1	2.3	3.2	4.3	5.4	6.6
P	0.35	0.03	<0.01	<0.01	<0.01	<0.01

3/21/90

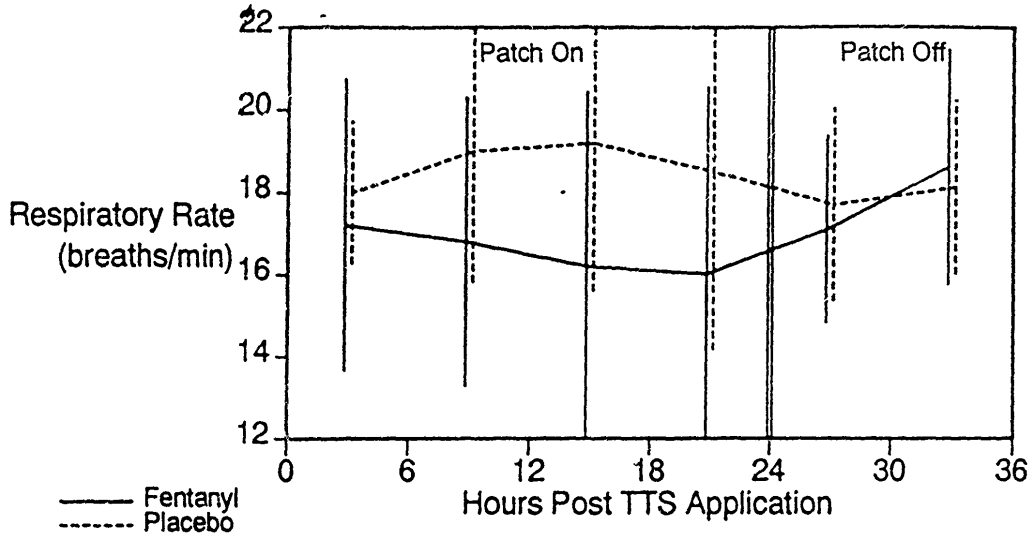
BENEFICIAL EFFECTS
PAIN INTENSITY RATINGS
Study: HOTCHKISS



FENTANYL							0-36
Mean	2.9	2.4	2.4	1.8	1.5	1.7	2.1
SD	3.1	2.4	2.1	1.8	1.3	2.0	1.6
N	14	21	22	21	19	19	22
PLACEBO							
Mean	5.7	5.3	4.9	4.3	5.1	3.8	4.8
SD	3.5	2.8	2.6	2.1	2.0	2.3	1.9
N	9	20	21	21	21	21	21
DIFFERENCE							
Mean	2.8	2.9	2.5	2.5	3.6	2.1	2.7
SE	1.4	0.8	0.7	0.6	0.5	0.7	0.5
P	0.05	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

3/21/90

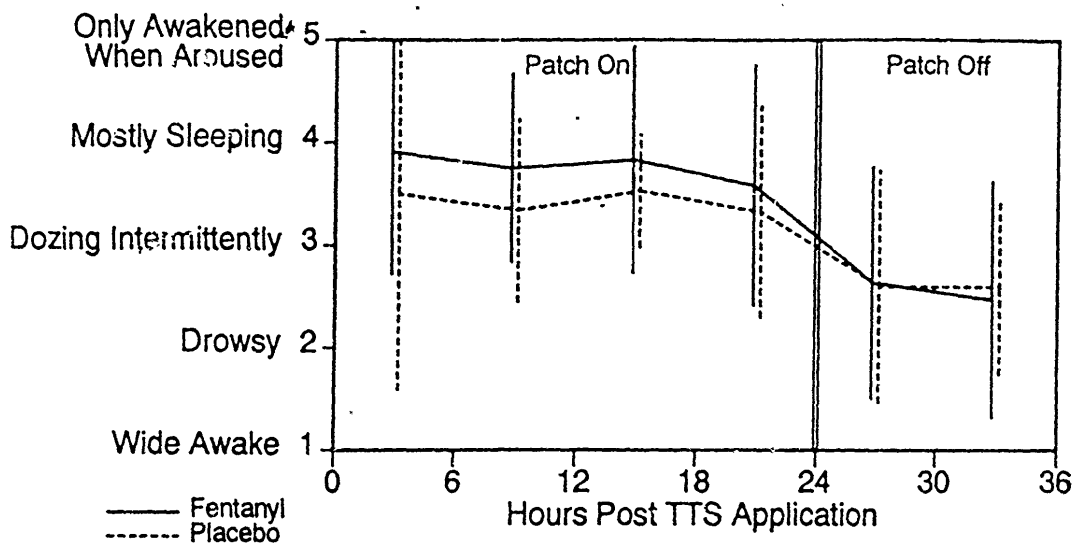
ADVERSE EFFECTS
RESPIRATORY RATE
Study: HOTCHKISS



FENTANYL							0-36
Mean	17.2	16.8	16.2	16.0	17.1	18.6	16.8
SD	3.6	3.5	4.3	4.6	2.3	2.9	3.2
N	16	20	20	20	19	19	22
PLACEBO							
Mean	18.0	19.0	19.2	18.5	17.7	18.1	18.5
SD	1.7	3.2	3.6	4.3	2.3	2.1	2.3
N	9	20	21	21	21	21	21
DIFFERENCE							
Mean	-0.8	-2.2	-3.0	-2.5	-0.6	0.5	-1.7
SE	1.3	1.1	1.2	1.4	0.7	0.8	0.9
P	0.54	0.05	0.02	0.08	0.42	0.54	0.05

3/21/90

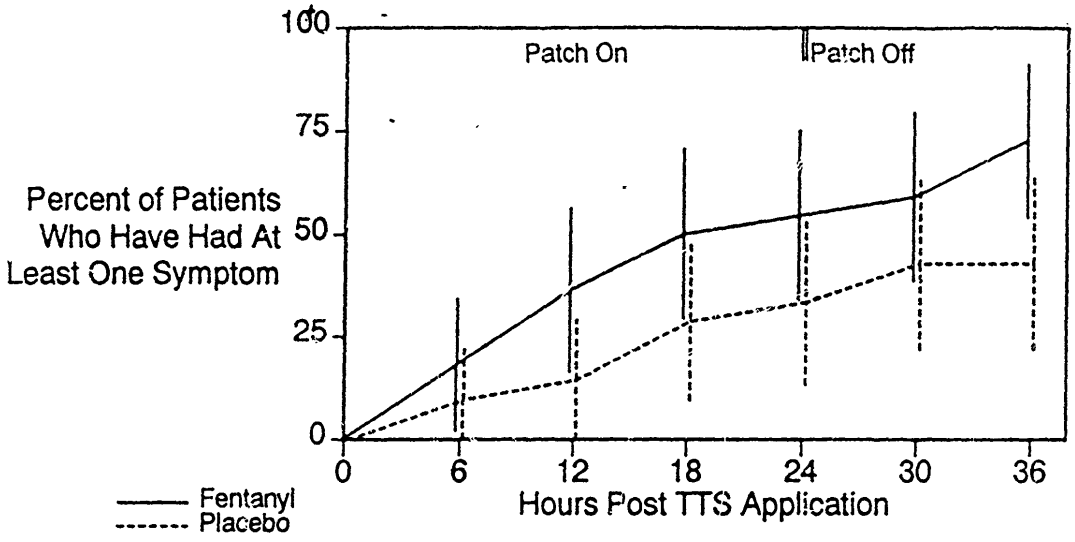
ADVERSE EFFECTS
SEDATION
Study: HOTCHKISS



FENTANYL							0-36
Mean	3.9	3.8	3.8	3.6	2.6	2.5	3.3
SD	1.2	0.9	1.1	1.2	1.1	1.2	0.7
N	15	21	22	21	19	19	22
PLACEBO							
Mean	3.5	3.3	3.5	3.3	2.6	2.6	3.1
SD	1.9	0.9	0.6	1.0	1.1	0.9	0.5
N	10	20	21	21	21	21	21
DIFFERENCE							
Mean	-0.4	-0.4	-0.3	-0.3	-0.0	0.1	-0.3
SE	0.6	0.3	0.3	0.3	0.4	0.3	0.2
P	0.52	0.15	0.27	0.45	0.92	0.70	0.18

3/21/90

ADVERSE EFFECTS
ADVERSE EVENTS CURVES
Study: HOTCHKISS



FENTANYL							
Mean	0.0	18.2	36.4	50.0	54.5	59.1	72.7
95% CI	-	2 -34	16-56	29-71	34-75	39-80	54-91
N	22	22	22	22	22	22	22
PLACEBO							
Mean	0.0	9.5	14.3	28.6	33.3	42.9	42.9
95% CI	-	0 -22	0 -29	9 -48	13-53	22-64	22-64
N	21	21	21	21	21	21	21
DIFFERENCE							
P	-	0.41	0.10	0.15	0.16	0.29	0.05

Hotchkiss

Adverse Events Requiring
Medical Evaluation or Intervention

TTS - Fentanyl

SCN 213	PH 7.25, PCO_2 55, RR 8; Lethargic & difficult to arouse. Naloxone given
SCN 215	Intraoperative bleeding. Blood transfusions intra and postoperatively. Continues to have bleeding. Expired 6 days later due to disease progression.
SCN 237	ABG's called for. Rouses easily. Falls back to sleep quickly, RR 10/min.
SCN 242	Very drowsy, PCO_2 increased, probably secondary to relaxant, $NAHCO_3$ given. 5% albumen 250cc, IVF's increased for decreased blood pressure. ? ventricular
SCN 243	Atrial fibrillation with rapid ventilatory response, lethargic, drowsy. During transfer to ICU, RR 8/min. Naloxone administered.
SCN 249	Drowsy, aroused and coached to breathe. Respiratory rate <8 and pCO_2 60. End tidal CO_2 monitor did not sense respiration. Patient requested patch not be removed because of good feeling and no pain. Naloxone administered. ? resp. depression ? ↑ pCO_2 ? pCO_2 is anka
SCN 255	Naloxone given for extubation intra-op. Hypotension, lethargy and increased pCO_2 in PAR.

Placebo

SCN 240	Complaint of dizziness. No focal deficit on neuro exam.

85-030-02 Nimmo 100 μg/h TTS Fentanyl

Abstract

This is a 46 patient randomized, double-blind, single-dose, parallel-group, placebo-controlled study of TTS Fentanyl in the relief of post-operative pain in men and women following major upper abdominal surgery. Each patient had a 100 μg/h or placebo system applied 2 hours before surgery, all received a 200 μg operative fentanyl bolus, and all were followed for 24 hours of system application and for an additional 24 hours post system removal. The investigators found significantly better pain control in 22 fentanyl patients over 18 placebo patients as measured by lower pain intensity ratings , less supplemental morphine use, and higher global pain control ratings in the fentanyl group. Mean blood levels of fentanyl ranged from 1.5-2.0 ng/ml during system application and in this study and the only withdrawal for an adverse event was from the placebo group.

Resume

This study was carried out by Walter S. Nimmo of the University of Sheffield Medical School in the United Kingdom between October 1986 and January of 1987. The study group consisted almost entirely (37 /46) of elective cholecystectomies. The majority of the subjects were female (28/46), but the study groups were otherwise comparable as to height, weight, & age . The study hypothesis was that patients who had a TTS 100 system applied 2 hours before induction of anesthesia would require less morphine analgesia in the 24 hours following system application than placebo. The outcome variables were identical to other studies in this series.

Efficacy	*Safety*
	Respiratory rate
Supplemental morphine use	*Blood levels of fentanyl*
Pain intensity scores	*Adverse effect counts*
Global pain control scores	*Withdrawals for cause*
	Episodes of respiratory depression
	Sedation scores

All patients had an active or a placebo system applied two hours before the induction of general anesthesia and received no pre-operative sedative. Induction of anesthesia was accomplished with a 200μg fentanyl bolus and 5 mg/kg thiopentone, following which anesthesia was maintained with nitrous, enflurane and a muscle relaxant (Vecuronium) if required. Post-operative analgesia was available to both groups via a patient controlled analgesia device (PCA) which was a computer-controlled infusions system which provided 2.5 mg/actuation IV morphine with a 10 minute lockout in the post anesthesia recovery room (PAR), and 1 mg/actuation morphine sulfate with a 20 minute lockout on the ward. This system provided a maximal rate (upper limit) of morphine

infusion of 15 mg/hr in the PAR, and 6 mg/hr thereafter. Actual usage rates were 6-26 mg/hr in the PAR and 0.1-5.7 mg/hr on the ward.

All patients were monitored for the 24 hours of system application and for 24 hours thereafter. This study differed from the other studies in this series in that the morphine was administered by PCA and in that pain scores, sedation scores, and adverse effect queries were collected at 4 hour intervals instead of hourly.

Patients who dropped out pre or intra-operatively due to changes in the operating schedule or type of surgical procedure (N=5) were excluded from efficacy analysis but included in the safety data.

Selection , Withdrawals, and Mistakes

This study provides information regarding the use of this medication in elective upper abdominal surgery in an older, heavier (70-75 kg) predominantly female group. It is a healthy group, containing 35 ASA class I patients & 11 ASA class II patients , and no ASA class III or IV. The study groups were equally matched, and represent a typical selection of cholecystectomy patients scheduled for elective inpatient surgery.

The 46 patients were randomized to two groups of 23 fentanyl and 23 placebo. Five of the patients in the placebo group were withdrawn at or about the time of surgery, as two had their surgery canceled, two had protocol violations, and one developed endotoxic shock. There were three intra- & postoperative withdrawals in the study, when one patient had the TTS removed by a student nurse who did not understand its function, one patient's PCA jammed, and one patient received morphine rather than fentanyl as a bolus. These withdrawals and violations are adequately explained and plausible and would not be expected to bias the results.

The investigators had five minor protocol violations in addition to the above, when the PCA device failed (after the 24 hour study interval). The investigator's handled this missing data for the post-TTS application interval by substituting the group means for the missing values for each of these five patients. While this is an unbiased method of extrapolation, it does reduce the power and the reliability of the data from the 24-48 hour periods. This would not be expected to bias the results for the TTS wearing period during the 0-24 hours interval.

Results and Analysis

The results of the study are shown on the following pages. As may be seen, the use of morphine by the fentanyl group was reduced over placebo at all time periods, as were pain intensity ratings. Serum fentanyl rose to therapeutic levels (1-2 ng/ml) over the first 12 hours and resulted in a lowed mean respiratory rate and an increase in opioid side effects over the placebo group.

This study differed somewhat from the American studies, since the pain, sedation, and adverse effects were collected twice per shift rather than hourly. In addition, the use of PCA rather than nurse administration of morphine or differences in anesthetic technique may have altered the total morphine use since the patients in this study used nearly twice as much total morphine (52 v. 27 mg) than in a parallel trial by Hotchkiss in which medication was administered by the study nurse..

Adverse Events

The investigators have shown that patients in the fentanyl group had a consistently better level of analgesia and required less morphine than the placebo group. They have also shown that the fentanyl group had a greater frequency of adverse opioid side effects than the placebo group. Both of these observations are most consistent with the observation that the fentanyl group probably received a higher total dose of opioid (fentanyl effect + morphine effect) than the placebo group, and that the greater analgesia is due to the patients having received more analgesic. The side effects reported in this trial consisted mainly of nausea & vomiting and were more common in the TTS fentanyl group. The very low numbers of adverse events in comparison with other trials (11 this trial/ 35-80 other trials) reflected a low sensitivity to adverse events due to the method of survey, the patient group, or the method of delivery of rescue medication (PCA). There were no episodes of significant respiratory depression or excessive sedation in any patient in this study.

Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal. These effects were seen in both fentanyl and placebo system groups. There were no reported episodes of delayed hypersensitivity or system allergy.

Pharmacologic Performance

The blood levels at 24 hours ranged from 0.97 ng/ml to 4.55 ng/ml, and the case reports for several of the patients with high values and low values were reviewed. Cases 638 & 648 had low fentanyl levels (0.97 & 0.98 ng/ml), were 99 & 58 kg respectively, and both had a cholecystectomy. Patient 638 had poor relief as shown by pain scores of 7-8 and high morphine use , while patient 648 had poor relief with scores of 7 and similar use of rescue medication.

Cases 654 & 635 had high blood levels (4.55 & 2.90 ng/ml), were 50.6 & 82.5 kg respectively, both had a cholecystectomy , neither reported significant pain (scores 2-4) or used morphine supplementation to any appreciable extent.

Conclusion

This study shows that post-operative pain experienced by patients who have had a TTS 100 fentanyl system applied is lower than that experienced by controls, as measured by both self-report and by the measurement of morphine demand. Fentanyl is clearly absorbed in amounts adequate to cause both intended and adverse effects, but it is

not possible to determine if the total narcotic demand (fentanyl + morphine) was reduced for these patients since the relative potency of fentanyl and morphine has not been tested in this system.

Study Type: Postoperative
C-85-030, II: TTS (fentanyl)-100 (40 cm^2)

NIMMO

This was a 46 patient randomized, double-blind, parallel-group, single-dose lev study of TTS fentanyl (100 μg/hr) vs placebo in the relief of post-operative pain in men and women following major upper abdominal surgery. Each patient had a 100 μg/hr or placebo patch applied two hours before surgery; all received a 200 μg operative fentanyl bolus; and all were followed for 24 hours of patch application and for an additional 24 hours post patch removal. Twenty-three patients receiving the fentanyl patch experienced significantly better pain control over 18 placebo control patients as measured by lower pain intensity ratings (fentanyl 3.5/placebo 5.3), less supplemental morphine use (fentanyl 50.0 mg/placebo 77.1 mg) and better global pain control ratings (fentanyl 2.0/placebo 3.4) in the fentanyl group. Mean blood levels of fentanyl ranged from 1.5-2.0 ng/ml during patch application and there were no withdrawals from the fentanyl group for adverse events.

	FENTANYL n=23	PLACEBO n=23	TOTAL n=46
SEX			
MALES	8	10	18
FEMALES	15	13	28
SURGERY			
MAJOR ABDOMINAL	23	23	46
ANESTHETIC			
NITROUS/NARCOTIC	23	23	46
TIME (MEAN HOURS)			
TTS APPLICATION TO INDUCTION	2.5	2.5	
SURGICAL PROCEDURE	1.6	1.7	
CONCOMITANT MEDICATIONS			
PREMEDICATIONS - NONE			
INTRAOPERATIVE NARCOTIC - FENTANYL 200 μg	23	23	46
ADJUNCTIVE MEDS - ANTI-EMETIC	10	5	15
- SEDATIVE/TRANQUILIZER	0	0	0
USE OF RESCUE ANALGESIC - MORPHINE	23	18	41
DROPOUTS			
PRE-SURGERY	0	2	2
DURING SURGERY	0	2	2
PROTOCOL VIOLATION	1	0	1
LACK OF EFFICACY	0	0	0
ADVERSE EVENTS	0	0	0
TOTAL	1	4	5
ADVERSE EVENTS REQUIRING MEDICAL EVALUATION	0	1	1

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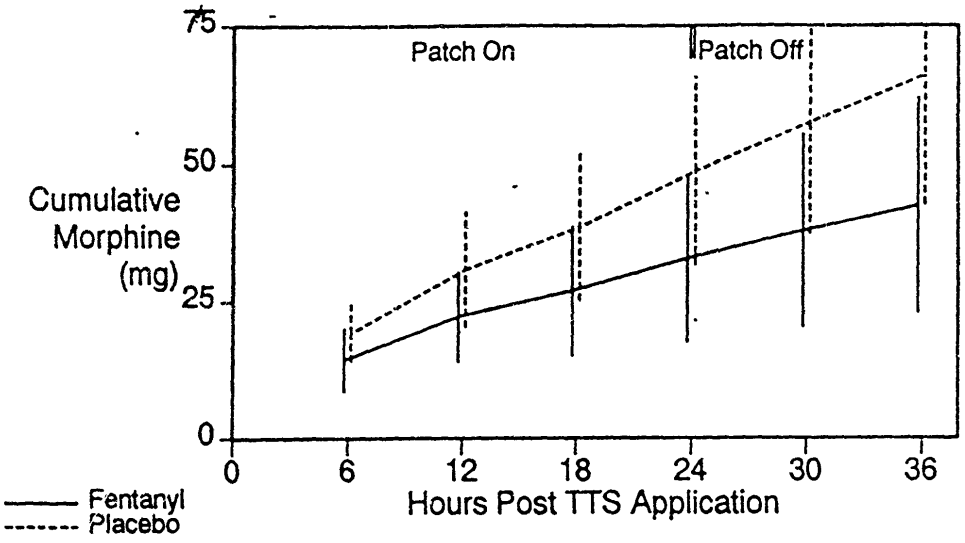
3/21/90

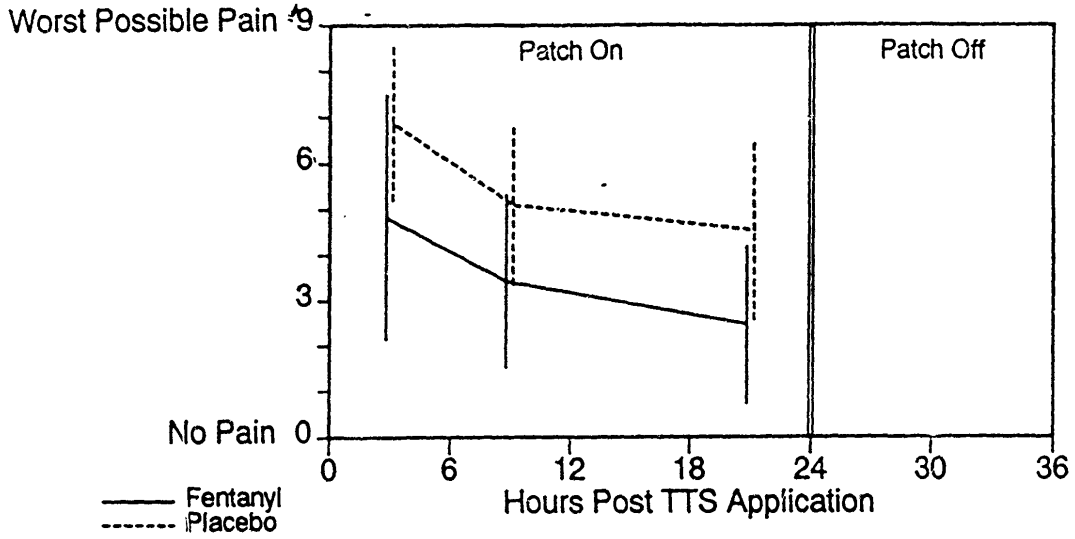
BENEFICIAL EFFECTS
CUMULATIVE USE OF RESCUE MEDICATION
Study: NIMMO



FENTANYL						
Mean	14.3	22.1	26.8	32.7	37.8	42.3
SD	5.9	8.3	11.9	15.3	17.6	19.6
N	23	23	23	23	23	23
PLACEBO						
Mean	19.2	30.8	38.5	48.6	57.5	66.0
SD	5.3	10.6	13.6	17.1	20.2	23.4
N	18	18	18	18	18	18
DIFFERENCE						
Mean	4.9	8.6	11.6	15.8	19.7	23.7
SE	1.8	3.0	4.0	5.1	5.9	6.7
P	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

3/21/90

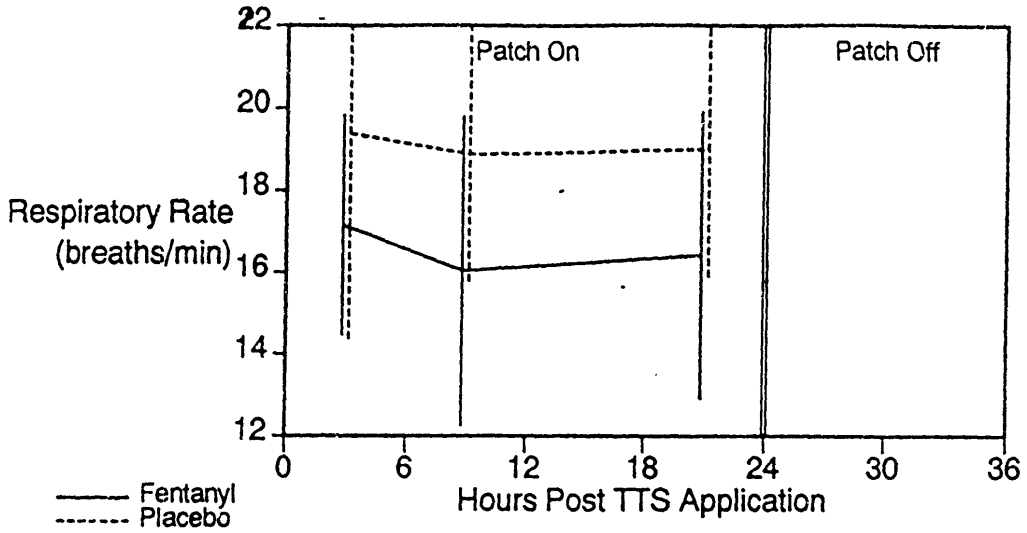
BENEFICIAL EFFECTS
PAIN INTENSITY RATINGS
Study: NIMMO



				0-36
FENTANYL				
Mean	4.8	3.4	2.5	3.5
SD	2.7	1.9	1.7	1.6
N	19	23	22	23
PLACEBO				
Mean	6.9	5.1	4.5	5.3
SD	1.7	1.7	2.0	1.5
N	15	18	17	18
DIFFERENCE				
Mean	2.1	1.7	2.1	1.9
SE	0.8	0.6	0.6	0.5
P	0.01	<0.01	<0.01	<0.01

3/21/90

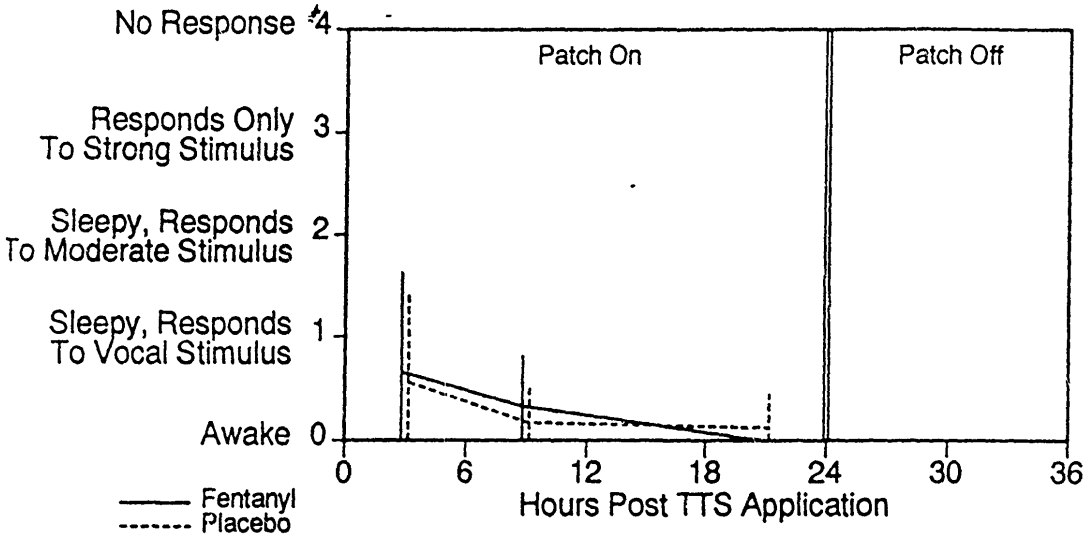
ADVERSE EFFECTS
RESPIRATORY RATE
Study: NIMMO



FENTANYL				0-36
Mean	17.2	16.0	16.4	16.4
SD	2.7	3.8	3.5	2.5
N	22	23	22	23
PLACEBO				
Mean	19.4	18.9	19.0	19.1
SD	5.0	3.1	3.1	2.4
N	18	18	17	18
DIFFERENCE				
Mean	-2.2	-2.8	-2.6	-2.7
SE	1.2	1.1	1.1	0.8
P	0.08	0.01	0.02	<0.01

3/21/90

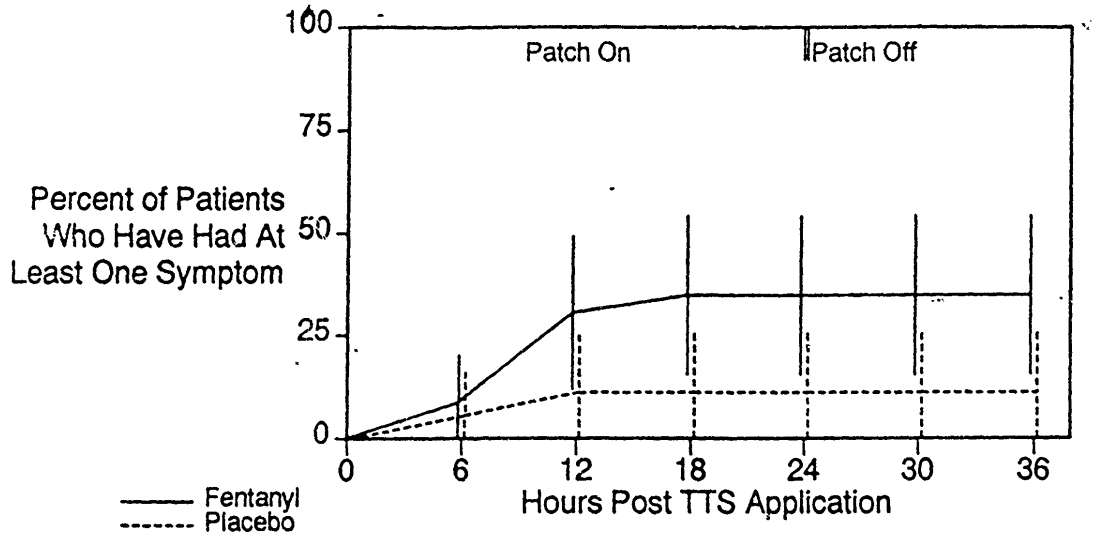
ADVERSE EFFECTS
SEDATION
Study: NIMMO



FENTANYL				0-36
Mean	0.7	0.3	0.0	0.4
SD	1.0	0.5	0.0	0.4
N	22	23	22	23
PLACEBO				
Mean	0.6	0.2	0.1	0.2
SD	0.9	0.3	0.3	0.4
N	18	18	17	18
DIFFERENCE				
Mean	-0.1	-0.2	0.1	-0.1
SE	0.3	0.1	0.1	0.1
P	0.73	0.25	0.10	0.39

3/21/90

ADVERSE EFFECTS
ADVERSE EVENTS CURVES
Study: NIMMO



FENTANYL							
Mean	0.0	8.7	30.4	34.8	34.8	34.8	34.8
95% CI	-	0 -20	12-49	15-54	15-54	15-54	15-54
N	23	23	23	23	23	23	23
PLACEBO							
Mean	0.0	5.6	11.1	11.1	11.1	11.1	11.1
95% CI	-	0 -16	0 -26	0 -26	0 -26	0 -26	0 -26
N	18	18	18	18	18	18	18
DIFFERENCE							
P	-	0.70	0.14	0.08	0.08	0.08	0.08

Nimmo

Adverse Events Requiring
Medical Evaluation or Intervention

TTS - Fentanyl

None

Placebo

SCN 626 Endotoxic shock in OR.

85-046-01 Caplan 75 μg/h TTS Fentanyl

Abstract

This is a 42 patient randomized, double-blind, placebo-controlled study of TTS Fentanyl in the relief of post-operative pain in men and women following major upper abdominal surgery. Each patient had a 75μg/hr or placebo system applied at induction of regional analgesia, received a 100 μg operative fentanyl bolus, and were followed for 24 hours of system application and for an additional 24 hours after system removal. The investigators found significantly better pain control in 20 fentanyl patients over 19 placebo patients as measured by lower pain intensity ratings , less supplemental morphine use, and better global pain control ratings in the fentanyl group. Mean blood levels of fentanyl ranged from 0.5-1.5 ng/ml during system application in this study and the only withdrawal for an adverse event was from the placebo group.

This study was a 42-patient, randomized, double-blind, placebo-controlled, parallel-group study of TTS-100 vrs placebo-system which was carried out by Robert A. Caplan of the University of Washington Medical School between January 1986 and February of 1987. The study group consisted of 30 men and 12 women with a mean age and weight of 41 years and 79 kg who were undergoing elective shoulder surgeries with regional anesthesia.

All patients had an active or a placebo system applied at the induction of regional anesthesia and received no pre-operative sedative. Interscalene block anesthesia was accomplished with 40 ml. carbocaine and accompanied by a 100 μg fentanyl bolus. Post-operative analgesia was available to both groups in the post anesthetic recovery room (PAR) as 2 mg morphine sulfate IV every 5-10 minutes, and as 5 mg morphine sulfate IM every 2 hours thereafter on the ward.

This system provided a maximal rate (upper limit) of morphine infusion of 12 mg/hr in the PAR, and 2.5 mg/hr thereafter. Actual usage rates ranged between 1-2 mg/h in both locations. After TTS removal the subjects could request either IM morphine or oral acetaminophen with codeine which was converted to an equivalent dose of morphine at a fixed ratio (Foley NEJM 313, 84-95) for both groups.

All patients were monitored for the 24 hours of system application and for 24 hours thereafter . Significant safety and efficacy variables included:

Efficacy

Supplemental morphine use
Pain intensity scores
Global pain control scores

Safety

Respiratory rate
Blood levels of fentanyl
Adverse effect counts
Withdrawals for cause
Episodes of respiratory depression
Sedation scores

The study hypothesis was that patients who had a TTS-75 system applied at induction of anesthesia would have better analgesia and require less supplemental morphine in the 24 hours following system application than the placebo-system group.

Patients who dropped out pre or intra-operatively were excluded from efficacy analysis but included in the safety data.

Selection , Withdrawals, and Mistakes

This study provides information regarding the use of this medication in elective orthopedic surgery in a 40 year old, 78-80 kg, predominantly male group. It is a healthy group, containing 30 ASA class I patients, 10 ASA class II patients , and no ASA class III or IV. The study groups were equally matched, and represent a typical selection of orthopedic patients scheduled for elective inpatient surgery..

The 42 patients were randomized to one group of 22 (fentanyl) and one group of 20 (placebo) . Two of the patients in the fentanyl group had the system applied at the time of induction but were excluded from the efficacy analysis after they required general anesthesia. Similarly, one of the placebo patients was removed for morphine associated nausea and vomiting.

These withdrawals and violations are adequately explained and plausible and would not be expected to bias the results.

The investigators had one minor protocol violation in addition to the above. Subject 425 could not tolerate codeine in the post-TTS removal phase and received oxycodone instead. This would not be expected to bias the results for the TTS wearing period during the 0-24 hours interval.

Results and Analysis

The results of the study are as shown on the following pages. The cumulative morphine use shows that TTS fentanyl application resulted in less use of morphine rescue medication during all study periods, and provides indirect evidence that the assay is sensitive since there is a markedly higher rate of use of morphine during the 4-12th postoperative hours than at later periods. Examination of the pain intensity ratings shows that the fentanyl group experienced less pain postoperatively, and expressed a greater global satisfaction with pain control than the placebo group.

The investigators have shown that patients in the TTS 75 group had a consistently better level of analgesia and required less morphine than the placebo group. They have also shown (below) that the fentanyl group has a greater frequency of adverse events and opioid side effects than the placebo group. Both of these observations are most consistent with the observation that the fentanyl group probably received a higher total dose of opioid (fentanyl effect + morphine effect) than the placebo group, and that the greater analgesia is due to the patients having received more narcotic.

Adverse Events

Review of the pattern of side effects reported in the study shows that fentanyl patients reported 69 adverse events while placebo patients had 38. These events were all episodes of opioid side effects such as nausea, and vomiting, urinary retention, pruritus, and similar complaints.

There were no episodes of significant respiratory depression or excessive sedation in any patient in this study, although three fentanyl patients had episodes of slowed respirations (respiratory rates of 5-10/minute) which were were recorded as adverse effects, but did not require medical intervention. Respiratory effects for the group as a whole were limited to a mean reduction of 1-2 breaths per minute during system application.

Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal (54% fentanyl/40% placebo) . These effects were seen in both fentanyl and placebo system groups. There were no reported episodes of delayed hypersensitivity or system allergy. One particularly hairy subject (452) had very poor adhesion and low uptake from the system (6.66 mg residual fentanyl in the system after 24 hours vrs group mean of 4.8 mg).

Pharmacologic Performance

The blood level profiles for all fentanyl patients are as shown in the figures. Observed blood levels at 24 hours ranged from 0.3 ng/ml to 4.00 ng/ml, and the case reports for several of the patients with high values and low values were reviewed. Cases 426 & 440 had low fentanyl levels (0.3 & 0.7 ng/ml), and were 100 & 67 kg respectively.

Patient 426 had average relief as shown by pain scores of 50-60 mm (max 100mm) and low morphine use , while patient 440 had excellent relief with scores of 2-20 mm and similar use of rescue medication.

Cases 415 & 447 had high blood levels (4.0 & 3.4 ng/ml), were 56 & 62 kg respectively, reported pain intensity scores of 27 & 68 mm respectively, and neither used morphine supplementation to any appreciable extent. Case 447 had one episode of slowed respiration, which required no intervention.

Conclusion

This study shows that post-operative pain experienced by patients who have had a TTS 75 fentanyl system applied is lower than that experienced by controls, as measured by both self-report and by the measurement of morphine demand.

This study establishes the efficacy of TTS fentanyl in postoperative pain.

Study Type: Postoperative
C-85-046, II: TTS (fentanyl)-75 (30 cm^2)

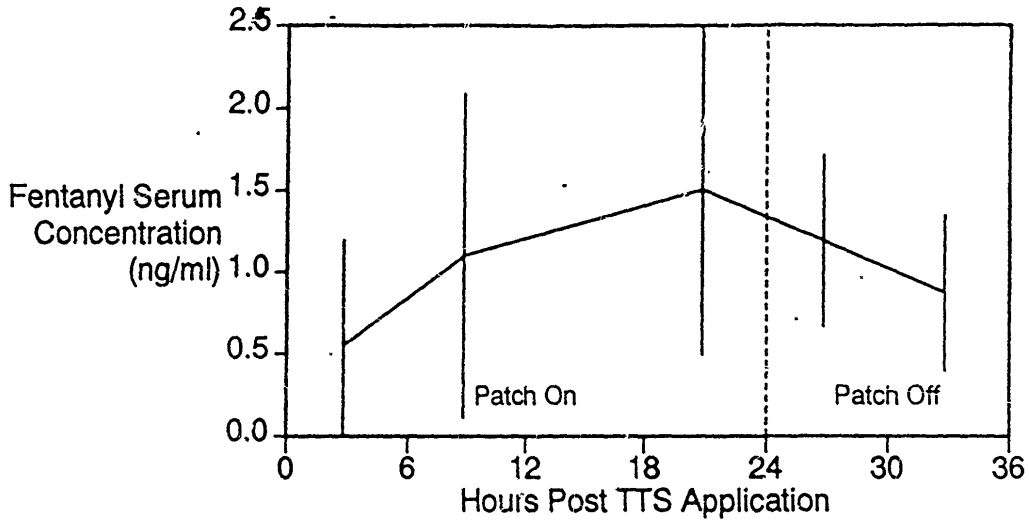
CAPLAN

This is a 42 patient randomized, double-blind, single dose level study of TTS fentanyl (75 μg/hr) vs placebo in the relief of post-operative pain in men and women following major upper abdominal surgery. Each patient had an active or placebo patch applied two hours before surgery, received a 100 μg intra-operative fentanyl bolus, and was followed for 24 hours of patch application and for an additional 24 hours after patch removal. The 20 fentanyl patients experienced significantly better outcomes than 19 placebo controls as measured by lower pain intensity ratings (fentanyl 2.5/placebo 4.1), less supplemental morphine use (fentanyl 21.7 mg/placebo 42.1 mg), and better global pain control ratings (fentanyl 36.2/placebo 56.2). Mean blood levels of fentanyl ranged from 0.5-1.5 ng/ml during patch application and the only withdrawal for an adverse event was from the placebo group.

	FENTANYL n=22	PLACEBO n=20	TOTAL n=42
SEX			
MALES	16	14	30
FEMALES	6	6	12
SURGERY			
ORTHOPEDIC	22	20	42
ANESTHETIC			
NITROUS/NARCOTIC	2	0	2
PERIPHERAL/LOCAL	20	20	40
TIME (MEAN HOURS)			
TTS APPLICATION TO INDUCTION	0.1	0.2	
SURGICAL PROCEDURE	3.2	2.8	
CONCOMITANT MEDICATIONS			
PREMEDICATIONS - DIAZEPAM	16	15	31
- OTHER	2	1	3
INTRAOPERATIVE NARCOTIC - FENTANYL 100 μg	22	20	42
ADJUNCTIVE MEDS - ANTI-EMETIC	12	8	20
- SEDATIVE/TRANQUILIZER	1	7	8
USE OF RESCUE ANALGESIC - MORPHINE	19	20	39
DROPOUTS			
PRE-SURGERY	0	0	0
DURING SURGERY	0	0	0
PROTOCOL VIOLATION	0	0	0
LACK OF EFFICACY	0	0	0
ADVERSE EVENTS	0	1	1
TOTAL	0	1	1
ADVERSE EVENTS REQUIRING MEDICAL EVALUATION	5	2	7

3/21/90

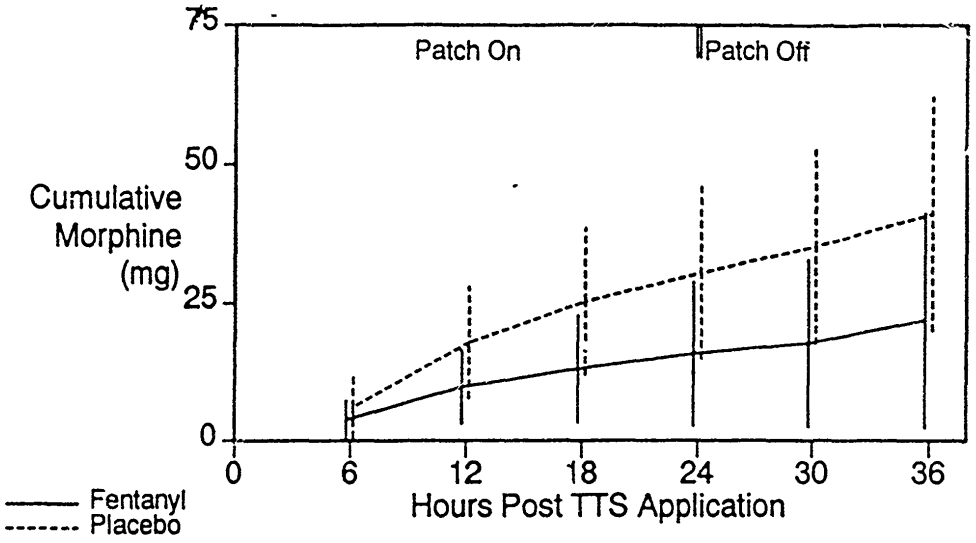
BENEFICIAL EFFECTS
FENTANYL SERUM LEVEL
Study: CAPLAN



FENTANYL					
Mean	0.6	1.1	1.5	1.2	0.9
SD	0.6	1.0	1.0	0.5	0.5
N	20	18	20	17	17

3/21/90

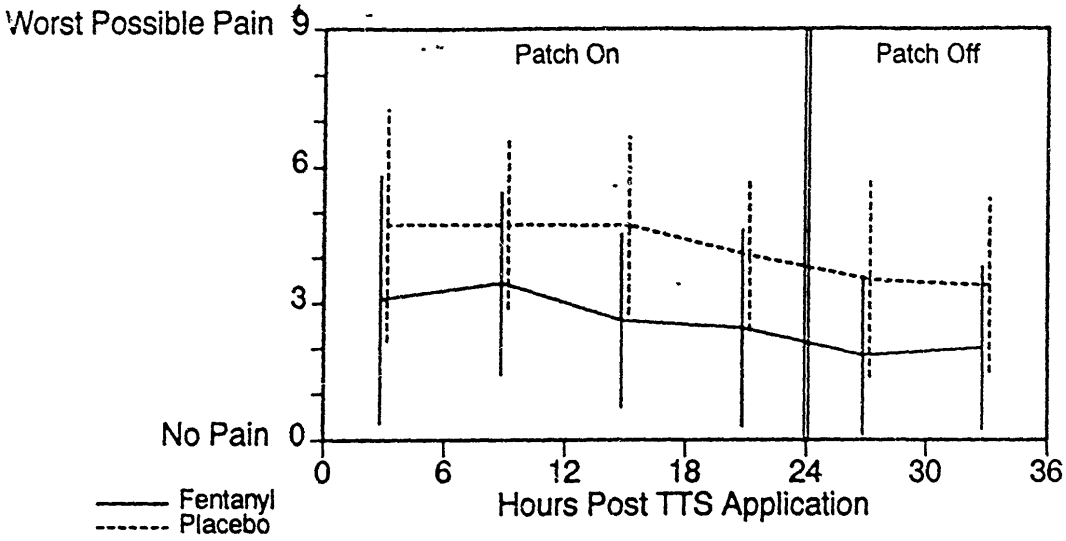
BENEFICIAL EFFECTS
CUMULATIVE USE OF RESCUE MEDICATION
Study: CAPLAN



FENTANYL						
Mean	3.7	9.7	13.0	15.7	17.5	21.7
SD	3.6	6.8	9.8	13.1	15.2	19.5
N	20	20	20	20	20	20
PLACEBO						
Mean	6.1	17.8	25.1	30.3	35.0	41.0
SD	5.6	10.2	13.4	15.6	17.7	21.2
N	20	20	20	20	20	20
DIFFERENCE						
Mean	2.3	8.1	12.2	14.6	17.5	19.3
SE	1.5	2.7	3.7	4.6	5.2	6.4
P	0.12	<0.01	<0.01	<0.01	<0.01	<0.01

3/21/90

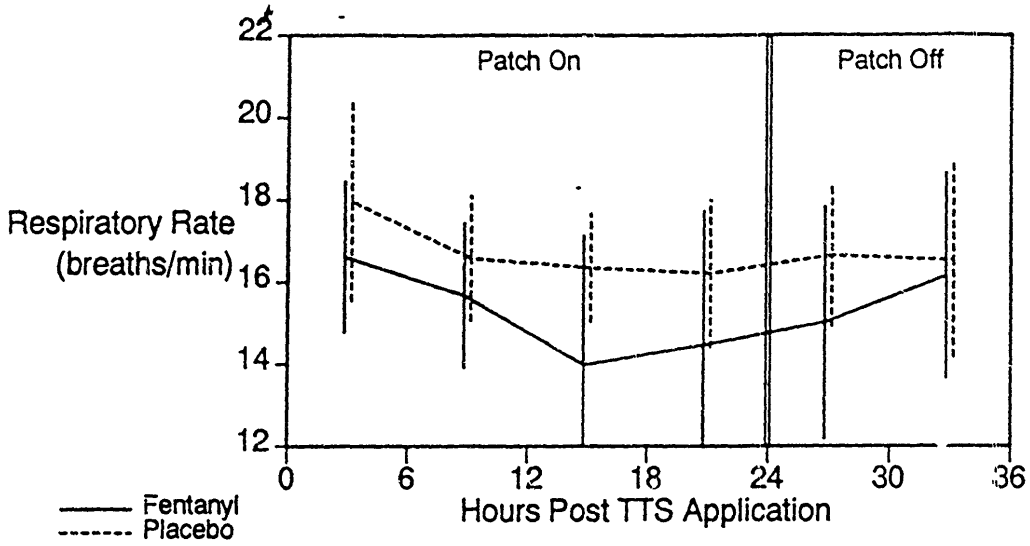
BENEFICIAL EFFECTS
PAIN INTENSITY RATINGS
Study: CAPLAN



FENTANYL							0-36
Mean	3.1	3.4	2.6	2.4	1.8	2.0	2.5
SD	2.7	2.0	1.9	2.2	1.7	1.8	1.7
N	17	20	20	20	20	20	20
PLACEBO							
Mean	4.7	4.7	4.7	4.0	3.5	3.4	4.1
SD	2.6	1.8	2.0	1.7	2.2	1.9	1.5
N	19	20	20	20	20	20	20
DIFFERENCE							
Mean	1.6	1.3	2.1	1.6	1.7	1.4	1.6
SE	0.9	0.6	0.6	0.6	0.6	0.6	0.5
P	0.07	0.04	<0.01	0.01	0.01	0.02	<0.01

3/21/90

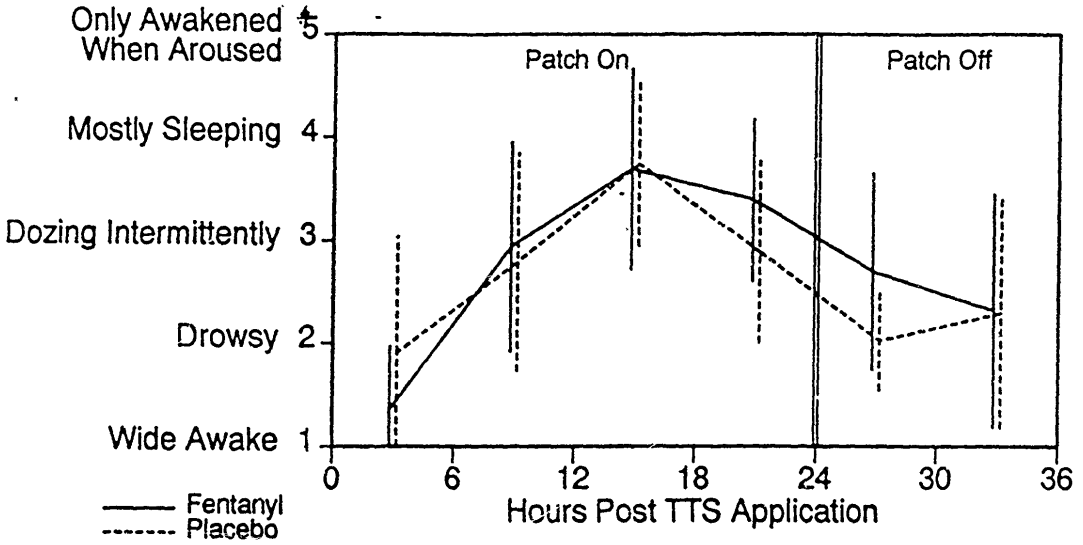
ADVERSE EFFECTS
RESPIRATORY RATE
Study: CAPLAN



FENTANYL							0-36
Mean	16.6	15.7	14.0	14.5	15.0	16.2	15.1
SD	1.8	1.8	3.2	3.3	2.8	2.5	2.3
N	18	20	20	20	20	20	20
PLACEBO							
Mean	18.0	16.6	16.3	16.2	16.7	16.5	16.5
SD	2.4	1.5	1.3	1.8	1.7	2.4	1.2
N	19	20	20	20	20	20	20
DIFFERENCE							
Mean	-1.3	-0.9	-2.4	-1.7	-1.6	-0.4	-1.4
SE	0.7	0.5	0.8	0.8	0.7	0.8	0.6
P	0.07	0.09	<0.01	0.04	0.03	0.62	0.02

3/21/90

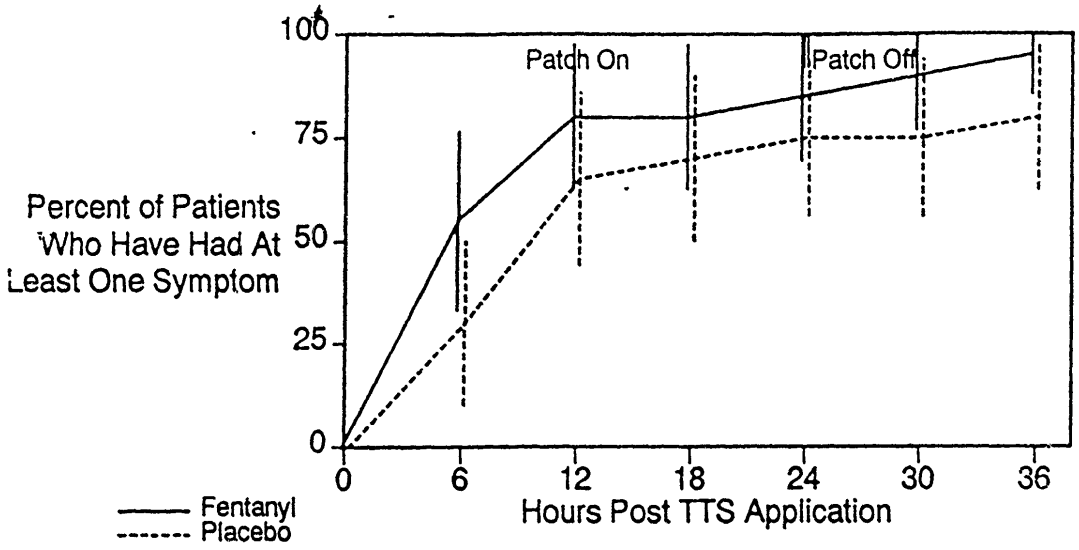
ADVERSE EFFECTS
SEDATION
Study: CAPLAN



FENTANYL							0-36
Mean	1.4	2.9	3.7	3.4	2.7	2.3	2.9
SD	0.6	1.0	1.0	0.8	1.0	1.1	0.5
N	18	20	20	20	20	20	20
PLACEBO							
Mean	1.9	2.8	3.7	2.9	2.0	2.3	2.7
SD	1.1	1.1	0.8	0.9	0.5	1.1	0.6
N	19	20	20	20	20	20	20
DIFFERENCE							
Mean	0.5	-0.1	0.1	-0.5	-0.7	-0.0	-0.2
SE	0.3	0.3	0.3	0.3	0.2	0.4	0.2
P	0.08	0.65	0.86	0.06	<0.01	0.94	0.23

3/21/90

ADVERSE EFFECTS
ADVERSE EVENTS CURVES
Study: CAPLAN



FENTANYL							
Mean	0.0	55.0	80.0	80.0	85.0	90.0	95.0
95% CI	-	33-77	62-98	62-98	69-100	77-100	85-100
N	20	20	20	20	20	20	20
PLACEBO							
Mean	0.0	30.0	65.0	70.0	75.0	75.0	80.0
95% CI	-	10-50	44-86	50-90	56-94	56-94	62-98
N	20	20	20	20	20	20	20
DIFFERENCE							
P	-	0.11	0.29	0.47	0.43	0.21	0.15

Caplan

Adverse Events Requiring
Medical Evaluation or Intervention

TTS - Fentanyl

SCN 428	Hemoptysis evaluated by physician. No treatment.
SCN 440	Physician called to evaluate RR of 8. No action required.
SCN 444	Chest heaviness. RR of 5. Physician called. Patient vomited. ABG's drawn. pCO_2 41. No action required.
SCN 447	RR 7. Sleeping soundly. Respiration slow and occassionally shallow. Physician called. No action taken.
SCN 451	Patient extremely agitated, tense, pale. Describes herself as "feeling weird." Calmed down and relaxed after conversation with physician.

Placebo

SCN 411	Hypotension related to hypovolemia from blood loss and possible requirement for steroid replacement. Head lowered, IV increased, hemovac 100 cc.
SCN 417	Shortness of breath and chest pain. Chest x-ray. ABG's; medical test and O_2. Physician called to evaluate. Attributed to anxiety.

85-051-02 McLesky 50 μg/h TTS Fentanyl

Abstract

This is a 54 patient randomized, double-blind, placebo-controlled study of TTS Fentanyl in the relief of post-operative pain in women following gynecologic surgery. Each patient had a 50 μg/hr or placebo system applied 2 hours before surgery, received a 100 μg operative fentanyl bolus, and was followed for 24 hours of system application and an additional 24 hours after system removal. The investigators found significantly better pain control in 26 fentanyl patients over 24 placebo patients as measured by lower pain intensity ratings , less supplemental morphine use, and higher global pain control ratings in the fentanyl group. Mean blood levels of fentanyl ranged from 0.86-1.0 ng/ml from 12-24 h after system application and no patients withdrew from the study by reason of adverse events.

This study was a 54-patient, randomized, double-blind, placebo-controlled, parallel-group study of TTS-50 vrs placebo-system carried out by Charles McLeskey of the University of Texas between July 1986 and April of 1987. The all-female study group had a median age of 43.5 years and weight of 72 kilos, was comprised of 26 whites, 16 blacks and 12 Hispanic women, and consisted of elective hysterectomies (52 of 54 patients). All patients had an active or a placebo system applied two hours before the induction of general anesthesia along with a dose of 10 mg oral diazepam. Induction of anesthesia was accomplished with a 100μg fentanyl bolus (both groups) and 4 mg/kg thiopental, following which anesthesia was maintained with nitrous, enflurane and a muscle relaxant if required. Post-operative analgesia was available to both groups as morphine sulfate 2 mg IV Q 2 hour PRN in the post-anesthetic recovery room (PAR) and up to 5 mg IM Q 2 hour thereafter. All patients were monitored for the 24 hours of system application and for 24 hours thereafter using the following efficacy and safety variables.

Efficacy Variables	***Safety Variables***
	Respiratory rate
Supplemental morphine use	***Sedation scores***
Pain intensity scores	***Blood levels of fentanyl***
Global pain control scores	***Adverse effect counts***
	Withdrawals for cause
	Episodes of respiratory depression

The study hypothesis was that patients who had a TTS-50 system applied 2 hours before induction of anesthesia would have better analgesia and require less supplemental morphine in the 24 hours following system application than a placebo-system group.

Patients who dropped out pre or intra-operatively were excluded from efficacy analysis but included in the safety data.

Selection , Withdrawals, and Mistakes

This study provides information regarding the use of this medication in healthy women undergoing elective gynecological surgery with benzodiazepine pre-medication. It is a young, healthy, female study group, with 54 of 54 ASA class I&II. Fentanyl and control groups differed in the number of vaginal hysterectomies (8/28 fentanyl v. 2/26 placebo), age (43 fentanyl v. 37 placebo), and height (fentanyl 160 cm v. placebo 163 cm). These differences would not be expected to significantly alter the results, although a case could be made that vaginal hysterectomy is potentially less painful than trans-abdominal hysterectomy.

Of the 54 patients who were randomized to two groups of 28 (fentanyl) and 26 (placebo) , two patients in each group were ineligible due to last minute alterations or cancellations of the proposed surgery. Since the patients had no surgery the systems were removed and these subjects were not included in the intent-to-treat analysis.

The investigators had 5 violations of protocol in 54 patients. These consisted mostly of single doses of unapproved analgesics (i.e. Tylenol #3, Demerol 75) given after the TTS had been removed and were handled by the investigator's converting the dose to an equianalgesic dose of morphine according to a fixed set of equivalencies provided by the company, and adding it to the patient's total morphine use. These violations would be expected to have no effect on the analysis of the period of system application.

Results and Analysis

The results of the study are shown on the next few pages. The first graph shows the cumulative use of rescue morphine by placebo and by the fentanyl group. Both the placebo and the fentanyl groups used morphine at a nearly constant rate (constant slope) for the first 36 hours of the trial, and the rate of use of morphine in the fentanyl group was significantly lower than in the placebo group. This finding is sufficient to establish efficacy, but when the morphine use is contrasted with the next graph showing pain intensity ratings, it can be seen that the fentanyl group not only used less morphine but experienced less pain while doing so. The findings seen in the pain intensity ratings are similar to those seen in the global ratings which are shown in the next graph. At all times the fentanyl group is reported as having better pain relief on global as well as interval ratings.

The fourth graph shows the blood levels of fentanyl for the active group during the study period, and shows that the group mean fentanyl level was within the therapeutic range for hours 12-36 of the trial, and analgesic efficacy might reasonably be expected. The finding of increased analgesic efficacy is also reasonable in light of the next figure which shows that the fentanyl group had a lower respiratory rate and a slightly higher level of sedation than the placebo group. The most reasonable interpretation is that the fentanyl group received a larger total dose (fentanyl + morphine) than the placebo group, and that this is reflected in higher levels of all opioid effects, including analgesia.

Adverse Events

The simultaneous use of morphine and fentanyl in this trial makes it difficult to interpret the pattern of adverse effects since both drugs have exactly the same profile of side effects in the doses used. Pure mu agonist drugs inevitably produce additive dose-related side effects such as anxiety, pruritis, insomnia, back & muscle ache, nausea, and urinary retention. Review of the pattern of side effects reported in the study shows that fentanyl patients had 43 adverse events while placebo patients had 25. These events were all consistent with narcotic side effects and reflected a general increase of all events rather than a large increase in one particular type.

There were no episodes of significant respiratory depression or excessive sedation in any patient in this study.

Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal. These effects were seen in both fentanyl and placebo system groups. There were no reported episodes of delayed hypersensitivity or system allergy.

Pharmacologic Performance

Observed blood levels at 24 hours ranged from 0.3 ng/ml to 2.0 ng/ml across the fentanyl group, and the individual case reports for several of the patients with high values and low values were reviewed. Cases 716 & 720 had low fentanyl levels (0.3 & 0.5 ng/ml), were 73 & 100 kg respectively, and both had a hysterectomy. Patient 716 had adequate relief as shown by pain scores of 2-4, while patient 720 had poor relief with scores of 7-9. Cases 713 & 739 had high blood levels (2.0 & 1.9 ng/ml), were 59 & 77 kg respectively, and had a hysterectomy and a laser ablation of the vulva respectively. Neither reported significant pain (scores 0-2) or used morphine supplementation to any appreciable extent.

Conclusion

This study shows that post-operative pain in patients who wore TTS 50 fentanyl systems was lower than that experienced by controls, both by self-report and by the measurement of morphine demand. Fentanyl is clearly absorbed in amounts adequate to cause both beneficial and adverse opiate effects, with the frequency of these effects being related to the total dose of opioid drugs rather than just to fentanyl. It is likely that any improved pain relief seen in the fentanyl group was due to a larger total narcotic dose rather than a specific fentanyl effect.

The TTS 50 μg/h group in this experiment had better pain relief with lower fentanyl blood levels than did the patients with TTS 100 μg/h systems in other studies. This study group was different in that it studied young, healthy, low-risk women recovering from modestly painful proceedures with excellent prognoses. It may be that the TTS system does a better job of relieving pain than relieving apprehension or suffering and is of most use when a strong psychic component of relief is not needed.

This study supports the efficacy of TTS fentanyl.

Study Type: Postoperative
C-85-051, II: TTS (fentanyl)-50 (20 cm^2)

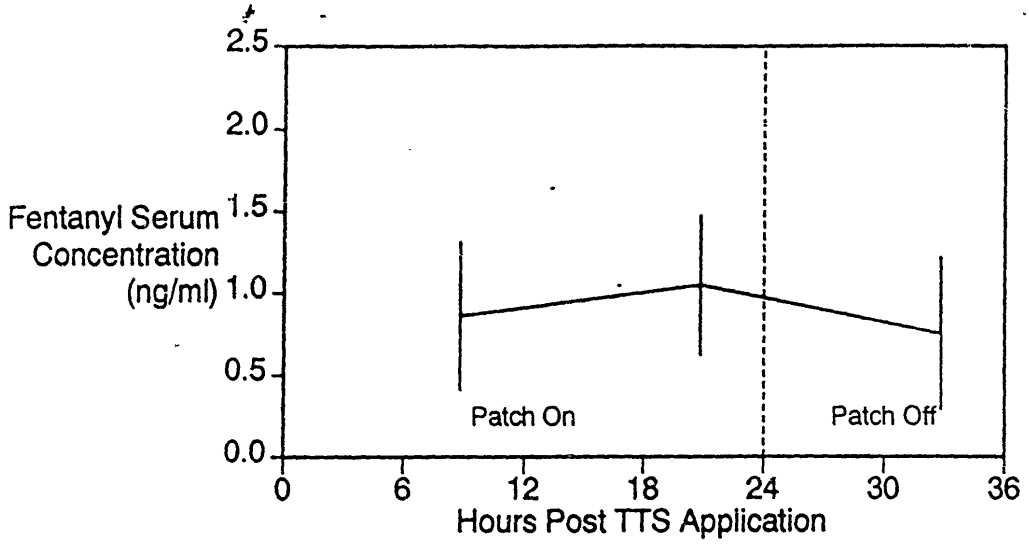
MCLESKEY

This is a 54 patient randomized, double-blind, single dose level study of TTS fentanyl (50 μg/hr) in the relief of post-operative pain in women following gynecologic surgery. Each patient had a 50 μg/hr or placebo patch applied two hours before surgery, received a 100 μg operative fentanyl bolus, and was followed for 24 hours of patch application and an additional 24 hours after patch removal. The 26 fentanyl patients experienced significantly better pain control as compared to 24 placebo patients as measured by lower pain intensity ratings (fentanyl 2.5/placebo 4.2), less supplemental morphine use (fentanyl 13.5/placebo 35.5) and better global pain control ratings (fentanyl 1.8/placebo 2.9) in the fentanyl group. Mean blood levels of fentanyl ranged from 0.75-1.0 ng/ml during patch application and no patients withdrew from the study by reason of adverse events.

	FENTANYL n=28	PLACEBO n=26	TOTAL n=54
SEX			
MALES	0	0	0
FEMALES	28	26	54
SURGERY			
GYNECOLOGIC	28	26	54
ANESTHETIC			
NITROUS/NARCOTIC	27	25	52
TIME (MEAN HOURS)			
TTS APPLICATION TO INDUCTION	2.4	2.5	
SURGICAL PROCEDURE	3.2	3.6	
CONCOMITANT MEDICATIONS			
PREMEDICATIONS - DIAZEPAM	28	26	54
- OTHER	0	0	0
INTRAOPERATIVE NARCOTIC - FENTANYL 100 μg	27	25	52
ADJUNCTIVE MEDS - ANTI-EMETIC	15	9	24
- SEDATIVE/TRANQUILIZER	1	0	1
USE OF RESCUE ANALGESIC - MORPHINE	17	24	41
DROPOUTS			
PRE-SURGERY	1	1	2
DURING SURGERY	0	0	0
PROTOCOL VIOLATION	0	0	0
LACK OF EFFICACY	0	0	0
ADVERSE EVENTS	0	0	0
TOTAL	1	1	2
ADVERSE EVENTS REQUIRING MEDICAL EVALUATION	2	3	5

3/21/90

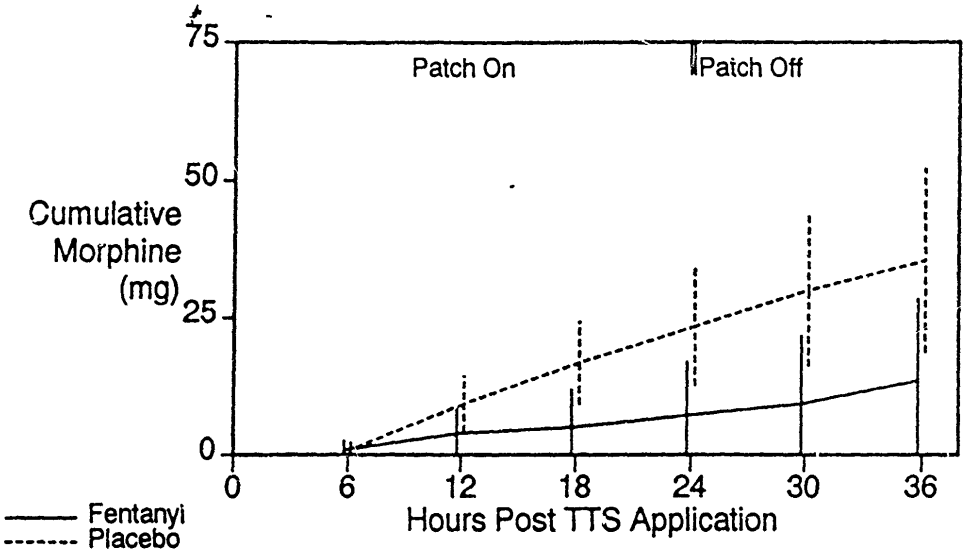
BENEFICIAL EFFECTS
FENTANYL SERUM LEVEL
Study: MCLESKEY



FENTANYL			
Mean	0.9	1.0	0.8
SD	0.5	0.4	0.5
N	26	25	24

3/21/90

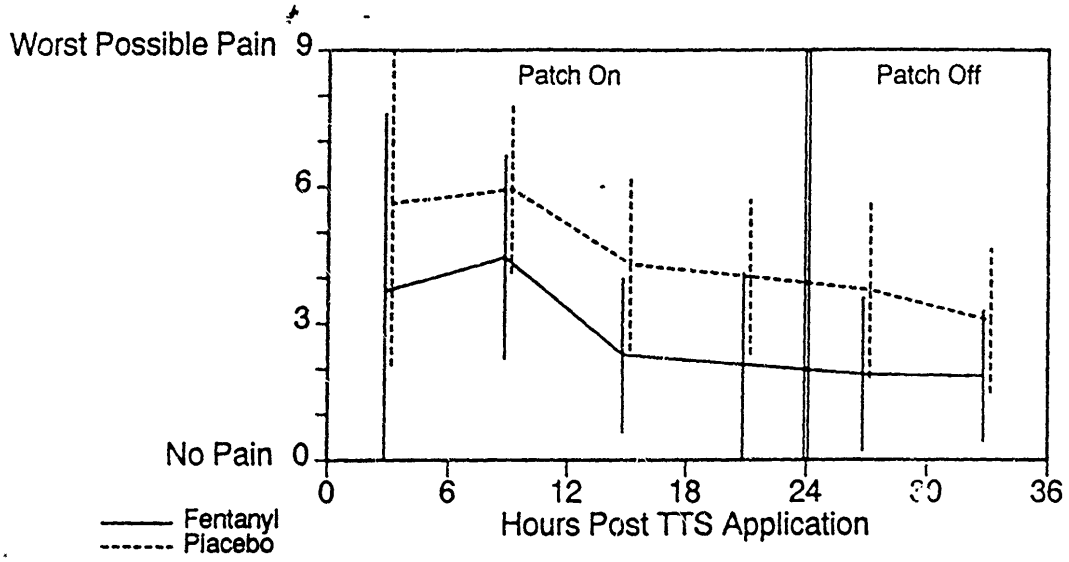
BENEFICIAL EFFECTS
CUMULATIVE USE OF RESCUE MEDICATION
Study: MCLESKEY



FENTANYL						
Mean	0.8	3.8	5.0	7.1	9.2	13.5
SD	1.8	4.6	7.0	9.9	12.5	15.1
N	26	26	26	26	26	26
PLACEBO						
Mean	1.0	9.2	16.8	23.4	30.0	35.5
SD	2.0	5.2	7.6	10.8	13.8	16.8
N	24	24	24	24	24	24
DIFFERENCE						
Mean	0.1	5.4	11.8	16.3	20.8	22.0
SE	0.5	1.4	2.1	2.9	3.7	4.5
P	0.84	<0.01	<0.01	<0.01	<0.01	<0.01

3/21/90

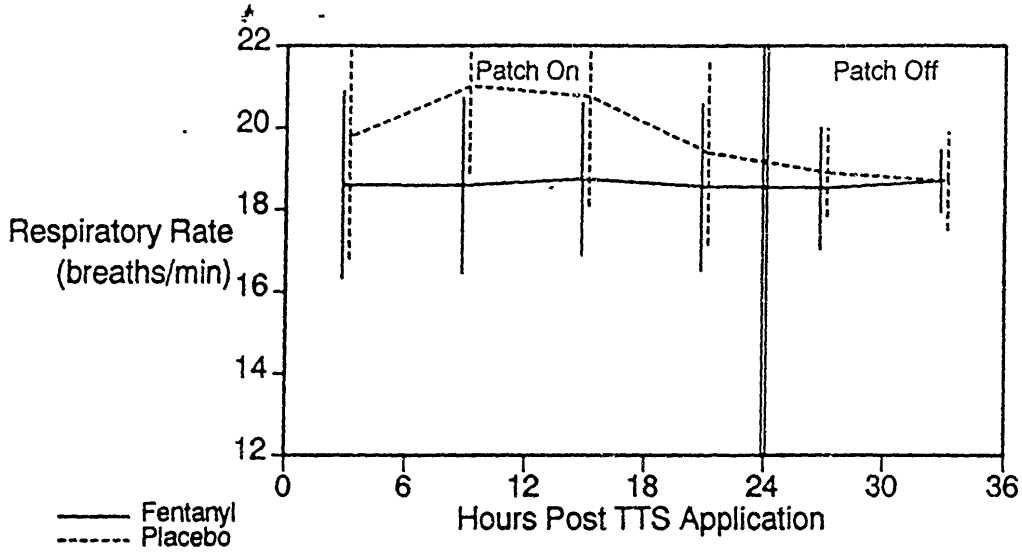
BENEFICIAL EFFECTS
PAIN INTENSITY RATINGS
Study: MCLESKEY



							0-36
FENTANYL							
Mean	3.7	4.5	2.3	2.1	1.9	1.8	2.5
SD	3.9	2.2	1.7	2.0	1.7	1.4	1.4
N	19	26	26	26	26	26	26
PLACEBO							
Mean	5.6	5.9	4.3	4.0	3.7	3.0	4.2
SD	3.6	1.8	1.9	1.7	1.9	1.6	1.6
N	15	24	24	24	24	24	24
DIFFERENCE							
Mean	1.9	1.5	2.0	1.9	1.9	1.2	1.7
SE	1.3	0.6	0.5	0.5	0.5	0.4	0.4
P	0.15	0.01	<0.01	<0.01	<0.01	<0.01	<0.01

3/21/90

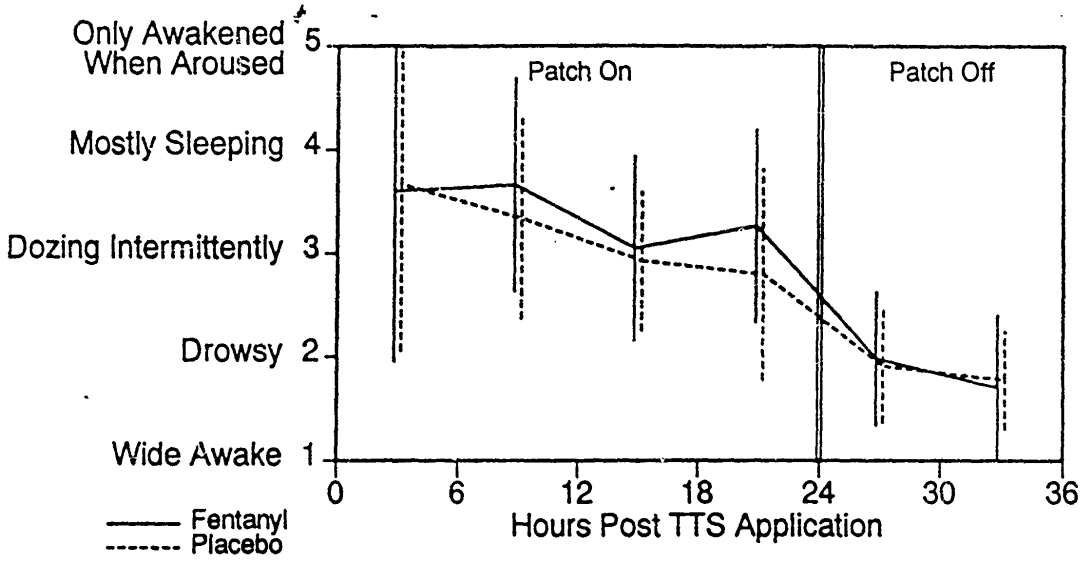
ADVERSE EFFECTS
RESPIRATORY RATE
Study: MCLESKEY



FENTANYL							0-36
Mean	18.6	18.6	18.7	18.6	18.5	18.7	18.6
SD	2.3	2.2	1.9	2.0	1.5	0.8	1.1
N	23	26	26	26	26	26	26
PLACEBO							
Mean	19.8	21.0	20.8	19.4	18.9	18.7	19.7
SD	3.0	2.1	2.7	2.3	1.1	1.2	1.2
N	19	24	24	24	24	24	24
DIFFERENCE							
Mean	-1.2	-2.4	-2.0	-0.8	-0.4	-0.0	-1.1
SE	0.8	0.6	0.7	0.6	0.4	0.3	0.3
P	0.16	<0.01	<0.01	0.18	0.32	0.99	<0.01

3/21/90

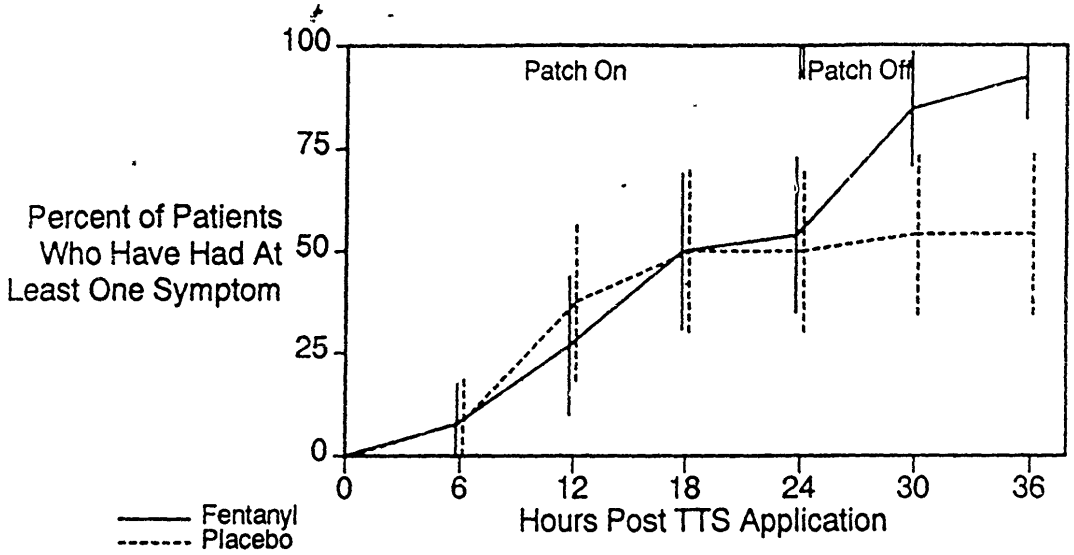
ADVERSE EFFECTS
SEDATION
Study: MCLESKEY



FENTANYL							0-36
Mean	3.6	3.7	3.0	3.3	2.0	1.7	2.8
SD	1.7	1.0	0.9	0.9	0.6	0.7	0.5
N	23	26	26	26	26	26	26
PLACEBO							
Mean	3.7	3.3	2.9	2.8	1.9	1.8	2.6
SD	1.6	1.0	0.7	1.0	0.5	0.5	0.5
N	19	24	24	24	24	24	24
DIFFERENCE							
Mean	0.1	-0.3	-0.1	-0.5	-0.1	0.1	-0.2
SE	0.5	0.3	0.2	0.3	0.2	0.2	0.1
P	0.90	0.25	0.59	0.10	0.65	0.68	0.17

3/21/90

ADVERSE EFFECTS
ADVERSE EVENTS CURVES
Study: MCLESKEY



FENTANYL							
Mean	0.0	7.7	26.9	50.0	53.8	84.6	92.3
95% CI	-	0 -18	10-44	31-69	35-73	71-98	82-100
N	26	26	26	26	26	26	26
PLACEBO							
Mean	0.0	8.3	37.5	50.0	50.0	54.2	54.2
95% CI	-	0 -19	18-57	30-70	30-70	34-74	34-74
N	24	24	24	24	24	24	24
DIFFERENCE							
P	-	0.93	0.42	1.00	0.79	0.02	<0.01

McLeskey

Adverse Events Requiring
Medical Evaluation or Intervention

TTS - Fentanyl

SCN 728	Decreased hematocrit. Atropine administered. Blood transfusions. Benadryl given.
SCN 732	Increased blood pressure. 0.1 mg clonidine given.

Placebo

SCN 718	Vagina was repacked; secondary bleeding; blood transfusion.
SCN 729	ABG's drawn for hematocrit determination. Low pO_2.
SCN 737	Physician notified of increased urinary output.

Supportive Studies in Postoperative Pain

C-85-047-02 Plezia

Abstract

This is a 43 patient randomized, double-blind, placebo-controlled study of TTS Fentanyl 75 in the relief of post-operative pain in men and women following a mixture of orthopedic and abdominal surgeries. Each patient had a 75 μg/hr or placebo system applied 2 hours before surgery, all received a 200 μg bolus of fentanyl at induction, and all were followed for 24 hours of system application and for an additional 24 hours after system removal. Pain relief and adverse events were monitored hourly by the investigators using the following efficacy and safety variables:

Efficacy	***Safety***
	Blood levels of fentanyl
Supplemental morphine use	***Sedation scores***
Pain intensity scores	***Adverse effect counts***
Global pain control scores	***Withdrawals for cause***
	Respiration

The investigators found a clinically but not statistically significant trend toward better pain control in 16 fentanyl patients over 21 placebo patients as measured by less supplemental morphine use. Mean blood levels of fentanyl ranged from 0.6-1.5 ng/ml during system application, for the magnitude of the surgeries seen in this study. The marginal performance of the TTS system in this study probably represents a combination of a low dose, an unacceptable number of drop-outs, multiple adverse events and high intra-subject variability.

Resume

This study was a 43-patient, randomized, double-blind, placebo-controlled, parallel-group study of TTS-75 vrs placebo, carried out by Patricia Plezia of the University of Arizona between February 1986 and September of 1986. The study group consisted of patients undergoing a mixture of orthopedic and abdominal procedures of varying severity under general anesthesia.

The subjects were stratified by surgery type, then randomized. Unfortunately, while the mixture of subjects for the entire group was nearly 50-50 male female (20/23), and each group started balanced, a disparate number of withdrawals unbalanced the final groups to fentanyl - 6 male/10 female, and placebo-12 male/9 female. This posed a problem in the later interpretation of the study, since there has been a trend across all studies for women to have a greater fentanyl - placebo discrimination than men. Other than this gender difference, there were little difference between the groups .

All patients had an active or a placebo system applied 2 hours before the induction of anesthesia with a 200 mg fentanyl bolus and 4 mg/kg thiopental. Anesthesia was maintained by nitrous - isoflurane, with

muscle relaxation by atracurium as needed. Post-operative analgesia was available to both groups in the post anesthetic recovery room (PAR) as 2 mg morphine sulfate IV every 5-10 minutes, and as 5 mg morphine sulfate IM every 2 hours thereafter.

This system provided a maximal rate (upper limit) of morphine infusion of 12-24 mg/hr in the PAR, and 2.5 mg/hr thereafter. Actual usage rates were about 5 mg/hr in the PAR and 1.0 mg/hr on the ward.

The study hypothesis was that patients who had a TTS-75 system applied 2 hours before induction of anesthesia would have better analgesia and require less supplemental morphine in the 24 hours following system application than a placebo-system group.

All data were analyzed for the entire period, and patients who dropped out pre or intra-operatively due to alterations in time or type of surgery were excluded from efficacy analysis but included in the safety data.

Selection , Withdrawals, and Mistakes

This study provides information regarding the use of this medication in a mixture of elective surgeries in a 40 year old, 60-75 kg patient group. It is a more seriously ill group than many other studies, containing 15 ASA class I patients, 15 ASA class II patients , and 6 ASA class III.

The 43 patients were stratified as to surgical type (orthopedic or abdominal) and randomized to one group of 22 (fentanyl) and a second group of 21 (placebo). Four patients in the fentanyl group were eliminated perioperatively for reasons not due to the medications (change in surgical procedure, intra-operative death from hemorrhage,surgery postponed, anesthesiologist altered technique) , and two additional were eliminated for respiratory depression on extubation which was treated with naloxone. Post-operatively one fentanyl patient was removed for inadequate analgesia, one for operative bleeding, and one for generalized pruritus. Three subjects in the placebo group were dropped, two for inadequate analgesia and one for respiratory depression requiring naloxone. Of these complications only the two respiratory depressions and the generalized pruritus are likely to be fentanyl effects as discussed below in the integrated safety summary.

The final numbers of subjects completing the protocol were 13 of a possible 22 in the fentanyl group, and 18 of 21 in the placebo group. These losses greatly diminished the worth of the study.

Protocol violations were numerous and significant. Five of the remaining patients received doses of fentanyl at induction other than the 200 µg required by the protocol, ranging from 100-250 µg. In addition, six patients received non-protocol narcotics during the study period which were converted to a "morphine equivalent" and added to the total morphine used. The conversion factors were approximate and taken from an article by Kathleen Foley in the NEJM (313:84-95, 1985).

The unbalanced gender ratios, the extensive drop-outs, and these protocol violations are likely to have biased the results in an

unpredictable fashion, raised the variability and thus lowered the power of the study.

Results and Analysis

The primary outcome variable for this study is the amount of morphine used in each interval and the total amount used in each group from hour 0 to hour 36. This is shown in tabular and graphic form. As may be seen, there is a small but consistent reduction in hourly morphine use for all periods and a clear divergence of the slopes of the cumulative morphine use plots. While the trend is clear, there is lack of statistical significance is due to small numbers and high variability as discussed above.

The pain experience of each group shows no clear advantage to either group for any time period, but does show marked parallelism of pain plots. Each group rated their pain at about 5 on a 10 point scale, with a modest decline in mean intensity over the first 36 hours post-operatively. There is a modest increase in pain relief in the placebo group from system removal to the end of the trial, which represents 3-4 placebo patients who had an unexplained improvement in pain control.

The investigators have shown that there is a consistent reduction in the morphine demand of fentanyl treated patients over placebo controls, but lacked the power to demonstrate statistical significance. Neither the placebo nor the fentanyl group achieved better than moderate pain relief, and neither group were particularly satisfied with their analgesia as shown by the nearly uniform distribution of global pain relief scores.

TTS Fentanyl 75 seems not to have delivered sufficiently improved analgesia to enable the differentiation from placebo in this trial.

Adverse Events

Review of the pattern of side effects reported in the study shows that nearly all adverse events were "opioid" or narcotic side effects. The fentanyl patients had 26 such adverse events while placebo patients had 18, with the excess events occurring during the period of system wearing.

Three fentanyl patients developed significant respiratory depression with blood levels of fentanyl >2.0 ng/ml. One placebo patient developed significant peri-operative respiratory depression from morphine and required naloxone reversal.

The fentanyl group had the consistent and modest reduction in mean respiratory rate as shown, but had no increase in sedation over the placebo system wearers.

Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal. These effects were seen in both fentanyl and placebo system groups. There were no reported episodes of delayed hypersensitivity or system allergy.

Pharmacologic Performance

Observed blood levels at 24 hours ranged from 0.2 ng/ml to 3.00 ng/ml, and the case reports for several of the patients with high values and low values were reviewed. Cases 536 & 538 had low fentanyl levels (0.2 & 0.6 ng/ml), and were 64 & 81 kg respectively. Patient 536 had average relief as shown by pain scores of 4-6 and low morphine use , while patient 538 had poor relief with scores of 5-9 and high use of rescue medication.

Cases 513 & 515 had high blood levels (2.9 & 3.0 ng/ml), were 49.9 & 44.5 kg respectively, both reported average pain relief (scores 4-7), and both used morphine supplementation at the group rate.

The system delivered fentanyl in a fashion consistent with the sponsor's claims, and resulted in an analgesic blood level of fentanyl (1.0-2.0 ng/ml) in the 12-24 hour interval in 11 of 18 patients wearing the system for that long.

Conclusion

This study did not have adequate statistical power to demonstrate the effect of TTS fentanyl, due to a combination of excessive patient variability, drop-outs, protocol errors, small sample size, and a significant number of patients who failed to achieve analgesic blood levels. The trial is inconclusive, not negative, since it failed for lack of power. Fentanyl was clearly absorbed by most patients in pharmacologic amounts, and the separation between the groups favored fentanyl, but the trial lacked enough statistical power to demonstrate statistical significance.

The significance of the episodes of respiratory depression at extubation is unknown, for they most likely reflect the combination of the intra-operative fentanyl bolus and isoflurane rather than the system. There was one such case of respiratory depression in each group, and the causative role of fentanyl in this is unproven. The fentanyl group clearly received more opioid drug than the placebo group, as shown by more opioid side effects, but did not show any clinically important increases in morbidity.

The sponsor's clinical hypothesis was not supported in this study, and while the the system was shown to be safe, it was not shown to be effective.

FIGURE 1

Disposition of Enrolled Patients

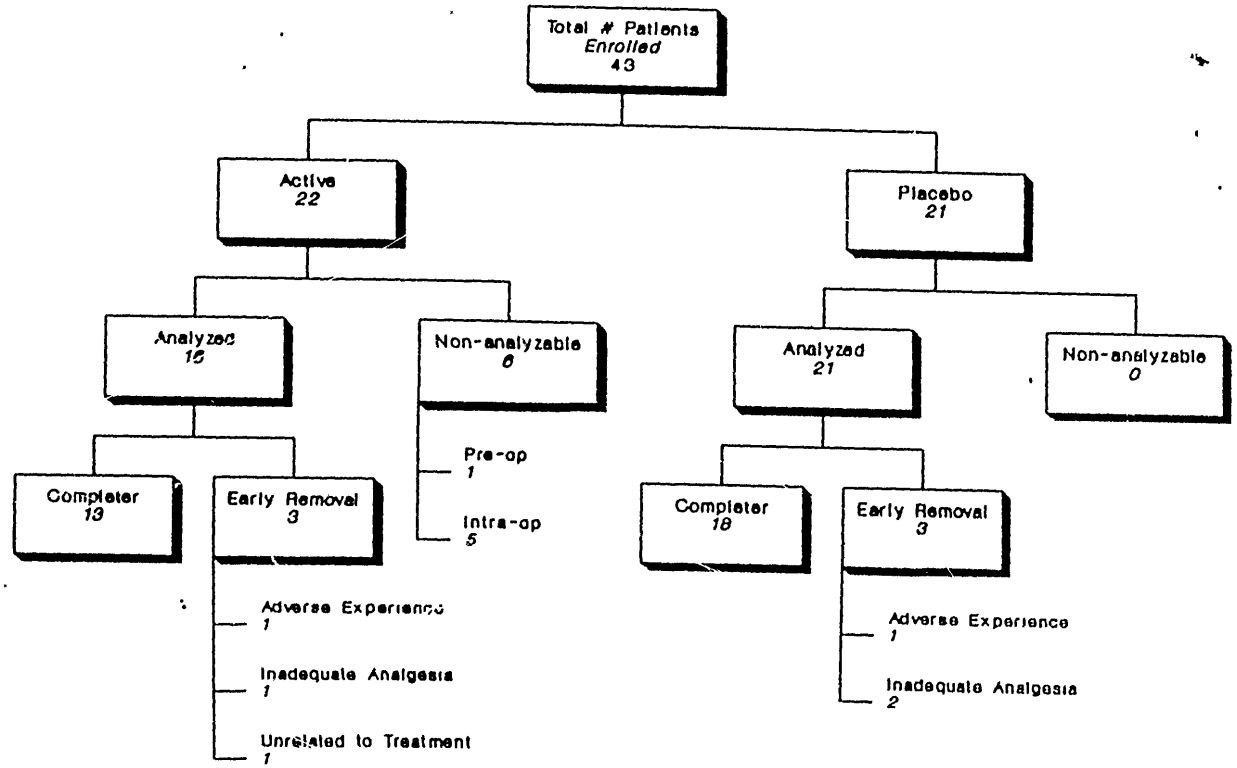
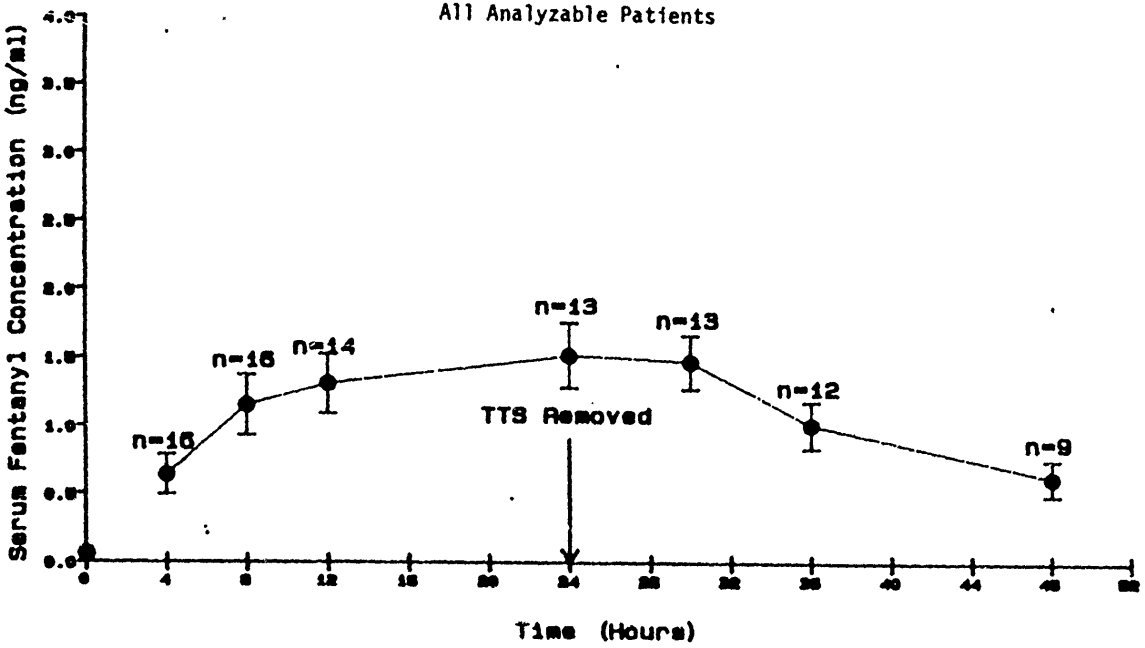


FIGURE 6
Mean (SE) Serum Fentanyl Concentration (ng/ml)
at Time from TTS Application*

All Analyzable Patients



*Values less than 0.1 ng/ml were reported as 0.05 ng/ml

FIGURE 4

Mean (SE) Cumulative Supplemental Morphine Sulfate Use
(Completers Only)

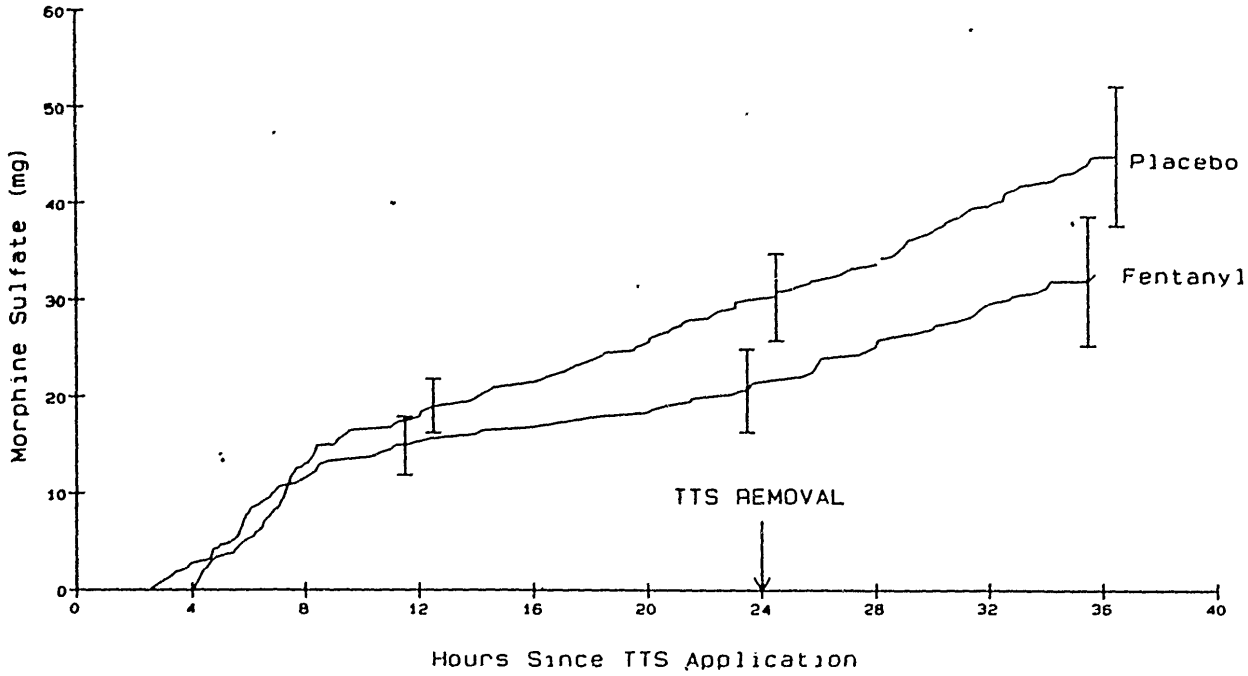


TABLE M. NUMBER OF PATIENTS WITH ADVERSE EXPERIENCES BY BODY SYSTEM
(All Enrolled Patients)

	FENTANYL (n=22)			PLACEBO (n=21)		
	OR/PAR	WARD-REMOVAL	AFTER REMOVAL	OR/PAR	WARD-REMOVAL	AFTER REMOVAL
NEUROLOGIC						
Headache	0	0	0	0	0	1 (5%)
Vivid dreams	0	1 (5%)	0	0	0	0
Dizziness	0	0	0	0	0	1 (5%)
Thick speech	1 (5%)	0	0	0	0	0
GASTROINTESTINAL						
Nausea/ Vomiting	2 (9%)	8 (36%)	3 (14%)	0 (0%)	5 (24%)	4 (19%)
CARDIOVASCULAR						
Asymptomatic hypotension	0	0	1 (5%)	0	0	0
Premature ventricular contractions	0	0	0	0	1 (5%)	0
RESPIRATORY						
Respiratory depression	2 (9%)	1 (5%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)
GENITOURINARY						
Urinary retention	0 (0%)	1 (5%)	1 (5%)	0 (0%)	2 (10%)	0 (0%)
SKIN & APPENDAGES						
Pruritus	1 (5%)	1 (5%)	1 (5%)	0*	0	0
Urticaria	0	0**	0	1 (5%)	0	0
Bleeding	0	1 (5%)	0	0	0	0
BODY AS A WHOLE						
Flushing	0	0	0	0	0	1 (5%)
Diaphoresis	0	0	1 (5%)	0	0	1 (5%)

* The investigator attributed this reaction, which occurred at the IV site, to a morphine sulfate allergy.
** Bleeding at the operative site was not related to study treatment per investigator. Refer to Appendix I.

REFERENCE: Appendix I

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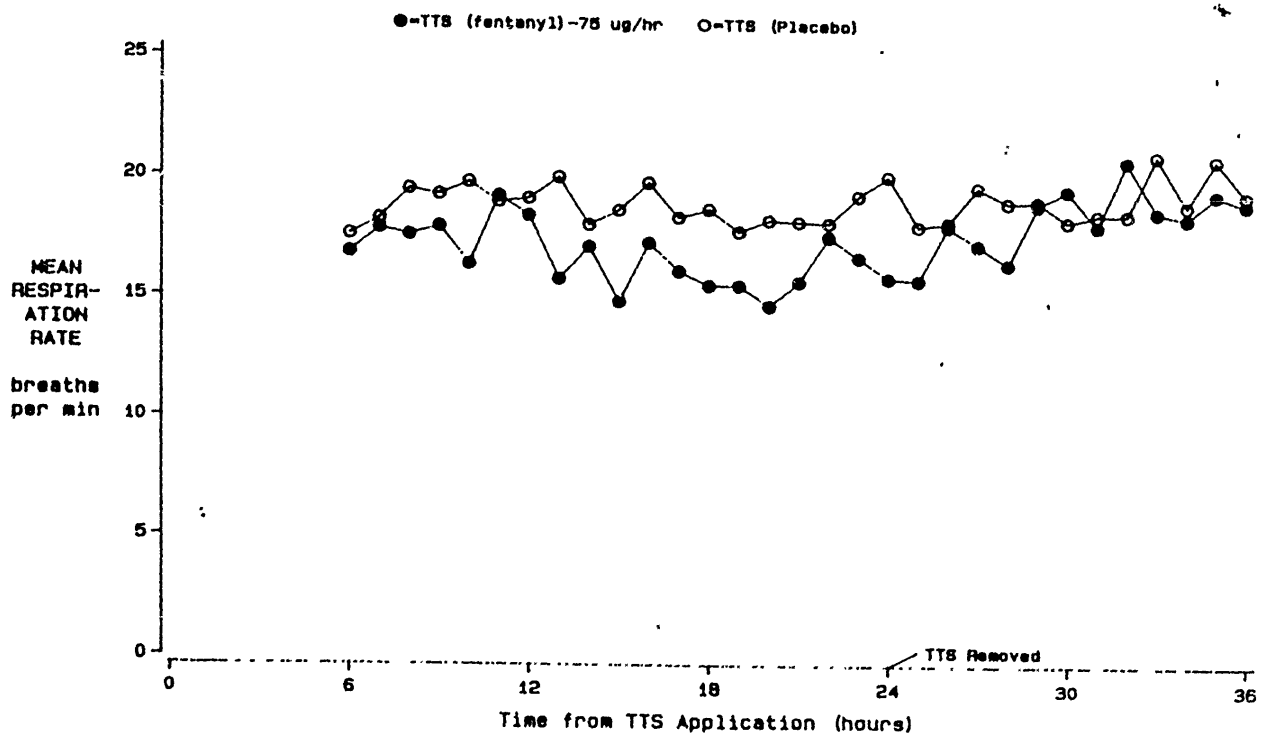
1.30/04

PROTOCOL C-85-047, Study II
Investigator: PLEZIA

FIGURE 7

Mean RESPIRATION RATE by Time from TTS Application
(All Analyzable Patients)



PROTOCOL C-85-047, STUDY II: PLEZIA

Table 7
Serum Fentanyl Concentration (ng/ml)

Patient Number+	Nominal Time (hours) 0	4	8	12	24	30	36	48
512 E	0.05++	0.5	1.5H	1.0*h	0.4*	0.2*	0.2*	0.05*
513	0.05	0.6h	2.0	2.1	2.9h	2.4	0.9	0.7
514	0.05	1.2	2.2	2.1	1.9	1.4	1.6	0.7
515	0.05	1.1	3.3	2.8	3.0	2.3	1.7	0.4
516 N	--	--	--	--	--	--	--	--
522	0.05	0.3	0.4	0.6	0.8	0.6	0.3	0.2
524	0.05	1.0	1.0	0.8	1.3	0.8	0.8	0.6
525	0.05	0.5	0.5	0.4	0.9	1.3	1.8	0.6
528	0.05	0.2	0.3	0.8	1.2H	0.7	0.4	1.1
529	0.05	2.5	2.3	2.6	2.4	3.0	1.4	--
533	0.05	0.3	0.6	1.5	1.6	1.6	1.5	1.3
534 E	0.05	0.05	0.9	0.8	--	--	--	--
535	0.05	0.6	0.9	1.3	1.6	1.7	1.1	0.1
536	0.05	0.05	0.05	0.1	0.2	1.0h	0.1	--
538	0.2	0.40a	0.3	0.8	0.6	1.0	0.5	--
569 N	--	--	--	--	--	--	--	--
570	0.05	0.5	0.9	1.6	1.4	1.3	--	--
571 N	--	--	--	--	--	--	--	--
574 N	0.05	1.95b	1.9	0.6	0.6	--	--	--
576 E	0.05	0.5	1.2	--	--	--	--	--
578 N	0.05	0.6	1.4	0.7	0.5	--	--	--
579 N	0.05	0.5	1.4	2.5	--	--	--	--
(Summary statistics exclude non-analyzable patients)								
N	16	16	16	14	13	13	12	9
Mean	0.06	0.64	1.15	1.31	1.52	1.47	1.01	0.63
SD	0.04	0.60	0.90	0.84	0.85	0.72	0.59	0.39
SE	0.01	0.15	0.22	0.22	0.24	0.20	0.17	0.13
Minimum	0.05	0.05	0.05	0.1	0.2	0.6	0.1	0.1
Maximum	0.2	2.5	3.3	2.8	3.0	3.0	1.8	1.3

+ Codes: E indicates TTS removed prior to 24 hours
N indicates non-analyzable patient

++ Values less than 0.1 ng/ml, the sensitivity of the assay, are reported as 0.05 ng/ml

* Values not included in summary statistics: patient had TTS removed early

a Value is the average of 0.4 ng/ml (3.0 hours) and 0.4 ng/ml (4.0 hours)

b Value is the average of 1.5 ng/ml (4.0 hours) and 2.4 ng/ml (5.7 hours)

h Slightly hemolyzed

H Hemolyzed

HS 22.66

3.3.4 Respiration

Respiratory Depression: One fentanyl patient (SCN 514) and 1 placebo patient (SCN 523) experienced respiratory depression postoperatively, defined as a respiratory rate of less than or equal to 8 breaths per minute and a pCO2 greater than 55 mm Hg (Table 10). Both patients had received supplemental morphine doses prior to respiratory depression. Two additional fentanyl patients (SCN 574 and 578) experienced respiratory depression upon extubation in the operating room. These patients are discussed in detail below.

SCN 514 (fentanyl); a 68-year-old female, ASA class III, who underwent Morton's neuroma removal of the right knee, was sedated throughout the study and experienced respiratory depression at study hour 24. Her fentanyl serum concentrations were 2.1 and 1.9 ng/ml, respectively at 12 and 24 hours post-application. She received a 5 mg morphine sulfate dose less than an hour before her respiratory rate fell to 7 at study hour 24. (Her total morphine dose was 10 mg.) Her respiratory status and vital signs improved within an hour following TTS removal without treatment. The investigator's letter in Appendix II provides a detailed explanation of this patient's event.

SCN 523 (placebo), a 67-year-old female, ASA class I, who underwent a right total hip revision, had received 16 mg morphine sulfate in the PAR shortly before her transfer to the ward. Upon arrival in the ward, her respiratory rate fell to 4 breaths per minute. Naloxone was administered with good response.

SCN 574 (fentanyl), a 38-year-old female, ASA class I, was breathing only on command and had a PCO2 of 64 following extubation after cholecystectomy. Intraoperatively, this patient received a lower fentanyl bolus (50 mcg) than that specified in the protocol (200 mcg) and a higher dose of thiopental (5.2 mg/kg rather than the specified 4.0 mg/kg); the investigator noted that this was done to avoid biliary sphincter spasm. Naloxone (0.15 mg) was administered in the OR, after which the patient's respiration rate increased to 24 and she became combative. Because the investigator felt that the dose of fentanyl used was low and was not consistent

with the apparent response, the TTS was left in place. The anesthesiologist administered 50 mg thiopental (5.8 mg/kg) to treat the combativeness, and the patient was transfered to the PAR with a respiratory rate of 24. Thirty-five minutes after arriving in the PAR, the patient's respirations decreased to 14 breaths per minute. The TTS was removed and the patient's respiratory rate increased to 16-20 breaths per minute. SCN 574's serum fentanyl concentration was 2.4 ng/ml, at the time of TTS removal (5.9 hours after application; 2.0 hours following the fentanyl bolus). (Refer to Appendix II for the investigator's letter of explanation and the patient's anesthesia record.)

SCN 578 (fentanyl), a 22-year-old female, ASA class II, failed to breathe following extubation in the OR. She had undergone an exploratory laparotomy with resection of a Meckles diverticulum and appendectomy. The anesthesiologist administered naloxone (0.12 mg) and removed the TTS, and the patient was admitted to the PAR in stable condition with a respiratory rate of 12. Her 8 hour serum fentanyl concentration (2 hr after TTS removal) was 1.4 ng/ml. (Refer to Appendix II for the investigator's letter of explanation and the patient's anesthesia record.)

Respiratory Rate: There were no statistically significant differences in mean respiratory rate between fentanyl and placebo groups during any time period except 12-24 hours (p=0.02). During that period, occurring during the night for most patients, the placebo group had a mean respiratory rate of 18.7 breaths per minute, versus the fentanyl group's mean rate of 16.1. (Table M and Figure 7).

Oxygen Saturation: Oxygen saturation was monitored continuously as a safety precaution. These data are listed by patient in Appendix 1.

1.30/0.

85-005-02 Stanski 100 μg/h TTS Fentanyl

Abstract

This is a double-blind, placebo-controlled, randomized study of the efficacy of TTS fentanyl 100 in relief of post-operative pain following inhalational anesthesia. Systems were applied 2 hours before surgery and supplemented in both experimental and control groups with a 300 μg intra-operative fentanyl bolus. There were better global pain control scores and less morphine use in the fentanyl group, but the differences did not reach statistically significance. Mean blood levels of fentanyl ranged from a low of 0.9 at four hours to a high of 1.8 ng/ml at 28 hours, with no observed differences in adverse events between groups.

This study was a 46-patient, randomized, double-blind, placebo-controlled, parallel-group efficacy study of TTS fentanyl 100 vrs placebo system. It was carried out by Donald R. Stanski at Stanford between Jan-Nov 1986 on a predominantly male (43 male/3 female) group of ASA class II & III patients who were undergoing abdominal (20), thoracic (9), lumbar(15), and orthopedic (2) surgeries. The study hypothesis was that patients who had a TTS 100 system applied 2 hours before induction of anesthesia with 300 μg fentanyl & 2-4 mg/kg thiopental (subsequent technique was nitrous-enflurane) would require less morphine analgesia in the 24 hours following system application than placebo. The outcome variables were identical to other studies in this series.

Efficacy	***Safety***
	Respiratory rate
Supplemental morphine use	***Blood levels of fentanyl***
Pain intensity scores	***Adverse effect counts***
Global pain control scores	***Withdrawals for cause***
	Episodes of respiratory depression
	Sedation scores

Outcome variables were assessed hourly for 24 hours of TTS application and for 12 hours after removal. Serum levels of fentanyl were taken at 0,4,8,12, & 24 hours after system application and 4,8,12,&24 hours after removal. Global pain ratings were done for 0-24, 24-36, and 36-48 hours after TTS application. The TTS skin site was examined at 1,6,& 24 hours after application.

Six patients dropped out pre or intra-operatively and were excluded from efficacy analysis but included in the safety data. In all cases this "drop-out" was due to changes in surgical type or intra-operative events which made the patients unsuitable for the trial.

Bias from Selection and Withdrawals

The initial group of 46 patients was randomized to two groups of 23, with 4 fentanyl patients and 6 placebo patients withdrawing from the

study after randomization. This left 19 fentanyl and 17 placebo patients in the study.

The subjects were typical for the predominantly male VA patient population, with a mean age of 52 years, weight of 80-83 kg, and ASA class II. As a group, this population has a higher degree of alcohol and drug use and anesthetic and analgesic tolerance than other sub-samples of the population, and this would be expected to reduce the difference between the fentanyl and placebo group by altering the pharmacodynamics of fentanyl.

As the system was applied pre-operatively, an "intent-to-treat" analysis should include all patients, but the 3 subjects in the fentanyl group who were withdrawn all had non-drug related protocol changes or surgical cancellations. The same was true of the 3 peri-operative placebo withdrawals. In consequence, the most unbiased method of handling the patients who had systems but no surgery is not to extrapolate their values, the method used by the sponsor.

The same cannot be said for the 1 placebo patient who was removed for respiratory depression and 2 placebo patients who dropped out for inadequate analgesia as well. No predictable bias was likely to have been introduced by these withdrawals, but they do degrade the power of the trial.

Results and Analysis

The results of the study are shown on the accompanying pages. As may be seen from the plot of morphine use, the use of rescue medication in the experimental and control group differed to the greatest extent in the first hours of the trial, and while the use of morphine was always less in the active system group, this difference was never significant. While a significant difference favoring the TTS system was seen in 0-24 hour global pain ratings, hourly pain ratings and observer ratings did not differ to any appreciable extent.

Safety

Review of the pattern of side effects reported in the study shows no obvious pattern other than a higher incidence of urinary retention (5 fentanyl vrs 2 placebo) and of anxiety (2 fentanyl vrs 0 placebo).

There were three patients in the study who had episodes of serious respiratory depression :

SCN 170, a fentanyl patient, had an episode of apnea after extubation in the PAR (fentanyl level 1.85) and required naloxone.

SCN 125, placebo, had hypercarbia after pulmonary lobectomy and receiving 16 mg morphine.

SCN 130, fentanyl, had an episode of hypopnea after receiving 50 mg diphenhydramine IV for hives (fentanyl level 0.61).

None of these episodes appeared related to TTS fentanyl overdosage, but did seem related to the residua of anethesia, use of narcotic analgesics or the combination of narcotics with sedatives.

Topical effects from the system were as expected. Both fentanyl and placebo system patients had mild erythema lasting 24 hours post system removal, while one patient had mild irritant dermatitis with pustules lasting over 24 hours.

Pharmacologic Performance

There was considerable variation in peak blood level, Tmax, and 24 hour dose in this study. Examination of the group mean revealed that it required about 4-8 hours for the patients to reach analgesic blood levels of fentanyl even with the bolus dose, and the peak level was not reached until 2 hours after the system was removed at 24 hours (hour 26).

Case reports for two of the individuals with the lowest blood levels and two with the highest blood levels were reviewed to examine the pharmacokinetic exceptions. Subjects 115 & 127 had low blood levels of fentanyl and were found to be males who weighed 108.9 and 104.3 kilos respectively, who were having a total knee repair (3.5 hr) and a cholecystectomy(4.5 hr) respectively. Cases 122 & 174 (who had high blood levels) were also male, 90 & 85 kg respectively, and having a low anterior resection (4.5 hr) and a Knodt rod fusion (5.5 hr). No satisfactory explanation for the differences other than the 20 % weight difference and its probable relationship to clearance could be discerned.

Reviewer's Evaluation

The investigator failed to show any difference between TTS 100 and placebo on any of the major outcome variables in the study. Although TTS 100 fentanyl did consistently outperform placebo in both supplemental morphine requirements and pain intensity scores, the difference was not of a magnitude such as to reach statistical significance given the power of the study. The safety findings are consistent with the efficacy outcome, and both seem to reflect the lack of sufficiently high blood levels of fentanyl to produce either analgesia or adverse effects. The claim of improved overall pain relief in the 0-24 hour ratings is not sufficiently robust to be accepted owing to the multiplicity of secondary variables.

Conclusion

This study gives useful information about the kinetics of the drug, but provides no information regarding either an analgesic effect or lack of toxicity in analgesic doses.

PROTOCOL C-85-005, STUDY II: STANSKI

Disposition of Enrolled Patients

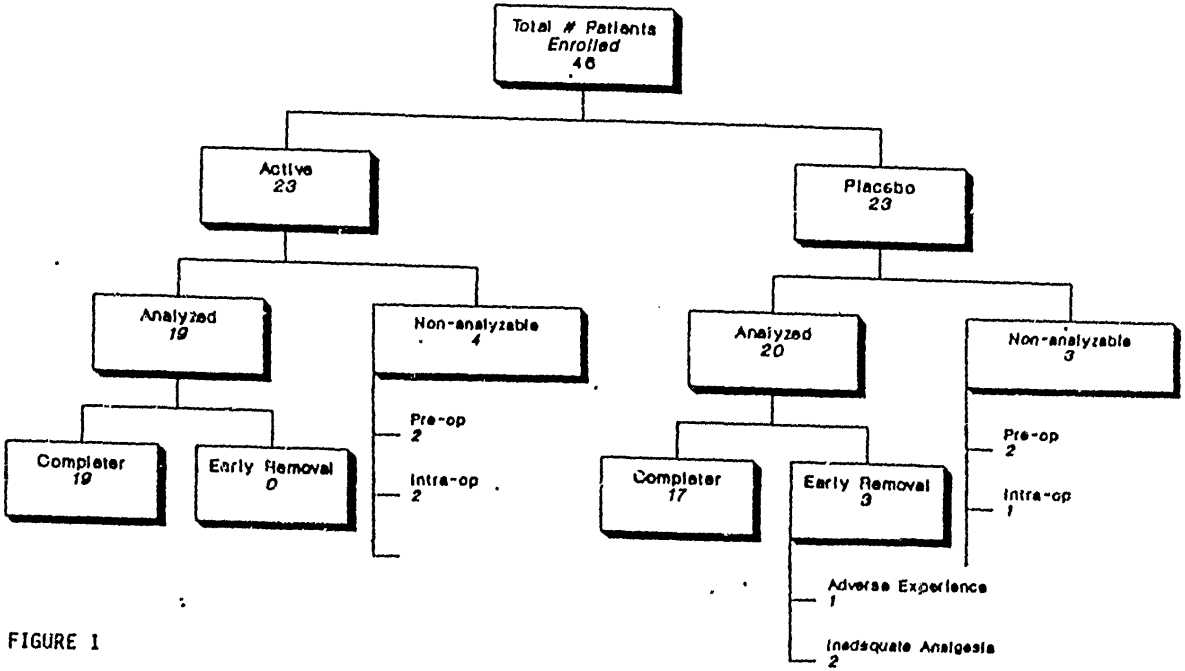


FIGURE 1

ABLE C. SUMMARY OF DEMOGRAPHICS, ALL ENROLLED PATIENTS

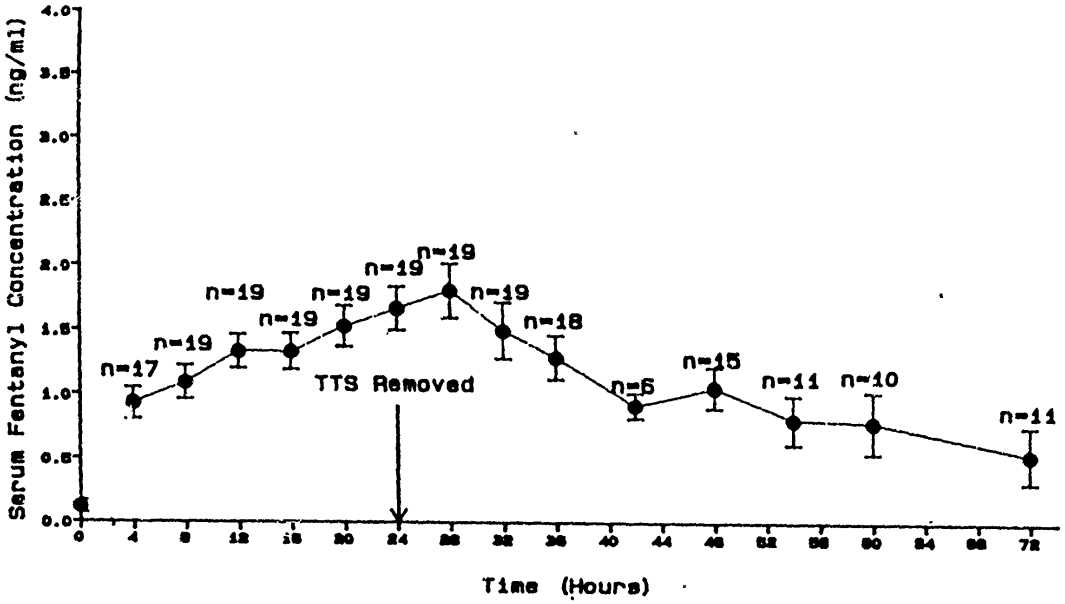
Measure	Treatment	N	Mean	SD	SE	p-value*
Height (cm)	Fentanyl	23	174.7	9.7	2.0	0.01
	Placebo	23	180.9	6.5	1.4	
Weight (kg)	Fentanyl	23	76.9	16.1	3.4	0.19
	Placebo	23	82.5	12.3	2.6	
Body Mass Index, (kg/m^2)	Fentanyl	23	25.0	3.9	0.8	0.90
	Placebo	23	25.2	3.2	0.7	
Age (Yrs)	Fentanyl	23	53.2	11.7	2.4	0.43
	Placebo	23	50.2	13.8	2.9	
Number of Previous Surgeries	Fentanyl	23	2.0	1.3	0.3	0.49
	Placebo	17	2.3	1.4	0.3	

	Fentanyl N	Fentanyl %	Placebo N	Placebo %	p-value
Sex					
Male	20	(87.0)	23	(100.0)	
Female	3	(13.0)	0	(0.0)	0.23**
Race					
Caucasian	16	(69.6)	17	(73.9)	
Hispanic	4	(17.4)	1	(4.4)	
Black	3	(13.0)	5	(21.7)	0.31+
ASA Rating					
I	3	(13.0)	5	(22.7)	
II	12	(52.2)	12	(54.6)	
III	8	(34.8)	5	(22.7)	0.56+
Surgery Type					
Orthopedic	2	(8.7)	0	(0.0)	
Abdominal	9	(39.1)	9	(39.1)	
Thoracic	3	(13.6)	5	(21.7)	
Lumbar	8	(34.8)	7	(30.4)	
Cancelled	1	(4.4)	2	(8.7)	0.58+

* t test ** Fisher's Exact Test +Chi square

REFERENCE: Table 1; Appendix I

FIGURE 6
Mean (SE) Serum Fentanyl Concentration (ng/ml)
at Time from TTS Application*

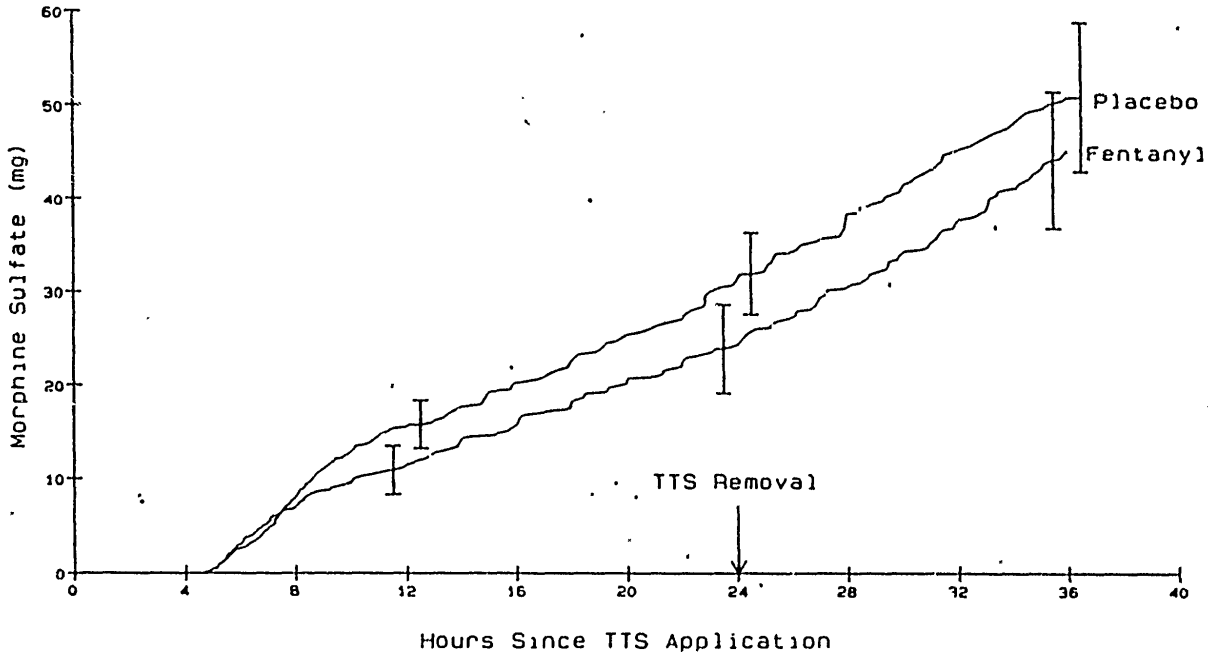


*Values less than 0.1 ng/ml were reported as 0.05 ng/ml

PROTOCOL C-85-005-02, STUDY II: STANSKI

Figure 4

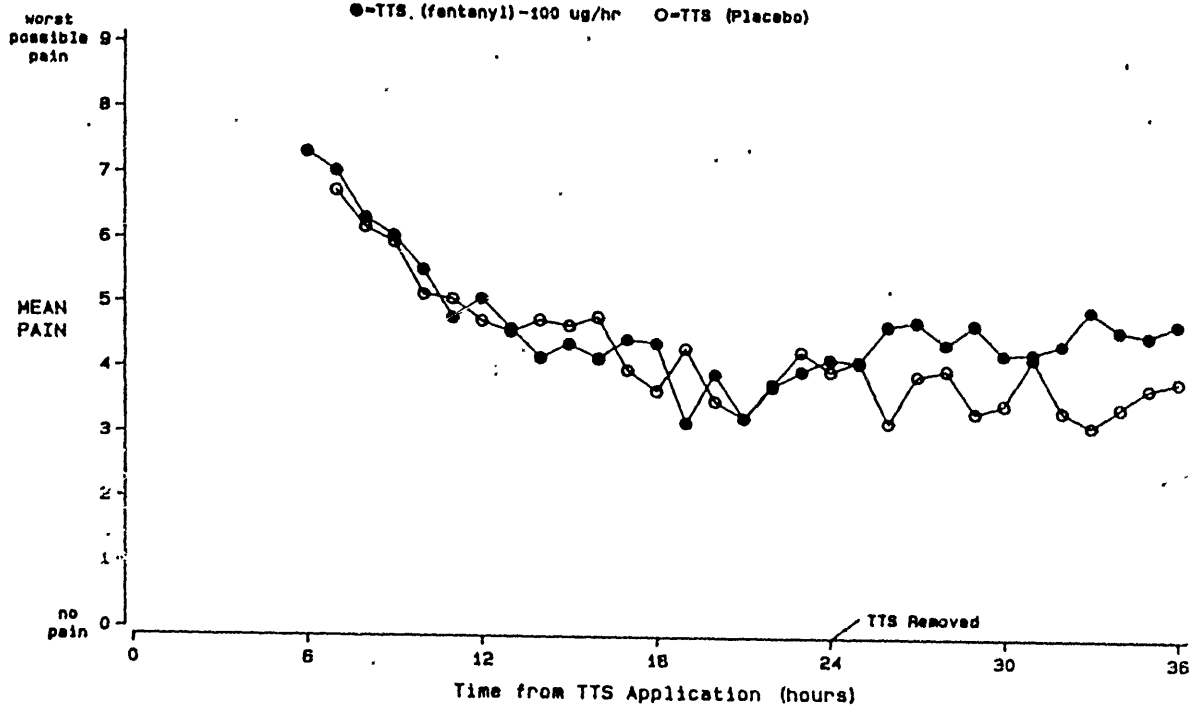
Mean (SE) Cumulative Supplemental Morphine Sulfate Use
(Completers Only)



PROTOCOL C-85-005, Study II
Investigator: STANSKI

FIGURE 5

Mean PAIN by Time from TTS Application
(All Analyzable Patients)



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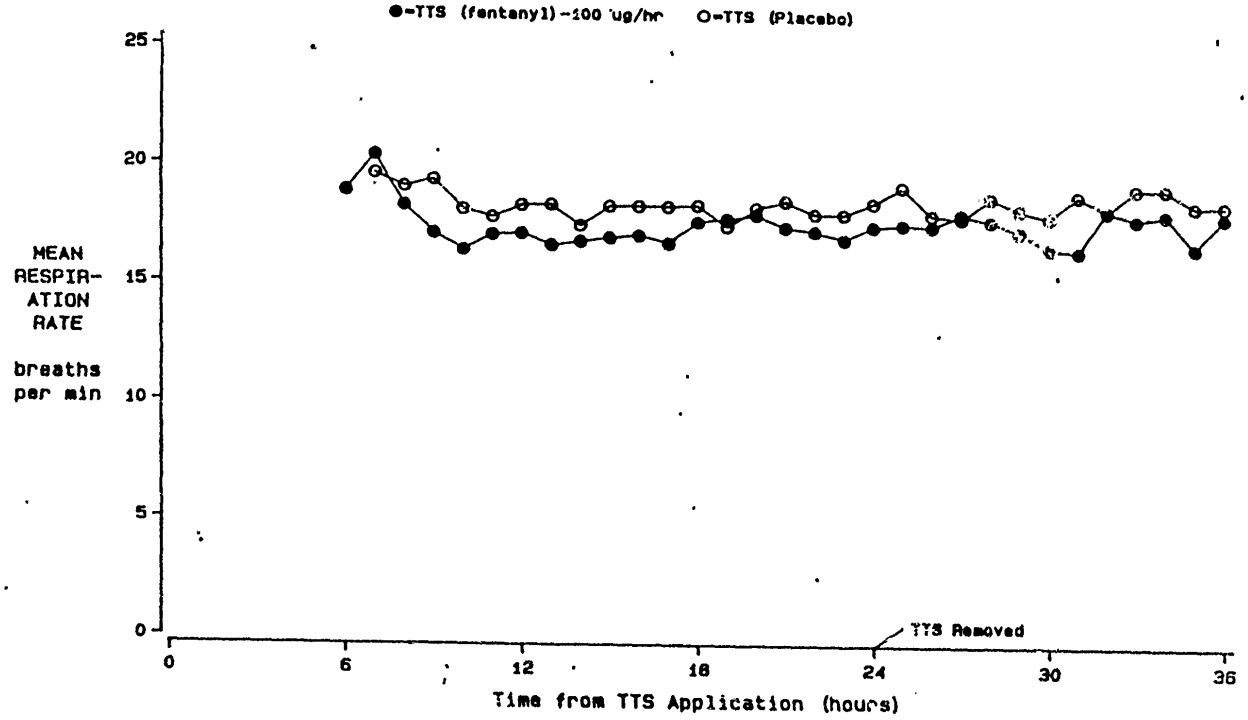
PROTOCOL C-85-005, Study II
Investigator: STANSKI

FIGURE 7

Mean RESPIRATION RATE by Time from TTS Application
(All Analyzable Patients)



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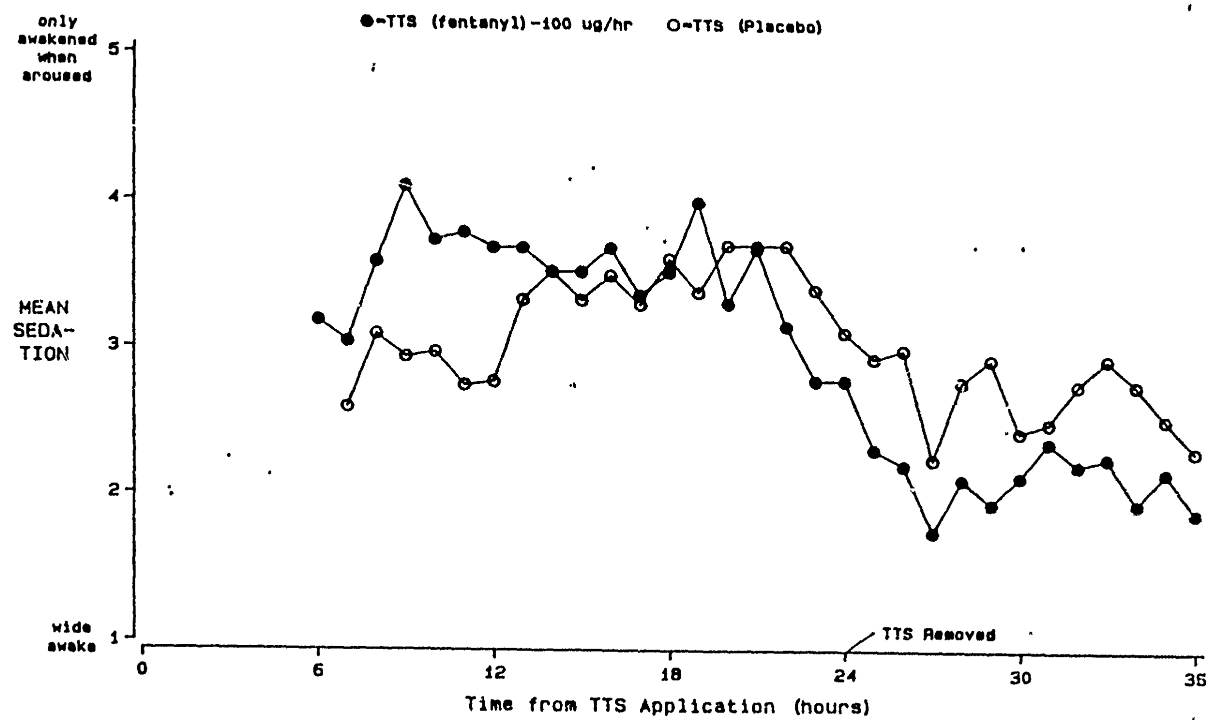
PROTOCOL C-85-005, Study II
Investigator: STANSKI

FIGURE 8

Mean SEDATION by Time from TTS Application
(All Analyzable Patients)



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1 05/045

pulmonary bypass for repair. The study code was broken and the study terminated.

3.3.3 Adverse Experiences

The overall adverse experience rates were quite comparable between groups during the postanesthetic recovery period, and only slightly higher in the fentanyl group following patient transfer to the ward and during the post-removal period. (Table K)

K. NUMBER (%) OF PATIENTS WITH ADVERSE EXPERIENCES*
(All Enrolled Patients)

	FENTANYL (n=23)	PLACEBO (n=23)
OR/PAR	4 (17%)	5 (22%)
WARD-REMOVAL	10 (43%)	6 (26%)
AFTER REMOVAL	7 (30%)	4 (17%)

* patients are counted in more than one time period.

Table L summarizes the number of patients experiencing each type of adverse reaction by body system. Nausea/vomiting was the most frequent adverse effect reported, occurring with equal frequency in the two treatment groups. Respiratory depression was noted in one patient on placebo, and 2 on TTS (fentanyl).

For the purpose of analysis, adverse experiences have been tabulated as described in Section 2.10, Statistical Analysis. Appendix 1, the Case Report Form Tabulation, lists all adverse experiences by patient at the actual time of occurrence. (Adverse experiences are highlighted with a black vertical bar.) These events, therefore, can be reviewed within the context of all other events occurring before, during, and after the adverse experience.

(Note: Sedation and topical effects are analyzed separately in Sections 3.3.5 and 3.4.)

C-85-005-02, STUDY II: STANSKI

3 Systemic Safety

3.3.1 Extent of Exposure

All 46 patients enrolled in the study have been included in the safety analysis, including 23 patients on TTS (fentanyl)-100 and 23 patients on placebo.

3.3.2 Early Removals Due to Adverse Experiences

One (1) patient in the fentanyl group and 2 in the placebo group discontinued the study before the end of the 24-hour wearing period because of adverse reactions.

SCN 170 (fentanyl), a 42-year-old female, 156 cm tall and 49.9 kg in weight, failed to breathe upon extubation in the operating room following lumbar laminectomy with Knodt rod fusion. Her PCO2 was 52 mm Hg. After naloxone administration (0.04 mg IV), the patient began to breathe spontaneously. The TTS (fentanyl)-100 was removed, and 9.5 hours later, the patient was alert enough that continuous study nurse monitoring was no longer required. Her serum fentanyl concentrations were between 1.8 and 1.9 ng/ml at the time of TTS removal. (SCN 170's anesthesia record is included in Appendix II.)

SCN 125 (placebo) was a 64-year-old male, 171 cm in height and 92.5 kg in weight, who underwent pulmonary lobectomy. While in the postanesthetic recovery room, the patient recived a total of 16 mg morphine sulfate IV and his PCO2 measurements were elevated (61 - 68 mm Hg). The TTS was removed at 12.7 hours post-application, when the PCO2 was 56 mm Hg. No treatment was administered. The investigator noted that this patient had chronic obstructive lung disease. (SCN 125's anesthesia record is included in Appendix II.)

SCN 118 (placebo), a 43-year-old male, 173 cm in height and 72.1 kg in weight, discontined the study during surgery due to surgical complications of the pneumonectomy procedure. The clamp holding the right pulmonary vein made a tear in the patient's heart, with massive bleeding requiring cardio-

TTS Fentanyl in Postoperative Pain- European Studies

(The following studies were performed in Europe and provide useful information regarding the clinical use of the TTS Fentanyl system, but are not directly comparable to earlier studies due to intrinsic design differences).

85-053-00 Muller 75 μg/h TTS Fentanyl

Abstract

This is a randomized, double-blind, parallel-group, placebo-controlled study of TTS Fentanyl 75 in the relief of post-operative pain. The subjects were 43 older men and women who had undergone elective total hip replacement under epidural anesthesia. Each patient had a 75 μg/hr or placebo system applied before surgery, no additional fentanyl was given, and all were followed for 24 hours of system application and for 12 hours after system removal. Pain intensity and adverse events were monitored for 24 hours by the investigators using the following efficacy and safety variables:

Efficacy	***Safety***
Hourly and total meperidine use	***Arterial blood gas results***
Pain intensity at 24 hours	***Pulmonary function testing***
Blood levels of fentanyl	***24 hr Adverse effect counts***

The study showed better pain control in 20 fentanyl patients over 19 placebo patients as measured by less supplemental analgesic use and better pain control scores. Mean blood levels of fentanyl ranged from 0.2-1.1 ng/ml during system application, taking 8-12 hours to rise to analgesic levels.

The strengths of this study were that it involved an older population, a painful but uniform surgery, and that information was available on the concomitant use of droperidol and midazolam.

A major weakness of the study was the failure of randomization causing a serious imbalance in the male-female ratio between the groups, and a four-step categorical pain rating scale which makes direct comparison with other studies using 100 mm VAS scales difficult.

Resume

This study was a randomized, double-blind, placebo-controlled, parallel-group study of TTS-75 vrs an equivalent placebo-system. It was carried out by Professor Hermann Muller of the University of Gieben in the FDR in 1988-1989. The study group (based on intent-to-treat) consisted of a group of 17 men and 24 women with a mean age of 60-62 years of age who were having elective total hip replacements.

All patients had an active or a placebo system applied at the time of the commencement of epidural anesthesia, and received no other fentanyl

during the procedure. Regional anesthetic was by bupivicaine (0.75%) epidurally, with the failure of regional analgesia being an exclusion criteria for the study. Significant concurrent medications included pre-operative midazolam and prn droperidol for nausea, adding a component of "neurolept" analgesia to both groups.

Post-operative analgesia was by meperidine (Pethidine) injection which was available prn at a rate of 50 mg IM every two hours to both groups. Observations for pain relief were made on a 4 point interval scale every 12 hours during system application.

The study hypothesis was that patients who had a TTS-75 system applied at induction of epidural anesthesia would have better analgesia and require less supplemental morphine in the 24 hours following system application than a placebo-system group.

Selection , Withdrawals, and Mistakes

This study provides information regarding the use of this medication in major bone surgery in a 60 year old patient group. No information was given regarding the ASA class of the patients, but serious heart disease other than angina, pulmonary insufficiency, and serious renal or hepatic disease were disqualifying.

There was a significant failure of randomization resulting in a fentanyl group consisting of 13 men and 7 women, while the placebo group consisted of 4 men and 17 women. This was both unlikely and unexplained ($p<.004$) and suggests that there was non-random allocation of patients .

Information from other studies suggests that men and women report different degrees of analgesia from the systems, and this study cannot yield an unbiased estimate of the efficacy of the system. Nevertheless, it is of value as it provides information regarding the interaction of the system with droperidol and midazolam, as well as significantly extending the experience with the system to an older surgical population.

Two patients were scheduled for admission to the study but did not actually participate. These patients (4 and 34) were randomized into the fentanyl group but never received any drug and were replaced by two sequentially admitted patients at the end of the study. An additional patient (SCN G-10) suffered an episode of respiratory depression with a fentanyl level > 2.0 ng/ml, was continued in the study, but was analyzed separately (see safety update for details). Two additional fentanyl patients were withdrawn, one for failure of the epidural and a second for an episode of angina pectoris which was probably unrelated to system application. One placebo patient withdrew from the study for inadequate analgesia.

There were thus 20 reported fentanyl subjects and 19 placebo subjects who completed the study. No information was given regarding protocol violations other than those above.

Results and Analysis

The primary outcome variable for this study is the amount of meperidine used in each group is as shown. As may be seen, there is reduced meperidine use for the fentanyl group for both the 0-24 hour interval and the post system period (25-36 h) . as well as a clear divergence of the slopes of the cumulative meperidine use plots. The subjects wearing fentanyl systems used about half the amount of meperidine rescue medication in the first post-operative day as the placebo-system wearers, and reported about half as much pain (0.4 vrs 1.1 on a 0-3 scale) at 24 hours.

The investigators have shown that there was a reduction in the meperidine demand of fentanyl treated patients over placebo controls, but have not addressed the problem of the unbalanced gender ratios and the non-random utilization of droperidol (prescribed for nausea) during the post-operative period. Both the midazolam and the droperidol would be expected to alter the pharmacodynamic effects of fentanyl (as in the neurolept analgetic combination Innovar), and these effects would interact with age and gender. This interaction was explored in our analysis and is discussed below.

Adverse Events

Adverse events were monitored both during system application and at exit as shown in the enclosures. One patient in each group had chest pain during the trial and this event was not judged to be related to TTS fentanyl. No episodes of respiratory depression occurred in the group as analyzed, although the fentanyl system group had a consistent but modest increase in $PaCO_2$, but no increase in sedation over the placebo system wearers. One subject was withdrawn for an episode of slowed respirations, but continued to wear the TTs system for 24 hours (see safety update).

Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal. These effects were seen in both fentanyl and placebo system groups. There were no reported episodes of delayed hypersensitivity or cutaneous allergy.

Pharmacologic Performance

The blood level profiles for the fentanyl patients are as shown, and reveal that a full 24 hours was required to achieve plateau values for the system, while significant amounts of fentanyl were still present in the blood twelve hours after system removal. Blood levels for the group overall ranged from a low of 0.7 ng/ml at 12 hours to a high of 1.1 ng/ml at 24 hours.

Additional Analyses

A number of post-hoc analyses were done using this investigator's data to attempt to understand this trial.

The first finding was that the trial was sensitive to the amount of fentanyl delivered by the system, as there was a graded and predictable fall in the amount of rescue medication used with increasing blood levels of fentanyl. The analgesic effects of the system became apparent when the patients achieved blood levels above 0.5 ng/ml, but maximal analgesia was reached about 1.5 ng/ml for the group as a whole.

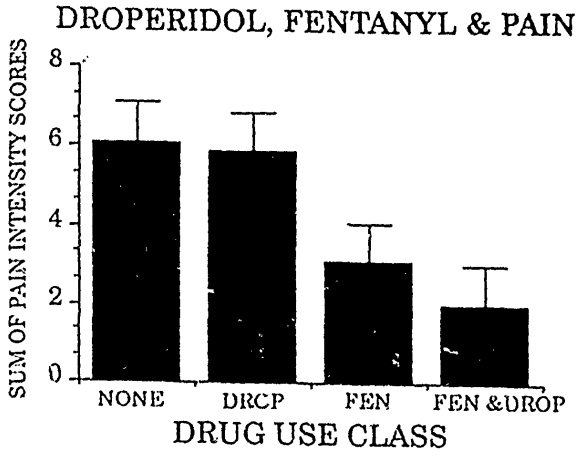
The second finding was that there was a probable interaction with droperidol. This interaction with droperidol is speculative, as the drug was prescribed on a prn basis for nausea during the postoperative period and not given in an orderly fashion. As shown , the patients who received droperidol for nausea had no greater blood levels of fentanyl than those who did not, and droperidol use was not related to fentanyl blood levels. When the four possible drug combinations were related to pain scores and meperidine use, the combination of fentanyl and droperidol was more effective than fentanyl alone in relieving pain and much more effective than droperidol alone.

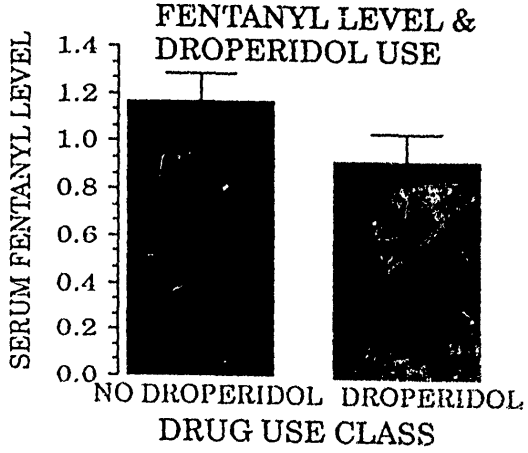
Although post-hoc and not statistically significant due to multiplicity, there was a clear and consistent falling trend in both pain scores and use of rescue meperidine in the order Placebo = Droperidol > Fentanyl TTS > Fentanyl & Droperidol.

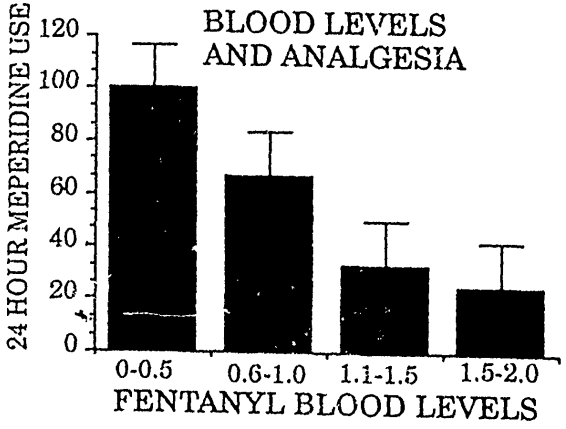
Conclusion

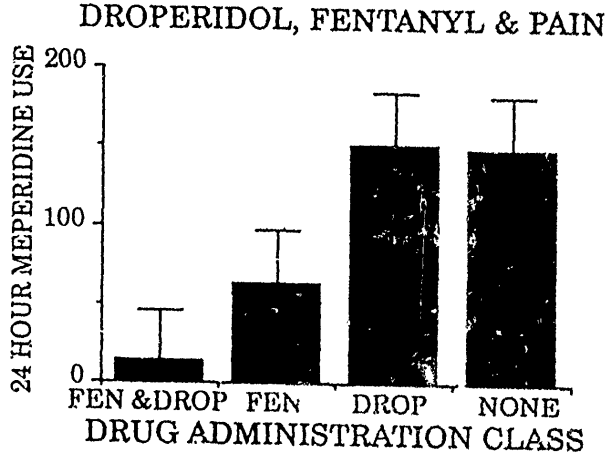
This study cannot be considered to prove a superior analgetic effect for TTS fentanyl, due to the failure of randomization, significant bias from unbalanced genders in the study groups, confounding by other medications and a significant number of patients who failed to achieve analgesic blood levels. The trial is not negative, since it showed better analgesia for TTS fentanyl, but must be considered to be only supportive due to the aforementioned bias and confounding.

The major finding of the study is that preoperative use of a benzodiazepine combined with postoperative use of the neurolept anti-emetic Droperidol may make the system more effective in relieving pain and may reduce the frequency of subjective adverse effects. Investigation of an orderly sequence of premedication, system application, and use of synergistic medication may be appropriate to develop a clinically sound strategy for the use of this product in postoperative pain.


DROPERIDOL, FENTANYL & PAIN
SUM OF PAIN INTENSITY SCORES
8
6
4
2
0
NONE
DRCP
FEN
FEN &DROP
DRUG USE CLASS


FENTANYL LEVEL &
DROPERIDOL USE
SERUM FENTANYL LEVEL
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
NO DROPERIDOL
DROPERIDOL
DRUG USE CLASS


BLOOD LEVELS
AND ANALGESIA
24 HOUR MEPERIDINE USE
120
100
80
60
40
20
0
0-0.5
0.6-1.0
1.1-1.5
1.5-2.0
FENTANYL BLOOD LEVELS


DROPERIDOL, FENTANYL & PAIN
24 HOUR MEPERIDINE USE
200
100
0
FEN &DROP
FEN
DROP
NONE
DRUG ADMINISTRATION CLASS

AKP

Table 4

MEAN SERUM FENTANYL CONCENTRATION (NG/ML)
at time from TTS-Application

	hours after TTS-Application *					
	0	6	12	24	30	36
Mean	0.01	0.22	0.71	1.12	0.86	0.64
SD	0.00	0.27	0.57	0.49	0.29	0.24
SE	0.00	0.06	0.13	0.11	0.06	0.06
Median	0.01	0.15	0.60	1.20	0.90	0.60
Minimum **	0.01	0.01	0.01	0.10	0.40	0.20
Maximum	0.01	0.90	1.90	2.10	1.30	1.00
N	19	20	20	20	20	19

Fig 8

* TTS was removed at 24 hours
** Values less than 0.1 ng/ml, the sensitivity of the assay, are reported as 0.01 ng/ml.

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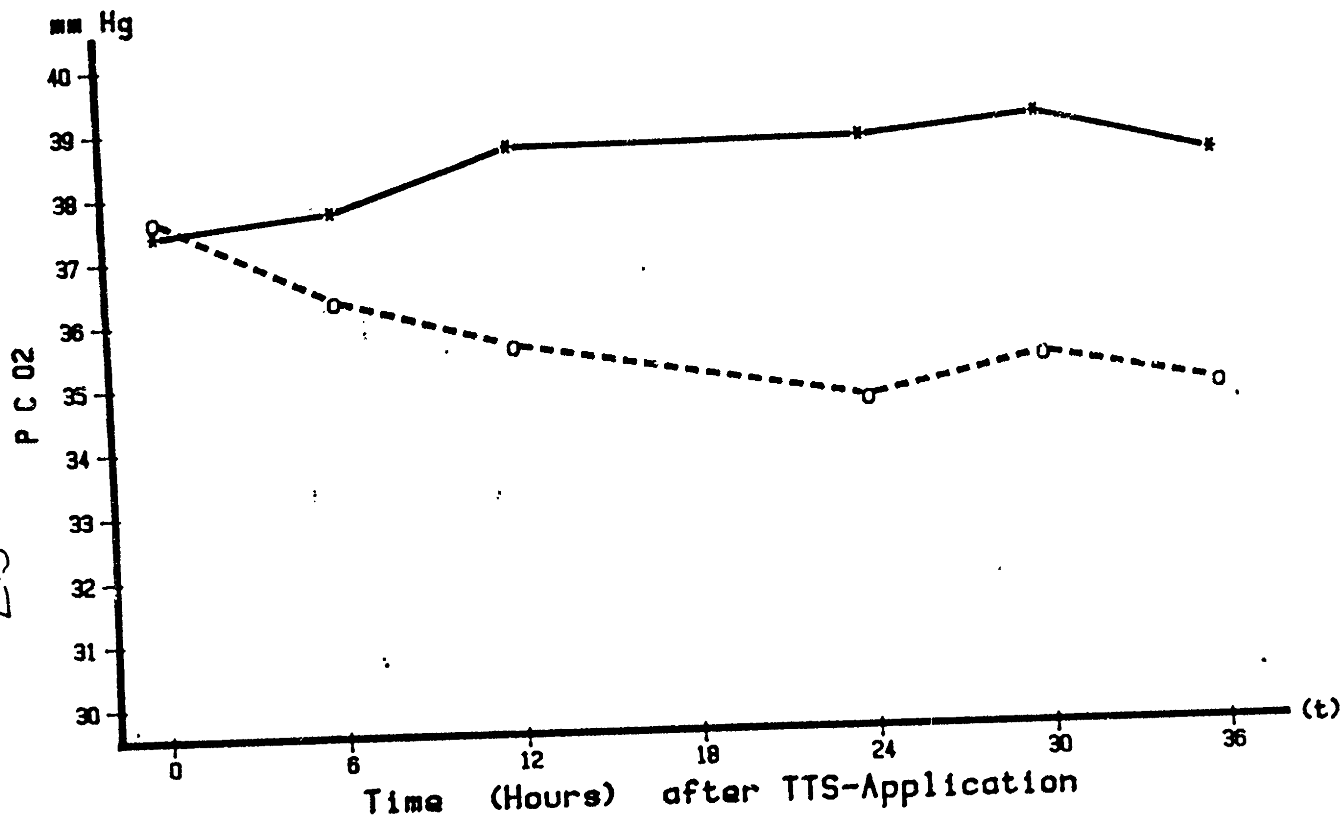
Mean PCO_2 at Time from TTS-Application



* = Group FENTANYL n = 20

o = Group PLACEBO n = 19

87

14 3/066

Euc(7)

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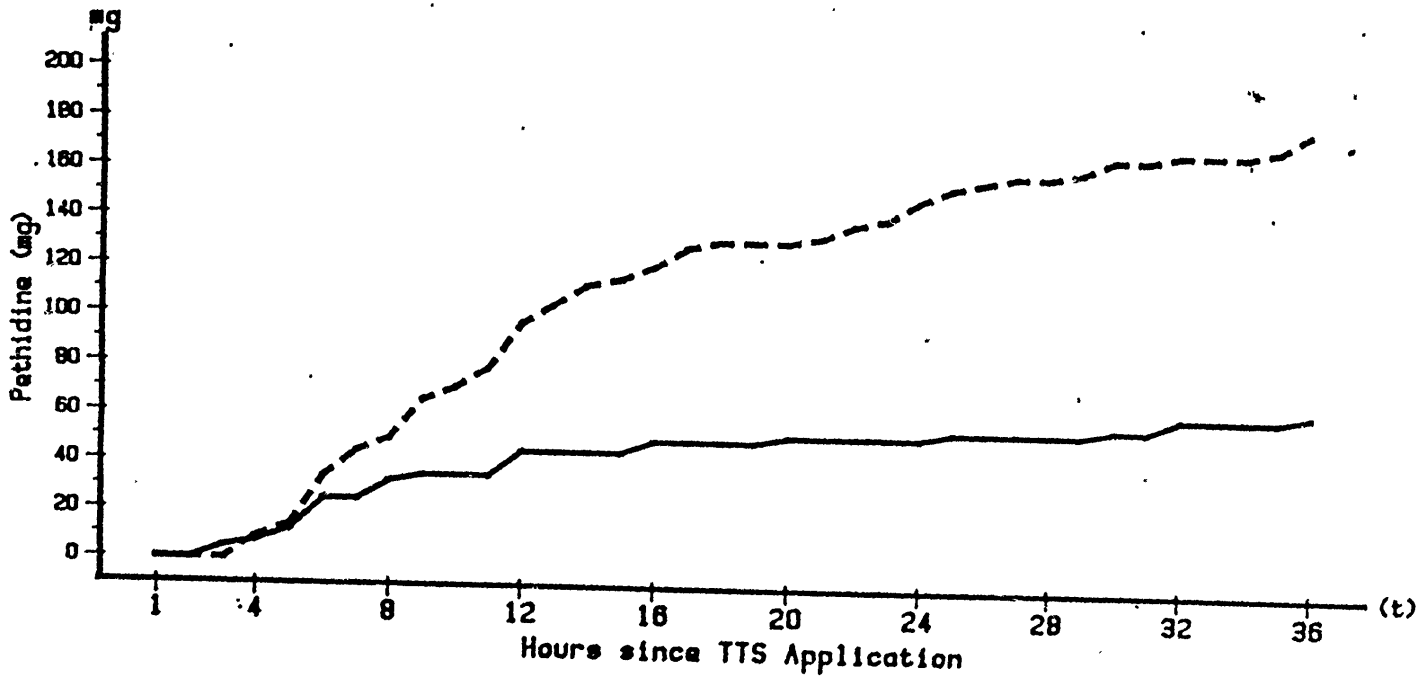
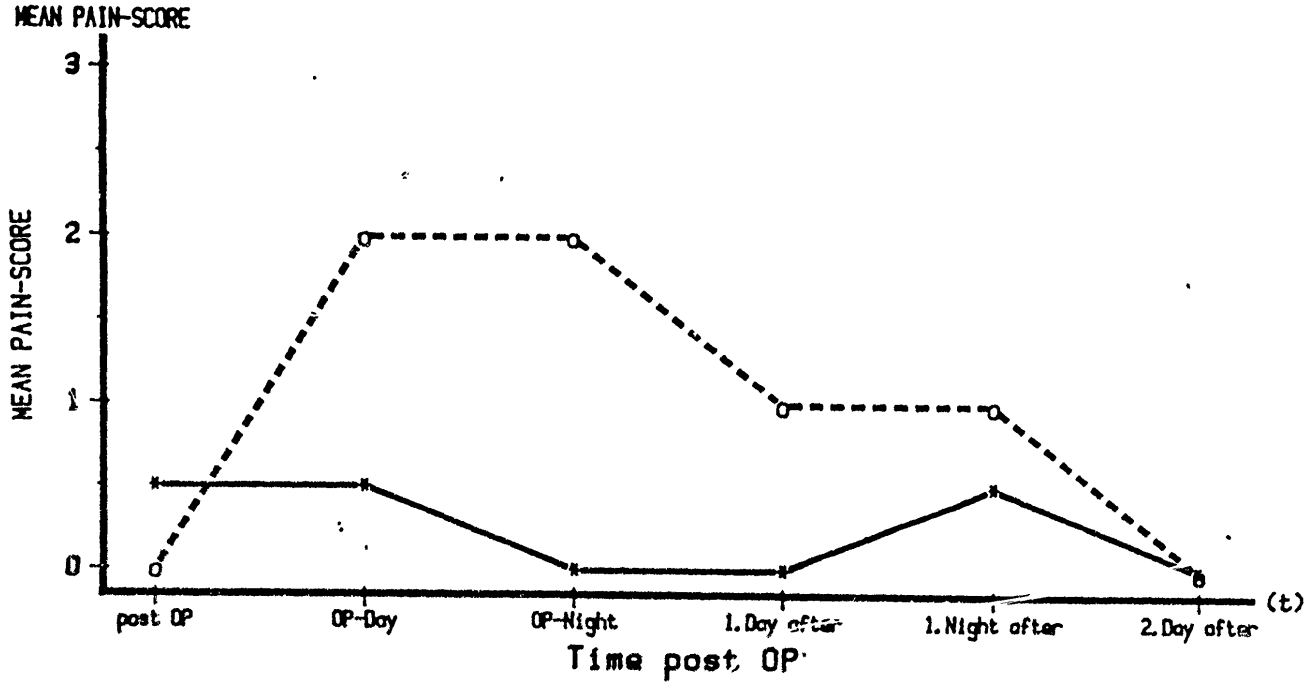
Mean Cumulative Supplemental Pethidine Use (mg/dose/Pat.)



ENC (2)

MEAN PAIN-SCORE POST OP.



* Group FENTANYL n = 20 o Group PLACEBO n = 19

Score : 0=None 1=Light 2= Moderate 3=Unbearable

ENC (3)

AKP

Table 5

Number (%) of Patients in Double-blind Study With Adverse Experiences by Body System During TTS Application

	TTS (FENTANYL) (n = 20)	TTS(PLACEBO) (n = 20*)
Patients with adverse experiences	13 (65%)	16 (80%)
CARDIOVASCULAR:		
Chest Pain	0 (0%)	1 (5%)
GASTROINTESTINAL:		
Nausea	8 (40%)	9 (45%)
Vomiting	6 (30%)	6 (30%)
GENITOURINARY:		
Urinary Retention	7 (35%)	8 (40%)
NEUROLOGICAL:		
Lethargy	1 (5%)	0 (0%)
OTHER:		
Dry Mouth	1 (5%)	0 (0%)

* Patient 17 was withdrawn after 20 minutes because of lack of anesthetic effect.

Enc 5

AKP

In an exit questionnaire at the end of the study (12 hours after TTS removal), patients were asked which of the specified side effects they experienced. The results are presented in table 7 below.

Table 7
Patient Reported Side Effects for 36-hour Study Period

Side effects	TTS (FENTANYL)	TTS (PLACEBO)
Headache	1	1
Itching	1	0
Dizziness	1	1
Nausea	12	12
Vomiting	7	7
Numbness	9	8
Tiredness	17	13
Cramp in Leg	1	2
Micturition Difficulties	10	7
Vision Defect	0	0
Ear Buzzing	0	0
Restlessness	1	2
Anxiety	2	2
Weak Legs	3	3

C-87-04- Latasch

Abstract

This is a 60 patient, randomized, double-blind, parallel-group, placebo-controlled study of TTS Fentanyl 75 in the relief of post-operative pain in men and women following hip or knee surgery under bupivicaine epidural anesthesia. Fifty-seven patients completed the protocol, 28 in the placebo group and 29 in the fentanyl group. Each patient had a 75 μg/hr or placebo system applied at the time of surgery, no fentanyl bolus was given, and all were followed for 24 hours of system application and for an additional 12 hours after system removal. Analgesic efficacy and adverse events were monitored for 24 hours by the investigators using use of rescue medication, global efficacy ratings every 12 hours, vital signs and serial blood gas measurements.

The investigators reported better pain control in the fentanyl patients as measured by less supplemental analgesic use and better global ratings. Mean blood levels of fentanyl rose slowly to between 0. 75 and 5.8 ng/ml at 24 hours after system application. The patients required 8-10 hours of system application to build up to analgesic levels of fentanyl, findings similar to other studies where no loading dose of fentanyl was given.

The strengths of this study were that it tested the efficacy of the TTS system in a group of relatively uniform surgeries under regional anesthesia using pre-medications and protocols such as might actually be used in clinical practice. A major weakness of the study was the dissimilarity to the American trials which makes comparison with other studies difficult.

Review

This study was a 60-patient, randomized, double-blind, placebo-controlled, parallel-group study of TTS-75 vrs placebo-system. It was carried out by Dr Latash in the FDR in 1988-1989. The study group consisted of a group of 40 men and 20 women, 18-50 years of age who were having elective hip and knee surgery under epidural anesthesia with bupivicaine.

There were no significant differences between the treatment groups after randomization with the majority of both groups (fentanyl 19/28, placebo 21/29) being males with an average weight between 70-80 kg. All patients received a premedication of atropine (0. 5 mg), meperidine (50 mg), and promethazine (50 mg), then had an active or a placebo system applied at the time of the commencement of epidural anesthesia, While sixty patients were randomized three patients received a bolus of narcotic during the procedure and were excluded from the protocol and the subsequent analysis.

Regional anesthesia was obtained by epidural bupivicaine (0. 50%) with the failure of regional analgesia being an exclusion criteria for the study.

Post-operative analgesia was by intravenous injection of the synthetic narcotic piritramid (Dipidolor) which was available at a rate of 7. 5 mg IV every two hours to both groups. Observation for pain relief was specified to be done at 24 hours after system application by questionnaire. All patients were monitored for the 24 hours of system application and for 12 hours thereafter.

The study hypothesis was that patients who had a TTS-75 system applied at induction of epidural anesthesia would have better analgesia and require less supplemental pain medication than a placebo-system group.

All data were analyzed for the 24 hours of system application as specified in the protocol, using relief medication dose and subjective pain relief at 24 hours as the major efficacy variables.

Selection , Withdrawals, and Mistakes

This study provides information regarding the use of this medication in a painful type of elective surgery. No information was given regarding the ASA class of the patients, although all were screened for significant cardiac, hepatic, or renal disease. Like other trials of this type, it tests the hypothesis that patients who receive TTs fentanyl will require less suplemental analgesia than those who wear a placebo system.

The two study groups were balanced for gender, age, weight, and type of surgery, and there were but three withdrawals out of 60, due to intra-operative narcotic administration as described above.

There were no reported late violations of protocol other than the failure of two TTS fentanyl patients to complete the postoperative pain global rating questionnaire given on the second postoperative day.

Results and Analysis

The primary outcome variable for this study is the amount of rescue narcotic used in each group from hour 12 to hour 24. This is as shown. As may be seen, the use of rescue medication by both groups is equivalent during the first 12 hours of system application, followed by markedly reduced use during the 12-24 hour period (0. 94 mg fentanyl group vrs 5. 95 mg placebo group).

The investigator chose to analyze the pain ratings as categorical variables, presenting the following table for the 24 hour pain results;

	Fentanyl group	Placebo Group
No Pain	3	0
Slight Pain	7	0
Moderate Pain	11	7
Intolerable Pain	5	22

(P<. 001)

TTS Fentanyl 75 delivered sufficiently improved analgesia to enable the differentiation from placebo in this trial, and to have provided better analgesia than prn narcotics alone.

Adverse Events

Examination of the number and severity of adverse events reported by the investigator shows that no adverse events were reported by the placebo group, while seven patients in the fentanyl group reported opioid side effects. The lack of any adverse events in the placebo group reveals that the patients were either very stoic or the trial was insensitive to adverse events, strengthening the presumed relationship between TTS fentanyl and the adverse events seen in the 7 TTS patients.

The adverse events in the patients in the TTS group were nausea, nervousness, pruritis, and other opioid side effects which did not require treatment, with two cases of transient hypotension which required atropine and/or fluids. A causal relationship cannot be established as two cases of post-operative hypotension out of 28 cases performed is reasonable in the setting of epidural anesthesia, IV narcotics, major joint surgery, and common use of narcotic rescue medication.

No cases of respiratory depression occurred, and there were no medically significant alterations in blood gases, pulmonary function test results, laboratory tests, or cardiovascular parameters. There was an apparent increase in PaCO2 in the fentanyl group from hours 12-24, suggesting that the fentanyl group probably received a greater total opioid effect than the placebo group, a finding that is consistent with less reported pain.

Adverse topical effects from the system were limited to mild erythema and pruritis for several hours after system removal. These effects were seen in both fentanyl and placebo system groups. There were no reported episodes of delayed hypersensitivity or system allergy.

Pharmacologic Performance

The fentanyl group did not achieve analgesic blood levels (0.6-0.75 ng ml) for at least 6-10 hours after system application. In this single dose study, with removal of the system at 24 hours, the group had no drop in blood fentanyl levels for six hours after system removal, and it took 12 hours after system removal for blood levels to fall to 66% of the 24 hour maximum value.

Conclusion

This study provides some evidence that the system provides improved analgesia and patient satisfaction over prn dosing. The most parsimonious explanation for this effect is that the combination of PRN analgesic & system provides a greater total dose of narcotic than prn dosing alone. The improved analgesia in the TTS fentanyl group was not associated with seriously increased risk of adverse effects in this study.

Table 1 SUMMARY OF DEMOGRAPHICS

Measure	Treatment	N	Mean	SD	SE	Median	Min	Max	p-value *
Height (cm)	Fentanyl	18 (2)	167.1	9.5	2.2	166.5	148	186	> 0.4
	Placebo	20 (1)	166.1	8.4	1.9	165.5	150	180	
Weight (kg)	Fentanyl	19 (1)	72.4	12.2	2.8	73	50	100	> 0.4
	Placebo	21	74.1	11.4	2.5	75	57	96	
Body Mass Index (kg/m^2)	Fentanyl	18 (2)	25.59	2.52	0.59	26.02	20.28	28.91	> 0.4
	Placebo	20 (1)	26.97	3.63	0.81	25.72	22.27	37.33	
Age (Yrs)	Fentanyl	20	61.3	7.9	1.8	61	47	70	> 0.4
	Placebo	21	61.1	9.1	2.0	61	41	70	
Duration of surgery (min)	Fentanyl	20 (1)	105.4	30.0	6.7	109.5	55	155	> 0.4
	Placebo	20	130.4	59.6	13.3	114.0	50	250	

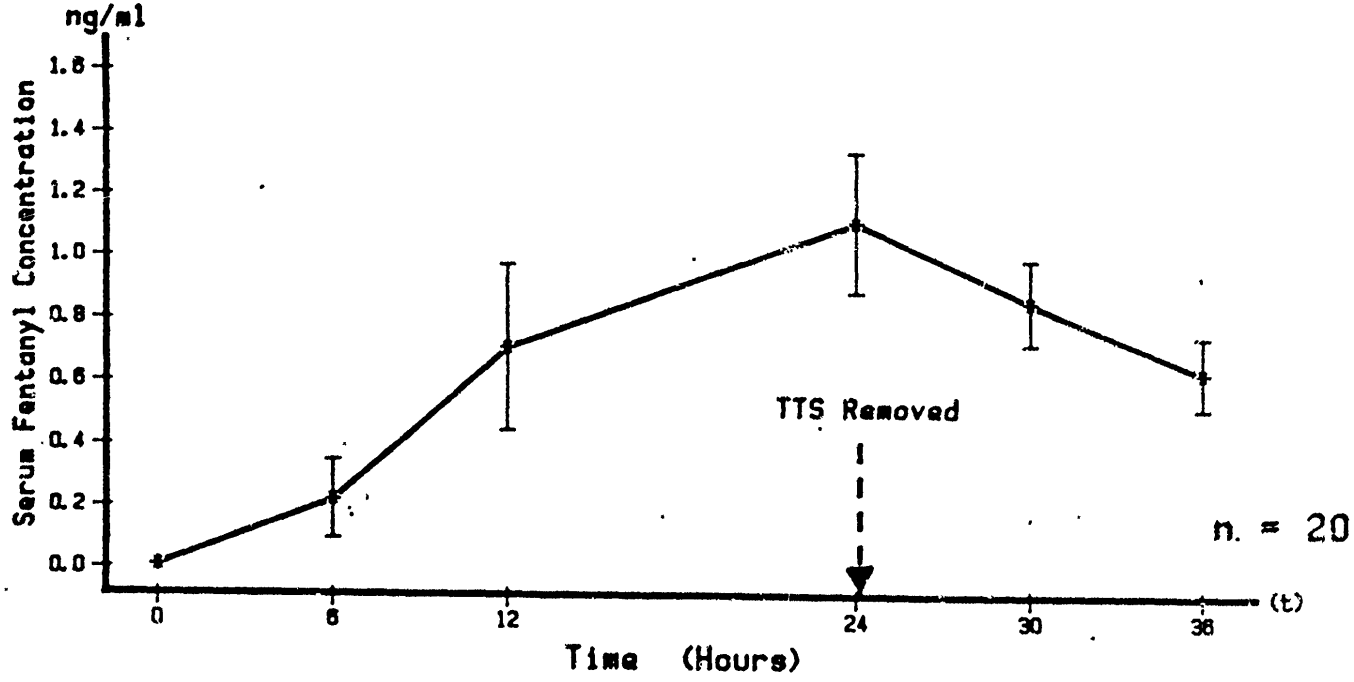
Sex	Fentanyl N	Fentanyl %	Placebo N	Placebo %	p-value **
Male	13	(65.0)	4	(19.0)	
Female	7	(35.0)	17	(81.0)	
Total	20	(100.0)	21	(100.0)	0.004

* Two-sample Rank Sum Test (Wilcoxon, Mann a. Whitney) ** Fisher's Exact Test

Missing data from (1) or (2) patient(s)

Mean (95% Confidence Interval) Serum Fentanyl Concentration

at Time from TTS Application



at Time 0 and 36 (h) n = 19

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98 14.3/063

Means and Standard Deviations of Blood Gas Parameters : PCO2

FENTANYL-TTS STUDY2

Figure 12

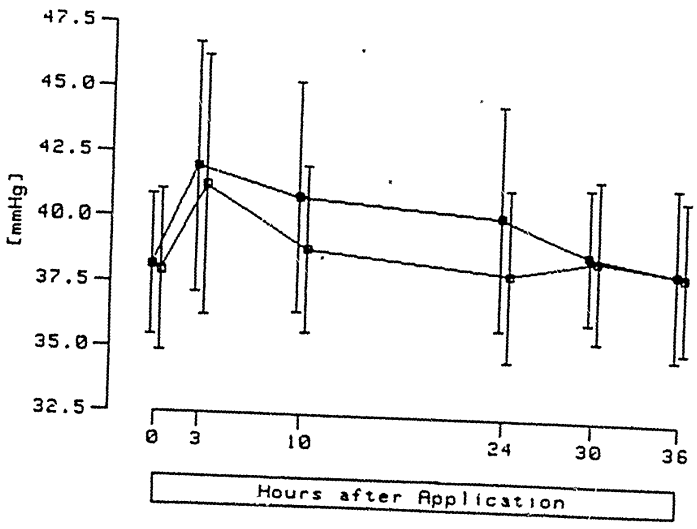

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Table 2

SUPPLEMENTARY PETHIDINE USE (MG)

	Study Period (hours since TTS-Application) *		
	0 to 24	25 to 36	0 to 36
FENTANYL			
Mean	52.5	12.5	65.0
SD	78.6	31.9	97.5
SE	17.6	7.1	21.8
Median	25	0	50
Minimum	0	0	0
Maximum	300	100	400
N	20	20	20
PLACEBO			
Mean	148.4	31.6	180.0
SD	84.9	44.8	111.2
SE	19.5	10.3	25.6
Median	125	0	150
Minimum	0	0	0
Maximum	350	150	400
N	19	19	19
p-value**	< 0.01	0.17	< 0.01

* TTS removed at 24 hrs
** Two-sample Rank Sum Test (Wilcoxon, Mann a. Whitney)

14.3/022

General Comments on the Efficacy of TTS Fentanyl in Postoperative Pain

Systematic Bias- Fentanyl has a very large apparent volume of distribution at steady state (4-6 l/kg), consistent with it's high lipid solubility. In consequence, it has been used in anesthesia in the same fashion as thiopental, using frequent bolus doses to obtain precise control over drug effects due to transient high CNS levels of the drug with the advantage of a short apparent half-life due to rapid redistribution. The clinical studies clearly show that if no fentanyl is given by bolus, that it takes 3-5 half-lives of system application (12-24 hours) to reach stable blood levels and 2-3 half-lives (8-12 hours) to reach analgesic blood levels. At the Cmax for the system, the total amount of drug in the body will be approximated by the blood level times the apparent volume of distribution. For a 100 μg/h system in the Hotchkiss study this is 1.9 ng/ml X 398 liters = 756 μg/70 kg. Since this is more than twice the usual bolus dose of fentanyl given in the studies (300 μg), it is clear that most of the patients had a trough in their fentanyl blood levels which occurred in the first 8 hours of the trial. Every one of these trials may be expected to show a bias or confounding which would tend to underestimate the true difference between the groups. This is because pain ratings and use of rescue medication data was collected on the fentanyl patients during a period in which it was pharmacokinetically impossible for them to have reached maximal drug effect. If this system is to be of maximal benefit in the postoperative setting then either a second bolus dose of fentanyl might be given after the procedure, or the system might be applied earlier than two hours prior to surgery.

Lack of Positive Controls- At least four of the clinical studies of this drug show statistically significant improvements in pain relief and reduced use of rescue medications, and all of the clinical trials show at least a trend toward such an effect. Unfortunately, none of the trials of this drug compared it to a fixed dose of a known analgesic, so that the magnitude of the pain relief offered by the system is unknown. It is clear from the trials that the application of the system reduced the total amount of morphine used by the patient by 25-75%, but it is not clear that the analgesia provided by the system is equal to either an equivalent dose of fentanyl given IV or IM, or to the decrement in the amount of morphine used administered over a like period. The sponsor has been asked to address the issue of the analgesic strength of the system , but these results are not yet available.

Proof of Efficacy- In the case of a known molecular entity such as fentanyl, which is being given in a new way, proof of the system's efficacy must be both pharmacokinetic and pharmacodynamic. While there is no need to show that fentanyl is an analgesic, the sponsor must prove that the system is able to deliver analgesic blood levels of fentanyl, and that the analgesic effects of fentanyl so delivered are not eliminated by the development of tolerance. Once these objectives have been reached, as they have with TTS fentanyl, then the sponsor needs not to continue to demonstrate efficacy in a series of pain models, but to demonstrate the collection of a sufficient body of experience with the

drug in different clinical settings to allow for appropriate estimations regarding it's safety and clinical utility.

Proof of Safety- As has been mentioned above, all of the TTS Fentanyl trials have been conducted with the concomitant administration of opioid rescue medication as an outcome measure in the design. In consequence, the safety of the system cannot be determined by the emergence of adverse effects, but by the relative frequency of adverse events considered in proportion to the beneficial outcomes. In most of the trials in this series the degree of pain relief experienced by the patients receiving the fentanyl system has been greater than that experienced by the placebo group. This is almost undoubtedly due to the fact that they received more active opioid drug than the controls, and in consequence they experienced a greater frequency and severity of opioid side effects such as anxiety, restlessness, nausea & vomiting.

In consequence, the measure of safety in these trials can best be determined by the relative frequency of serious adverse events the most common of which is respiratory depression. Initial review of the data suggests that of the seventeen episodes of respiratory depression which occurred among the 332 patients in the initial series of trials, eight could be attributed to the effects of underlying disease or surgery, coadministered medications other than fentanyl, or anesthetic technique. In the nine patients where some combination of fentanyl system and rescue medication resulted in the need for evaluation, system removal, or naloxone reversal the role of the system is complicated by the presence of the rescue narcotic. The sponsor has been asked to re-analyze this data using a pharmacodynamic analysis to attempt to discern a relationship between the blood level produced by the system and the probability of an adverse respiratory event. (see safety review vol. 4)

Studies of TTS Fentanyl in Cancer Pain-

The initial impetus for the development of the TTS fentanyl system was the problem of analgesia in chronic cancer pain. Despite the clinical utility of high dose oral morphines, there is a substantial population of cancer patients who are either intolerant of high oral doses of opiates or who do not achieve a sufficient duration of action by the oral route. In these cases, PCA analgesia with IV or intra-dermal fentanyl has been shown to be an effective alternative, but has the disadvantage of parenteral administration. When the sponsor first approached the agency with the proposal for a transdermal fentanyl dosage form, it was agreed by both sides that it had been unequivocally shown that fentanyl was effective as an analgesic, and that it would not be necessary to re-establish that fact. It would, however, be necessary to conduct clinical trials in a sufficient number of cancer patients to establish that:

1. The system provided pharmacologically active doses of fentanyl in a consistent, dose-proportional, and predictable fashion to almost every patient who received it in an appropriate dose.

2. That an appropriately sized system could be selected for initial therapy based on the patient's clinical history and/or clinical presentation.

3. That the majority (or an identifiable minority) of patients obtained satisfactory analgesia as measured by subjective and objective ratings, withdrawals, and subsequent clinical course.

4. That the system provided analgesia without an unacceptable rate of symptoms, adverse events, or undue development of opioid tolerance.

In response to this guidance the sponsor conducted several trials of the clinical utility of the system in chronic cancer pain, incorporating a placebo-controlled cross-over and a pharmacodynamic analysis into the better of the two. These are reported below.

Study # 86-003-01 Levy

Abstract

This is a multi-center, variable-dose, double-blind, randomized clinical trial of TTS fentanyl system analgesia utilizing a two-week placebo-controlled cross over design in cancer patients requiring chronic narcotic analgesia. The trial consisted of a period of conversion to TTS fentanyl system analgesia with prn oral morphine rescue, random assignment to a treatment group, a week of TTS or TTS-placebo, then cross over to the other limb. Efficacy outcome variables included self-reports of rescue medication use, pain intensity scores, nurse ratings of pain by standardized rating scales, and patient global ratings.
Safety was followed by physiologic measures (vital signs), subjective, and caretaker ratings.

The study claimed but failed to prove improved efficacy over placebo due to excessive drop-outs and missing data (of 46 patients only 10 completed the cross-over design with complete pain intensity ratings), and a clear pattern of under-dosing resulting in sub-therapeutic serum fentanyl levels in 7 of 19 patients for whom such data were available.

While the study did not succeed as a cross-over trial due to insufficient power and under-dosing, post-hoc pharmacodynamic analysis for those patients in which therapeutic fentanyl levels were achieved showed superior analgesia (pain ratings of 1.4 on TTS v 1.8 on placebo) whereas patients with sub-therapeutic blood levels did not (pain ratings of 2.5 on TTS v 2.5 on placebo).

The trial supports the clinical utility of TTS fentanyl in cancer pain.

Resume

This was a 46 patient, multi-center trial under the direction of Dr. Sandra M. Levy of the Pittsburgh Cancer Institute. It involved Montifiore Hospital (17 patients), Presbyterian Hospital (5 patients), Eye & Ear Hospital (3 patients), Forbes Hospice (6 patients), and the Pittsburgh VA Hospital (15 patients). Patients were admitted to the study during the latter months of 1986, converted to an individualized dose of TTS fentanyl, participated in a two-week cross-over trial, and then continued on TTS Fentanyl until death, discontinuation of the drug, or discharge from the trial.

The inclusion criteria for the study were terminal illness (<6 months life expectancy) from non-localized intermediate stage malignancy with severe pain requiring narcotic analgesics for control. Patients were to have normal hepatic, renal, and pulmonary function , no history of narcotic allergy, CO2 retention, drug abuse, or active skin disease.

Patients were given sequential case numbers and randomized in blocks of 10 to avoid imbalance among the centers. Supplies of TTS and placebo were prepared weekly, with only the safety monitor at each facility having access to the randomization codes in case of adverse reactions. The study plan was to admit the subjects to the hospital, convert the subjects from their pre-study medications to TTS fentanyl, titrate them to an individualized stable dose, then enter them as outpatients into one of two limbs of a two week cross-over with either TTS or TTS placebo systems. Following completion of the cross-over all patients could remain on TTS fentanyl at the discretion of their physician.

Each patient completed several self-rating scales, was observed by the visiting nurse, and had blood drawn for fentanyl levels and serum chemistries during the cross-over and open-label use of fentanyl. The patients completed the Present Pain Intensity Index as well as the Pain Rating Index of the McGill Pain Questionnaire, the Profile of Mood States, and the Manitoba Quality of Life Scale on a daily basis. The study nurses visited the subjects at home twice a week during the cross-over phase of the study, completing a pain behaviors instrument and reviewing the patient's diary of use of oral rescue morphine. Physician

evaluation in addition to the weekly visits by the study nurses were individualized, but were as frequent as every 24 hours when dosage adjustment was required or adverse events were encountered.

The PC-SAS Generalized Linear Model (GLM) procedure was used to analyze the pain scores and supplemental morphine use, using a three-term model with patient, treatment, and patient-treatment interaction terms.

The study hypothesis was that patients in the TTS fentanyl limb of the cross-over would report less pain and use less supplemental morphine than in the TTS placebo limb.

Selection , Withdrawals, and Mistakes

The 46 patients selected for the study were older (median age 61, range 21-81), most were terminal (29/46 died during the study) , were equally divided by gender (25 males/21 females), and a variety of metastatic cancers. Most were taking oral morphine (12), methadone (10), or oxycodone (23) for pain. Narcotic demand of the patients who completed the transition to TTS fentanyl was low, with 3/46 taking less than 60 mg oral morphine per day, 12/46 taking between 60-120 mg, and only 15/46 taking more than the equivalent of 120 mg oral morphine per day (patients who did not complete the transition to TTS fentanyl were excluded).

The patients did not spend a fixed amount of time in the stabilization period prior to starting the cross-over. Some spent only a week, while others were on TTS fentanyl for almost a month before starting the study. The reason for these delays were usually due to contemporary medical events due to the patient's serious medical conditions.

Because of the serious illness of most of the study participants there was considerable attrition during the study. Of the 46 patients randomized, only 23 completed both limbs of the cross-over, and of those that did do so, only 15 had complete information (most of the missing data was self-report inventories which these seriously ill patients tended not to keep on days they were not visited by the nurse). Of those who did not complete the protocol:

-**2** withdrew within 3 days of starting TTS due to death or disability.
-**4** withdrew due to adverse experiences from TTS (chiefly nausea)
-**3** withdrew due to inadequate pain control from TTS
-**2** withdrew due to unrelated complications of cancer.
-**1** withdrew due to unwillingness to participate
-**6** died prior to completing the cross-over
-**5** Withdrew due to protocol violations

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23 withdrawals prior to completing crossover.

Of possibly greater concern than a high (but expected) drop-out rate, was the number of patients who had TTS doses that were clearly too low applied during the trial. The patients admitted to the trials were taking a

variety of pain medications, but were converted to TTS fentanyl based on predicted 24 hour oral morphine demand and use of rescue medication during the titration phase of the study.

No attempt was made by the sponsor to perform a pharmacodynamic evaluation of the probable effects of tolerance on the dose-effect relationship for fentanyl. In consequence, it is difficult to determine the adequacy of the dosing of these patients from the blood level data. In consequence, it was necessary to make some (conservative) assumptions regarding the development of opioid tolerance in these chronic opiate users.

For purposes of analysis it was assumed that an opioid naive individual would obtain adequate analgesia from fentanyl levels above 1 ng/ml, that an individual taking the equivalent of 60-120 mg of long-acting oral morphine a day would require about twice as much or 2 ng/ml for analgesia, and that an individual taking over 120 mg oral morphine a day would require at least 3 ng/ml for a like effect. Using these estimates, in the 15 subjects for which complete data are available, the TTS systems prescribed provided subtherapeutic blood levels for 5 of the 15.

Review of the individual case report forms suggests that there may have been an unpredictable reporting bias in the patient's diaries of morphine use. In at least one case there are explicit comments that the subject had not been keeping an accurate morphine diary. Since there was no objective check (pill counts, PCA device, recording pill-box, etc.) it is possible that any of several kinds of error could occur undetected. The most likely forms that this could take would be fixed dosing with prn medication by the companion or the patient's recording of inaccurate amounts. In either case the bias would be in the direction of washing out the differences between treatment groups.

A reasonable conclusion regarding possible bias in the study is that the high drop-out rate, high percentage of subjects with subtherapeutic blood levels, and the variable length of stabilization on TTS fentanyl have introduced biase s that would be expected to reduce the apparent effectiveness of TTS fentanyl.

Results

The observed pain intensity scores and oral morphine use data are provided. As may be seen in the mean scores, there was no observed difference between self-reports of oral morphine use for the fentanyl and the placebo weeks. There is a difference between the daily mean pain scores, but the observed difference is very small (mean pain intensity scores fentanyl week 2.1, placebo week 1.8). If the patients are stratified by prior narcotic use and thus by probable tolerance and pharmacodynamic response the following results are seen:

Mean Pain Intensity Scores

	Fentanyl Week	Placebo Week
Patients with subtherapeutic fentanyl levels	2.5	2.5
Patients with therapeutic fentanyl levels	1.4	1.8

The probable interpretation is that the observed effect size of 15% reduction in pain scores (2.1-1.8/1.95) is actually low, and the more likely effect size for the system, prescribed in an appropriate size, is at least 25% (1.8-1.4/1.6).

Adverse Events

The real wealth of these studies lies in the availability of data for the patients who stayed on different doses of the systems for extended periods of time. This study utilized doses of up to five simultaneous 100 µg/hr systems, and involved blood levels of up 35 ng/ml of fentanyl. The forty-six patients in the study wore the systems for a total of 5500 patient-days. Of the 29 deaths during that period there were none that were not expected from the patient's underlying disease and no episodes of respiratory depression requiring naloxone reversal. Of the nine withdrawals for inadequate pain control or adverse events, four were for nausea and /or vomiting which was probably related to the TTS fentanyl, two were for drowsiness or confusion attributed to a combination of fentanyl and rescue medication, and three for inadequate pain control.

The remainder of the adverse events were reviewed to detect any unusual of frequent toxicities, and are presented. The adverse effect profile is appropriate for a combination of fentanyl and rescue medication and presents a typical mu-agonist set of CNS, GI, pulmonary, and dermatologic symptoms.

Pharmacologic and Pharmacodynamic Analyses

There was a definite relationship between system size and blood fentanyl level, even though the samples were taken at variable intervals after the last system application. These results are shown along with the degree of variation observed in the dose-blood level relationship as well as the range of doses employed (doses are absolute, not mg/kg). In addition, there was a definite trend in both prescribed fentanyl system size and blood levels over the first two weeks of therapy, during the open-label stabilization period. As pain ratings were not collected in a consistent manner until after the patient was stabilized on the system, the time course of the pharmacodynamic relationship of pain relief to blood levels cannot be determined from this data.

Post-crossover data was available for fourteen patients who were maintained on the fentanyl systems for open dosing periods of as long as three months, and are as shown. Of these fourteen patients, nine showed the unequivocal pattern of escalating dose shown, with a probable rate of dose escalation of 25-75% per month. Of the five patients who did not show this escalation in dose, two were taking high escalating doses of morphine (1061,1216), one had received radiation therapy with good results (1218) , one had a low level of pain and used little medication during the entire trial (1065), and one showed no escalation in use of either oral or system analgesics (1214).

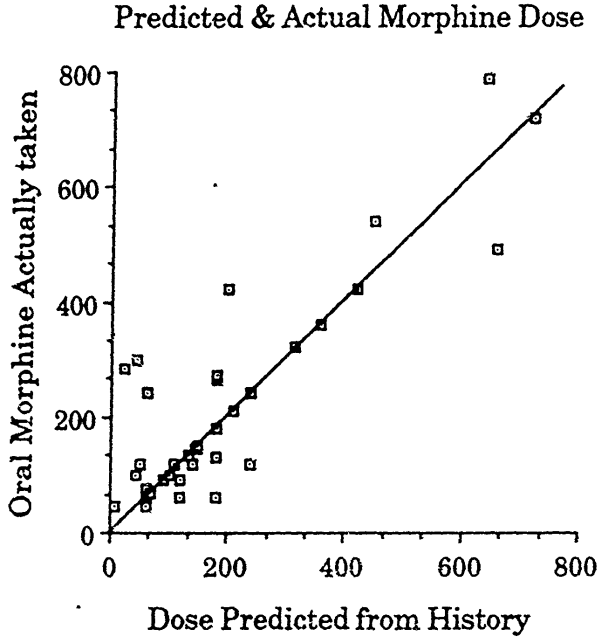
Conclusion

This study is strongly supportive of the clinical utility of TTS Fentanyl for pain control by cancer patients. The study revealed no unexpected hazards of the drug, and had a rate of adverse events requiring discontinuation of the drug of 5 per 100 patient-months and a rate of dose increase between 25-75% per month of therapy. There was evidence of accumulation of the drug with multiple dosing consistent with it's known kinetics, with approximately five to seven days being required to establish a plateau following a change in system size.

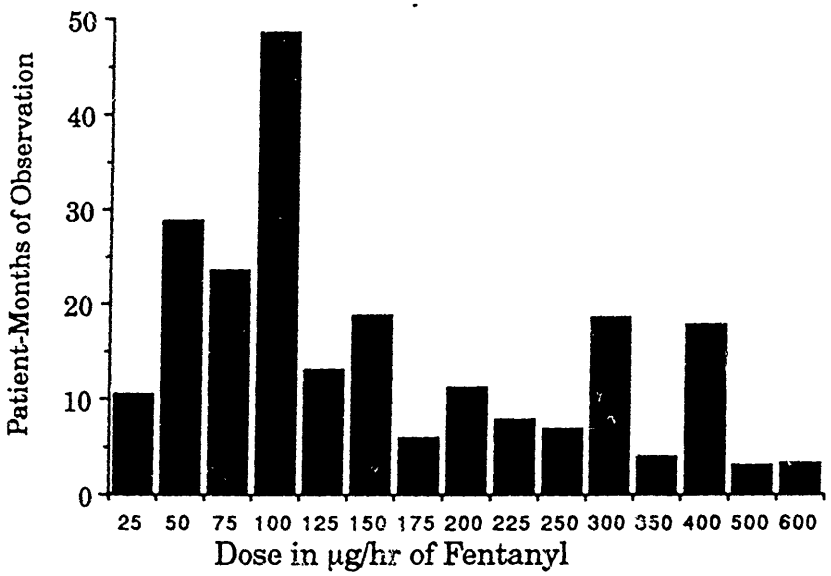
Both clinically and statistically the cross-over portion of the study lacked the power to demonstrate that TTS fentanyl was superior to placebo due to excessive dropouts, use of rescue medication in both groups, probable under-dosing, and a cross-over design that had no "wash-in" period to allow the subjects to establish plateau levels of drug. It is also possible that these opioid-experienced patients dropped-out after breaking the blind and realizing they were on placebo.

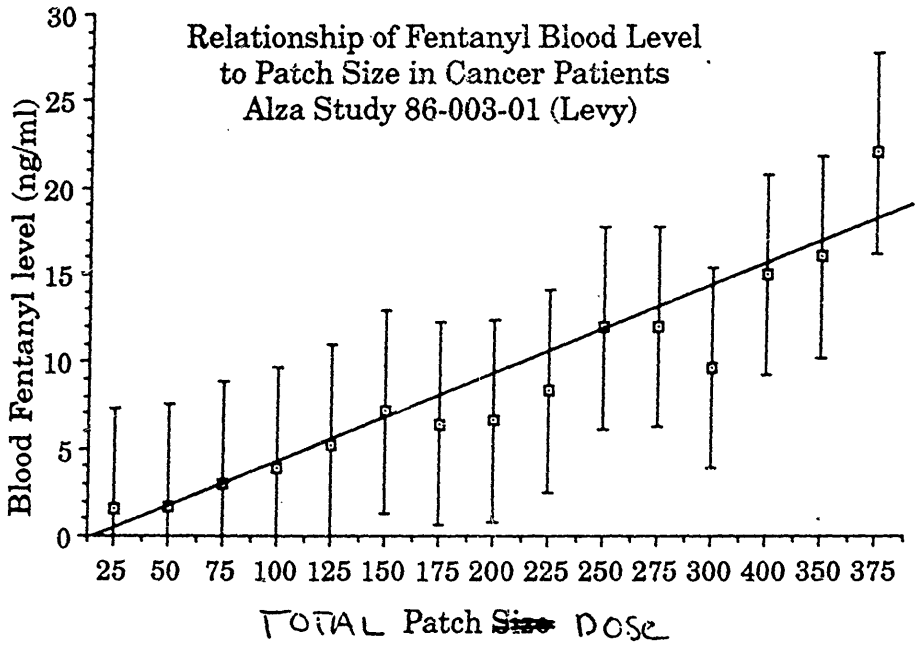
Table A: Patient Demographics

	Patients 46	(%)
Total No. of Patients		
Age (years)		
≤36	2	4.3
>36 - ≤47	1	2.2
>47 - ≤59	18	39.1
>59 - ≤69	17	37.0
>69	8	17.4
Sex		
Male	25	54.3
Female	21	45.7
Race		
Caucasian	39	84.8
Black	6	13.0
Asian	1	2.2
Height (cm)		
no data	4	8.7
≤163	10	21.7
>163-≤170	12	26.1
>170-≤179	16	34.8
>179	4	8.7
Weight (kg)		
no data	4	8.7
≤63	25	54.3
>63-≤74	10	21.7
>74-≤83	4	8.7
>83	3	6.5
Stage of Disease at Entry		
Intermediate	33	71.7
Terminal	11	23.9
Unknown	2	4.3
Diagnosis		
Sarcomas or AIDS	1	2.2
Head and Neck Cancers	5	10.9
Lung Cancer	5	10.9
Breast Cancer	6	13.0
Gastrointestinal Malignancies	17	37.0
Prostatic Cancer	3	6.5
Other Solid Tumors	5	10.9
Hematologic Cancers	4	8.7


Predicted & Actual Morphine Dose
Oral Morphine Actually taken
800
600
400
200
0
0
200
400
600
800
Dose Predicted from History

Alza Cooperative Trial C-87-010




Relationship of Fentanyl Blood Level
to Patch Size in Cancer Patients
Alza Study 86-003-01 (Levy)
Blood Fentanyl level (ng/ml)
0
5
10
15
20
25
30
25 50 75 100 125 150 175 200 225 250 275 300 400 350 375
TOTAL Patch ~~Size~~ Dose

Time Trend in Total TTS Dose for the Combined Chronic.Cancer Pain Studies

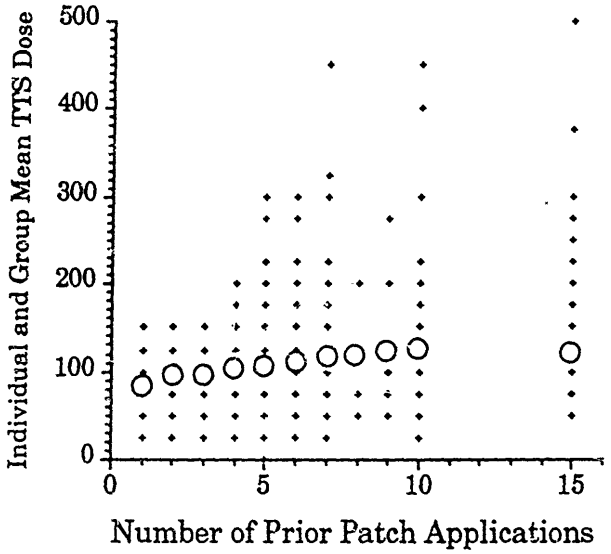


Table 3

Summary of Daily Supplemental Morphine Use (mg PO) by Study Period
Patients Who Completed the Double Blind Period

	In Hospital Titration				Stabilization				Active Week				Placebo Week			
SCN	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX
1061	19	28	0	60	2	5	0	15	17	22	0	45	40	28	15	90
1062	0		0	0	0	0	0	0	0	0	0	0	13	11	0	30
1063	71	41	15	120	30	13	15	45	41	14	15	60	61	21	30	90
1065	10		10	10	15		15	15	67	11	60	75	45	26	15	90
1066	144	69	20	270	159	29	120	180	171	15	150	180	148	46	75	210
1071	10		10	10	10	9	0	20	13	18	0	45	9	15	0	40
1074	205	244	15	540	92	24	60	135	73	10	60	90	56	35	15	120
1075	17	5	10	20	13	10	0	30	15	13	0	30	34	17	15	60
1077	9	6	5	14	0	0	0	0	0	0	0	0	0	0	0	0
1111	37	25	10	60	62	37	30	120	133	31	90	165	88	53	30	165
1112	48	27	30	90	50	15	30	60	116	32	90	180	116	36	90	180
1211	20		20	20	47	8	40	60	81	40	10	135	31	23	0	60
1213	37	29	20	70	17	8	10	30	37	10	20	50	68	10	60	80
1214	0		0	0	0	0	0	0	0	0	0	0	1	2	0	5
1216	20	10	10	30	30	8	20	40	43	48	0	100	54	24	10	80
1218	10	10	0	20	4	8	0	20	0	0	0	0	0	0	0	0
1219	79	41	20	180	163	24	150	210	159	23	120	180	154	21	120	180
1220	31	21	0	60	0	0	0	0	6	8	0	15	6	8	0	15
1221	15	15	0	30	13	34	0	90	47	44	10	120	43	10	30	60
1222	20	0	20	20	13	8	10	30	0	0	0	0	59	45	0	120
1224	95	44	40	140	10	11	0	20	10	9	0	20	20	0	20	20
1225	87	12	80	100	20	0	20	20	20	0	20	20	20	0	20	20
1265	15	0	15	15	11	7	0	15	11	7	0	15				
MEAN	43				33				46				48			
SD	50				46				53				45			

Table 4

Summary of Daily Supplemental Morphine Use (mg PO per day) by Study Period
Patients Not Completing the Double Blind Period

	In Hospital Titration				Stabilization				Active Week				Placebo Week			
SCN	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX
1011	29	24	0	105	15	17	0	30	19	8	15	30				
1012	38	13	30	60												
1013	35	18	10	60												
1014	15	7	10	20	61	35	15	150								
1064	36	17	15	60	36	18	15	60	43	18	30	75				
1067					36	14	10	50	72	38	10	110				
1068	40	31	15	75	58	16	45	90	115	77	30	180				
1069	14	5	5	20												
1070	62	53	18	120												
1072	200	136	20	390	73	22	60	120								
1073	15	0	15	15	24	12	15	45	30	15	15	45				
1076	38	15	30	60	30		30	30								
1113	29	19	15	60	36	13	15	50	106	60	45	165				
1114	138	109	60	330	133	62	30	180	146	195	20	540				
1115	140	28	120	160												
1212	48	25	16	80	10	8	0	16	45	23	15	75				
1215					10		10	10								
1217	15		15	15	43	14	20	60	20		20	20	43	18	20	60
1261	29	16	15	45	99	44	55	189	149	53	72	216	108	54	36	180
1262	114	29	72	160												
1263	20	14	10	40	12	4	10	20	8	4	0	10	302	307	10	804
1264																
MEAN	56				45				68				151			
SD	53				35				52				135			

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Table 7

Summary of Pain Scores by Study Period
Patients Who Completed the Double Blind Period

	In Hospital Titration				Stabilization				Active Week				Placebo Week			
SCN	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX
1061	1.5	1.2	0.0	4.0	0.7	0.5	0.0	1.0	1.8	1.0	1.0	3.0	2.3	1.1	1.0	4.0
1062	0.3	0.7	0.0	2.0									2.0	0.0	2.0	2.0
1063	1.9	1.1	0.0	5.0	3.1	1.0	1.0	4.0	2.8	0.7	2.0	4.0	3.1	0.4	2.0	4.0
1065	1.3	0.8	0.0	3.0	2.0		2.0	2.0	1.0	0.0	1.0	1.0	1.7	1.1	1.0	4.0
1066	1.8	1.0	0.0	4.0	2.8	0.6	2.0	4.0	2.6	0.6	1.0	4.0	2.9	0.7	1.0	4.0
1071					3.0	0.0	3.0	3.0	3.2	0.8	2.0	4.0	2.7	0.5	2.0	3.0
1074	2.8	1.6	1.0	5.0	1.6	0.8	1.0	3.0	1.1	0.2	1.0	2.0	1.1	0.3	1.0	2.0
1075	1.8	0.8	1.0	3.0	3.5	0.8	3.0	5.0	3.7	1.4	2.0	5.0	3.0	1.1	2.0	5.0
1077	1.3	0.5	1.0	2.0												
1111	1.7	1.0	0.0	4.0	1.8	1.3	0.0	4.0	1.5	0.6	1.0	3.0	1.9	0.8	1.0	3.0
1112	0.9	1.1	0.0	3.0	2.8	1.1	0.0	4.0	1.0	0.0	1.0	1.0	3.3	0.7	1.0	4.0
1211	3.0		3.0	3.0	2.3	0.5	2.0	3.0	2.0	0.4	1.0	3.0	2.6	0.5	2.0	3.0
1213	1.6	1.4	0.0	4.0	2.2	0.4	2.0	3.0	1.9	0.6	1.0	3.0	2.0	0.6	1.0	3.0
1214	0.8	0.5	0.0	1.0									2.0		2.0	2.0
1216	2.2	0.4	2.0	3.0	2.5	0.7	2.0	4.0								
1218	0.7	1.1	0.0	3.0	1.4	1.2	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1219	3.1	0.8	1.0	5.0	3.2	0.4	3.0	4.0	3.1	0.3	3.0	4.0	3.1	0.4	3.0	4.0
1220	1.6	1.2	0.0	4.0	1.1	0.5	0.0	2.0	1.3	0.4	1.0	2.0	1.0	0.0	1.0	1.0
1221	1.4	0.7	1.0	3.0	1.0	0.0	1.0	1.0	1.0	0.0	1.0	1.0	1.0	0.0	1.0	1.0
1222	1.1	0.9	0.0	3.0	3.4	0.5	3.0	4.0					2.8	0.6	2.0	4.0
1224	0.7	1.2	0.0	2.0	3.0	0.0	3.0	3.0								
1225	0.0	0.0	0.0	0.0	1.0	0.0	1.0	1.0	2.0	1.4	1.0	3.0				
1265	3.0		3.0	3.0					2.0	0.0	2.0	2.0				
MEAN	1.6				2.2				1.9				2.1			
SD	0.9				0.9				1.0				0.9			

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Table 8

Summary of Pain Scores by Study Period
Patients Not Completing the Double Blind Period

	In Hospital Titration				Stabilization				Active Week				Placebo Week			
SCN	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX	MEAN	SD	MIN	MAX
1011	1.0	1.1	0.0	3.0	1.0	1.3	0.0	3.0								
1012	0.3	0.8	0.0	2.0												
1013	1.7	0.9	0.0	4.0												
1014	0.8	0.8	0.0	2.0	2.8	0.6	1.0	5.0								
1064	2.2	1.4	0.0	5.0	2.7	1.5	0.0	5.0	3.7	1.4	1.0	5.0				
1067	2.5	0.8	1.0	4.0	2.9	1.0	1.0	5.0	3.3	1.0	1.0	5.0				
1068	0.5	0.6	0.0	1.0												
1069	1.8	2.0	0.0	5.0												
1070																
1072	3.9	0.9	3.0	5.0	3.5	0.7	3.0	4.0								
1073	1.9	1.2	1.0	5.0	2.6	0.8	1.0	4.0	3.0	0.9	1.0	4.0				
1076																
1113	1.0	1.2	0.0	3.0	3.4	1.0	1.0	4.0	2.8	1.2	2.0	5.0				
1114	1.6	1.5	0.0	5.0	2.6	0.9	1.0	4.0	2.3	0.5	2.0	3.0				
1115																
1212	1.8	1.4	0.0	5.0	3.0	0.8	2.0	4.0	3.6	1.4	1.0	5.0				
1215	0.0	0.0	0.0	0.0												
1217	2.5	1.7	1.0	5.0	2.7	0.5	2.0	3.0	2.0		2.0	2.0	2.1	0.3	2.0	3.0
1223																
1261	3.5	1.1	1.0	5.0	3.2	0.7	1.0	4.0	2.9	0.4	2.0	3.0	2.7	0.5	2.0	3.0
1262																
1263	1.2	0.9	0.0	3.0	2.2	0.8	1.0	3.0	3.5	2.1	2.0	5.0	3.0		3.0	3.0
1264	0.9	0.6	0.0	2.0												
MEAN	1.6				2.7				3.0				2.6			
SD	1.0				0.7				0.6				0.5			

Outcome		
Death	29	63.0
Discontinuation of Treatment		
Adverse Experience	6	13.0
Inadequate Pain Control	3	6.5
Personal Reasons Unrelated to Study	3	6.5
Protocol Violation	1	2.2
Continuing Treatment	4	8.7

Reference: Appendix VI

3.3 Initial TTS (fentanyl) Dose

If a patient's previous narcotic regimen was inadequate to control pain, a TTS (fentanyl) dose higher than the calculated equianalgesic dose was prescribed. A table in Appendix III illustrates the methodology used to convert each patient to their initial TTS (fentanyl) dose. This table includes the following:

a. prior narcotic use;

b. an equivalent IM morphine sulfate dose [based upon an equianalgesic drug chart derived from Foley (1), and included in Appendix III];

c. the calculated conversion dose to TTS (fentanyl).

The worksheet used for this calculation is also included.

TTS (fentanyl) doses were titrated within hospital surroundings over a period of three days.

If three days proved to be insufficient for a particular patient, the titration phase could be extended as long as necessary to achieve adequate dosage. During titration, study investigators were instructed to use an analgesic equivalency worksheet to calculate appropriate TTS (fentanyl) doses based on patients' prior narcotic use.

Guidelines given to study personnel included a recommendation to increase or decrease TTS (fentanyl) dosage in 25 mcg/hr increments as often as every 48 hours until adequate pain control was achieved. However, the final decision regarding titration schedules was left to the investigator's clinical judgment and dose changes were made as frequently as every 24 hours.

The TTS (fentanyl) doses on initiation of treatment ranged from 25 mcg/hr to 200 mcg/hr with the 50 and 75 mcg/hr doses being the

participants as of February 1, 1988. Appendices VI and VII describe reasons for individual patient terminations in detail.

3.5.1 Continuing TTS (fentanyl) Treatment

Four patients remained on TTS (fentanyl) as of February 1, 1988 (Table D). All have been using TTS (fentanyl) continuously for over one year and one patient has been receiving treatment for more than 1-1/2 years.

Table D

Summary of Patients Continuing Use of TTS (fentanyl)

SCN	TTS Dose (mcg/hr) Entry	Current	Days on Therapy
1067	50	125	536
1074	75	175	439
1218	50	50	576
1265	50	50	401

3.5.2 Patient Termination of TTS (fentanyl) Treatment

Table E below displays patient withdrawals by time in treatment.

Table E

Patient Withdrawals by Treatment Period

	1-3 Days	4-15 Days	16-30 Days	31-60 Days	61-90 Days	91-120 Days	Over 120 Days
No of pts. (n=42)	2	10	6	8	3	4	9

Only 2 (4%) of the patients were withdrawn from treatment within the first 3 days of TTS (fentanyl) wearing. They are discussed in detail below:

A 66 year-old female (SCN 1115) with a uterine sarcoma, who was classified as terminal at the time of study entry, discontinued the study on study day 2 due to increased pain, rapid respirations, and hypotension which culminated in

(26%), constipation (26%), pulmonary congestion (22%), confusion (22%), and anxiety/agitation (20%).

Table L: Adverse Experiences by Body System

	No.(%) Patients with Adverse Experiences N = 46
Total	43 (93%)
<u>Neurological System</u>	
Sedation	12 (26%)
Confusion	10 (22%)
Anxiety/Agitation	9 (20%)
Headache	5 (11%)
Dizziness	4 (9%)
Depression	3 (7%)
Euphoria	2 (4%)
Lethargy	2 (4%)
Hallucinations	2 (4%)
Vivid dreams	1 (2%)
Trembling	1 (2%)
Ataxic gait	1 (2%)
<u>Gastrointestinal</u>	
Nausea/Vomiting	25 (54%)
Constipation	12 (26%)
Diarrhea	3 (7%)
Flatulence	3 (7%)
Hiccoughs	2 (4%)
Gas pain	1 (2%)
<u>Respiratory</u>	
Pulmonary congestion	10 (22%)
Shortness of breath	6 (13%)
Irregular breathing	4 (9%)
Hemoptysis	2 (4%)
Rapid respirations	1 (2%)
Paroxysmal coughing	1 (2%)
Sleep apnea	1 (2%)

Table 2, continued

Cardiovascular	
Chest pain	4 (9%)
Tachycardia	2 (4%)
Hypotension	2 (4%)
Irregular Heart Beat	2 (4%)
Bradycardia	1 (2%)
Atrial fibrillation	1 (2%)
Cerebrovascular accident	1 (2%)
Skin & Appendages	
Pruritis	4 (9%)
Urticaria	1 (2%)
Genitourinary	
Urinary retention	4 (9%)
Body as a Whole	
Diaphoresis	4 (9%)
Flushing	1 (2%)
Other	
Dry mouth/throat	5 (11%)
Sore throat	1 (2%)

Reference: Appendix VIII

3.7.2 Respiratory Rates

Mean respiratory rates remained within clinically acceptable ranges for the period beginning with in-hospital titration and ending approximately three weeks after discharge from the hospital for both double-blind completers (Table 9) and patients who did not complete the double-blind trial (Table 10). No patient discontinued the study as a result of respiratory problems attributable to TTS (fentanyl).

3.7.3 Sedation

No patient terminated use of TTS (fentanyl) as a result of of over-sedation. Mean sedation ratings ranged from 1.1 (wide awake) to 2.0 (drowsy) among all 46 patients for the

Study # 87-010-01 Payne

Abstract

This multi-center, dose-ranging, open-label trial of the safety and acceptability of TTS Fentanyl was performed in pre-terminal cancer patients. Fifty-four patients were drawn from the clinic populations of four major cancer centers (18,21,8 & 7 patients per group), converted to an individualized dose of oral morphine solution, then crossed over to an individualized dose of Fentanyl TTS. The patients were kept on TTS Fentanyl until they died, could not comply with the requirements of the trial, were discontinued due to inadequate pain control or dropped out due to adverse effects. Outcomes for this study included the ease of conversion to TTS Fentanyl, trend in the patient's pain intensity scores, trend in fentanyl dose, withdrawals for lack of efficacy and adverse events, and rate of adverse effects over time.

Of the 59 patients screened 54 were eligible for the trial and were followed for 224 patient-months of observation. Doses of oral morphine ranged from 6-1320 mg/day at the onset of the trial, with TTS Fentanyl doses ranging from 25-600 μg/hr. Seventy percent (70%) of the patients were able to obtain analgesia equivalent to oral morphine (Pain Intensity ratings 2.5-4.5 on a 10 cm visual analog scale), and to continue on TTS fentanyl until death or the end of the trial. The dose of TTS fentanyl required for satisfactory analgesia increased over time during the trial, with a doubling of the dose after a month of therapy.

Adverse events were typical for high-dose opioid therapy and were mainly neurologic (confusion, excessive sedation, nervousness) and dermatologic (redness, stinging, & irritation of the system site.). The rate of all adverse events was relatively constant at 20-30 events per 100 patient-months, with a rate of events requiring medical evaluation or intervention of 8-10 per 100 patient-months of treatment.

Resume

This study was a multi-center open trial of the therapeutic utility of TTS fentanyl carried out at the University of Cincinnati, The Milton S. Hershey Medical Center, The Pittsburgh Cancer Institute, and M.D. Anderson in Houston. The investigational plan was to select 50-60 cancer patients who required narcotics for pain control, to convert them to oral morphine analgesia, and from thence to TTS fentanyl. This was one of several such trials in cancer patients which represent the first use of the system in multiple applications in man. This open trial was planned to investigate the acceptability and safety of the system in chronic cancer pain.

The inclusion criteria for the study were that the patients be taking narcotics for cancer pain, be able to communicate effectively, live with a constant caretaker, and achieve adequate pain control with oral morphine in the pre-study period. Patients expected to live less than a month, prior severe respiratory disorder, narcotic abuse, active skin

disease, mental disorder or liable to become pregnant were excluded. Fifty-nine patients were screened for the study and fifty-four were accepted into the protocol.

The patients were moderately ill at entry with a variety of tumors and tumor sites. All were taking oral or parenteral narcotics in doses ranging from 6 mg to 1300 mg of oral morphine equivalents a day. The patients were converted to oral morphine by the equivalencies provided, and had a median requirement for oral morphine between 120-240 mg/day.

Following stabilization on oral morphine the patients were switched to TTS Fentanyl using the formula: 360 mg/day oral morphine = TTS 100 μg/hr. TTS systems were re-applied every three days, and the dose was adjusted by the treating physician based on the patient's use of oral morphine rescue medication and reported pain relief. Included in the enclosures is the dosing experience of the group, showing that 35-65% of the patients increased their dose from visit to visit when the median dose was less than 200 μg/hr.

The patients were seen at 3 days, 7 days, and then monthly, with weekly telephone monitoring by the study nurses. Laboratory studies (chemistry & hematology) were done at baseline, one week, 1, 3, 6, &12 months after induction in the study. Pain control was assessed by weekly 10 cm visual analog ratings and global ratings by the clinicians at monitoring visits. There was no restriction on concomitant medication and the majority of patients were taking minor tranquilizers, anti-nauseants, and hypnotics.

The study hypothesis was that patients could be adequately stabilized on oral morphine and then converted to TTS Fentanyl with an acceptable frequency of adverse effects and analgesia satisfactory to treating clinician and patient.

Selection , Withdrawals, and Mistakes

The fifty-four patients in the study were grouped into the following treatment centers:

University of Cincinnati	18
Hershey Medical Center	21
Pittsburgh Cancer Institute	8
M. D. Anderson	7

The group included 30 males and 24 females, with breast cancer (13), lung cancer (12), and gastrointestinal cancer (11) being the most common diagnoses. The clinical status of each patients was by the Eastern Cooperative Oncology Group rating with 30% of the patients bed-ridden 50-100% of the time , and 54 % ambulatory with symptoms. Over half (54%) of the patients were on active chemotherapy during the trial with 13% receiving radiotherapy.

Seven patients did not complete the seven day period of stabilization on oral morphine specified in the protocol. Two patients (406&402) could not tolerate the high oral doses of morphine and were converted to TTS fentanyl without completing the week on oral morphine. Five patients were converted from their prior pain medication to TTS fentanyl directly on the basis that the clinicians felt that such conversion would provide the best analgesia for the patient.

At least half (24/54) of the subjects started at a higher dose of TTS Fentanyl than calculated from the 360 mg morphine = 100 μg TTS formula. This was done at the clinical judgement of the investigators who felt that the subjects were not taking enough prn morphine (over 40% of the patients had a a mean baseline VAS pain rating of greater than five out of ten and rated their analgesia on oral morphine as fair to poor). This finding is consistent with the later finding that 31 of the 54 patients required increased doses of TTS Fentanyl within one week of application.

There were five discontinuations which do not appear to be TTS Fentanyl related. Patient 404 persistently removed the system as part of a general pattern of non-compliance and was discontinued after less than 24 hours. Patient 104 requested discontinuation after less than three days as he preferred his old medications and thus had no chance to be titrated. Patient 211 developed gram negative sepsis within 5 days of system application and had the system removed, and patient 107 felt he did not need narcotics and requested system removal. The last patient, patient 105, had multiple family problems which included conflict over the systems and the study and which were resolved by withdrawing from the study.

Eight patients withdrew specifically due to problems with the TTS system system. Patients 202, 315, 320, 321, 402, & 404 all had to be switched to parenteral opioids after periods on TTS fentanyl. Maximal doses of the systems prior to discontinuation ranged from 200-600 μg/hr, and suggest that subjects who require doses above 250-500 μg/hr have exceeded that useful delivery range of the system.

Two subjects discontinued the system for adverse reactions. Patient 305 was withdrawn at the behest of the spouse from TTS 75, due to increasing confusion (subjective rating by spouse). Patient 101 stopped the system due to complaints of itching or burning after system removal (100μg/TTS), although no objective redness or skin injury was observed by the treating physician.

The cumulative effect of bias is difficult to establish. Fifty-four of fifty-nine patients seen were selected, the groups were balanced by gender, cancer type, severity, and test site. The withdrawals unrelated to TTS Fentanyl (5/54) were reasonable, but the protocol violations with respect to dose ranging (31/54) were not. The clinicians chose to use clinical judgement rather than the formula to establish dose, suggesting that the prn oral morphine stabilization dose converted into fentanyl (360 mg/day/100 μg/hr) does not adequately reflect the analgesic need of the patients. This will be discussed further below.

Results and Analysis

Since this is an open trial, it is exposed to the criticism that it may be biased by expectation effects on the part of both clinician and patient. This is mitigated by the fact that these were experienced narcotic users, most of whom had a substantial degree of physical dependence on narcotics. If TTS fentanyl had not delivered appropriate levels of narcotic these patients would be expected to promptly drop out as has been seen in trials of mixed agonist-anagonist narcotics in this setting. The enclosed plots show the cumulative experience of the group expressed as the probability of withdrawing from the trial as estimated by life table analysis (the raw data is biased by the large number of patient deaths). Patients who died from their underlying disease were withdrawn from the life tables without prejudice in all cases, while the two tables and graphs show the cumulated rate for discontinuation due to all causes, and for discontinuation due to adverse events. As may be seen, roughly 2% per month dropped out of treatment with TTS fentanyl, with an estimated 75% of patients persisting in adequate pain relief for one year of treatment. This is only an estimate, since the high mortality rate in the study group meant that many patients died while still on TTS fentanyl, but it suggests that this treatment is acceptable for most patients.

Also shown is the trend in pain scores over the period in which the majority of patients were on the therapy (eight weeks). As may be seen, the TTS system did not abolish the patient's pain, but did result in VAS pain scores at or below baseline pain ratings on oral morphine for the entire 8 weeks of the study.

The trend in TTS dose over time is confounded by the fact that half of the patients were started at doses that required immediate upward adjustment by the second dose. Nevertheless, there was a consistent trend over time toward increasing doses as shown. The time required to double the dose of TTS Fentanyl was about two months, with most patients requiring a gradual increase, a few maintaining a stable dose, and five or six rapidly escalating to very high doses (500-600 µg/hr) and having to be taken off the system as described above.

TTS Fentanyl in doses of 100-250 µg/hr was acceptable to the majority of patients in this trial and provided them with pain relief which they rated as similar to or slightly better than that provided by oral morphine.

Adverse Events

Enclosed are the rate of adverse events by body system expressed as raw counts and as rates per 100 patient-months on the therapy. These were plotted as both the raw data, and as mean-smoothed trends in order to try to observe any trends toward more adverse events at either the onset or later phases of therapy. As may be seen, the total number of adverse events shows a trend toward an increased number at the onset of therapy, but about half of the adverse events reported in the first few months are dermatologic (itching, burning, redness) , while the rates of the more serious CNS adverse events (confusion, agitation, "spaced-out")

remain constant. Serious adverse events (requiring medical evaluation or dosage adjustment) occurred at a rate of 8-10 per 100 patient-months, and had occurred in about half the patients by the end of the study.

The investigators & sponsor did not feel that any of the serious adverse events were directly related to the TTS Fentanyl, but review of the case report forms revealed a number of probable associations (in many cases the evaluating physician removed the system or adjusted the dose as the therapeutic intervention).

Patient 202- Hospitalized on day 46 for confusion, slurred speech & poor memory. System removed.

Patient 203- Hospitalized day 8 agitation, confusion, hallucinations. System removed.

Patient 205- Nausea, dizziness, mental confusion, fall at home, urinary retention. TTS continued.

Patient 209- Dose increased day 40, one day episode of emesis, dyspnea, weakness. TTS continued.

Patient 214- Mild confusion and disorientation during a period when TTS dose increased rapidly from 100-300 μg/hr. TTS continued.

Patient 215- Somnolence, woozy, shaky, unsteady gait, dizzy when TTS increased to 100. TTS reduced to 50.

Patient 218- Dysphoria, "weird spaced-out feeling" when TTS increased to 450 μg/hr. TTS reduced.

Patient 302- Increased sleepiness when dose increased to 300 μg/hr. TTS reduced.

Patient 315- Nausea & vomiting when TTS increased to 75. TTS removed.

These patients represent 9 of 54 for a total serious adverse reaction rate of 15-20%. No patient suffered any permanent injury or death attributable to TTS fentanyl, none suffered respiratory depression or was treated with naloxone, and all skin reactions resolved with system removal.

Laboratory screening data was available for most individuals during the period of TTS application, but much of it was abnormal due to prior disease. Scatter-plots of this data revealed no consistent trend signifying medication induced abnormalities.

Pharmacologic Performance

No pharmacokinetic or pharmacodynamic data were collected.

Additional Analyses

This study-used two methods of predicting analgesic demand, predicted demand based on the patient's reported use of analgesics, and actual 24 hours usage rates of oral morphine while under observation. The enclosed scatterplots show the predicted v. actual morphine demand, and the relationship of TTS dose to observed morphine use at the initial application of the TTS and after one week. Since TTS dose was set by the observed use of morphine in the stabilization period in the protocol, there should be a strong relationship between that two, and this is, in fact, observed. After a week in which the dose is adjusted to best analgesia, the doses of TTS are higher, with the relationship 300 mg/24 h oral morphine (50 mg/24 hour parenteral morphine) = 100 μg/hr TTS fentanyl. This probably represents a more accurate reflection of the analgetic relationship.

Conclusion

This study establishes the acceptability of TTS Fentanyl for pain control by cancer patients and suggests that that ratio of oral morphine to TTS Fentanyl for conversion to TTS fentanyl lies between 75-125 μg/hr TTS fentanyl per 360 mg/24 h oral morphine demand. The study revealed no unexpected clinical or laboratory hazards of the drug, a serious adverse events rate (mostly opioid side effects on the CNS) of 10 per 100 patient months, and a rate of dose increase of approximately 50% per month of therapy.

Scatterplot of VAS Pain Ratings at Entry and After One Month of TTS Use

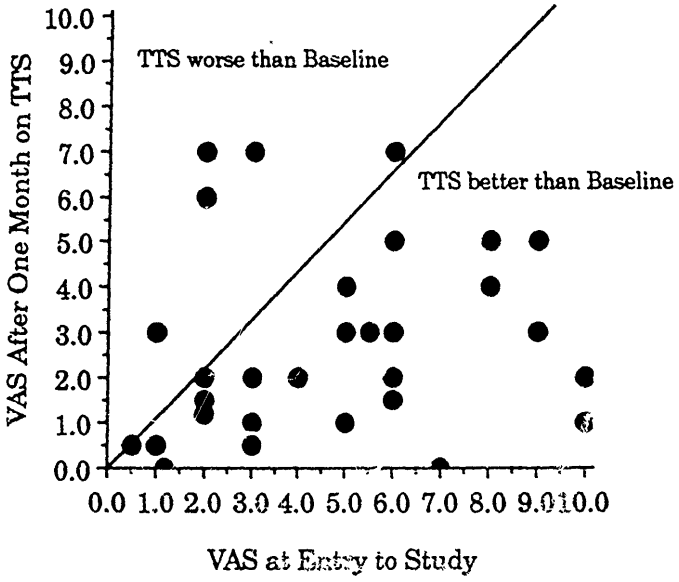

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TABLE 5

Distribution of Age, Sex, and Race *

Demographic Variable	Patients No. (n = 54)	(%)
Age (yrs):		
< 37	4	(7.4)
37-47	11	(20.4)
48-59	12	(22.2)
60-69	16	(29.6)
> 70	11	(20.4)
Mean	57.2	
Median	59.5	
Range	33-78	
Sex:		
Male	30	(55.6)
Female	24	(44.4)
Race:		
Caucasian	46	(85.2)
Black	8	(14.8)
Native American	0	
Asian	0	
Other	0	

* From screening visit.

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TABLE 6

Distribution of Primary Cancer Diagnoses *

Primary Diagnosis	Patients No.	(%)
Bladder	1	(1.9)
Breast Cancer	13	(24.1)
Colon Cancer	8	(14.8)
Head & Neck	5	(9.3)
Kidney Cancer	1	(1.9)
Lung Cancer	12	(22.2)
Malignant Melanoma	1	(1.9)
Pancreas Cancer	1	(1.9)
Prostate Cancer	4	(7.4)
Unknown Primary Cancer	2	(3.7)
Other		
Adenocarcinoma of the Appendix	1	(1.9)
Carcinoid	1	(1.9)
Fibrous Histiocytoma	1	(1.9)
Metastatic Renal Cell	1	(1.9)
Ovarian	1	(1.9)
Thyroid Cancer	1	(1.9)
Total	54	(100.5)

* From screening visit.

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TABLE 8

Distribution of ECOG Performance Status *

ECOG Status	Patients No.	(%)
Normal Activity	9	(16.7)
Ambulatory with Symptoms	29	(53.7)
Bedridden 50% of Time	8	(14.8)
Bedridden 75% of Time	6	(11.1)
100% Bedridden	2	(3.7)
Total	54	(100.0)

* ECOG = Eastern Cooperative Oncology Group status at study screening visit.

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14.2/050

TABLE 18

Summary of Morphine Sulfate Stabilization Dose *

MS Stabilization Dose (mg/day)	Patients No.	%
< 45	0	
45 - 134	23	(43.4)
135 - 224	9	(17.0)
225 - 314	9	(17.0)
315 - 404	5	(9.4)
405 - 494	2	(3.8)
495 - 584	1	(1.9)
585 - 674	0	
675 - 764	2 *	(3.8)
> 764	2 **	(3.8)
Total	53 ***	(100.1)

* Patient 406 received 720 mg/day morphine equivalents of injectable Dilaudid pretreatment and was switched to oral MS as the rescue analgesic at TTS (fentanyl) initiation. Patient could not tolerate high dose MS, but could tolerate low dose PO morphine.

** Patient 321 received 1,320 mg/day morphine equivalents of sustained release morphine and Dilaudid prior to TTS (fentanyl) therapy. The patient was prescribed 180 mg of immediate release MS during titration. Patient 104 received 768 mg/day morphine equivalent of Dilaudid (Hydromorphone) pretreatment. Patient 104 did not do well with change so was not switched to MS for titration.

*** Patient 318's stabilization dose was not available.

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TABLE 24

Distribution of Patient Reported Pain Control Ratings by Visit

Pain Control Rating	Pretreatment				Follow-up Visit											
	Pre-Screening Period		Morphine Sulfate Stabilization Period		1 Week		1 Month		3 Months		6 Months		9 Months		12 Months	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Excellent	3	(5.6)	4	(7.4)	1	(2.1)	4	(10.0)	1	(3.8)	1	(9.1)	0	0	0	0
Very Good	6	(11.1)	11	(20.4)	9	(19.2)	8	(20.0)	2	(7.7)	2	(18.2)	1	(16.7)	1	(33.3)
Good	14	(25.9)	14	(25.9)	19	(40.4)	18	(45.0)	15	(57.7)	7	(63.6)	3	(50.0)	1	(33.3)
Fair	19	(35.2)	21	(38.9)	16	(34.0)	7	(17.5)	3	(11.5)	1	(9.1)	2	(33.3)	1	(33.3)
Poor	12	(22.2)	4	(7.4)	2	(4.3)	3	(7.5)	5	(19.2)	0	0	0	0	0	0
Subtotal	54	(100.0)	54	(100.0)	47	(100.0)	40	(100.0)	26	(99.9)	11	(100.0)	6	(100.0)	3	(99.9)
Not Reported	0		0		1		2		0		0		0		0	
Total	54		54		48		42		26		11		6		3	

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Table 26

Distribution of Patient Visual Analogue Pain Score Prestudy vs. 1 Month TTS (fentanyl) Follow-up Interval*

Visual Analogue Pain Score at Screening (cm)	Visual Analogue Pain Score at 1 Month TTS (fentanyl) Follow-up Visit					Total
	0-2.5	2.6-5.0	5.1-7.5	7.6-10.0	Not Reported	
0- 2.5	5	1	0	0	3	9
2.6- 5.0	6	2	0	0	4	12
5.1- 7.5	3	1	1	1	3	9
7.6-10.0	1	1	2	0	2	6
Not Reported	1	1	1	0	3	6
Total	16	6	4	1	15	42

	No.	(%)
Patients with Improved Visual Analogue Pain Score	17	(63.0)
Patients with No Change in Visual Analogue Pain Score	8	(29.6)
Patients with Worsened Visual Analogue Pain Score	2	(7.4)
Total	27	(100.0)

Visual Analogue Pain Score	Screening	1 Month TTS (fentanyl)
N	36	27
Mean	4.70	2.87
Standard Deviation	2.64	2.42
Range	0.2-9.9	0.1-9.3

* Visual Analogue Pain Score recorded at the 1 month TTS (fentanyl) visit.

10/6/89 TBL26

14.2/071

ALZA Corporation
Protocol C-87-010-01

TABLE 30

Summary of Patient Discontinuations by Study Interval *

Reason for Discontinuation	Study Interval (days)										TOTAL
	1-3 (n=54) No. (%)	4-15 (n=52) No. (%)	16-30 (n=45) No. (%)	31-60 (n=44) No. (%)	61-90 (n=38) No. (%)	91-120 (n=29) No. (%)	121-180 (n=25) No. (%)	181-270 (n=14) No. (%)	271-360 (n=9) No. (%)	>360 (n=4) No. (%)	No. (%)
Pt. no longer required narcotics	0	0	0	0	0	1 (3.5)	0	0	0	0	1 (1.9)
Patient non-compliant	2 (3.7)	0	0	0	0	0	0	0	0	0	2 (3.7)
Patient/Investigator/ Caretaker Decision	0	1 (1.9)	1 (2.2)	1 (2.3)	0	0	0	0	0	0	3 (5.6)
Inadequate Pain Control	0	1 (1.9)	0	1 (2.3)	1 (2.6)	0	3 (12.0)	0	0	0	6 (11.1)
Concomitant Event	0	1 (1.9)	0	0	0	0	0	0	0	0	1 (1.9)
Death	0	4 (7.7)	0	4 (9.1)	7 (18.4)	3 (10.3)	7 (28.0)	2 (14.3)	1 (11.1)	2 (50.0)	30 (55.6)
Study Closure	0	0	0	0	1 (2.6)	0	1 (4.0)	3 (21.4)	4 (44.4)	2 (50.0)	11 (20.4)
Total	2 (3.7)	7 (13.5)	1 (2.2)	6 (13.6)	9 (23.7)	4 (13.8)	11 (44.0)	5 (35.7)	5 (55.5)	4 (100.0)	54 (100.2)

* See Appendix XIII for a listing of patient discontinuations by reason.

10/16/89 TBL30

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14.2/075

ALZA Corporation
Protocol C-87-010-01

TABLE 34

Distribution of Patients with Concomitant Events with Possible or Unknown Relationship to TTS (fentanyl) by Body System *

Concomitant Event	Patients No.	(%)
Neurological		
Confusion	8	(14.8)
Sedation	4	(7.4)
Abnormal Thinking	3	(5.6)
Dizziness	2	(3.7)
Agitation	2	(3.7)
Ataxia	2	(3.7)
Dysphoria	2	(3.7)
Anxiety	1	(1.9)
Lethargy	1	(1.9)
Hallucinations	1	(1.9)
Syncope	1	(1.9)
Aphasia	1	(1.9)
Thick Speech	1	(1.9)
Weakness	1	(1.9)
Gastrointestinal		
Nausea and Vomiting	3	(5.6)
Gas Pain	2	(3.7)
Vomiting	1	(1.9)
Constipation	1	(1.9)
Abdominal Distention	1	(1.9)
Diarrhea	1	(1.9)
Respiratory		
Respiratory Depression	1	(1.9)
Shortness of Breath	1	(1.9)
Dyspnea	1	(1.9)
Skin and Appendages		
Local Skin Reaction	5	(9.2)
Dermatitis	2	(3.7)
Special Senses		
Visual Disturbances	1	(1.9)
Body as a Whole		
Diaphoresis	2	(3.7)
Other		
Dry Mouth	1	(1.9)
Fall at Home	1	(1.9)
Patients Reporting at Least One Event	23	(42.6)

* See Appendix XIV for Concomitant Events Coding System.

10/9/89 TBL34

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ALZA Corporation
Protocol C-87-010-01

TABLE 35

Distribution of Patients with Concomitant Events with Possible or Unknown Relationship to TTS (fentanyl) and an Incidence of at Least Two Percent by Descending Order of Frequency

Concomitant Event	Patients No.	(%)
Confusion	8	(14.8)
Local Skin Reaction	5	(9.2)
Sedation	4	(7.4)
Abnormal Thinking	3	(5.6)
Nausea and Vomiting	3	(5.6)
Agitation	2	(3.7)
Ataxia	2	(3.7)
Dermatitis	2	(3.7)
Diaphoresis	2	(3.7)
Dizziness	2	(3.7)
Dysphoria	2	(3.7)
Gas Pain	2	(3.7)

10/9/89 TBL35

Concluding Comments

The pharmacologic studies presented in the NDA for TTS fentanyl unequivocally demonstrate that the system is able to introduce fentanyl into the body in effective doses, and that the rate of delivery is dose-proportional, reproducible, and predictable to the degree required for safety. The clinical studies show that TTS fentanyl produces a definite morphine-sparing effect in postoperative clinical trials and is accepted as adequate analgesia by chronic cancer patients, their custodians, and physicians. Although the full safety profile of the drug will be discussed in a separate review, the system has been shown to provide patients with a greater total narcotic delivery resulting in improved analgesia without marked increase in serious opioid side effects. In settings where there is clinically relevant under-dosing with opioid analgesics, the combination of TTS fentanyl system will provide superior analgesia to PRN dosing..

While the studies provided do demonstrate that the product is effective, they also show that it has all of the toxicity of a potent narcotic, and is of acceptable risk only if the clinical situation warrants the use of a potent opioid analgesic. This system is a delivery system which will deliver the pharmacologic equivalent of a continuous infusion of a potent narcotic at a nearly constant rate for up to 72 hours after application. Since it is a genuinely new product, and is likely to be the first of many such products, it is essential to comment on the studies which the sponsor has not conducted:

1. There are no studies of use of the product for "same-day" surgery, despite the apparent usefulness of the product in such settings.

2. There are no controlled studies of the interaction of the product with commonly used concomitant analgesic medication (NSAID's, benzodiazepines, phenothiazine anti-nauseants), despite evidence in the clinical trials that the concomitant use of these agents improves the efficacy and decreases the frequency of adverse events associated with the use of the system.

3. There are no studies of the use of the system in patients with chronic impairment of pulmonary function, or of the effect of the system on CO_2 sensitivity in volunteers.

4. There are no studies of the system in patients who have significant co-morbidity other than the cancer studies, and in those studies many of the patients were taken off the system during severe intercurrent illness.

5. The design of the clinical studies did not provide a positive comparison which would an estimate of the analgesic potency of the system, and there are only statistical estimates of the pain relief provided by each dose level.

In the opinion of the reviewer the system is approvable, but will require Phase IV obligations to be placed on the sponsor to ensure that the introduction of the system into clinical practice is not accompanied by extensive improper use and consequent morbidity and mortality.

The available data shows that use of the TTS fentanyl system will result in an increased total opioid dose to the patient over PRN dosing, which is a major advantage in clinical situations where under-dosing is the norm. If TTS fentanyl use is extended to clinical situations where this is not the case, opiate over-dosage is likely to occur. As use of the system spreads beyond the post-operative period and the "healthy" cancer patient it will be given to patients who are receiving concomitant medications which affect respirations and serious adverse events due to drug-drug and drug-disease interactions will occur. It is not possible on the basis of the available data to predict the probable frequency or severity of these reactions, but the advertising and detailing of the system will be critical in preventing overdose attributable to its use.

The fentanyl system is *not* a routine analgesic in exactly the same way that phenylbutazone is not a routine anti-inflammatory or chloramphenacol a routine anti-infective. All require particular cautions in their use and should be labeled so as to restrict their use to clinical settings where they are genuinely indicated. Fuller discussion of the clinical utility of the patch will be found in the safety review in volume 4.

Curtis Wright MD,MPH
Medical Review Officer
PDES (HFD-007)

Medical Officer Review
NDA #: 19,813
Alza Corporation

TTS Fentanyl

(Transdermal Therapeutic System)

Volume 2 - Pharmacokinetics & Pharmacodynamics

Executive Summary

This amendment was requested of the sponsor by HFD-007 in May 1990 in order to address concerns about the pharmacokinetic performance of the TTS system and to clarify the pharmacodynamics of fentanyl at blood levels between 0-5 ng/mL. The submission consists of a mixture of material from the open literature and new data from the sponsor. It shows that while the manufacturing controls and in-vitro performance of the TTS system are acceptable, there is a large variation in the blood level of the drug supplied by the system in clinical trials and that not all of this variation is due to individual variation in clearance. The data provided support a Ctox for opioid-naive postoperative patients of 3.0 ng/ml (2.0 ng/ml for patients with one or more respiratory risk factors such as chest surgery, concomitant administration of CNS depressants, poor ASA status, lung disease), and a MEC of 0.6 ng/mL.

Blood levels for patients wearing the TTS 50 system (50μg/hr) will be below the Minimum Effective Concentration (0.6 ng/ml) for 15%, hit the target zone (0.6-2.0 ng/ml) for 83% of the patients, be toxic (2.0-2.99) for 2% of vulnerables, but will not exceed 3.0 ng/mL. Of the three systems tested in clinical trials it is both safe and effective.

The 75 & 100 μg/hr systems both provide too much fentanyl (3% and 11% above 3.0 ng/ml) for unrestricted postoperative use and the sponsor has been advised that approval will depend on the adequacy of the labeling in identifying postoperative patients who should and should not be prescribed the larger systems, and the adequacy of carton/package/system warnings.

All systems (25,50,75,100) are reliable enough so that they will not dose-dump (Cmax < 5 ng/ml) and should not be toxic for opioid-tolerant individuals in the cancer pain indication.

Submitted: 5/16/90
Reviewed: 5/31/90 to 6/6/90
Curtis Wright MD,MPH

WRITTEN CWIV - 6/6/90
PEER REVIEWED RD- 6/18/90
SPONSOR'S COMMENTS MS -6/19/90

General Comments Regarding the PK-PD Amendment

One of the factors which has prolonged the review process for TTS fentanyl was a nearly universal concern about safety on the part of the regulatory staff who reviewed the original submission. This discomfort was due, in part, to the novelty of transdermal administration of a potent opioid, but was also the result of concerns about the pharmacokinetic reliability of this method of delivery of fentanyl. As a direct result, the sponsor was asked to examine the pharmacokinetics of the TTS systems in detail and to develop additional pharmacodynamic information about the pharmacodynamics of fentanyl in the 0-5 ng/ml range delivered by the system. This amendment is their response to this request.

Overview of the Amendment & Review

The submission consists of a series of discussions of the performance of the TTS system and a combination of new and old data which defines the system and evaluates the probable causes of variation in its pharmacokinetic performance.

Variability in the TTS System

The TTS system consists of a reservoir containing a gelled ethanolic solution of fentanyl, a membrane, and a silicone adhesive layer. While the adhesive holds no fentanyl at manufacture, during the first week after production about 10-12% of the reservoir dose migrates into the adhesive and is immediately available to the skin site at application. Immediately following application of the system to the skin, a flux of fentanyl from the adhesive and from the reservoir through the membrane begins to load the stratum corneum under the system and after a sufficient gradient is formed the drug begins to pass through the vital layers of the skin into the blood. Keratinocytes do not metabolize fentanyl in-vitro, and no skin metabolism of the drug has been seen in bio-availability studies which contrasted the fentanyl lost from the system with absorbed drug. Given these elements in TTS system functioning, each was investigated in turn to estimate its variability.

In-Vitro Delivery

The membrane-adhesive layer couple acts to limit diffusion from the reservoir and is measured by the in-vitro testing procedure which examines the release rate of a system discharging into a large test volume for 24 hours. Fifteen lots of TTS fentanyl 25-100 μg/hr systems were examined and found to deliver a large initial flux (256-972 μg/hr) followed by a slower release in hours 2-12 (50-190 μg/hr) and a slower still 12-24 hour phase (39-128 μg/hr).

TTS (FENTANYL)

SUMMARY OF IN VITRO DRUG RELEASE TESTING INDIVIDUAL DATA POINTS FROM LOT RELEASE

	TTS (fentanyl)-25 Control No. 720105 Code No. 04332	TTS (fentanyl)-25 Control No 720705 Code No 04332	TTS (fentanyl)-25 Control No. 750806 Code No 04332	TTS (fentanyl)-25 Control No 001608 Code No 04332	TTS (fentanyl)-100 Control No 720705 Code No 04325	TTS (fentanyl)-100 Control No 739065 Code No 04325	TTS (fentanyl)-100 Control No 750906 Code No 04325	TTS (fentanyl)-100 Control No 001708 Code No 04325
Release Rate Rate 0 - 2 hrs (mg/hr)	690 6	564 2	520 9	466 2	1004 7	647 6	777 7	581 4
	780 2	574 9	482 5	498 8	962 5	845 2	794 6	729 7
	648 9	534 5	500 1	535 5	953 0	858 3	818 6	874 6
	686 9	546 2	525 6	565 6	906 7	830 3	816 9	765 7
	860 5	565 2		496 3	1000 3	863 2	888 7	649 5
	716 1	590 0		512 2	972 2	888 7	757 3	672 9
	729 8	639 4		485 5	904 3	858 6	882 6	699 3
	700 8	586 0		567 6	903 8	866 4		653 4
Average	807 7	575 8	567 8	583 1	972 6	856 5	886 3	671 0
Std Dev	73 8	32 7	10 7	17 0	33 1	13 9	70 3	44 8
% Coef Var	9.3	5 7	3 9	3 4	3 4	2 1	4 9	6 7
Release Rate Rate 2 - 12 hrs (mg/hr)	145 5	114 3	107 4	140 3	173 8	136 5	153 9	161 8
	145 8	117 1	101 5	141 4	176 1	144 2	142 3	196 1
	134 4	105 8	112.9	158 7	179 4	144 4	162 5	179 4
	130 5	113 9	122 4	146 5	187 7	138 8	160 5	183 1
	134 4	121 2		140 8	218 9	138 8	166 1	171 4
	138 5	112 3		162 9	180 1	141 7	156 8	180 7
	144 3	132 9		141 7	206 8	146 6	156 5	193 6
	145 8	116 4		158 6	203 1	138 4	157 1	166 8
Average	141 8	115 6	111 1	149 9	190 8	146 8	157 9	179 6
Std Dev	4 9	8 1	8 8	8 8	16 4	5 4	7 4	12 2
% Coef Var	3 5	6 9	8 0	5 9	7 8	3 9	4 7	6 8
Release Rate Rate 12 - 24 hrs (mg/hr)	105 4	74 5	78 8	100 8	112 9	101 2	101.9	120 8
	100 2	73 8	72 8	100 9	126 2	90 8	93 5	143 5
	102 6	68 5	79 7	106 8	110 3	103 2	105 1	122 3
	101 7	79 6	86 2	107 1	123 3	100 1	107 8	121 5
	100 4	90 8		100 1	125 4	96 8	108 3	118 4
	104 1	74 8		115 2	124 4	103 6	91 6	120 2
	106 4	80 9		103 8	113 7	100 9	103 8	136 2
	107 7	74 4		113 6	120 4	102 5	100 4	117 9
Average	104 7	75 8	79 2	107 1	121 6	100 8	102 4	125 4
Std Dev	3 1	4 2	5 8	5 4	5 9	3 8	6 6	10 1
% Coef Var	2 9	5 5	7 3	5 1	4 8	3 8	6 5	8 0

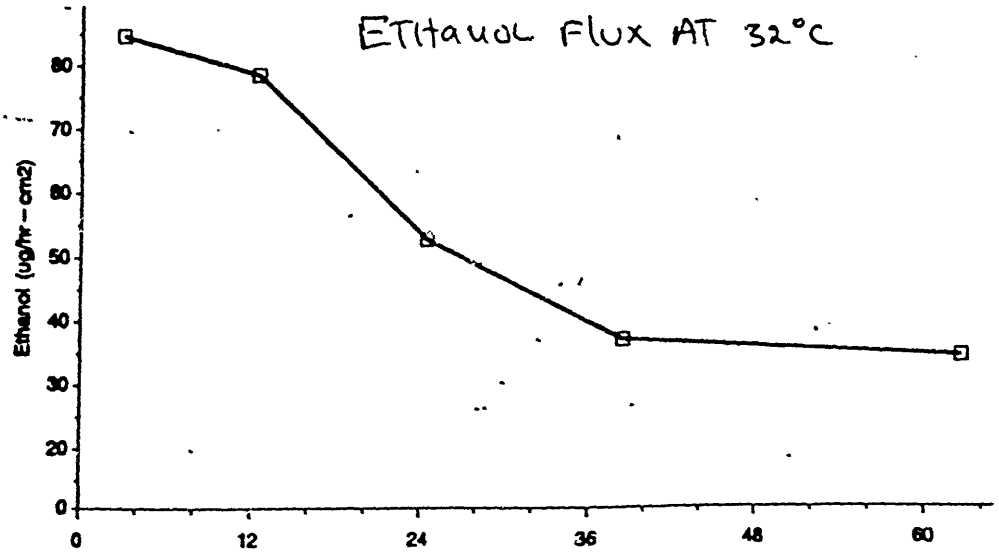
The following table shows the mean, standard deviation, and coefficient of variation for in-vitro delivery of drug from the systems for all four 100µg/hr TTS production batches used in the clinical trials:

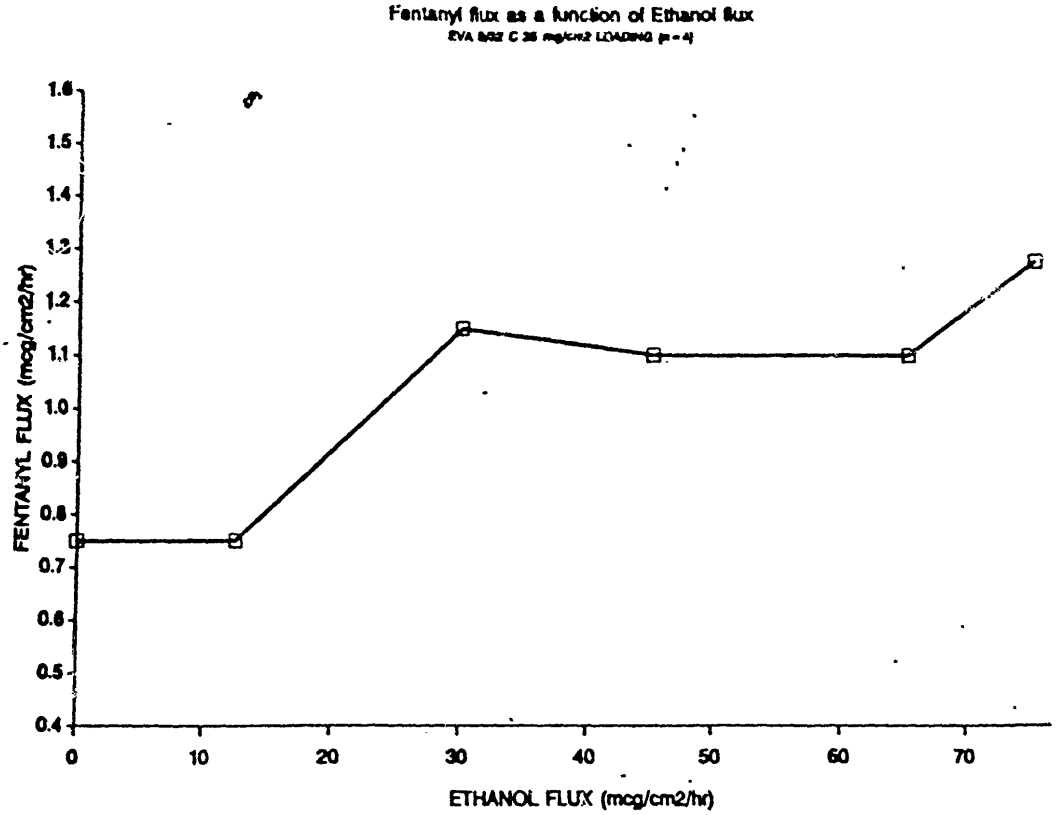
Lot Number	0-2 hours	2-12 hours	12-24 hours	24 hour total
1	691 (SD=86)	178 (SD=12)	125 (SD=10)	4670 SD=325
2	972 (SD=33)	190 (SD=14)	121 (SD=6)	5301 SD=190
3	797 (SD=20)	156 (SD=7)	102 (SD=7)	4386 SD=178
4	656 (SD=13)	139 (SD=3)	101 (SD=4)	3925 SD=97
Across all 100µg lots	**779** (SD=132) (CV=17%)	**166** (SD=22) (CV=13%)	**112** (SD=13) (CV=11%)	**4570** SD=546 (CV=12%)

It is likely that the variation in early release (0-2 hr) represents variability in the thickness and composition of the adhesive layer and that the late release rate (12-24 hr) represents variation in the reservoir-membrane assembly. Examination of the data shows a within-lot variation of 5% in early, late, and total delivery rates and an across-lot variation of three times as much or about 15%. The manufacturing controls for the prototype systems produce a product with a 24 hour in-vitro delivery of fentanyl of 4.57 +/- 0.54 mg, a clinically acceptable content uniformity.

Ethanol Flux

The TTS system reservoir contains a gelled aqueous solution of ethanol which acts to solubilize the fentanyl in the reservoir and alter the permeability of the stratum corneum under the system. The sponsor presents data which shows that there is a non-linear (probably first-order) loss of ethanol from the system during application with an initial ethanol flux of 85 µg/hr cm2 which falls to 30 µg/hr cm2 after 60-72 hours of system application. Since the permeability of the skin doubles (0.75 to 1.4 µg/cm2/hr) as a function of the ethanol flux, it is probable that the fall-off in ethanol in the system over time is related to the decline in the fentanyl flux observed after 24 hours of TTS system application.

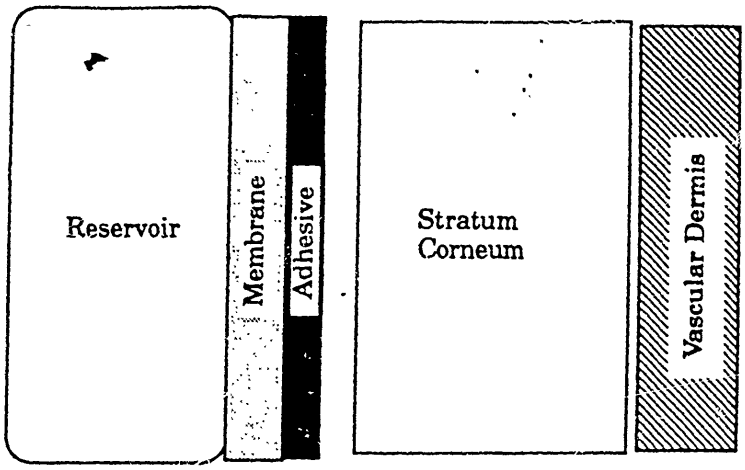




Variability in Skin Sites

Skin permeability differences to water or scopalamine of 10-fold and alterations in regional blood flow of 2-3 fold have been observed in normal humans. Both of these factors are expected to alter the flux through the skin along with alteration in skin temperature which affect blood flow, skin permeability, and functioning of the rate limiting membrane in the system. Each of these will be discussed in turn.

The driving force for fentanyl diffusion through the stratum corneum is the concentration gradient which is maximal just under the adhesive layer and minimal in the vascular dermal layers. The flux across the skin will be proportional to the size of this gradient, the area, and the permeability of the skin site. This is diagrammed on the next page:



When a drug solution is applied to a skin with a lower drug permeability (thicker) , the drug concentration gradient (per mm thickness) across the skin will be less for a thicker skin than a thinner skin because the same magnitude of concentration difference is established across a longer total distance (epithelial surface to basal layers). This lower gradient results in a decreased flux. If a solution applied to thick skin is to acheive the flux of a similar solution applied to thin skin, the total trans-epithelial concentration difference must be greater than for thinner skin. In the case of the TTS fentanyl system, the application of the system to thicker and thinner skin will result in an interaction between the rate limiting membrane and the skin "depot" of fentanyl to damp out large fluctuations in transepithelial flux.

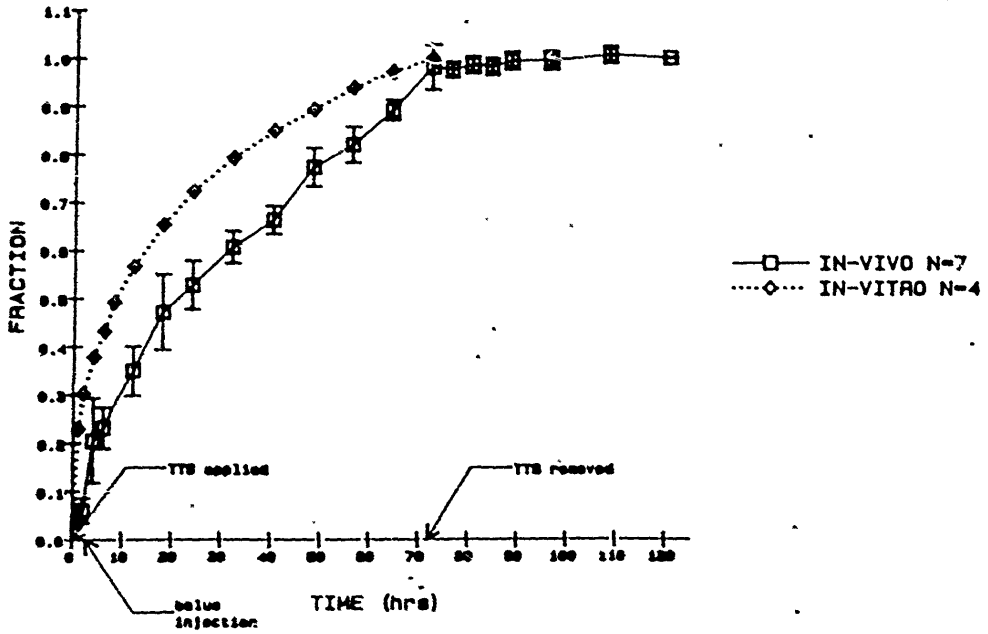
Application of the system to skin with lower permeability (thicker) will result in the need for a higher concentration under the system to achieve the same total flux. In such a case the flux through the membrane will exceed the flux into the blood and the trans-epithelial gradient will build up until the flux across the skin equals the flux across the membrane. As fentanyl is very soluble in both the ethanolic solution and the lipophilic lamellae the gradient can build to the required levels, and the flux across thicker skin will be expected to rise to nearly the levels of thinner skin. Even if the system is applied to raw or abraded thin skin the maximal flux cannot exceed the in-vitro rate of delivery of the system.

The difference between skin sites will be seen as a difference in the amount of time needed to establish a meaningful trans-epidermal flux, or more simply, in the lag between system application and the entry of fentanyl into the blood. The effects of such alteration in lag time have been modeled, and as may be seen in the accompanying figures will shift the onset of analgesia but have little effect on Cmax and Tmax. This is not true of failure of adhesion or partial application of the system which will alter the performance of the system in direct proportion to the degree of adhesion (few problems were observed with adhesion- see clinical trials review).

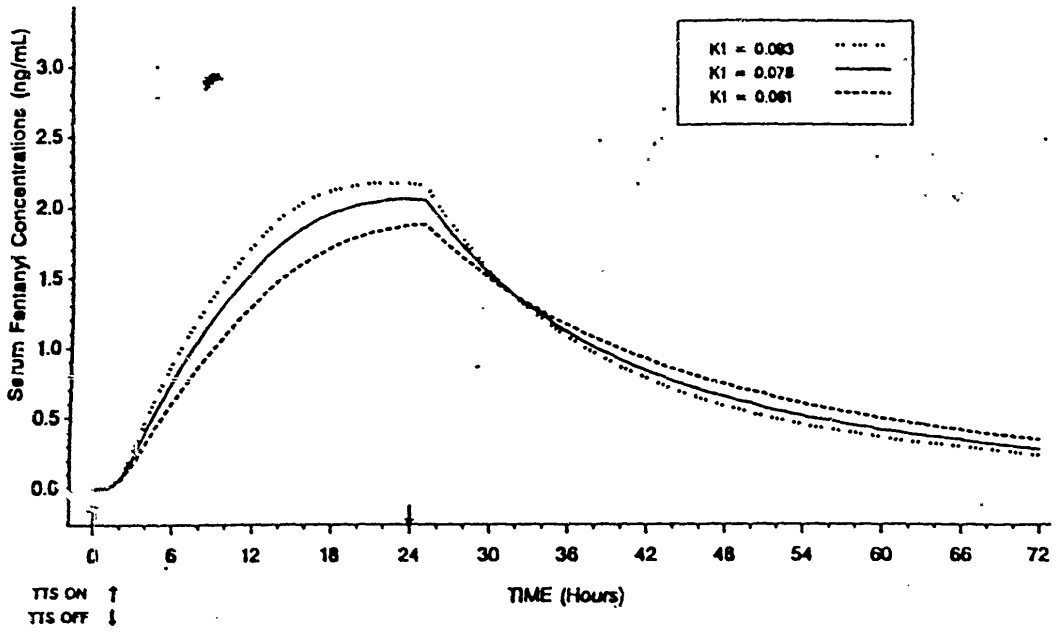
Pharmacokinetics

All of the initial pharmacokinetic evaluation of the TTS systems was done in patients in clinical studies due to company concern over possible risks of application of the higher strength systems to normal volunteers. Mean data from such studies is provided in this amendment (as was done in the initial application) and while such studies provide reasonable assurance that the products are dose proportional and have controlled release characteristics, the degree of variability observed and the confounding of peri-operative administration of fentanyl has led the division of Biopharmaceutics to request additional studies which are currently pending.

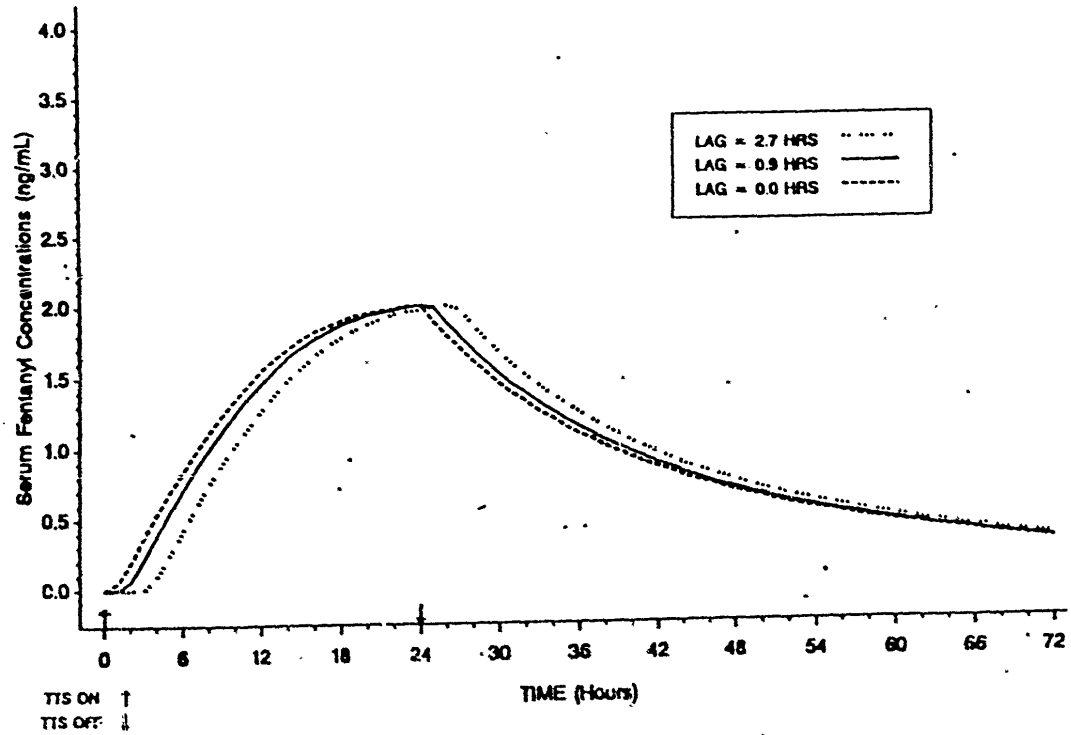
SINGLE APPLICATION TTS (fentanyl) 75 mcg/hr FOR THREE DAYS
MEAN (SE) IN-VIVO ABSORPTION and IN-VITRO DELIVERED DOSE



Simulated Serum Fentanyl Concentrations for TTS (fentanyl) – 100, 24 hour Application
Effect of Changes in Absorption Rate Constant



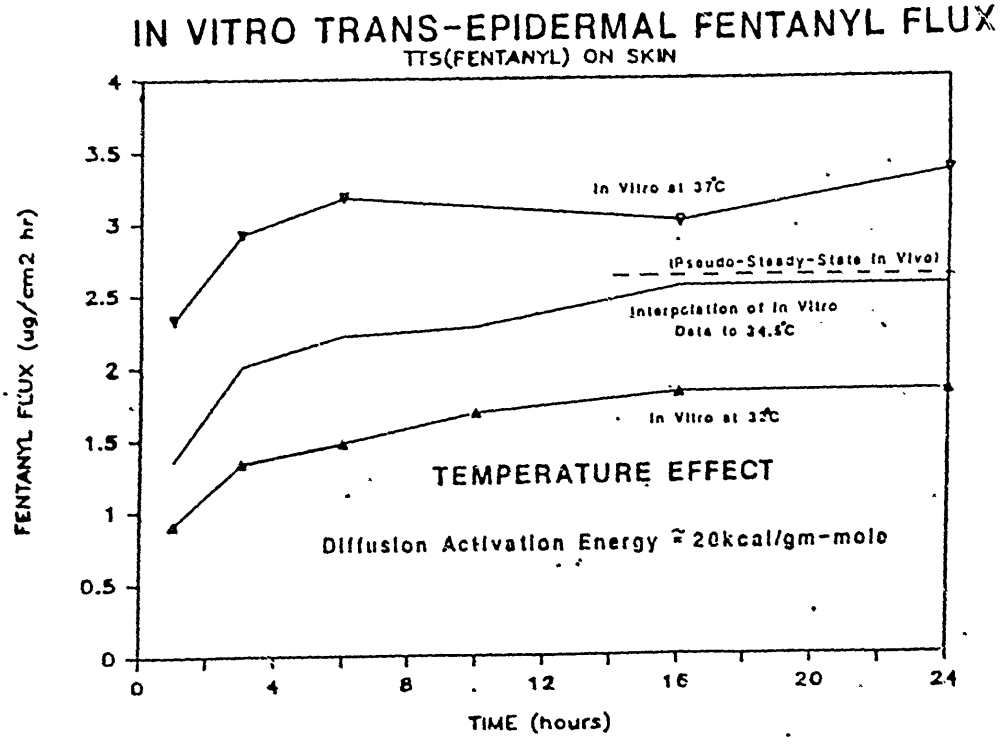
Simulated Serum Fentanyl Concentrations for TTS (fentanyl) – 100, 24 hour Application
Effect of Lag Time



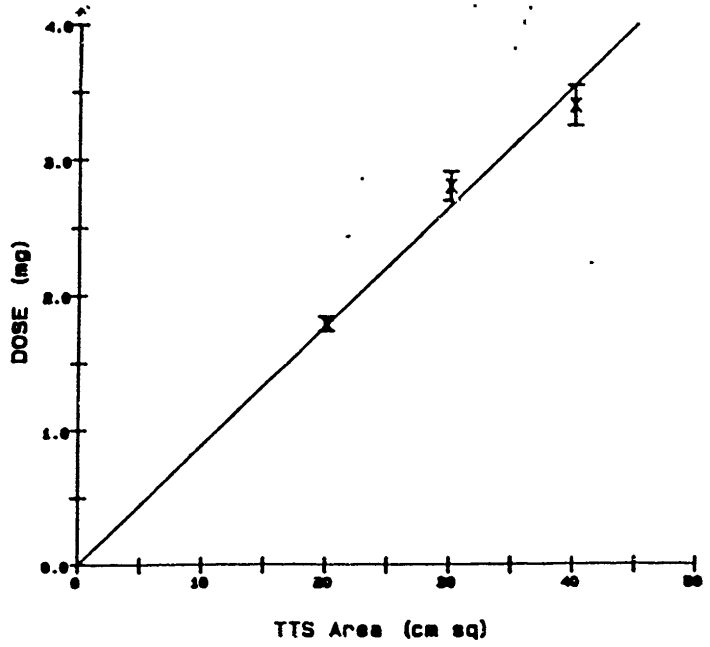
Temperature

One significant and poorly evaluated potential effect on system performance is temperature. In-vitro, the transdermal delivery of the system is doubled from 1.5 µg/cm2/hr to 3 µg/cm2/hr by a temperature change from 32 to 37 Centigrade. The sponsor has shown that in healthy volunteers the truncal skin temperature does not vary, but as yet has no data on the frequency of altered skin temperature in postoperative patients. Since anesthetic drugs, hypovolemia, peri-operative chilling, dressings, and postoperative temperature elevations are frequent, the effect of skin temperature on system delivery in clinical use should be investigated and commented on in the labeling. In a similar fashion the effects of sweating on system performance are not yet known, either with respect to adhesion or permeability.

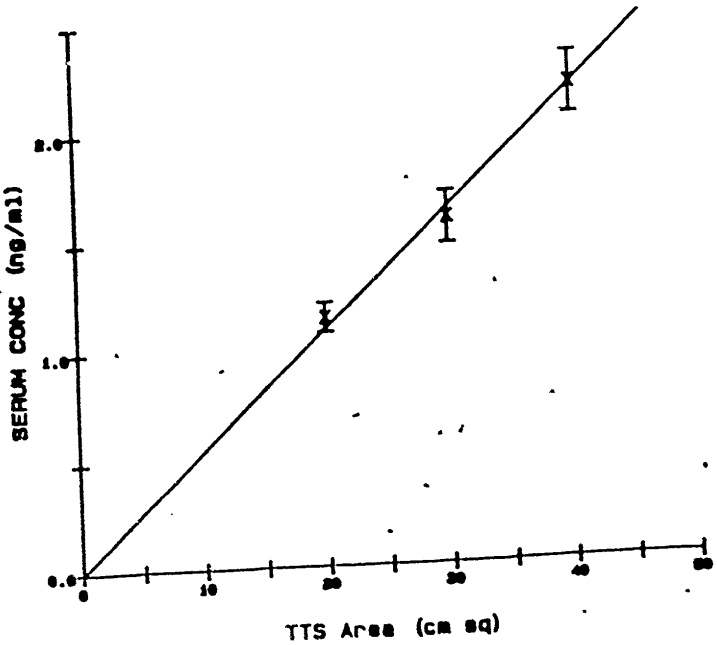
Another aspect of skin physiology is dermal blood flow. It is the sponsor's contention that in the case of this lipophilic drug that baseline dermal blood flow can clear 30-40 times the amount of drug that can penetrate the stratum corneum, and that this functional excess minimizes the effects of such flow on system. It is the opinion of the reviewer that dermal blood flow, skin hydration, and skin temperature are functionally and physiologically inseparable in man and that altered blood flow means altered temperature, and altered hydration of the dermal layers due to sweating. These variables are very probably related to system performance and answers to these questions should be sought as possible explanations of the variability in system performance.



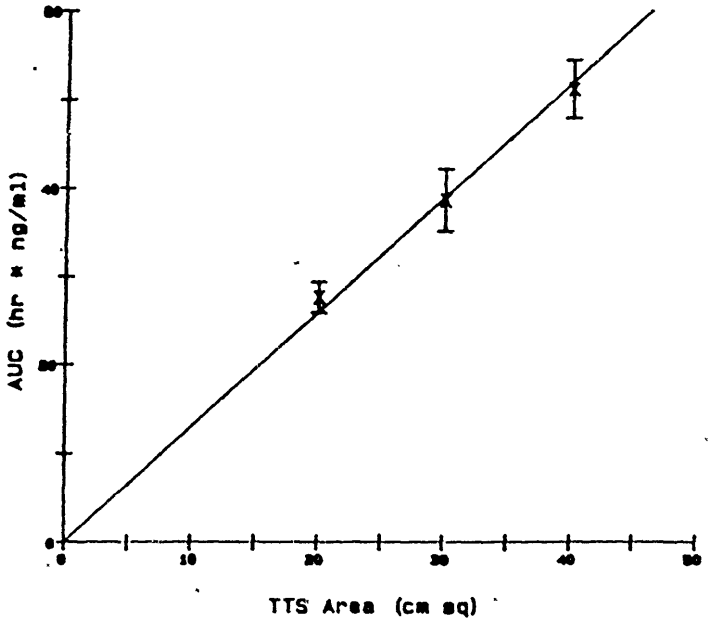
TTS (fentanyl) SINGLE 24 hr APPLICATION
MEAN (SE) DOSE OF DRUG DELIVERED (from RESIDUAL CONTENT)



TTS (fentanyl) SINGLE 24 hr APPLICATION
MEAN (SE) MAXIMAL SERUM DRUG CONCENTRATION



TTS (fentanyl) SINGLE 24 hr APPLICATION
MEAN (SE) AUC for 0-36 hr SERUM DRUG PROFILE



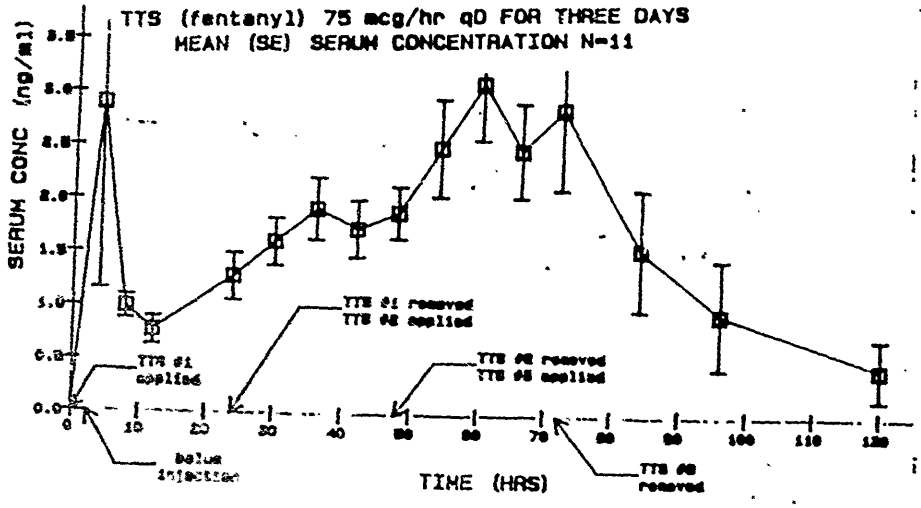
Serum fentanyl concentrations during and after the wearing of a Single TTS (fentanyl)-75 for 72 hours (ng/ml)

Time a (hr)	MEAN	SD	SE	N	Minimum	Maximum
0.0	0.24	0.26	0.10	7	0.05	0.8
2.0	0.38	0.39	0.15	7	0.05	1.1
4.0	0.98	1.14	0.51	5	0.3	3.0
6.0	0.85	0.21	0.15	2	0.7	1.0
12.0	1.10	0.44	0.16	8	0.6	1.8
18.0	1.41	0.71	0.27	7	0.9	2.8
24.0	1.36	0.54	0.19	8	0.9	2.6
32.0	1.25	0.33	0.12	8	0.7	1.7
40.0	1.11	0.38	0.13	8	0.7	1.8
48.0	1.18	0.42	0.15	8	0.7	1.8
56.0	1.03	0.31	0.11	8	0.6	1.5
64.0	1.01	0.59	0.21	8	0.3	2.3
72.0	1.16	1.08	0.38	8	0.5	3.8
76.0	0.91	0.36	0.13	8	0.6	1.6
80.0	0.78	0.36	0.13	8	0.3	1.4
84.0	0.68	0.27	0.10	8	0.3	1.2
88.0	0.56	0.28	0.10	8	0.1	0.9
96.0	0.41	0.24	0.09	8	0.1	0.8
108.0	0.33	0.14	0.06	6	0.2	0.5
120.0	0.19	0.17	0.06	7	0.05	0.5

Summary of Pharmacokinetic Parameters during and After the Wearing of a single TTS (fentanyl)-75 for 72 h

	CMAX (ng/ml)	TMAX (hr)	AUC (hr*ng/ml)	DOSE (mg)
N	8	8	8	7
MEAN	1.84	32.8	109.0	4.54
SD	0.85	22.0	40.9	0.70
SE	0.30	7.8	14.5	0.26
MAX	3.8	72	194.5	5.40
MIN	1.0	12	57.7	3.54

Critical inspection of the material provided shows that the system does not deliver fentanyl at a pseudo-first order rate but that the system has a definite lag, 24 hour Cmax, and a fall-off during hours 24-72 as shown on the enclosed figures. This supposition is confirmed by the data from a few studies where systems were replaced at 24 hour intervals, resulting in a average Cmax for the first system of 1.61 ng/ml at 24 hours, 2.0 ng/ml for the second system at 48 hours, and 3.0 ng/ml for the last system at 72 hours. This is consistent with a single system delivering approximately 50% of its dose in the first day, 30 % in the next, and 20 % in the last. Such a profile gives the peak at 24 hours seen in the appended study of eight patients who wore a single 75µg/hr system for three days, is consistent with the known chemistry of the TTS system, and explains the cumulation seen with daily patch application.



TIME (hr)	MEAN	SD	SE	N
0	0.050			11
4	2.891	5.753	1.735	11
8	0.991	0.362	0.109	11
10	0.900			1
12	0.770	0.416	0.132	10
18	0.800			1
24	1.282	0.735	0.221	11
30	1.609	0.734	0.221	11
36	1.918	0.959	0.289	11
42	1.736	0.870	0.262	11
48	1.891	0.812	0.245	11
54	2.500	1.452	0.459	10
60	3.110	1.695	0.536	10
66	2.480	1.401	0.443	10
72	2.870	2.385	0.754	10
84	1.556	1.696	0.565	9
96	0.963	1.439	0.509	8
120	0.456	0.801	0.283	8

Removal of the system results in an apparent half-life of 17 hours for fentanyl in the clinical studies, consistent with the resorption of the 10-30 μg/cm2 of fentanyl (0.5-1.5 mg) which was loaded into the stratum corneum to produce the concentration gradient. The pharmacokinetic consequences of this are seen in the single-dose curves which show that analgetic blood levels are maintained for 6-12 hours after system removal.

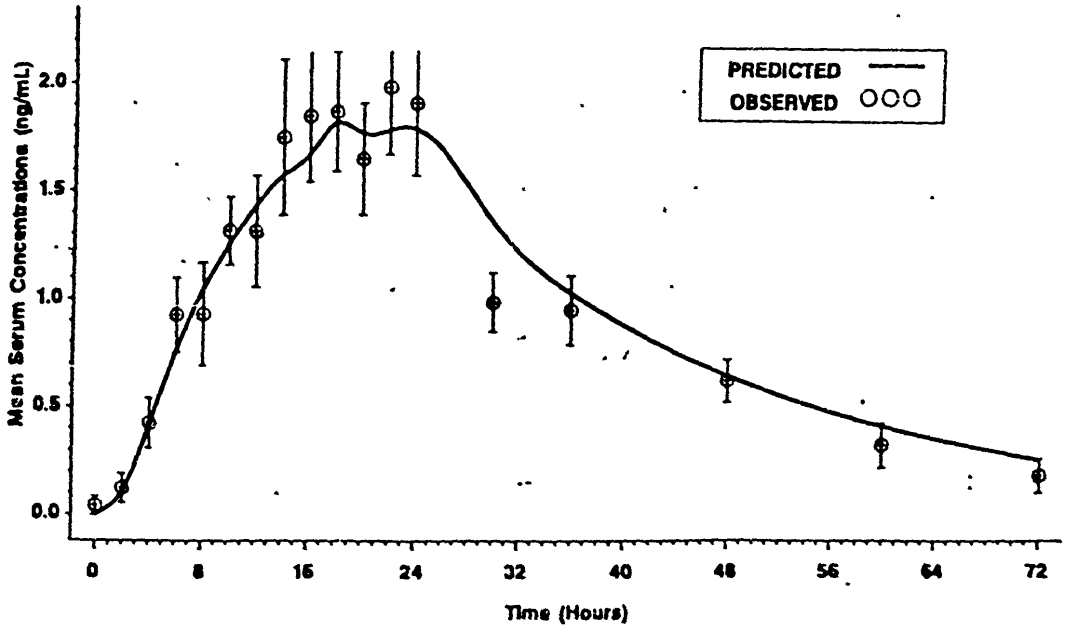
Pharmacokinetics in Hepato-Renal Disorders

The sponsor performed no studies in vulnerable sub-populations, submitting data from the general literature on fentanyl in liver and renal disease, obesity, and the elderly. The studies of hepato-renal disease and obesity showed little effect on Vd, Vss, Cl and t1/2, consistent with the view that fentanyl blood levels from the system are related to fentanyl clearance and not to volume of distribution. The sponsor has provided three mutually contradictory articles on the effects of fentanyl in the elderly, which argue that aging does and does not reduce clearance and that the elderly have altered pharmacodynamic responses to fentanyl.

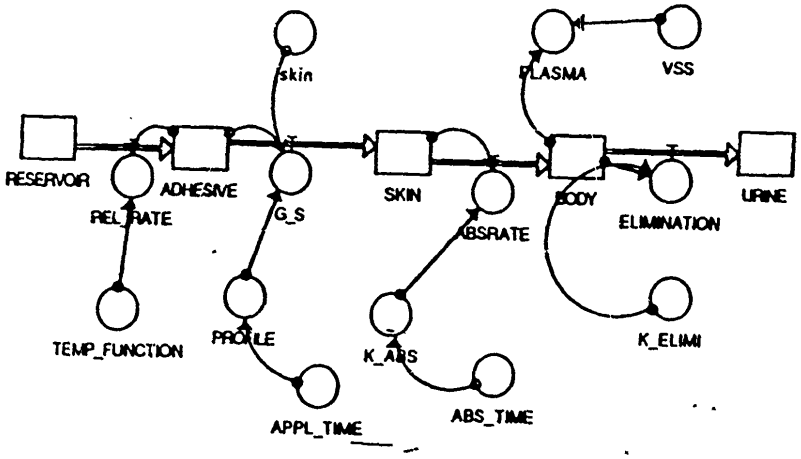
TTS System Modeling

The sponsor has provided two alternative kinetic models for the TTS fentanyl system. The first uses the known in-vitro release rate of the system, makes that assumption of first-order dermal absorption, and adjusts for the establishment of a skin depot by including a lag term in which the adhesive layer and the initial flux set up the skin gradient. This model was set up on SAS 6.03 PROC NLIN and used to derive estimated pharmacokinetic parameters for the system based on the clinical data.

Mean (SE) Predicted and Observed Serum Fentanyl Concentrations Using One Compartment Open Model with Two Absorption Rate constants

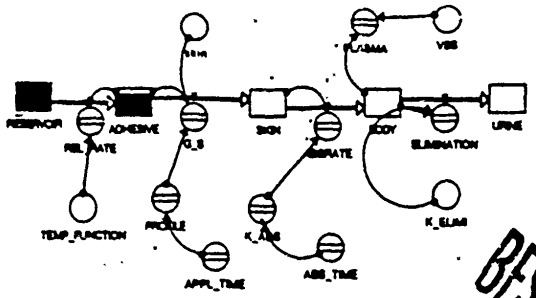


The second model was adapted from a model presented to the company by HFD-007 and modelled on STELLA T' is model provides a graphic model of the compartmental interactions among the reservoir, adhesive, dermal and central compartments and was used to estimate the effects of alterations in adhesive layer, rate controlling membrane, and skin permeability.

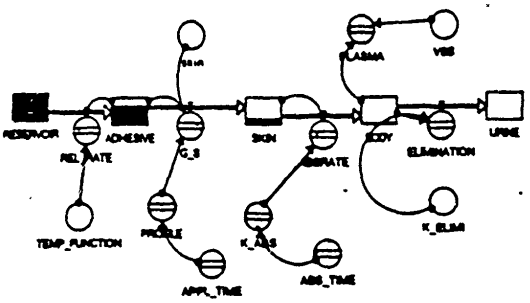


The results of this modeling are included, and show that alterations in the adhesive layer, dermal permeability, the patient's apparent volume of distribution and/or the ethanol flux would be expected to displace the blood concentration profile in time, but not alter the Cmax to any appreciable extent. Alterations in temperature, the permeability of the rate control membrane, and/or the patient's clearance of the drug would be expected to affect both Cmax and Tmax.

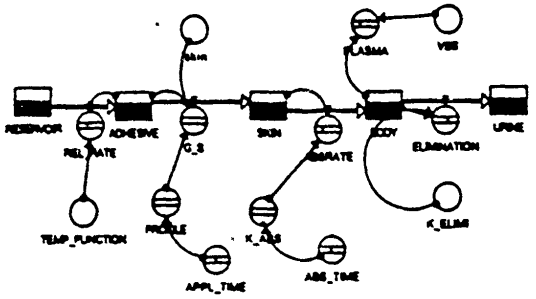
time= 0.1h



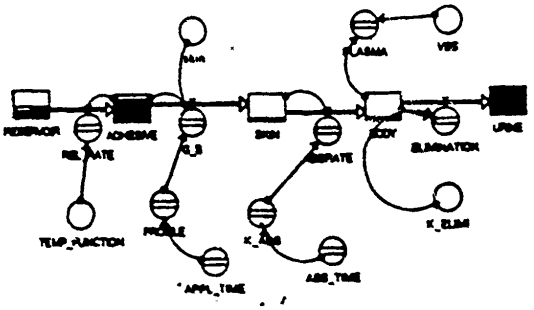
time= 6h

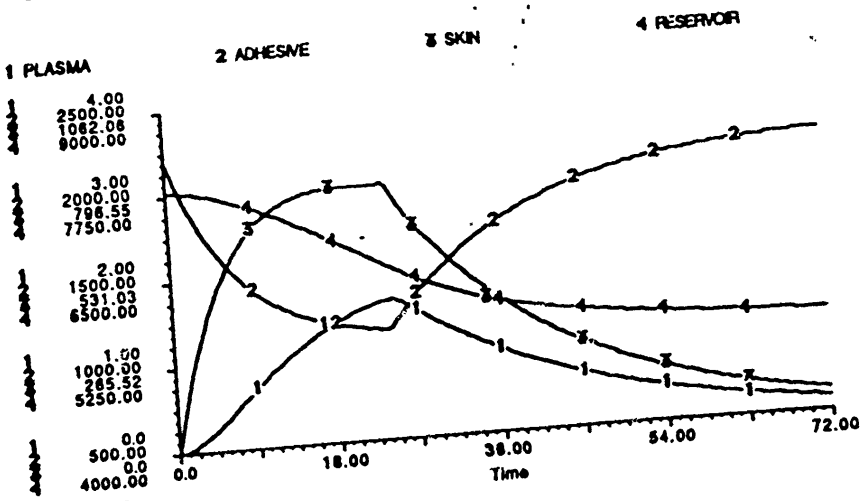


time= 24h



time= 72h





The sponsors did investigate the kinetics of fentanyl in a limited number of patients using a tri-exponential model of IV infusion with the following results:

Subject	Vc Liters	Vss Liters	Cl Liters/hr	MRT Hours
950	35.2	731	74.7	9.7
951	15.5	330	82.4	4.0
952	22.9	268	32.4	8.2
953	10.5	198	44.1	4.4
954	18.4	285	41.8	6.8
955	6.9	377	21.7	17.3
956	8.0	549	42.7	12.8
957	9.1	446	30.5	14.6
Mean	15.8	398	46.3	9.7
SD	10.2	185	22.8	5.1
CV	64%	46%	49%	52%

If this data is generalizable (N=8), and since the blood level at pseudo-steady state will be determined by the relationship between the flux into the body and the clearance of the drug, the observed 50% CV for the clearance of fentanyl suggests that the best that the system could achieve is a target blood level +/- 50%. This corresponds to the following distribution for 100 patients wearing the TTS 75 system,

assuming that the only variability was due to the clearance and the ideal target blood level was 1.5 ng/ml.

Blood Level	Estimated Distribution (n=8)	Observed Distribution (n>450)
0-0.49	8 %	6 %
0.5-0.99	14 %	26 %
1.0-1.49	22 %	36 %
1.5-1.99	23 %	12 %
2.0-2.49	19 %	10 %
2.5-2.99	9 %	6 %
> 3.0	5 %	4 %

The observed variability in clearance is 50%, the inter-lot variability in in-vitro delivery is 15%, and there is a theoretical variability (not experimentally determined in vivo) in delivery of 50% with a 5 degree centigrade alteration in skin temperature. Given this data the observed variability in blood level in the clinical trials is most likely due to individual differences in clearance, with lesser effects from differences in skin temperature and inter & intra-lot differences in the permeability of the membrane-adhesive layer.

Pharmacodynamics

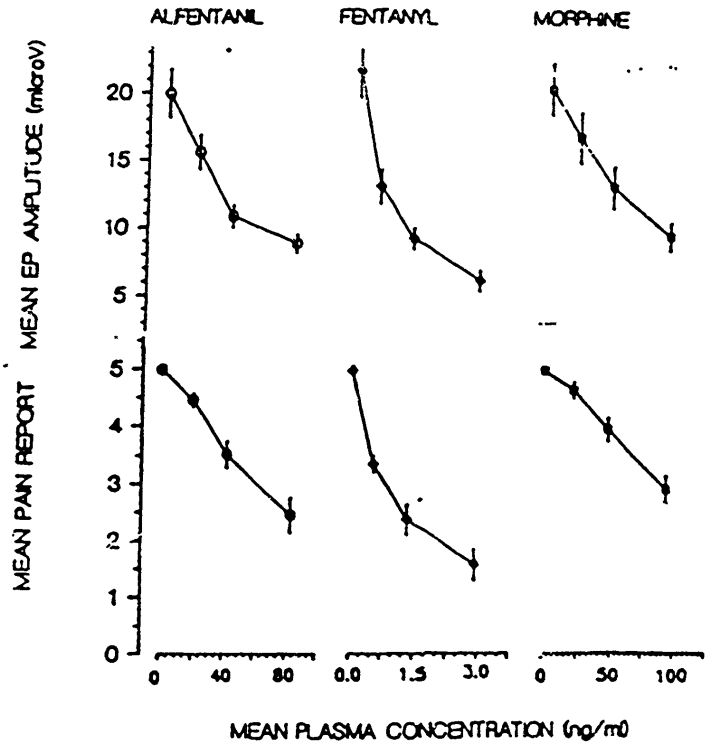
The sponsor has collected a number of papers from the literature which discuss various aspects of fentanyl pharmacodynamics which will be summarized. The initial papers discuss the cardiovascular effects of fentanyl which are known to be minimal (other than the occurrence of postural syncope in opioid-naive volunteers who ambulate after receiving any opioid). The respiratory effects are discussed at length, with the following summary of IV fentanyl data:

Author	Measure	Blood Level	Response
Hill 1989	**CO2 response**	**0.75-3.0**	**equivalent to morphine in equianalgesic dose**
Fung & Eisele	**CO2 response**	**4.6 ng/ml**	**50% reduction in CO2 response**
Cartwright 1983	**CO2 response**	**2.0 ng/ml**	**50% reduction in CO2 response**
Andrews 1982	**CO2 response**	**3.1 ng/ml**	**50% reduction in CO2 response**

The data presented makes a strong case that a fentanyl blood level of 2-4 ng/ml will cause a 50% reduction in CO2 sensitivity in normal volunteers, and is likely to produce clinically significant respiratory depression in post-operative patients.

Relative Potency, Time of onset, Analgesic Strength

The relative analgesic potency of IV bolus fentanyl has been estimated at 50-100 times that of morphine, based on a number of studies of the drug in animals and man. The sponsor has provided data from Hill et al. (1989) which shows the ablation of dental pulp pain by both morphine and fentanyl track in parallel curves with a relative potency of 1/50. While the dental pulp stimulation model is not a good model for the pain of inflammation, the data presented argues that blood fentanyl levels of 0.75-3.0 span the safe analgetic range in healthy volunteers in direct experiments.



This equivalency was also examined in the clinical trials of the drug. The design of the majority of the TTS fentanyl trials was to determine the morphine sparing produced by the system when contrasted with a placebo-wearing control group. The hypothesis of these trials was that the TTS group and the Placebo group would titrate themselves to equivalent pain relief and the "morphine-sparing" would provide the analgesic equivalents directly. This did not occur since the placebo group had substantially less pain relief that the TTS fentanyl group in nearly every study as may be seen by the enclosed charts of pain intensity ratings. Since direct comparison of morphine use in two parallel groups which had different levels of analgesia would seriously underestimate the potency of the TTS system, it became necessary to adjust the raw data to provide a useful estimate of relative potency.

This was done by three different methods in an attempt to find a robust and unbiased way of adjusting the data. All use the placebo group scores by estimating the group mean morphine demand for the placebo group, fitting a linear relationship for the placebo group of the form:

PAIN SCORE = K*MORPHINE USE + C

and then adjusting the morphine use data of the placebo group so as to determine what their morphine use would have to have been to give them the same degree of analgesia as the parallel group who received both morphine and TTS. This fit was done for the cumulative data (application to removal), the interval data (6 hour intervals), and the period from 12 hours to 24 hours. Both the six hour interval data and the 0-24 hour cumulative data gave similar results, while the 12-24 hour interval data resulted in a somewhat greater estimated morphine sparing across the trials. Using this technique the mean adjusted morphine sparing was 1.6 mg morphine per hour corresponding to a 24 hour morphine dose of 39 mg (range 30-50 mg/24 hr). This data gives a relative potency of 1.8 mg fentanyl/24 hours = 39 mg morphine /24 hours = 20:1. This is consistent with the lower limit for studies of IV fentanyl, but may not be directly comparable since it includes the effects of a large intra-operative fentanyl bolus, data from the period (0-8 hr) in which the system had not built up adequate fentanyl levels, and the confounding effects of residual anesthetics. It does reflect the "as-used" potency of the TTS system and is the best current estimate of the analgesic strength of the system.

Comparison of TTS (fentanyl) to Morphine at Doses Estimated to Produce Equivalent Pain Intensity Scores Adjustment Based on Interpolated Cumulative Data Analysis Post Surgery to TTS Removal

Investigator	TTS Dose (mcg/hr)	Morphine (mg) Actual	Adjusted[4]	Between Group Difference	Rate/ Hour[5]
Nimmo	100	33.53			
	Placebo	49.67	66.43	32.9	1.6
Hotchkiss	100	9.46			
	Placebo	28.35	44.26	34.3	2.0
Caplan	75	17.10			
	Placebo	32.49	44.07	27.0	1.3
McLeskey	50	9.53			
	Placebo	25.59	38.75	29.2	1.6

Comparison of TTS (fentanyl) to Morphine at Doses Estimated
to Produce Equivalent Pain Intensity Scores
Adjustment Based on Cumulative Data Analyzed by Six-Hour Intervals
Post Surgery to TTS Removal

Investigator	TTS Dose (mcg/hr)	Morphine (mg) Actual	Adjusted[a]	Between Group Difference	Rate/ Hour[b]
Nimmo	100	32.74			
	Placebo	48.58	62.41	29.7	1.5
Hotchkiss	100	7.85			
	Placebo	25.90	41.09	33.2	1.9
Caplan	75	15.70			
	Placebo	30.28	45.03	29.3	1.4
McLeskey	50	7.12			
	Placebo	23.38	32.83	25.7	1.4

Comparison of TTS (fentanyl) to Morphine at Doses Estimated
to Produce Equivalent Pain Intensity Scores
Adjustment Based on the 12-24 Hour Interval
Post TTS Application

Investigator	TTS Dose (mcg/hr)	Morphine (mg) Actual[a]	Adjusted[b]	Between Group Difference	Rate/ Hour[c]
Nimmo	100	10.00			
	Placebo	19.50	26.00	16.00	1.3
Hotchkiss	100	0.00			
	Placebo	14.00	25.20	25.20	2.1
Caplan	75	5.00			
	Placebo	12.50	19.12	14.12	1.2
McLeskey	50	0.00			
	Placebo	15.00	26.47	26.47	2.2

The sponsor's submission discussed the onset of analgesia following the application of the system in terms of time (3-7 hours) to reach a known MEC of 0.6-0.75 ng/ml using a combination of intra-operative fentanyl bolus and concurrent system application. While this is adequate to describe the conjoint use, most of the trials did not allow the estimation of onset of analgesia in the absence of such bolus. Data from trials in

which a bolus was not given (Stanski & Plezia) shows that a MEC of 0.6 ng/ml is reached at 5-8 hours after application of a TTS 75 & 100.

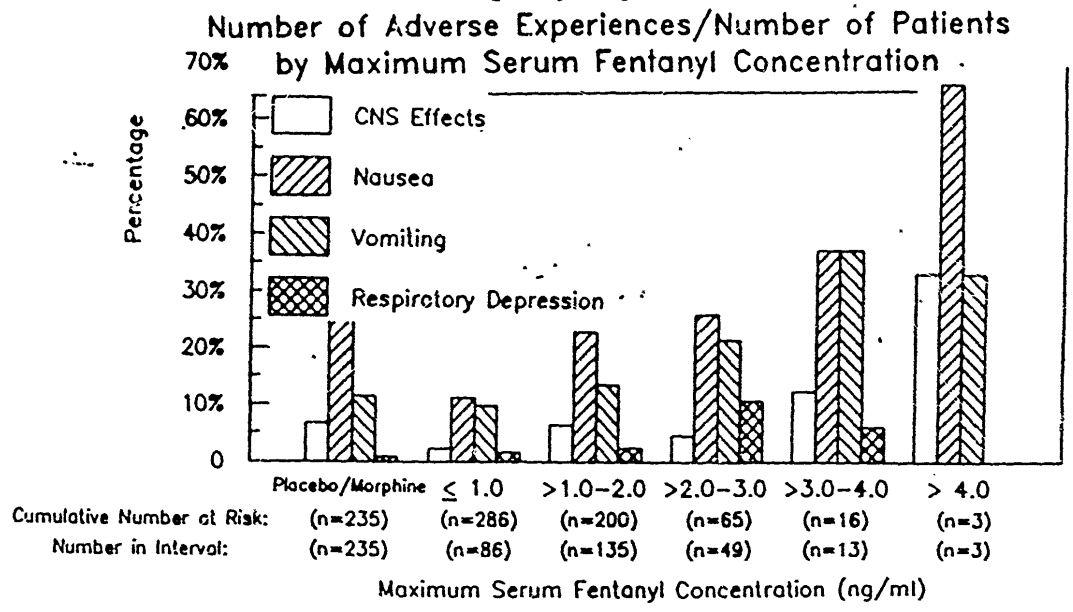
Hysteresis, Tolerance, and Blood Fentanyl Level

The sponsor was asked to select patients who did not require additional morphine and to attempt to plot the time course of pain scores against time. This was not a true hysteresis study since each such patient had received an initial bolus of fentanyl at the time of surgery which would obscure any early rapid (< 1-2 hours) alterations in response. As this was the only data available on acute tolerance effects, the loops were calculated and prepared. **(Since pain scores are inversely related to fentanyl blood levels, the normal sense of hysteresis curves are reversed.)** Of the 29 subjects the majority (18/24) had clockwise hysteresis loops, suggesting the the effect-site concentration lags the blood level and that significant acute tolerance does not occur. While not definitive, the hysteresis plots suggest that at least up until 24 hours there is no shift in analgesic effects due to constant exposure to the drug at levels of 0-3 ng/ml, and no probable shift in the pharmacodynamic effect curve.

Pharmacodynamics of Adverse Effects

The sponsor discusses the 18 episodes of respiratory depression which occurred in the clinical trials and correctly reason that the frequency of these events rise from less than 3% at blood levels under 2 ng/ml to 7/65 or 11% for patients with blood levels over 2 ng/ml. TTS fentanyl induced respiratory depression (see safety summary) becomes unacceptably frequent at blood levels over 2 ng/ml and is most likely to occur in individuals who are subject to respiratory compromise for another reason (thoracotomy, concurrent medical illness, poor ASA status, etc.) For these reasons the adverse effect level for respiratory depression should be set at 2 ng/ml for susceptible individuals.

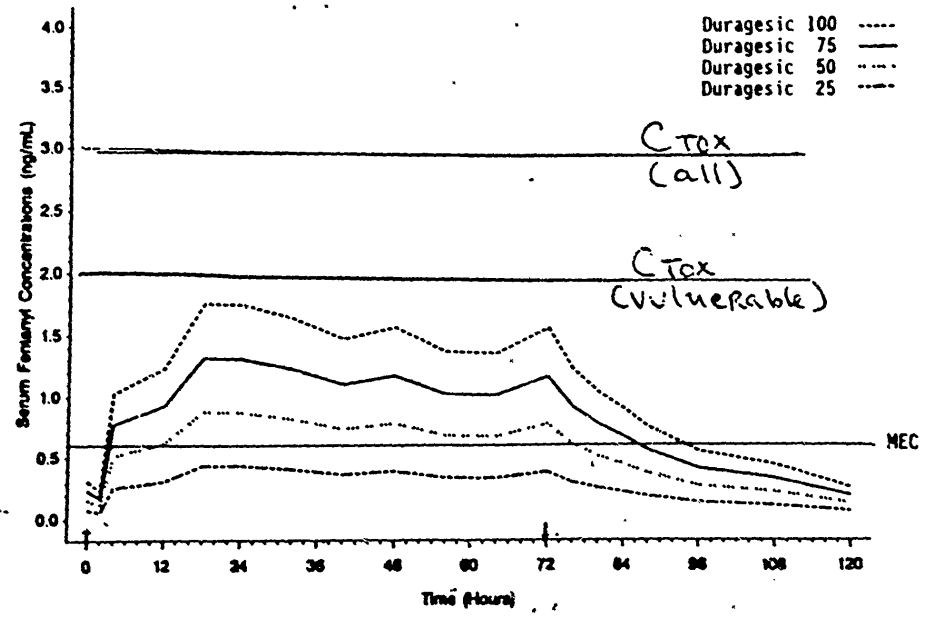
The sponsor was also asked to do a pharmacodynamic analysis of nausea, vomiting, and adverse CNS effects. These results are presented, and show that vomiting begins to emerge at blood levels above 2 ng/ml, and all such effects are unacceptably frequent at levels above 3 ng/ml.



The reviewer concluded that the absolute adverse effect level for fentanyl for postoperative analgesia in opioid-naive patients was 3.0 ng/ml, and the adverse effect level for susceptible individuals was 2.0 ng./ml. The cumulative percentage profiles for the Cmax observed for each system size in the clinical trials are appended and show that for each system the following pharmacokinetic performance is expected:

System Size	% *0.00-0.60* *(Ineffective)*	% 0.6-1.99 (Target Level)	% 2.0-2.99 (Toxic to some)	% above 3.0 (Toxic to all)
TTS 25	*50% (EST)*	50% (EST)	0%	0%
TTS 50	*15 %*	83%	2%	0%
TTS 75	*7%*	78%	12%	3%
TTS 100	*1%*	58%	30%	11%

Mean Serum Fentanyl Concentrations After Duragesic Application

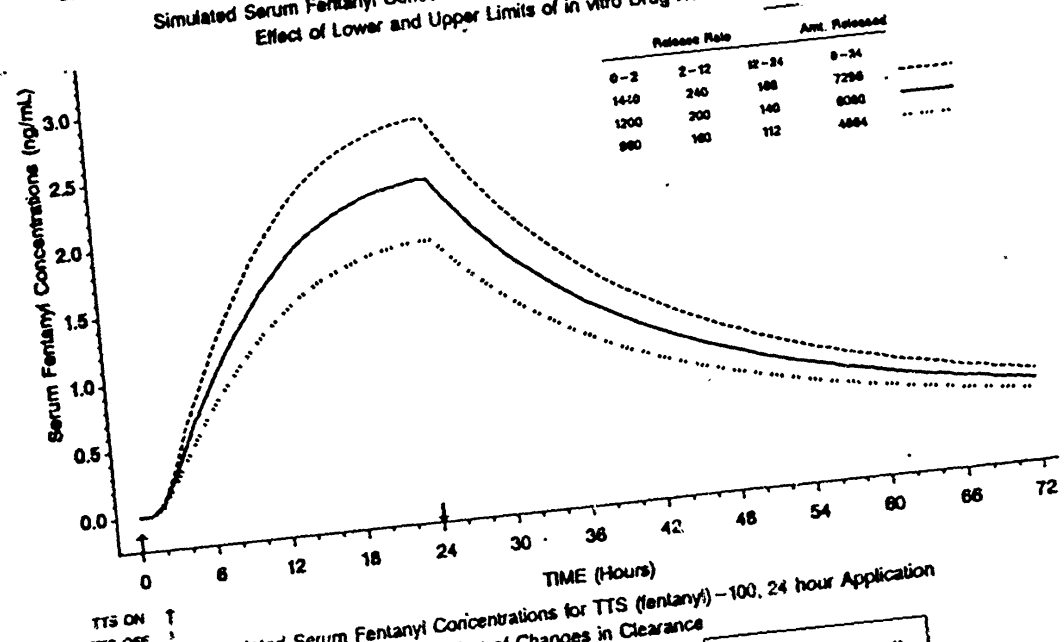


Reviewer's Conclusions

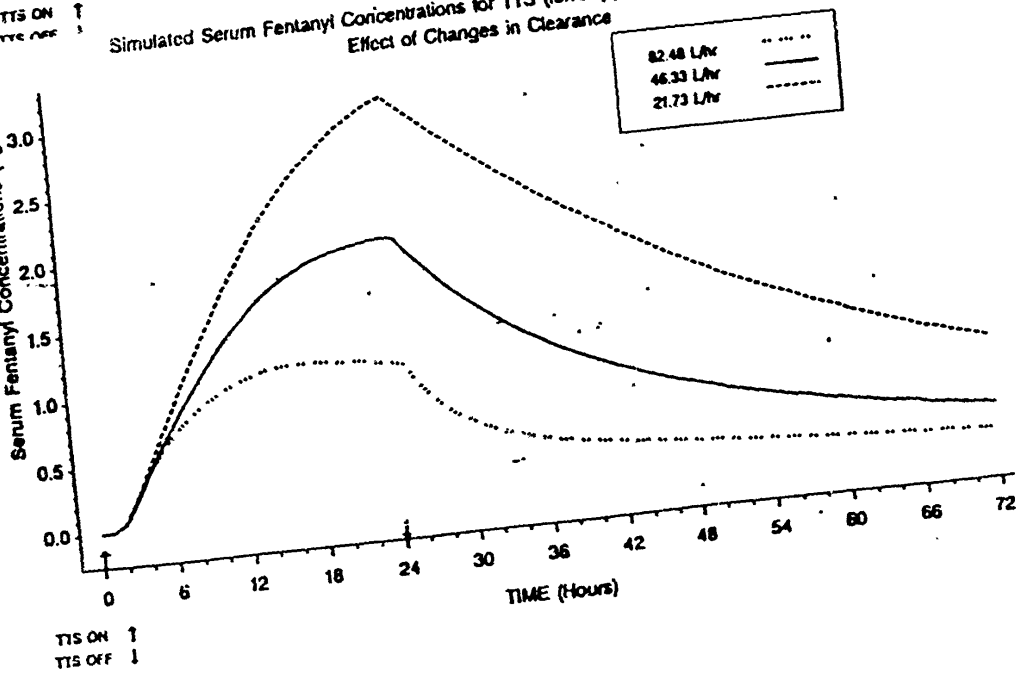
This amendment provides a more rational explanation of the pharmacokinetic performance of the TTS fentanyl system than the

original NDA, and explains about half of the variability in the pharmacokinetic performance of the system seen in the clinical trials. The following STELLA simulations show how the expected manufacturing variability in the TTS system are less critical than the wide range in clearance seen in the population. They also show that while weight is a good estimator of Vd, it is not a particularly good estimator of Cl for this drug. Unlike conventional PRN dosing where the major determinant of the acheived blood level is the apparent volume of distribution (Vd) and the rate of absorption/dissolution, this product is insensitive to these factors , but very sensitive to clearance.

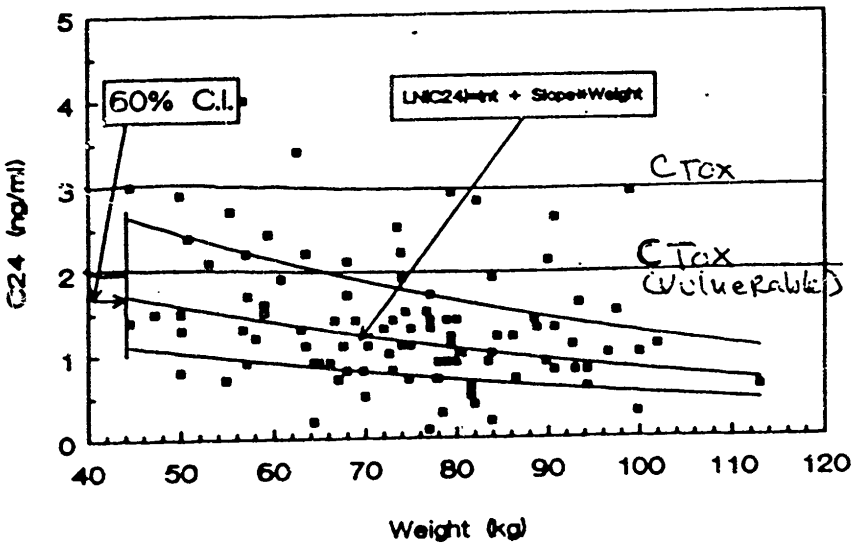
Simulated Serum Fentanyl Concentrations for TTS (fentanyl) – 100, 24 hour Application
Effect of Lower and Upper Limits of in vitro Drug Release Rate



Simulated Serum Fentanyl Concentrations for TTS (fentanyl) – 100, 24 hour Application
Effect of Changes in Clearance



Serum Drug Level vs Body Weight for TTS fentanyl-75



In conclusion, this amendment describes:

1.How variations in skin permeability, ethanol flux, thickness of the adhesive layer, and the Vd of the patient may be expected to significantly alter the lag time between application and the achievement of analgetic blood levels, but not Cmax.

2. How variations in skin temperature, function of the rate control membrane, and individual clearance of fentanyl will alter both the timing of peak effect and Cmax.

3. How the TTS system proportions the delivery of fentanyl over 72 hours (imprecisely), and why repeated applications of new TTS systems at 24 hour intervals results in an increase in Cmax over application of a single system for the same period.

4. That the manufacturing controls (as established by in-vitro testing) are adequate to control the product to within an in-vitro CV of 20%.

5. That the major determinant of the performance of the TTS system is individual variability in clearance of fentanyl.

6. That the probable role of variations of truncal skin temperature with fever, hypovolemia, and surgical chilling is likely to be significant, but its magnitude is unknown.

7. That the Ctox for the general patient population is likely to be 3.0 ng/ml and the Ctox for (opioid-naive) vulnerable patients is 2.0 ng/ml.

8. That the MEC for fentanyl in opioid-naive patients is approximately 0.6 ng/ml.

9. That the proposed 75 & 100 μg/hr TTS fentanyl system sizes are capable of delivering toxic doses of fentanyl to a significant fraction of the clinical populaiton and that labeling must provide sufficient information to allow physicians to prevent, identify, and manage such cases.

It is the opinion of the reviewer, based on the performance of the systems in the clinical trials, that the TTS 50 is the largest size system which can be applied without exceeding the toxic level for a significant fraction of vulnerable patients. If the sponsor can clarify how to select the system size safely for post-operative pain, based on skin temperature (fever), estimated clearance, lean body mass, body weight, surgical or anesthetic risk factors, or other means the 75 μg/hr system may be approvable for this indication.

Medical Officer Review
NDA #: 19,813
Alza Corporation

TTS Fentanyl

(Transdermal Therapeutic System)

Volume 3 - Metanalysis and Cross-Study Comparisons

Curtis Wright MD,MPH

WRITTEN CWIV - 7/14/90
PEER REVIEWED JGH -7/16/90
SPONSOR'S COMMENTS MS - 7/15/90
Revised CWIV 7/16/90

General Comments Regarding the Analysis

The Problem

Five of the studies submitted with the NDA (Stanski, Hotchkiss, McLeskey, Plezia and Caplan) had nearly identical design, and were intended to be directly compared and contrasted in the course of the analysis. Several studies (Nimmo, Muller, Latasch) were similar, but used different routes of administration (PCA) or different rescue medications (meperidine) and may not be directly compared with the others. All of the five pivotal studies followed a common design:

1. Patients were selected and randomized.
2. A TTS system or placebo system was applied.
3. TTS dose (system size, fentanyl flux) was not varied by weight.
4. Anesthesia was induced and a bolus dose of fentanyl was given.
5. Periodic assessments of Pain Intensity (VAS) were performed for 36 hr.
6. Periodic serum fentanyl levels were drawn for 36 hr.
7. Morphine was given to both groups prn for 36 hr.
8. The TTS and placebo systems were removed at 24 hours.
9. Cumulative morphine use for each treatment group was then analyzed

Using this technique the investigators found that in all cases the TTS wearers used less PRN morphine than the placebo group and had lower mean VAS pain scores. When the results obtained for each TTS size in each trial were then compared, the following results were obtained:

One Factor ANOVA X1: TTS SYSTEM SIZE Y1: Morphine Used

Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	3	3112.07	1037.359	28.113
Within groups	581	21438.966	36.9	p = .0001
Total	584	24551.042		

Group:	NO. OF PATIENTS	MEAN MS USE	Std. Dev.:	Std. Error:
PLACEBO	99	8.193	6.866	.398
TTS 50µg/hr	26	2.09	3.739	.423
TTS 75µg/hr	33	4.192	4.674	.47
TTS 100µg/hr	37	4.766	6.229	.591

As may be seen, the placebo patients required 8 mg MS /q6hr, the TTS 50 2mg, the TTS 75 4 mg, and the TTS 100 4.7 mg. This lack of correspondence between TTS size and analgesic effectiveness was unexpected, but is clearly shown in the data.

One possible reason for the inconsistencies across the trials is the difference between the pain models used in testing each system size. As may be seen from the following table, two doses of TTS were never tested against each other in any single trial. Thus, the analyst is left to compare the degree of morphine sparing of the TTS 50 in gynecologic surgery (Mcleskey) with a similar test of TTS 100 in a predominantly male thoracotomy trial (Hotchkiss). The analytical problem is that the design is incomplete, which tends to confound dose size, trial conditions, gender, and pain model. As the placebo group is present in all the trials it may be used to attempt to overcome this difficulty.

Number of Patients for Each TTS size by Trial

Clinical Trial Name

TTS size	MCLE	CAPL	PLEZ	HOTC	STAN	Totals:
PLACEBO	24	19	18	21	17	99
TTS 50µg/hr	26	0	0	0	0	26
TTS 75µg/hr	0	20	13	0	0	33
TTS 100µg/hr	0	0	0	18	19	37
Totals:	50	39	31	39	36	195

One Solution for Cross-Study Metanalysis

Since the outcome variable is continuous (mg of morphine sulfate used per 6 hour period), and since each trial had a placebo group, then it is possible to look for trial and pain model effects across the placebo groups, and to attempt to adjust the values for the TTS groups and make use of the values so developed. The actual mechanics of this analysis were developed jointly by the sponsor, this reviewer, and Richard Stein (HFD-007 Biometrics). Highlights of the analysis follow, and computer diskettes containing the actual spreadsheets (5 1/4=MSDOS, 3 1/2 = MAC) are attached to the inner cover of this review.

(DATA SET #1- "EFFICACY" ON THE DISKETTE)

The data set was provided by the sponsor, and consisted of the raw data on 195 patients (96 TTS & 99 controls) from the five named trials divided by six hour time periods from TTS application. Since it was known prior to the analysis that it takes about 6-8 hours after system application for the average patient to reach analgesic serum levels, and the TTS systems were removed at 24 hours, the 6-24 hour interval was selected for analysis. While it would be more kinetically appropriate to select the 12-24 hour interval for analysis as more nearly reflecting the steady state, the sponsor is interested in the 6-12 hour interval for labeling claims and it was included in the analysis for that reason.

The 6-24 hour interval was divided up into three intervals, and the times of 9,15 & 21 hours were taken as the midpoints of those six hour segments . Each patient in this initial data set has <u>three values</u>, one at 9,15, & 21 hours. In all cases where a serum fentanyl level was not drawn at the midpoint of an interval the appropriate value was interpolated from the two adjacent known values. Each line of the spreadsheet consists of one of 3 observations for each subject, with the following variables.

Subject	Age	Gender	Height(cm)	Weight(kg)
Investigator	TTS size	Treatment	Surgery Type	
Time	MS=mg/q6hr	Pain=VAS	Serum Fentanyl=ng/ml	

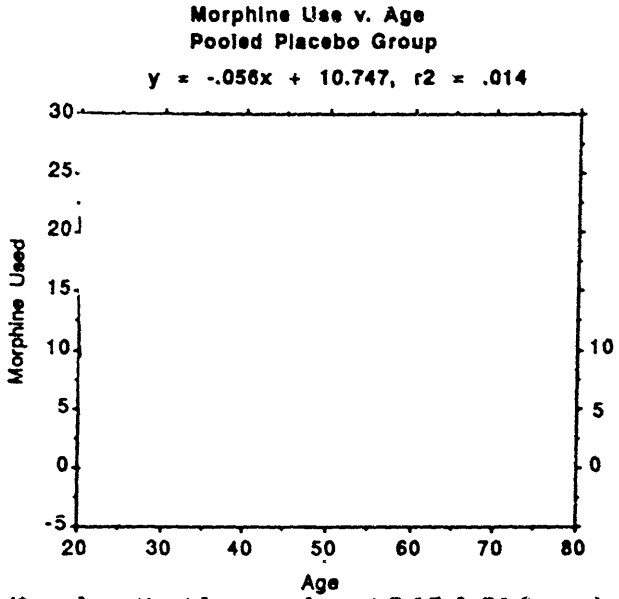
(in all tables in this section the count is the actual number of patients, but the degrees of freedom may reflect the number of observations)

AGE

As a first step each patient variable was regressed against morphine use to identify possible adjustments to be made. Of the variables Age, Gender, Height, Weight, Investigator, Surgery Type, and Time, the variables AGE, TIME, SURGERY TYPE, & INVESTIGATOR were significant by univariate analysis. An adjustment strategy of

partial regression (as opposed to fitting all adjustments "en-bloc") going from the most independent variables (presumably least confounded) toward the more highly confounded ones was then selected.

Using this strategy the first adjustment was performed using the placebo group and regressing age against MS usage:



(* each patient has a value at 9,15 & 21 hours)

As may be seen, there is a small age effect in the trials, which accounts for less than 1-2% of the variance, and corresponds to a hypothetical 7.5 mg/q6hr morphine demand for a 20 year old declining to a 5 mg/q6hr morphine demand for an eighty year-old. This finding is consistent with altered pharmacodynamics for opioids with aging, the magnitude of the adjustment is small.

The values for morphine use for the entire data-set were thus adjusted to the grand-mean for age, subtracting 0.056 mg/q6hr for every year below the mean age of 46 and adding 0.056 mg/q6hr for every year above age 46 for every data-point. This adjustment was then rechecked against the original variable and the adjustment was found to have collapsed the age effect as intended.

Checking the effect of the adjustment on the data, the effects are barely perceptible.

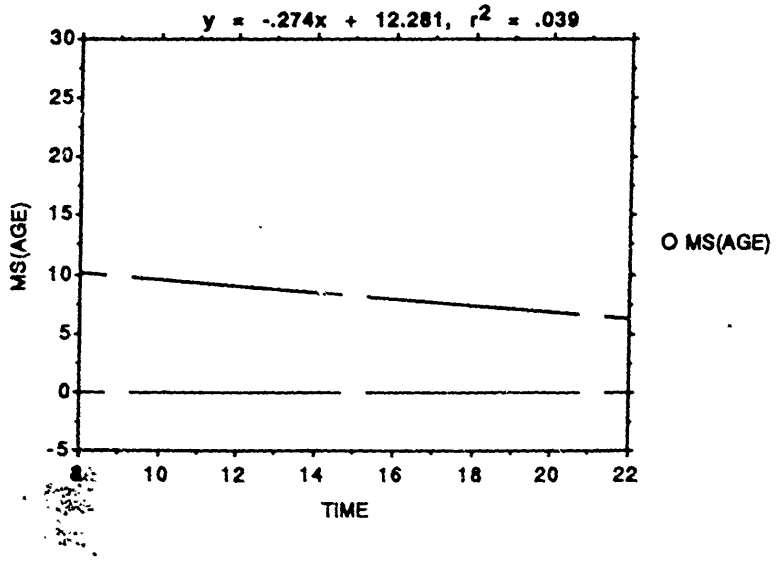
Results of Age Adjustment

One Factor ANOVA X1: TTS SYSTEM Y1: MS(AGE)

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
PLACEBO	99	8.167	6.818	.396
TTS 50µg/hr	26	1.939	3.722	.421
TTS 75µg/hr	33	3.91	4.605	.463
TTS 100µg/hr	37	5.164	6.159	.585

TIME

The next adjustment applied to this data is for time, since it was reasonable to assume that there was likely to be either a circadian or a trend effect resulting in a change in morphine use over time (as these were all elective cases in academic centers the surgeries all started in the mornings and time effects are nearly synchronous). Regressing time against morphine use:



This finding suggests that morphine requirements are maximal in the first interval, falling from a mean of 10 mg/q6h at six hours to a projected mean of 7.0 mg/q6hr at 24 hours. This trend is reasonable in both magnitude and direction and may be adjusted for by subtracting 0.274 mg for every hour before 15 hours and adding 0.274 for every hour after 15 hours in the data set. The adjustment was then checked by re-checking against the initial variable (time) as before.

GENDER

Despite a perception that there might be a gender effect, no difference was seen between the sexes in the pooled placebo group.

Relationship of Gender to Morphine Use
Pooled Placebo Group Adjusted for (Age & Time)

One Factor ANOVA X1: GENDER Y1: MS(AGE,TIME)

Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	1	.639	.639	.014
Within groups	98	13223.586	44.826	p = .9051
Total	99	13224.226		

Group:	Count:	Mean MS USE:	Std. Dev.:	Std. Error:
F	44	8.115	5.186	.451
M	55	8.208	7.691	.599

SURGERY

The next adjustment is for surgical type. The following table shows how this is problematic, since there is a highly non-uniform distribution of surgery types among investigators:

Surgery Type by Investigator

Observed Frequency Table

	GYN	ORTHO	ABD-II	CHEST	H & N	ABD-I	Totals:
MCLE	50	0	0	0	0	0	50
CAPL	0	39	0	0	0	0	39
PLEZ	4	25	2	0	0	0	31
HOTC	1	0	8	24	6	0	39
STAN	0	15	14	6	0	1	36
Totals:	55	79	24	30	6	1	195

In view of the observed non-random distribution of surgical type by trial there is built in confounding between investigator-specific effects and pain-model effects in this analysis. Since the adjustments are made sequentially it may be that some of the observed pain-model (surgical type) effects are actually trial effects, but as both effects will be adjusted out the net effect is the same no matter what the order of regression. The observed effects were:

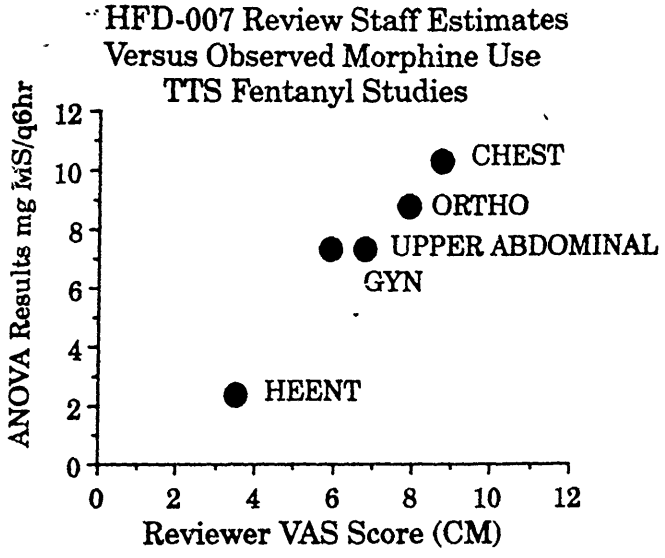
Adjusted Morphine Usage by Surgery Type

One Factor ANOVA X1: SURGERY TYPE Y1: MS(AGE,TIME)
Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	4	721.993	180.498	4.216
Within groups	292	12502.233	42.816	p = .0025
Total	296	13224.226		

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
GYN	27	7.359	4.835	.537
ORTHO	38	8.847	7.612	.713
ABD-II	15	7.361	6.593	.983
CHEST	15	10.234	6.463	.963
H & N	4	2.431	5.513	1.591

The observed effect of surgical model on postoperative morphine use is the strongest effect seen so far, with a rank order of EENT< GYN< ABDOMINAL< ORTHO< CHEST. In order to get an independent evaluation of this rank order, the analgesic reviewers in HFD-007 were asked to complete a visual analog scale rating of their estimates of the relative analgesic requirements of these surgeries which is shown below plotted against the results of the regression.



As there was good agreement between raters and data the ranking and magnitude of the adjustment was accepted and it was deemed reasonable to adjust the morphine use based on the observed differences between the means for different types of surgery. Each TTS value was then adjusted by the difference between the average values for each surgery and the overall mean for the placebo group of 8.167. The magnitude of the adjustment was less than 1 mg/q6hr for all but CHEST (-1.9) and HEENT (5.6).

This adjustment had a considerable effect on the relative TTS performance as shown, and clearly shows how the TTS 50 values were all drawn from gyn surgeries:

Results of Adjustment for Age, Time, and Surgery Type

One Factor ANOVA X1: TTS SYSTEM Y1: MS(AGE,TIME,SURGERY)

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
PLACEBO	99	8.167	6.499	.377
TTS 50µg/hr	26	2.747	3.834	.434
TTS 75µg/hr	33	3.275	4.38	.44
TTS 100µg/hr	37	4.632	6.774	.643

INVESTIGATOR

The next (and final) adjustment was to take the values which had been adjusted for type of surgery and examine them for investigator effect (conditions of trial). This was done by finding the mean adjusted morphine use for each investigator (MS(Age,Time,Surg) as follows:

One Factor ANOVA X_1: INVESTIGATOR Y_1: MS(AGE,TIME,SURGERY)

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
MCLE	72	7.821	4.634	.546
CAPL	57	7.248	5.765	.764
PLEZ	54	7.958	8.105	1.103
HOTC	63	8.333	6.151	.775
STAN	51	9.699	7.884	1.104

This analysis showed that there was a small site effect as seen in the mean use of morphine for each investigator's patients as seen above (min=CAPL=7.2, max=STAN=9.6). The differences between each site's placebo mean and the placebo group mean of 8.167 were subtracted from the scores for each site's fentanyl and placebo group to achieve a data set which was adjusted for patient age, time after surgery, type of surgery, and conditions of the trial, based on the observed relationships in the placebo groups. Further univariate regressions showed that there were no further useful adjustments to be done and the values obtained in this step were used in all later analyses.

OUTCOME OF ADJUSTMENT

The direction and magnitude of the adjustment were then re-examined for reasonableness as follows :

The raw data was first adjusted for age, using the observed relationship in the placebo group that a 70 year-old patient would require 1/3 less morphine than a 20 year-old patient; an adjustment that is reasonable in direction and magnitude.

The raw data was then adjusted using the observation that the morphine requirement of the "mean" placebo patient would fall by 1/3 between the first six hours postoperatively and the beginning of the second postoperative day.

The third adjustment was that the morphine requirements after different surgeries would be expected to be different, with cholecystectomy, thoracotomy and major joint procedures taking 8-11 mg morphine /

q6hr, and lower abdominal, gyn, and head & neck procedures taking 3-7 mg morphine / q6hr.

The final adjustment was that the conditions of the trials differed, such that McLeskey, Caplan & Plezia's patients used an average of 7.3-7.7 mg/q6hr, while Hotchkiss & Stanski's patients used 8.2-9.6 mg/q6h.

ADJUSTED TTS EFFECTS

The most important result was that there was a clear distinction between TTS fentanyl and placebo for the adjusted data:

One Factor ANOVA X1: TREATMENT Y1: MS(AGE,TIME,SURGERY,INVESTIGA...

Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	1	3003.876	3003.876	87.222
Within groups	194	20078.178	34.439	p = .0001
Total	195	23082.053		

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
Placebo	99	8.165	6.452	.374
All TTS Systems	96	3.633	5.199	.306

The mean amount of morphine used by the placebo group from 6-24 hours was 8.1 mg/q6hr, while the mean amount used by the TTS fentanyl group was 3.6 mg/q6hr, corresponding to a morphine sparing (for a mixture of all three TTS sizes) of 4.50 mg/q6hr (18 mg/24 hours).

Examined by TTS system size:

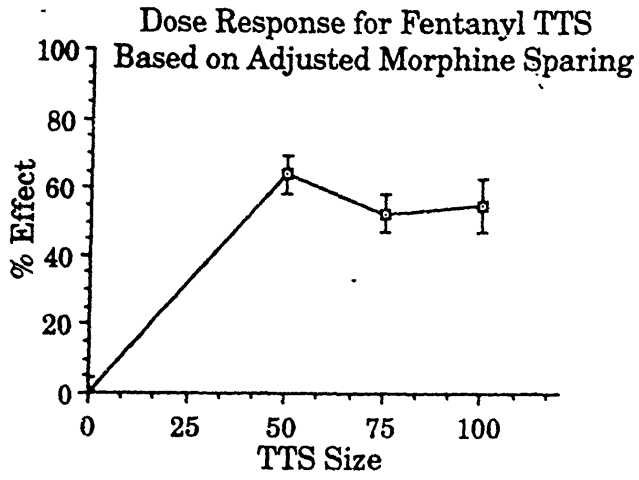
Final ANOVA of TTS System Size versus Adjusted Morphine Use

One Factor ANOVA X1: TTS SYSTEM Y1: MS(AGE,TIME,SURGERY,INVESTIG...

Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	3	3036.906	1012.302	29.341
Within groups	581	20045.147	34.501	p = .0001
Total	584	23082.053		

Group:	Count:	Mean MS USE q6hr:	Std. Dev.:	Std. Error:
PLACEBO	99	8.165	6.452	.374
TTS 50µg/hr	26	3.087	3.834	.434
TTS 75µg/hr	33	3.915	4.363	.438
TTS 100µg/hr	37	3.765	6.555	.622



This analysis shows that while the placebo group is significantly different from the TTS fentanyl groups, the TTS 50,75 & 100 do not distinguish each from the other. Based on the data presented in the bioavailability studies in the NDA a hypothesis was proposed that the pharmacokinetic variability between patients was sufficiently great to wash out the dose-response relationship. If this was true, then such a hypothesis could be tested looking for a pharmacodynamic relationship between serum fentanyl levels and the q6hr morphine use in the adjusted data set.

Relationship Between Categorical Fentanyl Use and Adjusted Morphine Use in mg/q6hr

One Factor ANOVA X1: CAT 2 FEN Y1: MS(AGE,TIME,SURGERY,INVESTIGAT...

Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	4	3074.461	768.615	22.282
Within groups	579	19972.417	34.495	p = .0001
Total	583	23046.878		

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
none	99	8.165	6.452	.374
0.0-0.5	16	4.801	5.488	.784
0.5-1.0	28	3.699	4.292	.468
1.0-2.0	36	3.164	5.667	.543
Over 2.0	15	3.451	5.24	.781

This analysis shows that there is a consistent and significant relationship between serum-level of fentanyl collected in the clinical trials and the amount of rescue morphine used. This relationship may be checked by dong a similar analysis for the UN-ADJUSTED or "RAW" morphine use data to see if the same relationship is seen.

Relationship Between Fentanyl Serum Level Category and UNADJUSTED Morphine Use

One Factor ANOVA X1: CAT 2 FEN Y1: Morphine Used

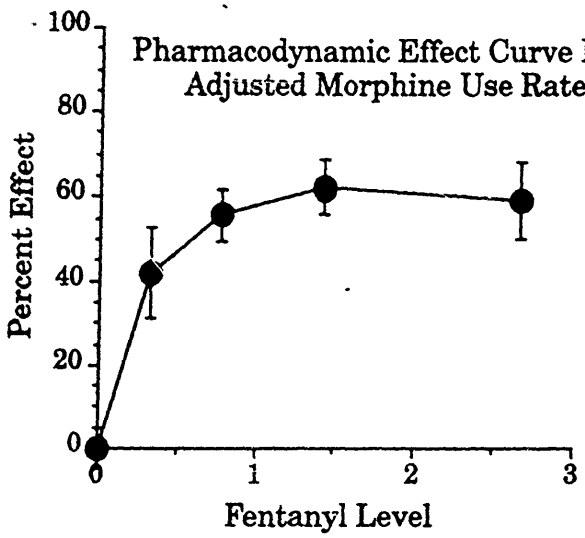
Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	4	2923.236	730.809	19.598
Within groups	579	21591.119	37.29	p = .0001
Total	583	24514.355		

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
none	99	8.193	6.866	.398
0.0-0.5	16	5.49	6.062	.866
0.5-1.0	28	3.583	4.529	.494
1.0-2.0	36	3.248	5.37	.514
Over 2.0	15	4.067	4.901	.731

This Table shows how the pharamcodynamic relationship is sufficiently powerful as to be seen even in the raw data confounded by differences in pain model and trial site.

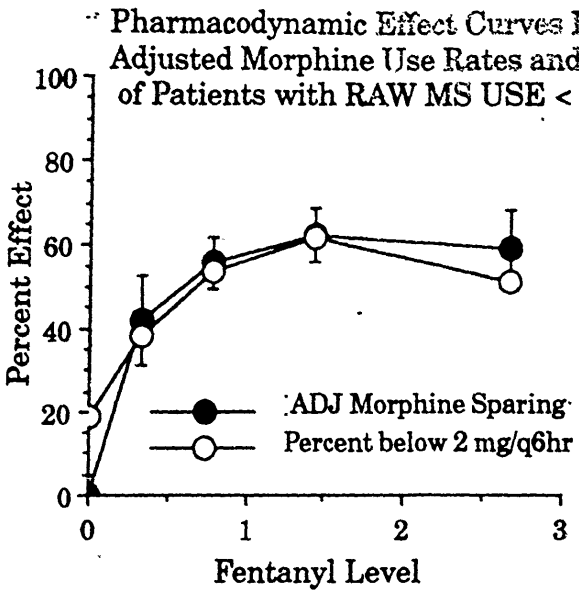
The relationship may be transformed into a more usual form by re-expressing the "Y" axis as a percentage of the maximal effect. Since the maximum morphine use is 8 mg/q6hr and the minimum is 0 mg/q6hr, then the amount of rescue medication may be transformed as % effect=((8.096-Observed MS) /8.096) x100.



The plot suggests that in the pain models tested, fentanyl has reached half-maximal activity at serum levels below 1 ng/ml. If this is true, then the difference between 1 ng/ml and 3 ng/ml in terms of efficacy will be slight, and it may explain the inability to show dose effects between the TTS 50,75 & 100 µg/hr systems, since the observed mean and 95% CI for each system size is as follows:

TTS 50	1.10 ng/ml	(0.1-2.1 ng/ml)
TTS 75	1.45 ng/ml	(0.2-3.0 ng/ml)
TTS 100	2.05 ng/ml	(0.3-3.6 ng/ml)

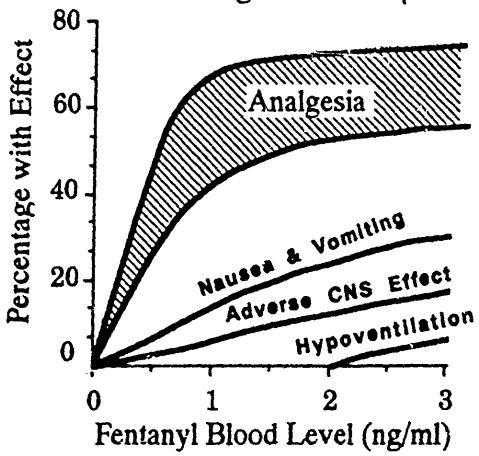
Another way of looking at the pharmacodynamics of analgesia in the clinical trials is to plot the percentage of patients in each serum level strata who use little or no morphine. For this analysis patients who took less than 2 mg/q6hr were considered to have used morphine at a rate clearly different from that used by the placebo group (this level was chosen as it was more than one standard deviation below the placebo group mean). These were plotted along with the data obtained above in order to see the agreement between alternative estimates of the PD effect curve :



In each case, the linear portion of the sigmoid effect curve is below 1 ng/ml, with the curve reaching toward an asymtote above 1.5 ng/ml. This suggests that regardless of upward or downward shifts due to differences in the definition of "successful" analgesia, that the pharmacodynamic effect curve rolls over in the vicinity of 0.75- 1.0 ng/ml. In consequence, in the opioid-naive individual in the post-operative setting who has not developed tolerance, increasing the serum fentanyl level above 1.0-1.5 ng/ml affords little increase in analgesia.

The percentage of various adverse reactions were plotted versus serum fentanyl level. This provided an estimate of the effect curves for adverse reactions for fentanyl when given with rescue morphine as done in the trials. In order to place the analgesic effects in perspective, the curves for nausea and vomiting, CNS effects (anxiety, nervousness) and hypoventilation (hypercarbia, resp. rate < 8, unresponsive) were plotted along with the upper and lower bounds for the analgesic effect.

Fentanyl Blood Level- Effect Relationships
in Trials of Duragesic in Postoperative Pain



Pharmacokinetics of SAFETY for the Different Strengths

Since the TTS systems are labeled to be used in conjunction with rescue medication, and since the most serious adverse effect is hypoventilation, it would be most desirable to find a way to use the systems that provides analgesia to most of the patients and does not expose more than 5% of the patients to serum levels that are associated with hypoventilation. In the safety review it was noted that in the observed cases of hypoventilation in the clinical trials (n=12 as we do not have the serum fentanyl level for patient G-10, see safety summary), all cases took place at serum levels between 1.8-3.5. Half of such cases were associated with known pulmonary risk factors (thoracotomy, RUQ incision, ASA status > III, concurrent medical illness) and somewhat less than half were probably due to a mixture of high fentanyl levels and concurrent morphine administration. Given these factors and the known pharmacodynamics of fentanyl in normals (50% reduction in ventilation at serum levels of 3-4 ng/ml), a reasonable Ctox for fentanyl in the non-tolerant patient is probably 2.5 ng/ml, although the data could support a Ctox of 2.0 and a Ctox of 3.0 equally well.

The minimum effective concentration is more difficult to determine. In the studies submitted with the NDA the MEC is about 0.5-0.75, while in the clinical trials the lowest fentanyl strata (0-0.50 ng/ml) had significantly reduced morphine use (on a population, not individual, basis). Under these circumstances a MEC for fentanyl could be chosen anywhere between 0.250-0.750 ng/ml, but is most likely to be 0.5 ng/ml.

With Ctox & MEC estimated, it is possible to look at all the clinical and pharmacokinetic trials and estimate the percentages of the population which fall within, above, and below the therapeutic range.

TTS Size and Serum Fentanyl Levels as Tested in the Clinical Trials

	TTS 25	TTS 50	TTS 75	TTS 100	Totals:
BELOW .5	0	4	5	3	12
0.5-2.0	2	63	78	85	228
2.0-2.5	0	3	11	7	21
2.5-3.0	0	1	5	2	8
OVER 3	0	0	4	0	4
Totals:	2	71	103	97	273

(NEW DATA SET - FILE #2 "SAFETY' ON THE DISKETTE)

The sponsor did not adjust the dose of TTS according to the patient's weight in the clinical trials, since a definite relationship between weight and serum fentanyl was only seen after the aggregate data was collected. In an attempt to improve the safety profile of the system, it was decided to look at the possibility of adjusting dose by weight. To examine this question, the sponsor provided a data set consisting of a total 273 applications of TTS fentanyl systems across all studies which included all reported cases of hypoventilation.

Composition of the SAFETY DATASET

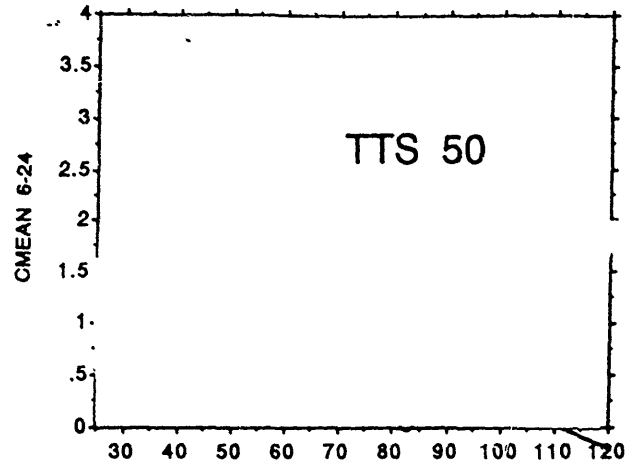
	TTS 25	TTS 50	TTS 75	TTS 100
Mather-E	2	13	4	
Jackson-E		4		
Mcleskey-E		26		
Jackson-P		8		
Mcleskey-P		8		
Mather-P		2	10	1
Stanekl-P		10		
Plezia-E			14	
Caplan-E			20	
Stada I-E			19	
Hotchkiss-P			1	4
Caplan-P			10	
Plezia-P			7	
Larijani I			10	
Larijani II			8	
Stanekl-E				20
Hotchkiss-E				22
Nimmo-IB-P				10
Nimmo-E				22
Nimmo-IA-P				10
Stanekl BA				8
Totals:	2	71	103	97

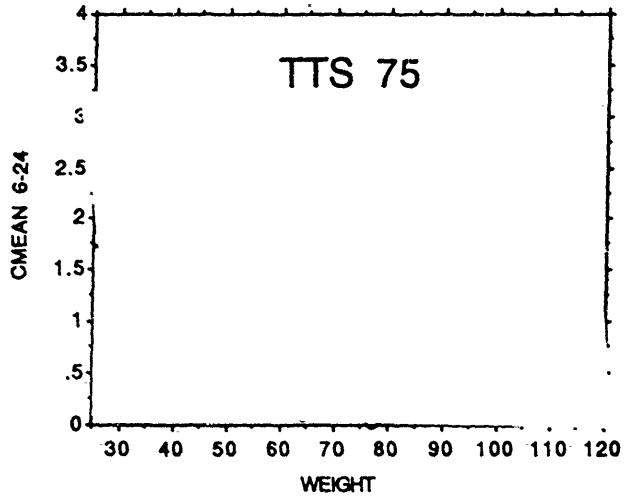
Using this data set, serum fentanyl level was then regressed against patient weight, lean body mass, ideal body mass, surface area, body mass index, and total body water. All regressions were significant, but no derived measure was sufficiently better than weight in kilos to warrent their increased complexity and weight was used in subsequent calculations. The sponsor did a similar exploration using the data from the Stanski BA study in which fentanyl clearance was measured directly. The relationships they observed were:

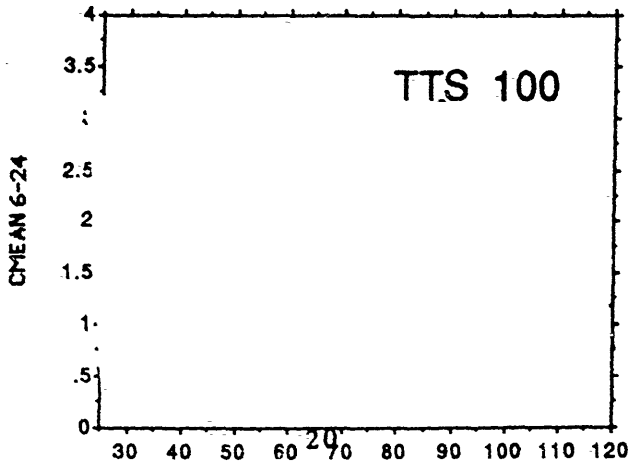
Stanski BA study
IV Fentanyl
Clearance v. Demographic Variables

Variable	F Value	R-Square	p-Value
Weight	4.561	.0559	.0359
Height	5.025	.0491	.0279
Surface Area M sq.	5.666	.0685	.0198
Lean body Mass (Peck)	5.216	.0634	.0251
Age	0.000	0.000	.999
Body Mass Index	.922	.0118	.3398
Ideal Body Weight	5.171	.0629	.0258
Lean Body Mass (H20)	5.368	.0652	.0232

The scatterplots for each TTS size by body weight are as shown:


TTS 50
CMEAN 6-24
4
3.5
3
2.5
2
1.5
1
.5
0
30 40 50 60 70 80 90 100 110 120


TTS 75
CMEAN 6-24
4
3.5
3
2.5
2
1.5
1
.5
0
30 40 50 60 70 80 90 100 110 120
WEIGHT


TTS 100
CMEAN 6-24
4
3.5
2.5
2
1.5
1
.5
0
30 40 50 60 70 80 90 100 110 120

Thus there is a relationship between patient weight and fentanyl serum level for all three TTS systems tested. This observed relationship allows the TTS 50, TTS 75, & TTS 100 groups to be adjusted for between-group differences in patient weight by using the observed relationship (1 kilo heavier results in a 0.012 ng/ml drop in serum fentanyl level for a given TTS system).

The data-set was then adjusted to a common mean weight of 70 kilos, and the mean 6-24 hours fentanyl serum level was determined for each TTS size:

Relationship of Adjusted Serum Fentanyl Level to TTS Size

One Factor ANOVA X1: TTSDOSE Y1: MEAN FENTANYL (KG)

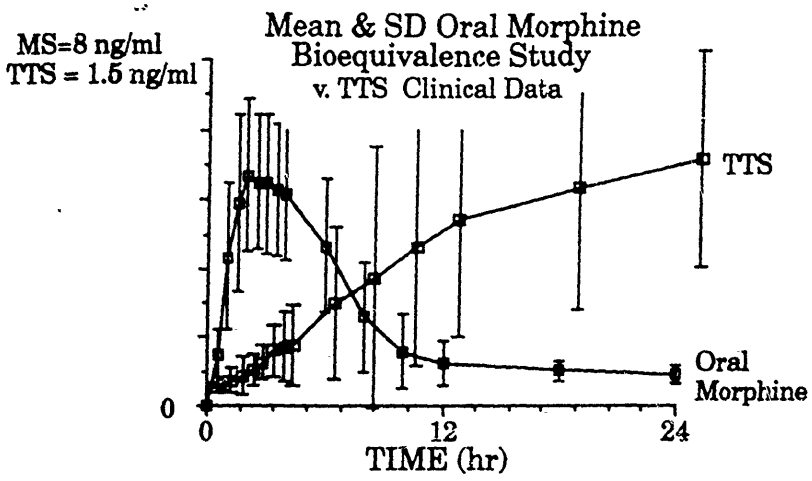
Analysis of Variance Table

Source:	DF:	Sum Squares:	Mean Square:	F-test:
Between groups	3	27.659	9.22	27.043
Within groups	268	91.369	.341	p = .0001
Total	271	119.029		

Group:	Count:	Mean:	Std. Dev.:	Std. Error:
TTS 50	71	.886	.404	.048
TTS 75	102	1.098	.636	.063
TTS 100	97	1.625	.638	.065

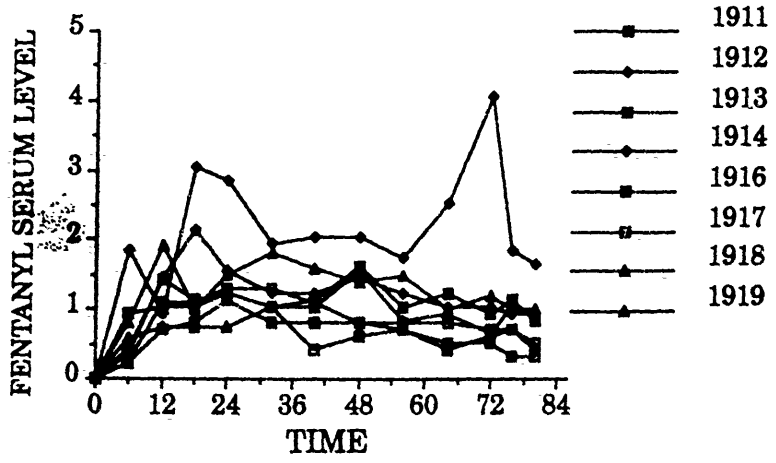
The observed values show dose proportionality in mean serum fentanyl level for the 6-24 hour period, with an inter-subject coefficient of variation of 45% for the TTS 50, 58% for the TTS 75, and 39% for the TTS 100.

There is no currently approved 72 hour analgesic product, and thus there is no pre-existing standard against which to judge this product. The most similar kind of products are the oral morphines, which are used in cancer analgesia. To allow the reader to put the pharmacokinetic variability of the TTS systems in perspective the following graph is offered in which the data for TTS is plotted on the same axis with data from a typical oral morphine. In using the figure for comparison please remember that the TTS data is for all patients in all trials and the morphine data is for 20 healthy males of normal body weight in a single kinetic study.



Performance over 72 Hours

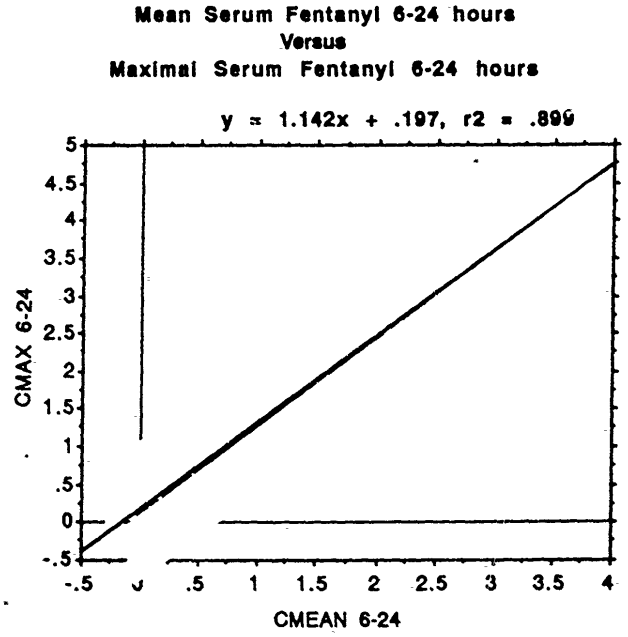
There is little data in the NDA supporting the use of the TTS system for 72 hours for post-operative pain, although there is a lot of supporting evidence in the oncology trials. One trial (Larijani-II), did follow the serum levels of eight patients for 72 hours following a single application of a TTS 75. The data for this trial are as follows:



Although not conclusive, this small trial does support the pharmacokinetic modeling and projections previously reported and suggests that the TTS system does reach a steady-state serum level within 12 hours and hold it for 72.

Dosage Recommendations

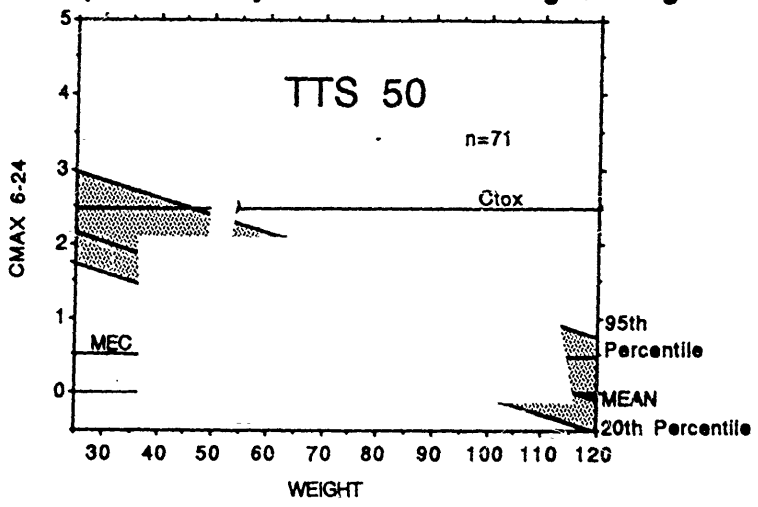
With a known MEC, a known Ctox, and the assumption that no more than 5% of the patients should be above Ctox nor more than 20% below MEC, it is possible to plot the intersection of Ctox and MEC with the band which reflects the 20th to 95th percentiles of the serum levels seen in patients of different weights receiving each TTS size. In doing this analysis it was assumed that analgesic efficacy is best predicted by mean serum level, while toxicity is best predicted by peak blood level. In consequence, it is important to know if mean and peak blood level are related in the observations:



While this analysis suggests good agreement, it must be confirmed by a followup analysis where the Cmax is compared with the Cmean for all points other than Cmax. This analysis will be done before NDA DAY but is not available in this packet. Accepting the hypothesis that there is good agreement between the Cmax and Cmean for the serum fentanyl values, it becomes even more certain that the inter-patient variability is much larger than the intra-patient variability .

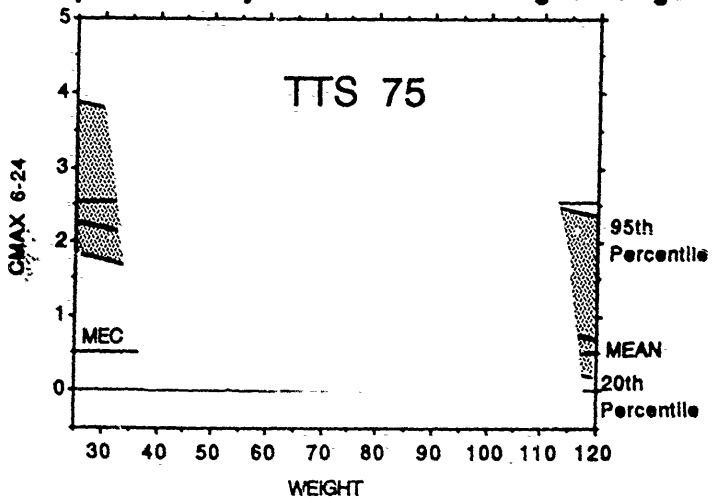
Given the closeness of the Cmax & Cmean, I have chosen to use the Cmax for the following graphical analysis of the TTS 50, TTS 75, & TTS 100 systems, since lack of safety at the high end is of more concern than loss of efficacy at the low end for a product intended to be used with rescue medication.

Graphical Analysis of TTS 50 Weight Range



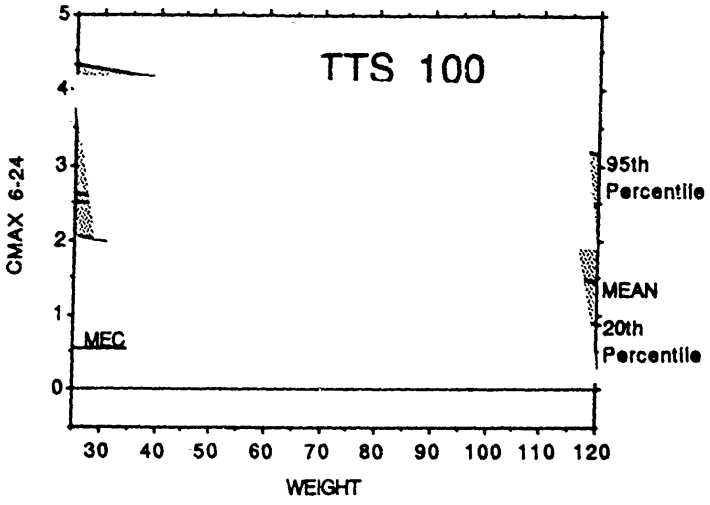
The 20-95th percentiles for TTS 50 are in zone for patients who weigh 50-75 kilos, with two subjects having serum levels in the toxic range.

Graphical Analysis of TTS 75 Weight Range



The 20-95th percentiles for TTS 75 intersect the Ctox & MEC at about 90-100 kilos, suggesting that some patients will have blood levels in the toxic range when the TTS 75 is applied to patients under 100 kilos, while more than 20% will have reduced efficacy if it is applied to patients over that weight.

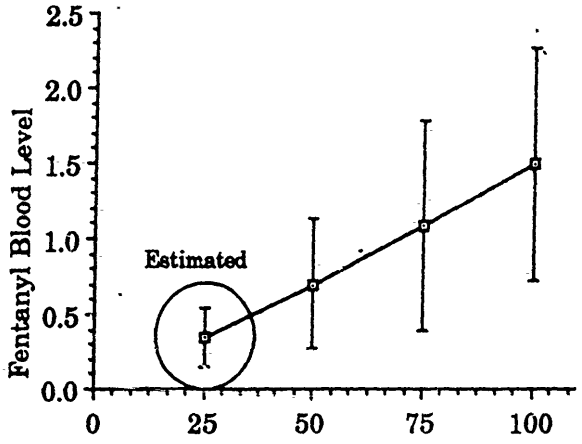
Graphical Analysis of TTS 100 Weight Range



The application of the TTS 100 system to a population of opioid-naive patients will a wide range of clearances result in overdose for those who weight below 105-110 kilos, but will underdose half of of those above weight range. In consequence, the TTS 100 system will probably only be useful and safe in situations where dose can be individually titrated and not in the postoperative setting.

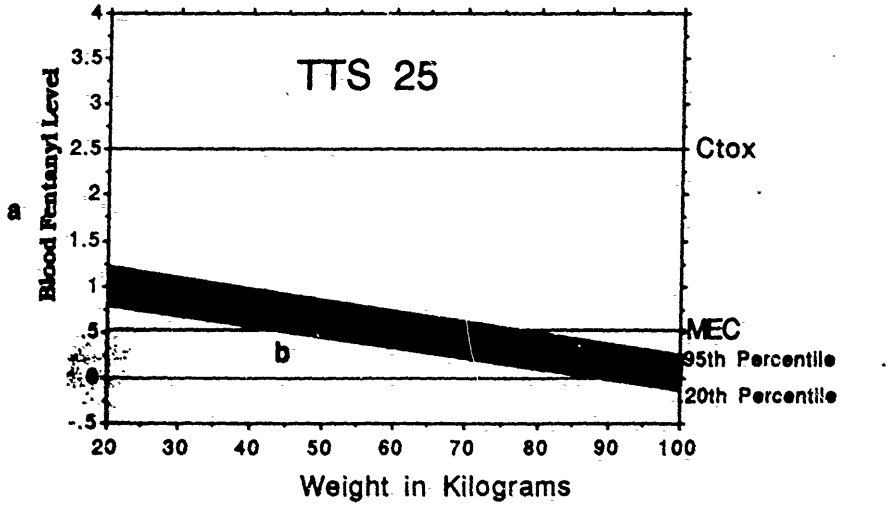
The TTS 25 was not tested in clinical trials, but it's performance can be estimated from the performance of TTS 50 and the trend established by TTS 50,75, & 100:

Mean and SD of TTS Fentanyl Clinical Data
(6-24 hours following a single application)



TTS Size

Given this data the probable dose-weight relationship can be constructed:



While TTS 25 is in zone for patients under 40 kilos, no patients under 40 kilos were tested in the trials, and no pediatric trials were performed. It's usefulness is limited pending such tests. although it is a useful titration dose for oncology patients, and may be of use in 25-50 kilo patients, or

patients with known or suspected pulmonary risk factors or known sensitivity to opiates.

Conclusions

The metanalysis was performed in an attempt to understand the lack of dose-response seen in the clinical trials by analysis of the blood level data from the clinical trials. The systems are very likely to deliver fentanyl in the stated amount and in a dose-proportional fashion, but the achieved serum level is likely to exhibit considerable intra-individual variation. So much intra-individual variation in the mean and peak blood level after system application was observed that only systems 50 µg/hr and under were "safe" in the post-operative trials conducted by the sponsor. This result is, in part, the consequence of the assignment of TTS size by surgical type, not by weight, in the original research design. Post-hoc analysis of the data shows that the 75 µg/hr system is likely to be safe for individuals who weight above 75 kilos, but such a dosing schedule has not been tested.

The dosing recommendations proposed by the sponsor are to use TTS 25 on patients weighing 25-49 kilos, the TTS 50 on patients weighing 50-74 kilos, and the TTS 75 on patients weighing 75 kilos or more. This dosing schedule can be tested on the whole patient data-set.

The observed cases of hypoventilation occurred at the following serum levels:

Hypoventilation and Fentanyl Serum Level Observations in the TTS Clinical Trials

	No Hypoventilation	Hypo-Ventilation	Totals:
BELOW 1.5	157	0	157
1.5-2.0	49	1	50
2.0-2.5	24	5	29
2.5-3	16	5	21
OVER 3	15	1	16
Totals:	261	12	273

The original dosing design gave the following numbers of cases:

TTS Size and Serum Fentanyl Levels as Tested in the Clinical Trials

	TTS 25	TTS 50	TTS 75	TTS 100	Totals:
BELOW .5	0	4	5	3	12
0.5-2.0	2	63	78	85	228
2.0-2.5	0	3	11	7	21
2.5-3.0	0	1	5	2	8
OVER 3	0	0	4	0	4
Totals:	2	71	103	97	273

And the proposed dosing adjustmetn by weight (25,50,75) gives the following projected values:

Predicted Distribution Based on Post-Hoc Weight Analysis

	TTS 25	TTS 50	TTS 75	Totals:
BELOW .5	3	17	26	46
0.5-2.0	7	127	80	214
2.0-2.5	0	5	3	8
2.5-3.0	0	3	1	4
Totals:	10	152	110	272

This dosing recommendation can be expected to put 78% of the patients at a serum level likely to be analgesic, 16 % at a serum level likely not to be analgesic (these patients will require prn supplementation), 3 % at a blood level with a 15% risk of hypoventilation (2-2.5ng/ml) and 1.5% at a serum level with a 25% risk of hypoventilation (2.5-3.0 ng/ml).

Figure 1
Mean (SE) Plasma Fentanyl Concentrations (ng/mL) for TTS (fentanyl) 25
n=5

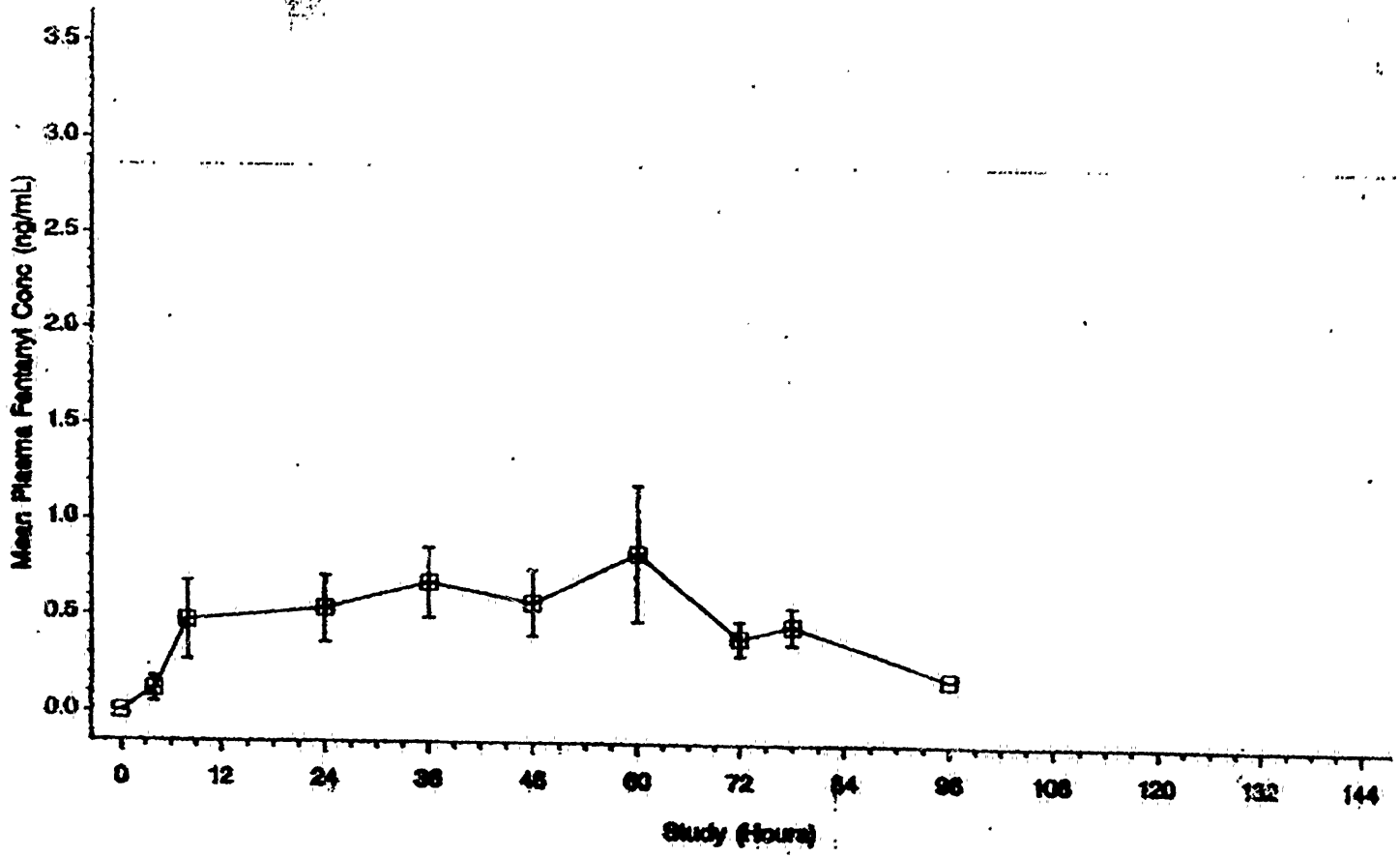


Figure 2
Mean (SE) Plasma Fentanyl Concentrations for TTS (fentanyl) 75
n=5

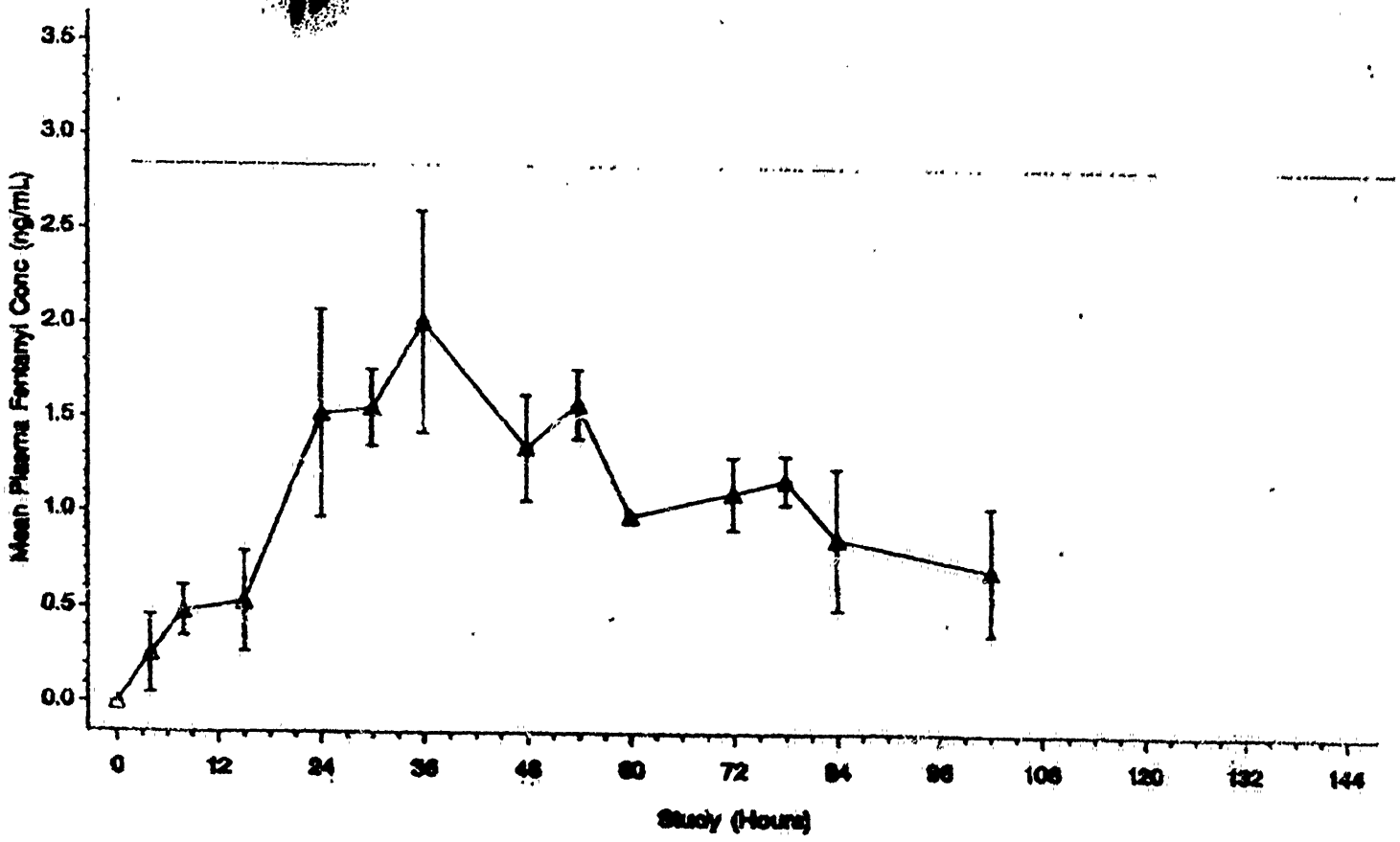


Figure 3
Mean (SE) Plasma Fentanyl Concentrations (ng/mL) for TTS (fentanyl) 100
n=3

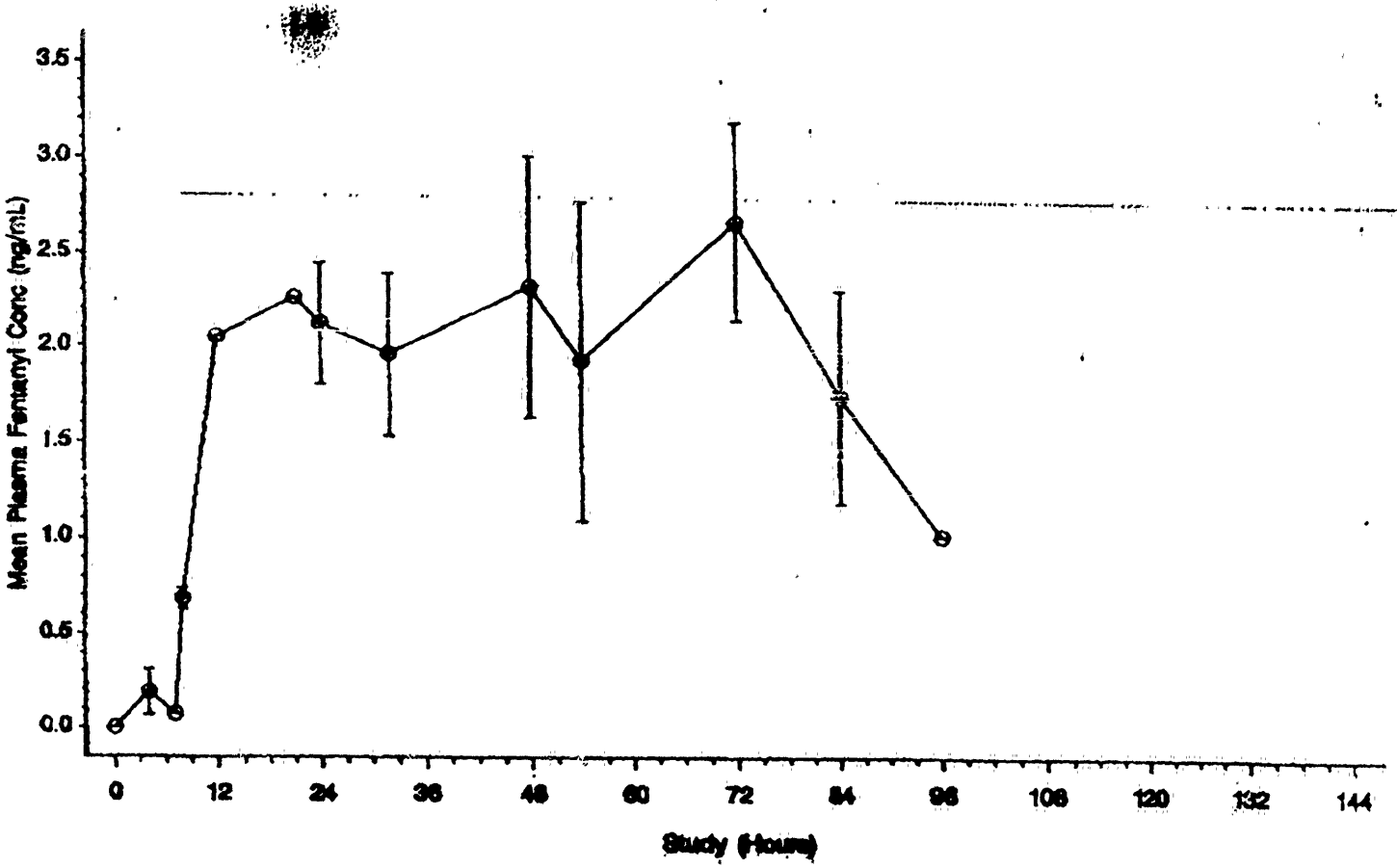
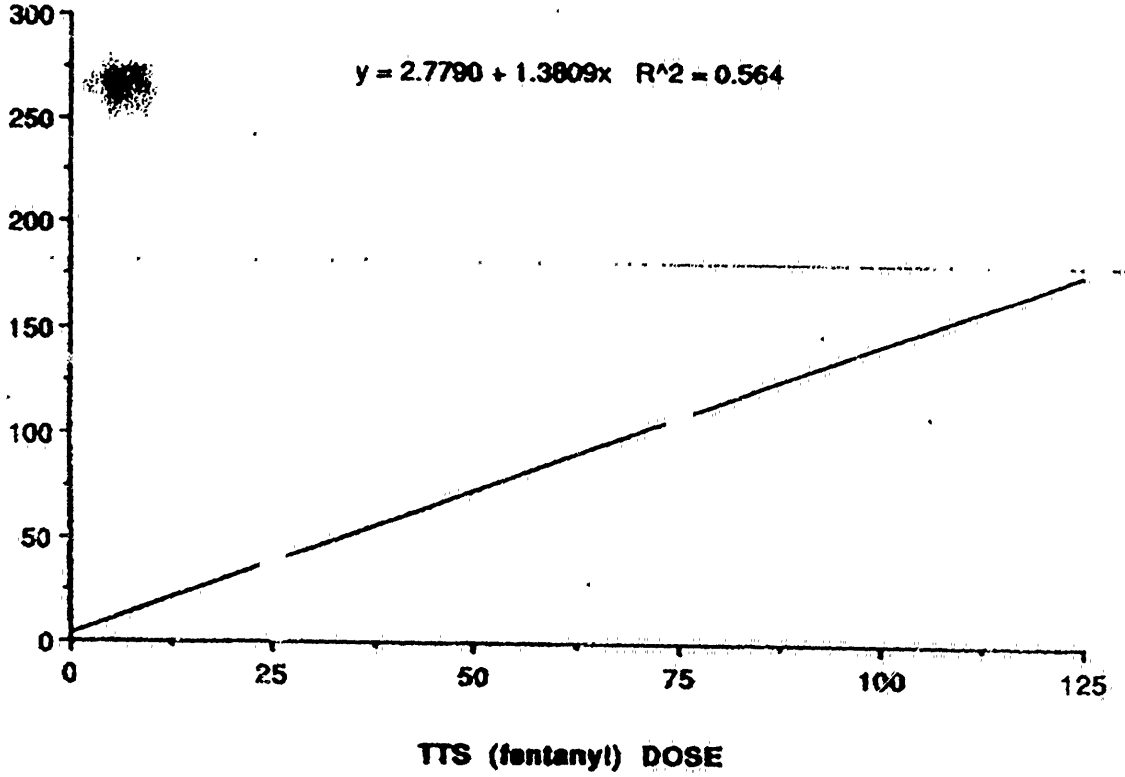


FIGURE 4

Effect of TTS (fentanyl) Dose on Plasma Fentanyl AUC

(Protocol C-89-096-00, UK STUDY, Kenny)



ALZA CORPORATION, PALO ALTO, CA 94303-0802

FIGURE 5

Effect of TTS (fentanyl) Dose on Fentanyl AUC (72 hour Application)

[C-89-006-00 UK Study, Kenny,(N=13) & C-88-032-00, Portenoy ,(N=5)]

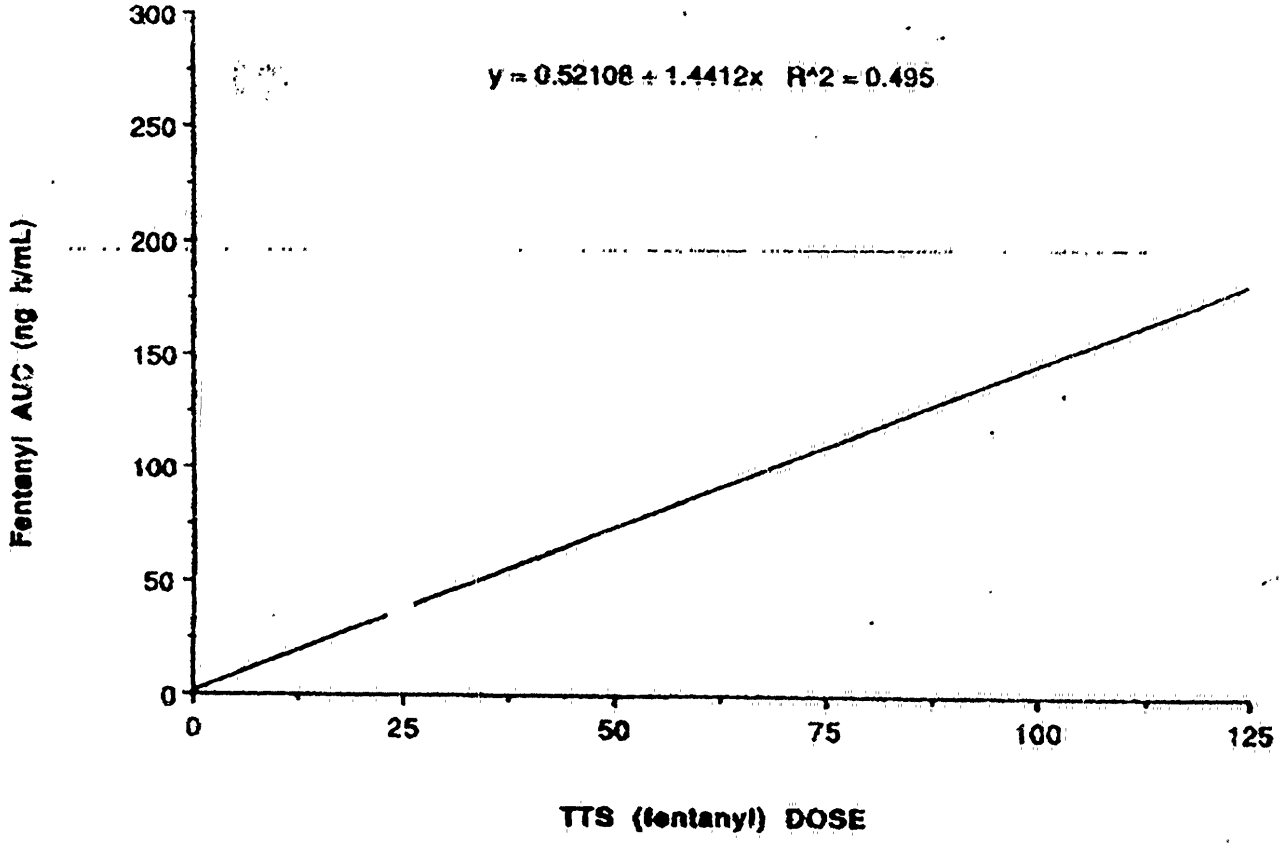
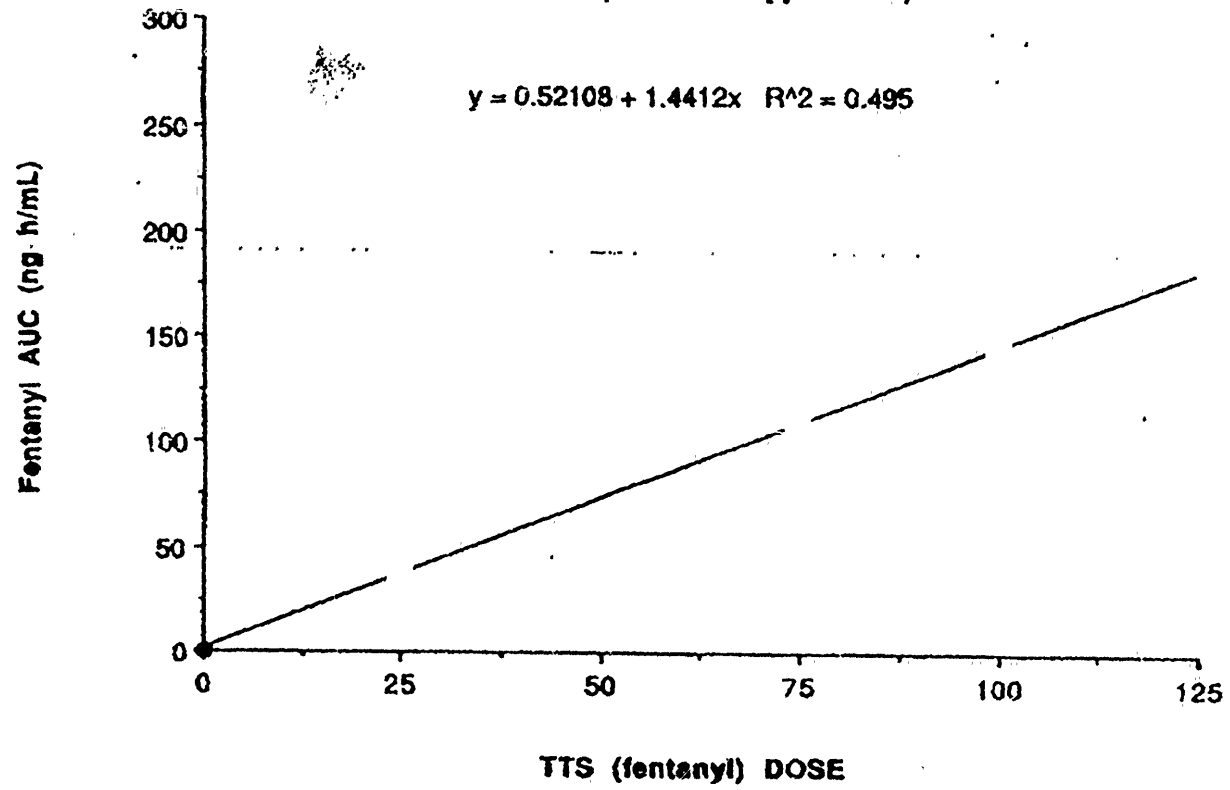


FIGURE 6

Effect of TTS (fentanyl) Dose on Fentanyl AUC Values

(72 Hour Application)



□ : Data From Protocol C-89-006 and C-88-032-00 (N=18)
● = Mean Data From Protocol C-85-047 , Larijani Study (N=8)

Medical Officer Review
NDA #: 19,813
Alza Corporation

TTS Fentanyl

(Transdermal Therapeutic System)

Volume 4 - Safety

Submitted: 12/31/87
Reviewed: 5/2, 90 to 5/12/90
Curtis Wright MD,MPH

WRITTEN CWIV - 5/12/90
PEER REVIEWED RL 5/18/90
SPONSOR'S COMMENTS MS 5/25/90

General Comments Regarding the Safety of TTS Fentanyl

Fentanyl has been used in anesthetic practice for over 20 years. It has been shown to be a safe and effective drug with predictable mu-agonist narcotic properties whose only unexpected toxicity is chest-wall rigidity occasionally seen when the drug is used in high dose as an anesthetic induction agent. Fentanyl has been used successfully as a solution for patent-controlled analgesia for acute and chronic pain and has no known idiosyncratic toxicity in patients above 3 months of age. In consequence, it is not necessary for the sponsor of TTS fentanyl to prove the basic safety of the drug fentanyl, but only to prove the safety of the delivery system for the drug. Establishing the safety of TTS fentanyl will involve the sustained application of pharmacokinetic and pharmacodynamic analysis.

As a pure mu opioid agonist, fentanyl will interact with another mu opioid in a quantitative additive fashion. Since the TTS fentanyl system is planned for use in conjunction with concomitant opioid and non-opioid analgesia, no attempt should be made to partition the adverse effects observed in the trials between the narcotic provided by the TTS system and the narcotic provided by the rescue analgesic. If the TTS fentanyl system is to be labeled for use with the simultaneous administration of another opioid analgesic, the safety of the combination is the safety of the system under conditions of intended use.

Mu Agonist Toxicity

Primary mu agonists such as fentanyl and morphine have an adverse effect profile determined by their basic pharmacologic profile. Patients receiving such drugs complain of nausea, vomiting, postural syncope, nervousness or "drive", itching, confusion, dizziness, altered breathing, blurred vision, disordered micturition, constipation, and rare episodes of psychosis and/or hallucination. Serious toxicity is almost entirely confined to injury from falls due to postural syncope, respiratory depression, and rare cases of acute allergic reactions or histamine sensitivity. Blood levels of opioid agonists which are effective in relieving pain are likely to cause the patient some degree of symptomatic distress, and to cause respiratory depression in vulnerable patients. TTS Fentanyl can be expected to cause nausea, vomiting, itching and some degree of CNS disturbance, but should not cause an unacceptable degreeof respiratory depression.

Fentanyl Induced Rigidity

Fentanyl, like other opioids, is able to interact with the dopaminergic system to alter muscle tonus, cause muscular rigidity and alter chest wall compliance in patients who receive the drug rapidly for induction. Discussion of this point at the anesthesia advisory committee meeting of 4/20/90 revealed a consensus that the phenomena begins to be seen when IV fentanyl is delivered at rates above 1-2 μg/kg/**min** and would not be expected with the 1-2 μg/kg/**hr** rates of delivery from the system. No episodes of muscular rigidity or respiratory paralysis were seen in any study of TTS fentanyl.

Overview of the TTS Fentanyl Studies

TTS fentanyl has been studied in 5 chronic use studies in 153 cancer patients and in 24 postoperative studies involving 592 patients of which 357 received TTS fentanyl. There were no patient deaths attributable to fentanyl in either type of trial, and the withdrawals for all causes are as shown below:

Cancer Studies

Trial	Total size	Number of Withdrawals (all causes except death)
84-011-01	5	5
85-018-01	10	0
86-003-01	57	19
86-003-01 (3)	7	2
87-010-01	54	13
88-006-00	20	0
TOTAL SIZE	153	WITHDRAWALS 39 (25.5%)

TTS Fentanyl Patients in Postoperative trials

Trial	Total size	Number of Withdrawals (all causes)
Pharmacokinetic	38	2
Uncontrolled Studies	76	4
Controlled Studies	243	26
TOTAL SIZE	357	WITHDRAWALS 32 (9.0%)

These 71 patients will be scrutinized in detail along with the adverse effect profile for the patients completing the trial.

Cancer Pain Trials

The enclosed figures and tables show that the 153 cancer patients were representative of the clinical population, covering a wide range of ages, weights, primary malignancy and functional status. Doses of TTS fentanyl ranged from 25-600 micrograms an hour, applied for periods of from 1-866 days. Thirty-nine patients withdrew from the trials for the following reasons:

Reason	Number of Withdrawals
Inadequate Pain control	11
Nausea & Vomiting	7
Narcotic related side effects	3
CNS side Effects	1

Intercurrent Illness	**5**
Narcotics no longer required	**3**
Lack of compliance	**3**
Patient-Caretaker Decision	**3**
Admission to non-participating hospital	**2**
Protocol violation	**1**

Table 16 gives the overall frequency of adverse experiences by order of frequency, and shows a profile typical for high dose opioid drug treatment similar to oral high dose morphine. There is not enough data to support an analysis of the comparative frequency of adverse effects or for the sponsor to make claims of fewer side effects.

Major Side Effect	Frequency (Percent)
Nausea	**23**
Vomiting	**22**
Somnolence	**17**
Sweating	**14**
Constipation	**14**
Confusion	**13**
Dry Mouth	**13**
Asthenia	**12**
Anorexia	**8**
Dizziness	**7**
Lung Disease	**7**
Nervousness	**6**
Diarrhea	**5**
Dyspepsia	**5**
Dyspnea	**4**
Pruritis	**4**
Hypoventilation	**4**
Topical Reaction	**4**
Urinary retention	**3**
Apnea	**3**
Hallucinations	**3**

Respiratory Depression

Case 1- 57 y.o. W.M. with metastatic pancreatic cancer started on 200 µg/hr TTS system, advanced to 275 µg/h and found to have a nocturnal respiratory rate of 6/min. TTS was reduced and respiratory depression resolved.

Case 2- 68 y.o. W.M. with metastatic prostate cancer started on TTS at 150 µg/hr and escalated over 5 months to 275 µg/hr. One episode of depressed respirations while sleeping to 6 breaths/min. He was roused w/o difficulty and TTS was continued with no recurrence of respiratory depression.

Case 3- 67 y.o. male with metastatic small cell of the lung started on TTS at 125 µg/hr. The patient was advanced over a six week period to 500 µg/hr with morphine supplement (7.5-45 mg prn). TTS fentanyl was

reduced by 100 µg/hr after the patient was observed to have an episode of bradypnea (6 /min). TTS was continued without difficulty up to the time of the patients death from cancer.

Case 4- 66 y.o. male with metastatic bladder cancer started on TTS at 100µg/hr. TTS was maintained at 100 µg/hr for two months when the patient developed Cheyne-Stokes respirations and died from his cancer. TTS was worn at the time of death but not implicated.

Case 5- 21 y.o. male with metastatic medulloblastoma was started on TTS at 75 µg/hr and advanced over six months to 200 µg/hr. By day 171 the patient appeared terminal with Cheyne-Stokes respiration and died the next day. TTS was not judged to be involved.

Case 6. 78 y.o. male with malignant carcinoid was started on TTS 50 and advanced to TTS 100, remaining at that dose for 135 days. On day 136 he was obtunded and brought to the hospital where TTS was removed and naloxone given. He became alert and was converted to IV morphine which resulted in a return of obtundation. He was shown to have decreased hepatic clearance due to disease progression and died on the fifth hospital day. TTS was involved, but the respiratory depression was judged to be due to altered clearance due to disease progression.

Of the six documented cases of TTS associated respiratory depression three are probably due to TTS effect and three are probably due to disease progression and cancer morbidity.

Safety of Conversion to TTS Fentanyl

In the studies of TTS fentanyl in cancer pain in this NDA the formula for conversion of analgetic requirement to TTS dose was based on the prior use of opiod drugs by the patient. One TTS 100 µg/h system was considered to be the equivalent of 360 mg/day of oral morphine or 60 mg/day of parenteral drug. Post-hoc analysis of the data suggested that the actual equivalence was more likely to be 100 µg/h TTS system = 300 mg/day oral morphine, but the 360 mg/day= 100 µg/hr ratio proved to be effective without causing overdose. This may be seen by a review of the withdrawals from TTS in the first three days of treatment (first TTs application) which are reported below:

SCN 1115- 66 y.o. female hospice patient who started on TTS fentanyl but died of her cancer within 3 days.

SCN 1223- 66 y.o. male with metastatic adenocarcinoma was started on TTS fentanyl but withdrawn on the second day due to the absence of a caretaker as required by the protocol.

SCN-1051 57 y.o. female with metastatic breast cancer who was started on TTS 50 µg/h and terminated on the second day due to nausea related to chemotherapy. This patient re-entered the study and continued on TTS for 721 days.

SCN 21- 58 y.o. male with leiomyosarcoma who was on TTS for only 3 days before he was withdrawn from the study to undergo surgery.

SCN 403- 42 y.o. female with metastatic breast cancer who removed her TTS within 12 hours of application and did not desire another.

SCN 1080- 64 y.o. female with small bowel cancer refused TTS after 9 hours due to opioid side effects.

SCN 104- 55 y.o. male whose physician reported he was unable to cope with the change from his previous pain medicine.

Of the seven subjects who terminated TTS during the first application of the system 3 were withdrawn for reasons not connected with the system, 1 withdrew by reason of adverse side effects, 2 withdrew for reasons that were related to their disease and 1 withdrew for unknown reasons. No patient withdrew for reasons of safety when converted at the 360 mg/day morphine = 100 μg/hr TTS ratio.

Cardiovascular and Laboratory Safety

No cardiovascular effects (other than a modest increase in liability to postural syncope) or laboratory abnormalities were expected based on the known safety profile of fentanyl, and none were found (other than the expected increased frequency of abnormalities in pre-morbid patients).

Conclusion Regarding Safety in Chronic Cancer Pain

The enclosed plots of adverse effect frequency as expressed in terms of the fentanyl dose delivered by the TTS and the duration of treatment show that the highest frequency of adverse reactions occurred at the initiation of treatment (lower doses & shorter times), and that there was no trend toward the emergence of adverse effects at the higher dosage levels and/or longer wearing times. This profile is consistent with a drug whose adverse effects and desired pharmacologic effects occur in concert, and it provides some assurance that the TTS system has a low level of non-opioid toxicity.

A sample size of 153 patients allows (at best) the detection of a single very adverse event at the 1% level and a doubling of common adverse events with a power of 80%. When the trial is conducted in a patient population that is dying of intercurrent illness and the control group is historical then all that can be said is that the patient population could be converted to TTS systems, did not suffer any detectable early morbidity from over or under-dosage at a 360 mg oral morphine:100 μg TTS system ratio, and experienced opioid side effects at a rate which might be expected for the population. Respiratory depression which was probably related to the TTS system did occur in 4 of 153 patients, of which one required naloxone therapy and three responded to stimulation or reduction in the TTS dose.

TTS safety in Postoperative Analgesia

Subjects receiving TTS fentanyl in postoperative pain were nearly always involved in 24 hour, single TTS application, controlled clinical trials and received either TTS or placebo as shown in the following table:

System Size	Number
Placebo	235
25	2
50	73
75	177
100	105

Among these 357 TTS fentanyl wearers there were 32 TTS fentanyl wearers who did not complete the study for the reasons shown in the following table:

Reason	Number
Respiratory Depression	10
Other Adverse Reaction	4
Inadequate Pain Control	2
Surgery Postponed or Altered	11
Surgical Complications	3
TTS removed in Error	2

Of the 32 withdrawals 16 were probably related to the TTS system for an overall withdrawal rate of 16/357 or 4%.

TTS related Respiratory Depression

In addition to the 10 cases of respiratory depression which led to withdrawal from the trials there were 8 other cases in which the subject did not do so for a total of 18 total cases of respiratory depression. Of these 18 cases four (#'s 578, 505, 602, 130) were cases in which respiratory depression was seen only upon reversal of the anesthetic at a time when the fentanyl blood level < 1.0 ng/ml. These cases were judged not to be related to the TTS system but to the anesthetic technique. Of the remaining 14 cases one (205) was an asthmatic alcoholic with pneumonia who had bronchospasm unrelated to the TTS system (fentanyl blood level <1.0 ng/ml). Thus there were 13 patients who experienced respiratory depression due to a combination of the TTS system, morphine rescue medication, and/or routine postoperative anti-nauseants & hypnotics.

SCN	Weight	Age	Sex	ASA	TTS Dose	Time	Blood Level	Other Factors
170	50	42	F	I	100	7 h	1.9	hypothyroidism
243	100	53	M	IV	100	12 h	2.7	verapamil
249	53	34	F	II	100	12 h	3.0	adrenal insufficiency
255	54	59	F	III	100	6 h	2.1	volume depletion

574	77	38	F	I	75	6 h	2.4	thiopental
213	57	66	F	II	100	15 h	3.1	none
611	60	28	F	I	100	16 h	3.3	none
696	73	60	M	I	100	7 h	2.3	none
514	61	67	F	III	75	23 h	1.9	none
823	60	30	F	I	75	21 h	2.2	none
825	82	20	F	I	75	20 h	2.8	none
832	57	33	M	I	75	17 h	2.0	none
G 10	57	66	F	II	75	15 h	2.0	none

Reference to the above table reveals that there were no episodes of depressed respirations below a blood level of 2.0 ng/ml (excluding one hypothyroid patient), and no cases involving the 50 µg/h TTS system. The single major determinant of respiratory depression was the blood level of fentanyl at the time of the event. Respiratory depression observed in the fentanyl trials started six hours after TTS application and could occur at any time up to the removal of the TTS at 24 hours. Clinical synopses of the cases follow:

SCN 170- TTS-100 patient with prior history of hypothyroidism (not on replacement) who underwent Knodt rod fusion and required TTS removal and naloxone administration for reversal at the conclusion of surgery.

SCN 213- TTS-100 patient s/p lobectomy had a respiratory rate of 8/min and pCO2 of 55 after 15 hours of TTS wearing. TTS removed and naloxone given resulting in an uneventful recovery.

SCN 243- TTS 100 patient (ASA class IV) 12 hr s/p pneumonectomy developed atrial arrythmia requiring 17.5 verapamil. One hour later the patient developed a respiratory rate of 8/min and a pCO2 of 52. TTS removed, naloxone given, recovery uneventful.

SCN 249- TTS 100 patient s/p lobectomy had had a prior bilateral adrenalectomy but had not been given replacement at the time of surgery. Five hours after surgery an attempt was made to correct for this omission by giving 100 mg hydrocortisone IV. One hour later the patient had a respiratory rate of 4/min and a pCO2 of 60. TTS removed, naloxone given, recovery uneventful thereafter.

SCN 255- TTS 100 patient s/p right lower lobectomy required naloxone for reversal of anesthesia. Recovery room course troubled with pCO2 of 53 and hypotension. The TTS was removed at two hours, naloxone was given and recovery was uneventful.

SCN 514- TTS 75 patient s/p right total knee and Morton's neuroma excision who received a dose of 5 mg rescue morphine 17 hours after surgery. One hour after that dose of morphine the patient became groggy with a repspiratory rate of 7/min. The patient was stimulated, followed by uneventful recovery from the episode.

SCN 574- TTS 75 patient s/p cholecystectomy who required naloxone at reversal of anesthesia (pCO2 64). Following naloxone administration the patient became combative and was given IV thiopental and the anesthesiologist requested the removal of the TTS system. Uneventful recovery followed.

SCN 611- TTS 100 patient s/p cholecystectomy who had "slow and noisy respirations" 11 hours postoperatively. TTS removed, naloxone given, uneventful recovery.

SCN 696- TTS 100 patient s/p hernia repair who had a respiratory rate of 3/min six hours after surgery. TTS removed, naloxone given, uneventful recovery.

SCN 823- TTS 75 patient s/p cholecystectomy who became sleepy with a respiratory rate of 6-10 /min 19 hours after surgery. TTS replaced with 50 µg/h system which the patient wore for another 25 hours during an otherwise uneventful recovery.

SCN 825- TTS 75 patient s/p cholecystectomy who had two episodes of respiratory rates of 5-6 /min at 14 & 18 hours postoperatively. TTS dose was reduced to 50 µg/h and a single dose of 0.1 mg naloxone was given. The patient wore the smaller system for another 48 hours during an uneventful recovery.

SCN 832- TTS 75 patient s/p laparotomy who developed a bradypnea of 7-10 breaths /min 14 hours after surgery. TTS dose was reduced to 50 µg/h for the remainder of the study period, followed by uneventful recovery.

SCN G 10- TTS 75 patient s/p hip arthroplasty who became somnolent 15 hours after TTS application. ABG showed pO2 72 & pCO2 59. TTS left in place and 2.6 mg naloxone given over 5 hours to allow the TTS system to remain in place a full 24 hours as per protocol. No sequelae.

Of the cases who had respiratory depression, nine of thirteen (69%) had had a combination of a procedure which impaired respiratory mechanics and a blood fentanyl level above 2.0 ng/ml. Twenty five individuals who wore TTS 100 µg/h systems had thoracic surgery, and four of those had respiratory depression (4/25=**16%**). Eighty individuals wore TTS 100 µg/h systems had surgeries other than chest surgery and three had respiratory depression (3/80=**4%**). In the absence of additional data it is presumed that the combination of impaired ventilatory mechanics and the high dose (TTS 100) patch results in an unaccpetable frequency of respiratory depression (Relative Risk = 4).

No individual information is available regarding the fentanyl clearance of the individuals who had adverse respiratory events, but the following table shows the relationship between body weight, TTS dose, blood level, and the risk of respiratory depression.

Weight Class	Number At Risk	Cases of Respiratory Depression	75 µg TTS	100 µg TTS	Frequency (Percent)
< 63 kg	97	9	4	5	9%
64-74 kg	98	1	0	1	1%
75-83 kg	83	2	2	0	2%
> 84 kg	77	1	0	1	1%

While such finding can only be suggestive when such small numbers are involved, it seems that the combination of impaired respiration, small habitus, possible reduced fentanyl clearance, and the TTS 100 may result in an unacceptable high blood level of fentanyl and an unacceptable frequency of respiratory depression. Such events, when they occurred, were successfully treated in all cases by stimulation, TTS removal and/or naloxone administration (if required). In 5/13 cases the patients were continued on the TTS without a second episode of respiratory problems.

Opioid Side Effects

The adverse effect profile observed in the postoperative studies is as follows:

Effect	Count (TTS fentanyl)	Percentage	Placebo
Nausea	**115**	**32 %**	**26 %**
Vomiting	**80**	**22 %**	**12 %**
Urinary Retention	**37**	**10 %**	**9 %**
Pruritis	**20**	**6 %**	**3 %**
Sweating	**18**	**5 %**	**6 %**
Hypoventilation	**17**	**5 %**	**< 1%**
Headache	**13**	**4 %**	**2 %**
Hypotension	**11**	**3 %**	**1 %**
Dizziness	**9**	**2.5 %**	**3 %**
Confusion	**5**	**1 %**	**0 %**
Constipation	**4**	**1 %**	**2 %**
Dry Mouth	**4**	**1 %**	**< 1 %**
Hypertension	**4**	**1 %**	**< 1 %**
Nervousness	**4**	**1 %**	**< 1 %**
Rash	**4**	**1 %**	**< 1 %**

This pattern of adverse events is typical for an opioid agonist and is probably related to the total dose of fentanyl (TTS system) and morphine

(rescue medication) given to each patient. The combination is more likely to reflect the actual adverse effect profile in use than the TTS system when given alone.

There was no clear trend in adverse effects across all doses, although this was confounded by the use of spinal anesthesia in the 75 µg/h group. There is a suggestion that confusion and hypoventilation are dose related, but the numbers are too small to draw any definitive conclusions.

	TTS 50	TTS 75	TTS 100
Number at Risk	73	177 83 Neuraxial 94 General	105
Nausea	36	61	17
Vomiting	22	47	10
Urinary Retention	9	25	3
Pruritis	6	12	2
Sweating	1	17	0
Hypoventilation	**0**	**8**	**9***
Headache	6	6	1
Hypotension	3	4	4
Dizziness	2	6	1
Confusion	**0**	**1**	**4***

Topical Safety

The following is a tabular representation of the topical observations across 357 subjects in the postoperative studies.

Hours after Removal	Possible Erythema	Definite Erythema	Beet Red	Edema	Papules or Pustules	Itch
1	87	27	3	6	21	35
6	64	12	1	0	25	26
24	13	3	1	0	16	7

The rapid fall-off of the initial irritation suggests that there is a about a 5-10% frequency of moderate irritation (possibly related to the ethanol permeability modifier) which results in itching and a rapidly resolving irritant dermatitis. Since no patient with known skin disease was entered into the trial, and since defatting agents such as ethanol are known provocative agents in eczematoid illness, the risk of skin irritation in vulnerable indivduals is unknown.

Omissions

The following is a tabular representation of the studies not done by the sponsor in the development of this dosage form:

Study	Extent of Current Knowledge	Studies In NDA	Need for Additional Information
Kinetics in Hepatic/Renal Disease	Moderate	None	**High**
Pharmacodynamics of Respiratory Depression in Normal Subjects	Moderate	None	Moderate
Cardiovascular Effects	High	None	None
Head Injury	Low	None	None
Known Pulmonary Disease	Low	None	**High**
Biliary Surgery	Low	None	Moderate
Use in Combination with other CNS Drugs or ethanol.	Low	Limited	**High**
Use in Combination with non-narcotic analgesics (NSAIDS)	Low	None	**High**
Use in Ambulatory Patients	None	Limited	**High**
Use in Labor and Delivery	Moderate	None	Low
Use in Nursing Mothers	Low	None	Low
Use in the Aged	Moderate	Limited	Moderate
Abuse Liability Testing In Man	None	None	**Depends on Scheduling**

The opinion of the sponsor is that since the drug will be intended for use in chronic cancer pain and acute postoperative analgesia in the in-hospital setting, a full evaluation for the drug in outpatient settings and broad clinical use need not be performed. It is the opinion of the reviewer that once the clinicians learn that the TTS fentanyl system can provide continuous opioid analgesia through the night, that the system will be used in a much broader clinical population than intended. This spread beyond the use which has been evaluated in clinical trials is common to many drugs and represents an unknown hazard for all of them. It is not unsafe, by itself, but the extent of such use should be estimated, the risks identified, and their management outlined.

Based on the probable widespread use of this convenient dosage form the following phase IV studies should be considered:

1. Either find in the literature or perform an experimental study of the volume of distribution and clearance of fentanyl in patients with hepatic disorders resulting in impaired drug metabolism.

2. Performing an experimental study of the pharmacodynamic effects of TTS or IV fentanyl on oxygen saturation, respiratory rate, paCO2 (or end expiratory CO2), and CO2 sensitivity in normal volunteers in the presence and absence of a typical postoperative CNS sedative and/or alcohol. It would be prudent to include some measure of the magnitude of time course (hysteresis effects) in such a study.

3. Performing an experimental study of the pharmacodynamic effects of TTS or IV fentanyl on oxygen saturation, respiratory rate, pCO2, and CO2 sensitivity in patients with compensated COPD such as might receive the patch for same day surgery.

4. Perform abuse liability testing in experienced drug users if any schedule other than CII is desired (CIII may be possible).

Safety Conclusions

Postoperative use

The TTS fentanyl system had been shown to have typical opioid safety characteristics in clinical trials in postoperative pain. The most significant side effect observed in the trials was the capacity of the system to produce hypoventilation, hypercarbia, and hypoxia at times when the patient was asleep. This effect was clearly related to blood fentanyl level and did not occur at blood levels below approximately 2.0 ng/ml. In consequence, the 50 µg/h dose produced no such episodes, the 75 µg/h resulted in 6 episodes in 177 applications (**3%**), and the 100 caused 7 in 105 applications (**6%**). Respiratory depression was more common in patients who had had **pulmonary surgery**, received full doses of **concurrent CNS medication**, had received large amounts of **rescue analgesic**, who were **under 63 kilos in weight**, and who were **ASA Class III & higher**. It may reasonably be expected that the frequency of this adverse effect will increase should TTS use spread into more debilitated populations on the medical services and into less well supervised postoperative settings.

Until more is known about the pharmacodynamics of respiratory depression caused by low dose fentanyl it would be prudent to allow the 50 µg/h dose into general use, restrict the 75µg/h dose to clinical settings which would allow immediate recognition of hypoventilation, and restrict the postoperative use of the 100 µg/h dose to patients in closely monitored settings who have known opioid tolerance, high estimated clearance, or procedures known to cause several days of intense pain.

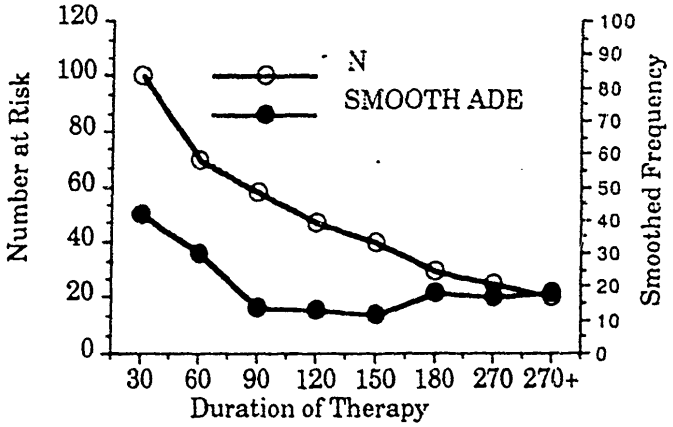
Unanswered is the question as to how clinicians should modify the doses of other concurrent analgesic or CNS active medication in patients

wearing the patch (1/2 dose?, 1/3 dose ?, 1/4 dose ?). In the absence of experimental human or animal studies a tentative suggestion would be half the usual dose, but additional data is needed in this area.

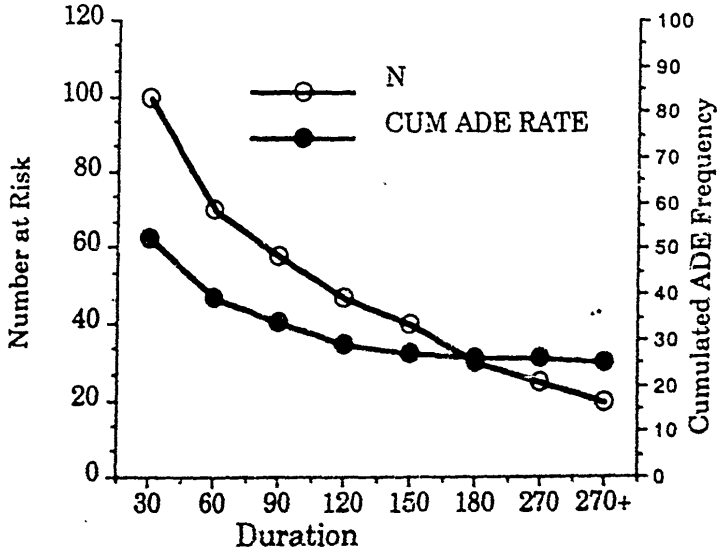
Cancer Pain

The clinical studies of TTS fentanyl in cancer patients supported its safety when used in doses of 100μg/h = 360 mg oral morphine /day. Clinicians should be advised of the desirability of starting at a low patch dose and "fading-out" the use of rescue medication as the patch dose in increased. Labeling should advise prescribers of the time course of opioid side effects seen with the system, which may be a frequent as 50% in the first month of treatment declining to 15-20% after 30-60 days. Close followup and individualized odsage adjustment during the first few weeks of treatment with TTS fentanyl in these opioid tolerant populations should allow for the clinical introduction of the TTS system without undue risk. Clinicians should be advised of the probable potentiations of respiratory depression due to common sedative drugs (hydroxizine, diphenhydramine, benzodiazpines) in individuals wearing the system and of the risk of precipitating withdrawal if naloxone must be given to individuals tolerant to high dose TTS systems.

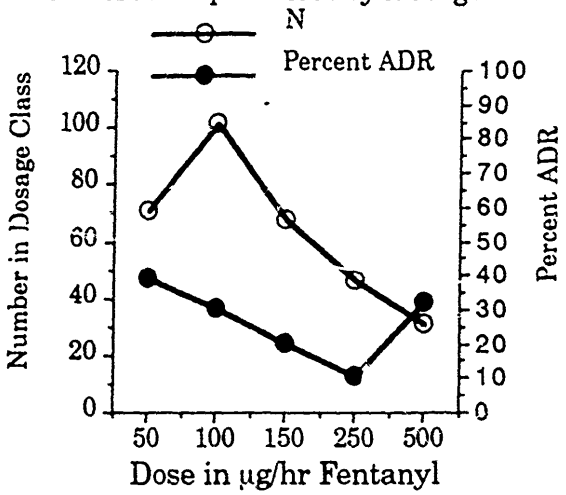
Frequency of Adverse Effects by Duration of TTS Use (Mean Smoothed Frequency)



Cumulative Frequency of Adverse Effects Plotted by Duration of TTS Therapy



Sample Size and Frequency of Adverse Experiences by Dosage



Cumulated Frequency Of Adverse Events According to TTS Size

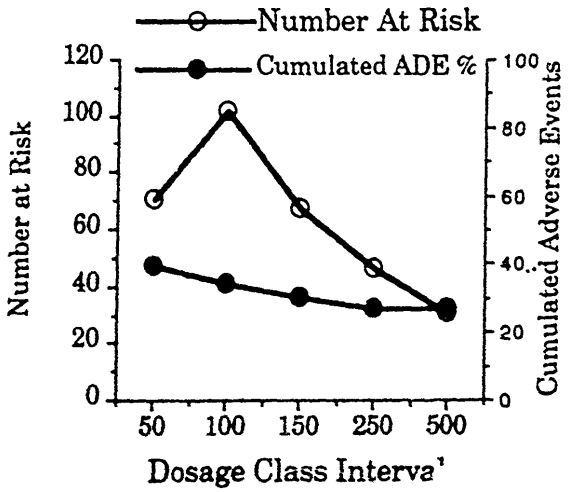


TABLE 2
PATIENT DEMOGRAPHICS

	NUMBER (%) OF PATIENTS (n=153)
Age (years):	
≤ 36	9 (5.9%)
37-47	19 (12.4%)
48-59	47 (30.7%)
≥ 60	78 (51.0%)
Sex:	
Male	77 (50.3%)
Female	76 (49.7%)
Race/Ethnic Group:	
Caucasian	135 (88.2%)
Black	17 (11.1%)
Asian	1 (0.7%)
Weight (kg):	
≤ 63	65 (42.5%)
64-83	50 (32.7%)
≥ 84	23 (15.0%)
ND*	15 (9.8%)
Height (cm):	
≤ 163	35 (22.9%)
164-179	71 (46.4%)
≥ 180	29 (19.0%)
ND*	18 (11.8%)
Diagnosis:	
Gastrointestinal Malignancies	39 (25.5%)
Breast Cancer	29 (19.0%)
Lung Cancer	23 (15.0%)
Other Solid Tumors	21 (13.7%)
Head and Neck Cancers	17 (11.1%)
Prostatic Cancer	11 (7.2%)
Hematologic Cancers	9 (5.9%)
Sarcomas or AIDS	4 (2.6%)

* ND = No Data Reported

TABLE 3

Patient Exposure by Initial TTS (fentanyl) Dose*

TTS (fentanyl) Dose (mcg/hr)	Number of Patients (n=153)
25	28 (18.3%)
50	50 (32.7%)
75	32 (20.9%)
100	18 (11.8%)
125	7 (4.6%)
150	9 (5.9%)
175	1 (0.7%)
200	5 (3.3%)
225	1 (0.7%)
275	1 (0.7%)
300	1 (0.7%)

* NOTE: When the required TTS (fentanyl) dose exceeded 100 mcg/hr, multiple systems were applied to achieve the appropriate delivery rate.

TABLE 4

Duration of TTS (fentanyl) Therapy*

	1-3 Days	4-15 Days	16-30 Days	31-60 Days	61-90 Days	91-120 Days	Over 120 Days
No. of Pts. (n=153)	153	136	94	85	65	52	43
Percent (%)	100	88.9	61.4	55.6	42.5	34.0	28.1

* Includes days on therapy under compassionate use amendment.

TABLE 7

Patient Withdrawals by Treatment Period

	1-3 Days	4-15 Days	16-30 Days	31-60 Days	61-90 Days	91-120 Days	Over 120 Days
No. of Pts. Terminating Therapy (n=115)	7	22	9	20	13	9	35

TABLE 16

ADVERSE EXPERIENCES WITH FREQUENCIES
>1 IN DESCENDING ORDER

Cancer Patients

ADVERSE EXPERIENCE	NUMBER (%) OF PATIENTS (n = 153)
Nausea	35 (23%)*
Vomiting	33 (22%)*
Somnolence	26 (17%)
Sweating	22 (14%)*
Constipation	22 (14%)*
Confusion	20 (13%)
Dry Mouth	20 (13%)*
Asthenia	19 (12%)*
Anorexia	12 (8%)*
Dizziness	11 (7%)*
Lung Disease	10 (7%)
Nervousness	9 (6%)
Diarrhea	8 (5%)*
Dyspepsia	7 (5%)*
Dyspnea	6 (4%)
Pruritis	6 (4%)*
Hypoventilation	6 (4%)
Application Site Reaction	6 (4%)
Urinary Retention	5 (3%)*
Apnea	5 (3%)
Hallucinations	5 (3%)
Anxiety	5 (3%)
Gas Pain	5 (3%)
Headache	4 (3%)
Depression	4 (3%)
Euphoria	4 (3%)
Thinking Abnormal	3 (2%)
Hemoptysis	3 (2%)
Arrythmia	3 (2%)
Coordination Abnormal	3 (2%)
Speech Disorder	3 (2%)
Tremor	3 (2%)
Pharyngitis	3 (2%)
Flatulence	2 (1%)
Tachycardia	2 (1%)
Dreams Abnormal	2 (1%)
Chest Pain	2 (1%)
Rash	2 (1%)
Hiccoughs	2 (1%)
Hypotension	2 (1%)
Numbness	2 (1%)
Gait Abnormal	2 (1%)
Agitation	2 (1%)
Parasthesia	2 (1%)
Amnesia	2 (1%)
Hiccoughs	2 (1%)
Paranoid Reaction	2 (1%)

TABLE 9

ADVERSE EXPERIENCES WITH FREQUENCIES > 1% IN DESCENDING ORDER DURING 0-24 HR PERIOD*
ALL PATIENTS

	Treatment	
	TTS (fentanyl)	TTS Placebo
No. of Patients Treated:	357	235
Time at which Adverse Experience Occured:	0-24 hrs*	0-24 hrs*
No. (%) of Patients with Adverse Experiences:	214 (59.9%)	107 (45.5%)
	No. (%) Patients with Adverse Experience	
Adverse Experience:		
Nausea	115 (32.2%)	61 (26.0%)
Vomiting	80 (22.4%)	27 (11.5%)
Urinary Retention	37 (10.4%)	22 (9.4%)
Pruritus	20 (5.6%)	7 (3.0%)
Sweating	18 (5.0%)	14 (6.0%)
Hypoventilation	17 (4.8%)	2 (<1%)
Headache	13 (3.6%)	5 (2.1%)
Hypotension	11 (3.1%)	3 (1.3%)
Dizziness	9 (2.5%)	8 (3.4%)
Confusion	5 (1.4%)	0
Constipation	4 (1.1%)	4 (1.7%)
Dry Mouth	4 (1.1%)	1 (<1%)
Hypertension	4 (1.1%)	1 (<1%)
Nervousness	4 (1.1%)	2 (<1%)
Rash	4 (1.1%)	1 (<1%)

TABLE 3
(page 2 of 2)

DEMOGRAPHICS AND TYPE OF SURGERY SUMMARY BY TREATMENT ASSIGNMENT

	Total Number of Patients	Number (%) of Patients Receiving TTS (fentanyl) N = 357	Number (%) of Patients Receiving TTS Placebo N = 235
Type of Surgery:			
Abdominal	251	162 (45.4%)	89 (37.9%)
Orthopedic	152	85 (23.8%)	67 (28.5%)
Lumbar	71	44 (12.3%)	27 (11.5%)
Urologic	51	26 (7.3%)	25 (10.6%)
Thoracic	40	25 (7.0%)	15 (6.4%)
Vaginal	10	8 (2.2%)	2 (<1%)
Head and Neck	7	2 (<1%)	5 (2.1%)
Mastectomy	1	1 (<1%)	0
Cancelled Surgeries	9	6 (1.1%)	5 (2.1%)

TABLE 15
(Page 1 of 2)

ADVERSE EXPERIENCES DURING TTS APPLICATION
(0-24 HRS) BY TTS (FENTANYL) DOSE
ALL PATIENTS

	TTS (fentanyl) Dose (mcg/hr)			
	TTS-25	TTS-50	TTS-75	TTS-100
Patients Treated:	2	73	177	105
	No. (%) of Patients			
Adverse Experience:				
Body as a Whole				
Headache	0	6 (8%)	6 (3%)	1 (<1%)
Chills	0	0	3 (2%)	0
Pain Abdominal	0	1 (1%)	1 (<1%)	0
Cardiovascular				
Hypotension	0	3 (4%)	4 (2%)	4 (4%)
Hypertension	0	3 (4%)	1 (<1%)	0
Arrhythmia	0	2 (3%)	1 (<1%)	0
Bradycardia	0	0	3 (2%)	0
Vasodilation	0	0	3 (2%)	1 (<1%)
Fibrillation Atrial	0	0	1 (<1%)	0
Pain Chest	0	0	1 (<1%)	0
Palpitation	0	0	1 (<1%)	0
Tachycardia	0	0	1 (<1%)	0
Digestive				
Nausea	1 (50%)	36 (49%)	61 (34%)	17 (16%)
Vomiting	1 (50%)	22 (30%)	47 (27%)	10 (10%)
Constipation	0	0	4 (2%)	0
Dry Mouth	0	1 (1%)	3 (2%)	0
Nervous				
Dizziness	0	2 (3%)	6 (3%)	1 (<1%)
Confusion	0	0	1 (<1%)	6 (4%)
Nervousness	0	0	2 (1%)	2 (2%)
Agitation	0	0	1 (<1%)	2 (2%)
Speech Disorder	0	0	2 (1%)	1 (<1%)
Dream Abnormal	0	0	1 (<1%)	1 (<1%)
Somnolence	0	0	2 (1%)	0
Anxiety	0	0	1 (<1%)	0
Depersonalization	0	0	1 (<1%)	0
Hallucinations	0	0	1 (<1%)	1 (<1%)
Hostility	0	0	0	1 (<1%)
Paresthesia	0	0	1 (<1%)	0
Tremor	0	0	1 (<1%)	0
Other				
Bleeding at Operative Site	0	0	0	0

TABLE 15
(Page 2 of 2)

ADVERSE EXPERIENCES DURING TTS APPLICATION
(0-24 HRS) BY TTS (FENTANYL) DOSE
ALL PATIENTS

	TTS (fentanyl) Dose (mcg/hr)			
	TTS-25	TTS-50	TTS-75	TTS-100
Respiratory				
Hypoventilation	0	0	8 (5%)	9 (9%)
Asthma	0	0	1 (<1%)	0
Dyspnea	0	0	1 (<1%)	0
Hemoptysis	0	0	1 (<1%)	0
Hiccups	0	0	1 (<1%)	0
Infection	0	0	0	1 (<1%)
Pharyngitis	0	1 (1%)	0	1 (<1%)
Stertorous Breathing	0	0	1 (<1%)	0
Skin and Appendages				
Pruritus	0	6 (8%)	12 (7%)	2 (2%)
Sweating	0	1 (1%)	17 (10%)	0
Rash	0	0	3 (2%)	1 (<1%)
Special Senses				
Amblyopia	0	1 (1%)	2 (1%)	0
Urogenital				
Urinary Retention	0	9 (12%)	25 (14%)	3 (3%)
Pain Bladder	0	0	3 (2%)	0
Oliguria	0	1 (1%)	0	1 (<1%)

NUMBER (%) OF TTS (FENTANYL) PATIENT-DAYS WITH TOPICAL EFFECTS
FOLLOWING TTS REMOVAL COMPARED TO PLACEBO
DOUBLE-BLIND STUDIES

Hours After Removal	Treatment Group	Barely Perceptible Erythema	Definite Erythema	Beet Red Erythema	Edema	Papules*	Pustules*	Papules/ Pustules**	Itching***
1	Fentanyl (n = 256)	42 (16%)	21 (8%)	2 (<1%)	6 (2%)	8 (4%)	1 (<1%)	6 (8%)	20 (8%)***
	Placebo (n = 256)	28 (11%)	14 (5%)	0	8 (3%)	2 (1%)	1 (<1%)	1 (1%)	2 (<1%)
6	Fentanyl (n = 252)	33 (13%)	9 (4%)	0	0	9 (5%)	2 (1%)	5 (7%)	13 (5%)
	Placebo (n = 252)	22 (9%)	10 (4%)	0	0	3 (2%)	1 (<1%)	5 (7%)	2 (<1%)
24	Fentanyl (n = 244)	10 (4%)	3 (1%)	0	0	6 (4%)	1 (<1%)	3 (4%)	7 (3%)
	Placebo (n = 256)	5 (2%)	2 (<1%)	0	0	2 (1%)	1 (<1%)	2 (3%)	2 (<1%)

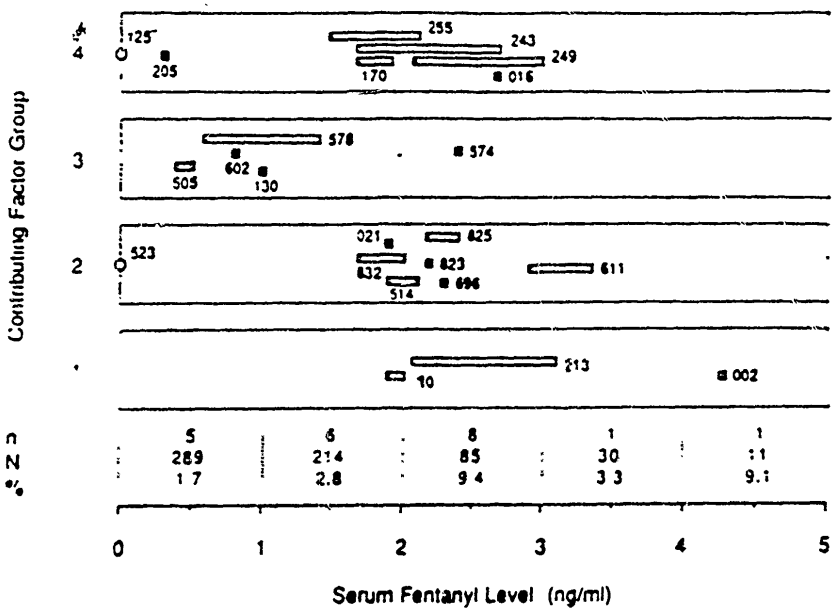
Hour 1: Fentanyl - n=183, Placebo - n=183 Hour 6: Fentanyl - n=179, Placebo - n=179 Hour 24: Fentanyl - n=171, Placebo - n=183

** The [illegible] German studies combined observations of papules and pustules (N=73 for both fentanyl and placebo groups).

*** [illegible] and moderate itching

Figure 3

ALL PATIENTS IDENTIFIED WITH
RESPIRATORY DEPRESSION OR OVERSEDATION



CONTRIBUTING FACTOR GROUPS:

4 Contributing effect of an underlying medical condition
3 Contributing effect of residual anesthesia or a concomitant non-narcotic
2 Contributing effect of a concomitant narcotic
1 No obvious contributing factor (primary effect of TTS fentanyl)

---

n Number of cases occuring within the specified interval

N Number of patients at risk (see text)

% n/N (as percent)

■ Denotes a serum fentanyl level that was obtained within 1 hour of an episode of respiratory depression

▭ Denotes the most proximate serum fentanyl levels before and after an episode of respiratory depression, when neither was obtained within 1 hour of the episode

o Denotes a placebo patient with an episode of respiratory depression (no serum fentanyl level)

Figure 3

ALL PATIENTS IDENTIFIED WITH
RESPIRATORY DEPRESSION OR OVERSEDATION

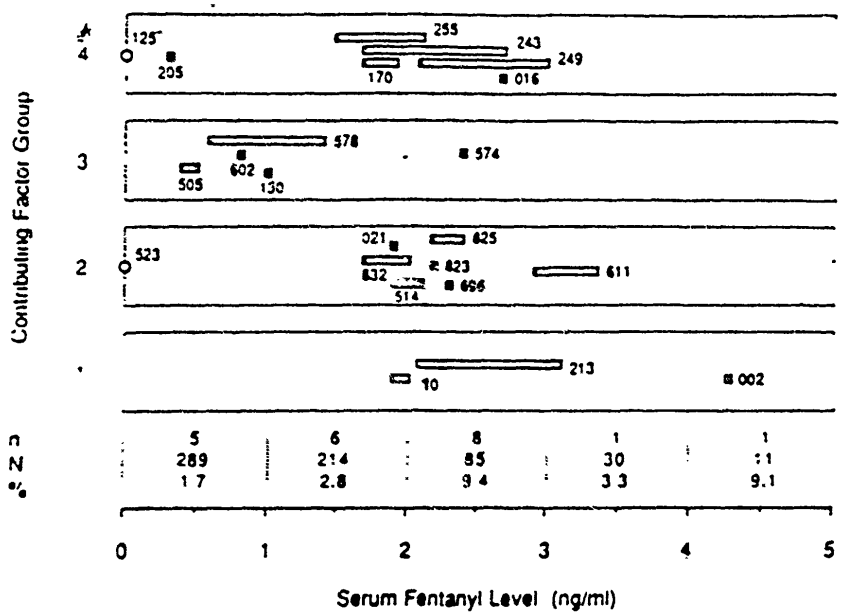


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TABLE 23

DEMOGRAPHICS AND TYPE OF SURGERY SUMMARY FOR TTS (FENTANYL)
PATIENTS WITH RESPIRATORY DEPRESSION DURING WARD TO REMOVAL PERIOD

	Number of TTS (fentanyl) Patients with Respiratory Depression (n=18)	Percent (%) of Patients at Risk (n=357)
Age (years):		
≤36	7	8.2%
37-47	3	3.4%
48-59	3	3.2%
≥60	5	5.7%
Sex:		
Male	6	3.6%
Female	12	6.4%
Weight (kg):		
≤63	10	10.3%
64-83	6	3.3%
≥84	2	2.6%
ASA Classification*:		
I	8	5.9%
II	5	4.3%
III	3	6.4%
IV	2	50.0%
Type of Surgery:		
Abdominal	9	5.6%
Orthopedic	3	3.5%
Lumbar	1	2.3%
Thoracic	5	20.0%
Head and Neck	0	
Mastectomy	0	
Vaginal	0	
TTS (Fentanyl) Dose		
100 mcg/hr - 40 cm^2	9	8.6%
75 mcg/hr - 30 cm^2	9	5.1%
50 mcg/hr - 20 cm^2	0	
25 mcg/hr - 10 cm^2	0	

* No Data

TABLE 24

NUMBER (%) OF PATIENTS WITH RESPIRATORY DEPRESSION ON ITS (FENTANYL) THERAPY BY WEIGHT, PATIENT LOCATION AND DOSE

Weight Group:	≤ 63 Kg		64-74 Kg		75-83 Kg		≥ 84 Kg		Total	
ITS (fentanyl)										
Number at Risk:	97		98		83		77		357	
	OR/PAR*	Ward to Removal**	OR/PAR	Ward to Removal	OR/PAR	Ward to Removal	OR/PAR	Ward to Removal	OR/PAR	Ward to Removal
ITS (fentanyl) Dose										
ITS (fentanyl) - 100	2 (2%)	3 (3%)	0	2 (2%)	0	1 (1%)	0	1 (1%)	2 (<1%)	7 (2%)
ITS (fentanyl) - 75	1 (1%)	4 (4%)	1 (1%)	0	1 (1%)	1 (1%)	1 (1%)	0	4 (1%)	5 (1%)
ITS (fentanyl) - 50	0	0	0	0	0	0	0	0	0	0
Total	3 (3%)	7 (7%)	1 (1%)	2 (2%)	1 (1%)	2 (2%)	1 (1%)	1 (1%)	6 (2%)	12 (3%)
ITS Placebo										
Number at Risk:	49		61		67		58		235	
Placebo	0	1 (2%)	0	0	0	0	0	1 (2%)	0	2 (<1%)

Medical Officer Review
NDA #: 19,813
Alza Corporation

TTS Fentanyl

(Transdermal Therapeutic System)

Volume 5 - Abuse and Diversion

Submitted: 4/10/90
Curtis Wright MD,MPH

Written CWIV 5/16/90
Peer Reviewed MK 5/25/90
Reviewed by Sponsor MS 6/19/90
Rewritten CWIV 6/19/90

General Comments Regarding the Abuse Liability of TTS Fentanyl

The submission by this sponsor of an NDA for a new dosage form for fentanyl posed a new regulatory problem. It was the first of many "non-injection" parenteral delivery systems for older drugs, where modification of the pharmacokinetics of the delivery of an agent reveals a new dimension of the pharmacodynamic spectrum of the drug. Recent experience with the enhancement of the addictive potential of intranasal cocaine by its conversion to smoked cocaine or "crack", stands as a warning of the possibility of significantly altering the abuse pattern of a known drug of abuse by a change in the dosage form. As our ability to predict the abuse liability of drugs improves the relationship of the pharmacokinetics of the delivery system to the pharmacodynamics of abuse has become an important dimension in the evaluation of both licit and illicit narcotic drugs.

Fentanyl is not currently a drug of abuse for the general population, although the persistence of clandestine synthesis and illicit distribution shows that it is a desirable drug of abuse. The current low prevalence of abuse is probably due to the relative scarcity of access to the drug. Among health care providers with high access to the drug (anesthesiologists, operating room personnel, intensive care unit staff) it remains a significant drug of abuse and is second only to meperidine in total number of addicted health care professionals.

The TTS fentanyl system will be available from pharmacies, clinics, and patient's homes as well as the relatively controlled operating and recovery room environment. In order to evaluate the abuse liability of this new dosage form it will be necessary to answer the following questions:

1. What is the abuse and dependence potential of the TTS system to the intended users when used as directed?

2. What is the risk of abuse and dependence of the TTS system to health care providers handling the system?

3. What is the abuse and diversion potential of the intact TTS system?

4. What is the magnitude of the risk posed by the fentanyl in used or removed patches and what measures should be taken to control such risks?

In an attempt to answer these questions a meeting was held on the 21st of February 1990 between representatives of the sponsor, FDA, NIDA, and DEA. The following is a review of that meeting and material provided by DEA, NIDA, and the sponsor addressing these questions.

Risk of abuse of TTS When Used as Directed

There was universal agreement among the parties to the meeting that the TTS system had pharmacokinetic properties which gave it less abuse potential than IV or IM fentanyl when used as directed. The TTS system

provides a slow onset of narcotic effect (6-8 hours), sub-euphoric peak levels (0.75-2.5 ng/ml), and a long duration of action (>72 hours). This profile is similar to phenobarbital which is not subject to frequent abuse. When the TTS system is contrasted with the alternative drugs used in both post-operative pain and in cancer pain (morphine, hydromorphone, codeine, meperidine, pentazocine), the TTS system has a profile which predicts a lower rate of de-novo abuse than similar mu agonist narcotics with a more rapid onset and a higher peak-to-trough difference in the magnitude of opioid effects.

In consequence, there was consensus that the TTS system, when used as directed, poses no greater risk of abuse and addiction in the opioid-naive user and has less theoretical risk of abuse than current therapy.

Risk of Abuse and Diversion by Health Care Providers

Fentanyl is an attractive drug of abuse for health care providers with established opioid drug dependence. Its abuse among the public is currently limited by poor availability and is greatest in settings where covert medical diversion by the impaired professional is easiest (anesthesiologists, OR nurses, ICU staff). Fentanyl addiction is rare outside of medical personnel with direct access to the drug in daily practice owing to the fact that use of the drug outside of the usual settings would be extremely conspicuous and easily detected. A major concern about TTS fentanyl would be if the system itself, or the contents of the system could be used to provide a medical professional with an abused dose of the drug.

Risk of Abuse by TTS Application- The sponsor made inquiries to rehabilitation programs handling impaired professionals and determined that the minimum abused dose of fentanyl was about 250 micrograms IM or IV used 10-15 times a day. Fentanyl IV has been fit with tri-exponential kinetic models with the duration of action controlled by redistribution into a large Vss of 280 liters for a 70 kg adult. Given an apparent central volume of 5-10 liters the probable euphoric blood level for IV abuse in the experienced and tolerant user is at least 25 and may be as great as 50 ng/ml which require application of as many as 10-20 intact TTS systems to acheive this blood level. Given the controlled rate of delivery of the system, abuse for euphoria of the intact system is not likely, but it may be used by impaired professionals who might use it to control opiate withdrawal symptoms. Such usage poses no increased risk over diversion of other opiates available to such individuals.

Abuse of the Fentanyl Contained in the system- The TTS system consists of a gel-filled reservoir, a membrane, and a sticky adhesive-covered surface. It was the opinion of the meeting that abuse by health care providers would take the form of attempting to abuse the fentanyl gel in the reservoir, rather than abusing the intact unit. This was verified by interviews conducted by the sponsor with ten health professionals undergoing treatment for opioid drug dependence, half of whom reported they would attempt to recover the contents of a fentanyl system. To investigate this possibility the sponsor and the DEA were set about parallel investigations regarding the ease of recovery of abusable fentanyl from the TTS.

ALZA DATA- The sponsor tried a variety of methods of removing the fentanyl from new systems with a nominal initial drug content of 10 mg (TTS 100) with the following results:

Technique	Amount Recovered	% of Daily Addict Dose
Direct withdrawal by 24 ga. needle from adhesive side of patch (undetectable)	None (Too Viscous)	0
Withdrawal from upper surface via 19-ga needle (Easily detected by inspection)		
Single extraction	0.14 mg	3%
Multiple extractions	2.20 mg	58%
Cut corner-squeeze out gel	2.40 mg	64%
Inject water-withdraw with syringe	2.80 mg	74%
Inject water-cut and squeeze	3.90 mg	100%

Given a mean daily usage of 2.5-4.0 mg/day as 10-15 separate injections the most that could be easily removed from a TTS system without chemical extraction would be a single day's worth of fentanyl for a single addict, and systems which had been subject to such tampering would be easily detected in the hospital environment.

Diversion of Used Systems- A second concern involved the possible diversion of used patches for their fentanyl content by hospital personnel. This was addressed by the sponsor and DEA, with the sponsor providing the following data on the 75 µg/h (7.5 mg) TTS system.

Drug Distribution	Fentanyl (mg)
Total in TTS system at start	7.5 mg
Remaining after 72 hours	3.0 mg
Held in adhesive	1.9 mg
Held in membrane	0.5 mg
Free in reservoir	0.6 mg

It was the conclusion of the sponsor that no fentanyl remained free in the system for direct withdrawal after use, and that methanol extraction would be required to remove it from the adhesive layer. While such "re-manufacture is possible and may be attractive if a criminal group has access to a large number of systems, easy abuse by an individual addict is unlikely.

Risk to Health Care Providers- Conclusion

The data presented provides significant assurance that the new dosage form of fentanyl does not provide widened, easy access to the drug in an abusable form. There does not appear to be any increased risk to this vulnerable population, owing chiefly to the fact that less than 25% of the fentanyl may be recovered without using extraction techniques, and only half of the interviewed addicts would consider ever attempting to inject fentanyl removed from the systems.

Diversion- NIDA Perspective

Dr. Jim Cooper of NIDA reviewed the data on the TTS system and provided an opinion that the recoverable fentanyl posed no more of a threat of diversion than the usual post-operative analgesics in the hospital environment, and that TTS systems were less prone to diversion than the currently used oral morphines and hydromorphone cancer analgesics.

Safety and Handling of TTS systems

There was considerable discussion of the possible abuse of the TTS system as well as a possible safety hazard if the reservoir was breached and the contents were spread over a wide skin area. Investigation showed that the skin permeability in the absence of the ethanolic enhancer (0.75 µg/sq.cm/h) was about 1/2 of the flux observed under the system (1.4 µg/sqcm/h). It was also learned that the amount of fentanyl required to establish a concentration gradient across the stratum corneum was about 5 µg/cm2, and that a 1.0 ml volume of thickened gel could be spread across 200-400 cm2. These values for the amount required to establish the gradient, the area, and the amount in the gel, can predict the probable result of intentional misuse of the product. Of the 2.4 mg in the gel, 1.5 mg would be used up in establishing the gradient and the probable peak flux would be 200-300 µg/h for 3 hours or so giving a peak blood level of below the euphoric or analgesic range.

Of greater probable importance is the possibility of diversion of the new or used systems and criminal "de-manufacture" to obtain the fentanyl for resale. Mr. Howard McClain Jr. of DEA requested new and used TTS systems to determine the ease of recovery by re-manufacture of fentanyl from new or used systems and assessment of the risk posed by the used patches. The results of their analysis may not be available by NDA day, but will allow them to prepare for possible criminal activity in this area. The current DEA quoted median wholesale price of a kilo of heroin is $60,000 establishing a wholesale floor price of $0.06/mg for heroin and a wholesale price of $6.00 per 100 mg/day habit. If there is 9 mg of

recoverable fentanyl per new 100 μg/h system (90% extraction) and the typical fentanyl habit is 3 mg/day (Gallegos data) then if the cost of obtaining the TTS system exceeds $18.00 heroin is more profitable.As the estimated wholesale price of the system exceeds $20/unit, wholesale diversion will result in a net loss to the criminal and is unlikely. Individual extraction and use remains possible, but its frequency will depend on the complexity of the technique required to separate the abusable fentanyl from the irritant carboxymethylcellulose in the reservoir.

Manufacture of the TTS systems will require substantial increases in the quota for fentanyl owing to the increased use. The current wholesale price of fentanyl is $6000/kilo, and a kilo of fentanyl corresponds to about 20-30 kilos of heroin. Increased manufacture of the bulk drug will make diversion more likely since diversion of a kilo of fentanyl represents a potential profit at the wholesale level of approximately 2 million dollars. This was discussed with the representative of DEA who said that such a risk was acceptable to the law enforcement community if there was good evidence that the new product would serve a legitimate medical need.

Disposal of Used Systems- Considerable time went into discussions of how best to dispose of the used TTS which might contain significant amounts of fentanyl. Discussions and proposals ranged from return to the manufacturer, return to the hospital pharmacy, and on-site destruction. Ultimately it was decided that the best method was to fold the system in half, sticky sides together, and flush it down the toilet. The sponsor was then asked for an environmental analysis and obtained the following data.

According to the Association of Metropolitan Sewage Agencies, the Water Pollution Control Federation and the National Water Resources Federation, the folded system (a 4 x 10 sq cm polyester plastic square) would be treated as a skimmable non-biodegradeable similar to a condom. Current wastewater system condom loading is 156 million flushed per year, such that if the current projection of 4 million TTS systems flushed per year the addition to the skimmables would be less than 2%, which was deemed acceptable by those surveyed. None of those surveyed felt that there was a real risk of anyone attempting to recover the TTS from among the skimmed material at the sewage treatment plant. There was agreement that flushing should not be a routine recommended measure of disposal for all transdermal systems, but that to do so with products subject to abuse would pose no problem.

Abuse and Diversion- Conclusion

Although the attendance at the meeting was evidence that there was significant concern regarding the possibility of abuse associated with TTS fentanyl, the data presented by the sponsor suggests that the risk to addicts, health care professionals, and the general public from the new dosage form is minimal. There is no bar to the approval of TTS fentanyl on the basis of excessive risk of abuse or diversion.

As fentanyl is currently a schedule II controlled substance no new action need be taken to schedule the TTS system, although it might be argued by the sponsor that the system should have a less-restrictive Schedule III classification. Consideration might be given to such an action for the TTS dosage form of fentanyl as part of an ongoing policy to enhance the attractiveness of less abusable alternatives to parenteral morphine in medical practice.

Curtis Wright MD

NDA 19813

ENVIRONMENTAL

IMPACT

STATEMENT

alza

CONFIDENTIAL

ENVIRONMENTAL ASSESSMENT

TYPE 1 - PROPOSED DRUG APPROVAL

PRODUCT: TTS (Fentanyl)

1. Date: 22 October 1987

2. Name of Applicant: ALZA Corporation

3. Address: ALZA Corporation
950 Page Mill Road
Palo Alto, CA 94304

4. Description of Proposed Action

The proposed action is approval of the New Drug Application (NDA) for TTS (fentanyl). The NDA is needed in order to make available to the public this medication for the treatment of moderate to severe pain. The product will be used by consumers throughout the United States. Unused portions of the dosage form will be discarded by consumers.

The product will be manufactured, packaged and labeled by ALZA Corporation at their Palo Alto, CA facility. This plant is located in the Stanford Industrial Park, a short distance south of Stanford University. The area is zoned Industrial and is primarily occupied by research oriented, light industrial firms. A residential neighborhood is located a block away and major building and site improvements have to receive approval from an Architectural Review Committee.

Components of the dosage form may also be manufactured, under contract to ALZA, by the following:

5. Identification of Drug Substance

Drug substance is fentanyl base.

Nomenclature: N - Phenyl - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] propanamide

alza

CONFIDENTIAL

ENVIRONMENTAL ASSESSMENT

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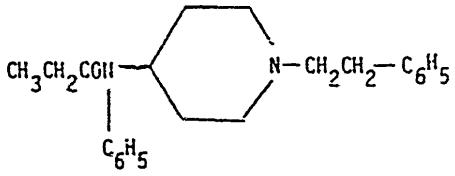
CAS Registration Number: 437-38-7

Molecular Weight: 336.46

Physical Description: White to off-white crystalline solid

Empirical Formula: $C_{22}H_{28}N_2O$

Structural Formula:



6. Introduction of Substances into the Environment

The following substances may be emitted:
- formulation components
- defective or damaged dosage systems
- waste paper
- waste foil
- trace amounts of solvent -

The applicable Federal, State and Local emission regulations for the Palo Alto Plant are:
- Federal Clean Air Act
- Federal Resource Conservation and Recovery Act (RCRA)
- State of California Hazardous Waste Control Law
- Bay Area Air Quality Management District Regulations
- San Francisco Regional Water Quality Control Board
- City of Palo Alto Sewer Use Ordinance

The plant is in compliance with the applicable emission requirements.

Approval of the NDA will have no adverse effect upon compliance with emissions regulations at the Palo Alto Plant.

For manufacturing sites other than ALZA, see attached list of substances that may be emitted, along with a citation of applicable Federal, State, and Local requirements for each site.

7. Fate of Substances Emitted into the Environment

Non-hazardous items (spent air filters, solids from formulation components, used cleaning implements, waste paper from packaging and labeling) will be drummed for disposal in approved land fills or by incineration, as necessary. Since the active ingredient is a controlled substance, waste drug and/or dosage systems will be delivered to a regional office of the Drug Enforcement Agency for disposal.

Trace amounts of formulation components not trapped by filters and trace amounts of solvent vapor not trapped by pollution abatement equipment will be liberated to the atmosphere.

As a result of equipment cleaning, trace amounts of formulation components, after dilution, filtering, and neutralizing, will be fed to the sanitary sewer system.

8. Environmental Effects of Released Substances

Trace amounts of solvent will be emitted into the air, in accordance with applicable environmental regulations. The solvent will be at negligible concentration in the air stream. Landfilling of the non-hazardous components such as paper will not release significant quantities of harmful compounds into the ground.

9. Use of Resources and Energy

There will be minimum depletion of natural resources used to manufacture components of this system. Energy will be used in the operation of the equipment.

There will be no effect on any endangered species.

There will be no effect on any property listed in the National Register of Historic Places.

10. Mitigation Measures

The handling measures outlined herein have been implemented as a measure to mitigate the effect of this production process on the environment. No further measure is required. The entire production operation will be carried out under the supervision of qualified personnel, with training provided for normal and emergency operations.

11. Alternative to Proposed Action

The alternative to approval of the NDA is to prevent this medication from being available to the public.

12. List of Preparers

Douglas S. Burhyte, Manager, Process Engineering, ALZA

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13. The undersigned official certifies that the information presented is true, accurate, and complete to the best knowledge of the firm or agency responsible for preparation of the environmental assessment.

11/3/87
Date

Signature of Responsible Official

V.P. MFG
Title