

discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light, should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

The anti-anabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Usage in Pregnancy

(See above **WARNINGS** about use during tooth development).

Doxycycline for injection has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in Children

The use of doxycycline for injection in children under 8 years is not recommended because safe conditions for its use have not been established. (See above **WARNINGS** about use during tooth development).

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

PRECAUTIONS:

Prescribing doxycycline in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

In venereal diseases when coexistent syphilis is suspected, a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

Pregnancy

Teratogenic Effects: Pregnancy Category D

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS—the Teratogen Information System—concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.¹

A case-control study (18,515 mothers of

infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. (Sixty-three (0.19%) of the controls and 56 (0.3%) of the cases were treated with doxycycline). This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases.²

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.³

Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown.⁴ Because of the potential for adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see **WARNINGS**).

Information for Patients

Patients should be counseled that antibacterial drugs including doxycycline should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When doxycycline is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by doxycycline or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

ADVERSE REACTIONS:

Gastrointestinal

Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Skin

Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see **WARNINGS**).

Renal Toxicity

Rise in BUN has been reported and is apparently dose related (see **WARNINGS**).

Hypersensitivity Reactions

Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus.

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Blood

Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSE AND ADMINISTRATION:

NOTE: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE FOR INJECTION (100 TO 200 MG/DAY) DIFFERS FROM THAT OF THE OTHER TETRACYCLINES (1 TO 2 G/DAY). EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Studies to date have indicated that doxycycline hyclate at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Adults

The usual dosage of doxycycline for injection is 200 mg on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg depending upon the severity of infection, with 200 mg administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

For Children Above Eight Years of Age

The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg/lb of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used (see **WARNINGS, Usage in Children**).

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 1 mg/lb (2.2 mg/kg) of body weight, twice a day in children weighing less than 100 lb (45 kg). Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

General

The duration of infusion may vary with the dose (100 to 200 mg/day), but is usually one to four hours. A recommended minimum infusion time for 100 mg of a 0.5 mg/mL solution is one hour. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly or subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

PREPARATION OF SOLUTION:

To prepare a solution containing 10 mg/mL, the contents of the vial should be reconstituted with 10 mL (for the 100 mg/vial container) or 20 mL (for the 200 mg/vial container) of Sterile Water for Injection or any of the 10 intravenous infusion solutions listed below. Each 100 mg of doxycycline for injection (i.e., withdraw entire solution from the 100 mg vial) is further diluted with 100 mL to 1,000 mL of the intravenous solutions listed below. Each 200 mg of Doxycycline for Injection (i.e., withdraw entire solution from the 200 mg vial) is further diluted with 200 mL to 2,000 mL of the following intravenous solutions:

1. Sodium Chloride Injection, USP
2. 5% Dextrose Injection, USP
3. Ringer's Injection, USP
4. Invert Sugar, 10% in Water
5. Lactated Ringer's Injection, USP
6. Dextrose 5% in Lactated Ringer's
7. Normosol-M[®] in D5-W (Abbott)
8. Normosol-R[®] in D5-W (Abbott)
9. Plasma-Lyte[®] 56 in 5% Dextrose (Baxter)
10. Plasma-Lyte[®] 148 in 5% Dextrose (Baxter)

This will result in desired concentrations of 0.1 to 1 mg/mL. Concentrations lower than 0.1 mg/mL or higher than 1 mg/mL are not recommended.

Stability

Doxycycline is stable for 48 hours in solution when diluted with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to concentrations between 1 mg/mL and 0.1 mg/mL and stored at 25°C. Doxycycline in these solutions is stable under fluorescent light for 48 hours, but must

be protected from direct sunlight during storage and infusion. Reconstituted solutions (1 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Doxycycline, when diluted with Ringer's Injection, USP, or Invert Sugar, 10% in Water, to a concentration between 1 mg/mL and 0.1 mg/mL, must be completely infused within 12 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Reconstituted solutions (1 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Diluted solutions (0.1 to 1 mg/mL) prepared using Normosol-M[®] in D5-W (Abbott); Normosol-R[®] in D5-W (Abbott); Plasma-Lyte[®] 56 in 5% Dextrose (Baxter); or Plasma-Lyte[®] 148 in 5% Dextrose (Baxter) may also be stored up to 12 hours prior to start of infusion, if refrigerated and protected from sunlight and artificial light. The infusion must be completed within 12 hours. Solutions must be used within these time periods or discarded.

When diluted with Lactated Ringer's Injection, USP, or Dextrose 5% in Lactated Ringer's, infusion of the solution (ca. 1 mg/mL) or lower concentrations (not less than 0.1 mg/mL) must be completed within six hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.

Solutions of doxycycline for injection, at a concentration of 10 mg/mL in Sterile Water for Injection, when frozen immediately after reconstitution are stable for eight weeks when stored at -20°C. If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED:

Product NDC

| No. | No. | |
|-------|--------------|--|
| 1311 | 63323-130-11 | Doxycycline for Injection, USP (equivalent to 100 mg Doxycycline with 480 mg ascorbic acid and 300 mg mannitol), lyophilized in a flip-top vial, in packages of 10. |
| 16420 | 63323-164-20 | Doxycycline for Injection, USP (equivalent to 200 mg Doxycycline with 960 mg ascorbic acid and 600 mg mannitol), lyophilized in a flip-top vial, packaged individually. |

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

PROTECT FROM LIGHT.

Retain in carton until time of use.

REFERENCES:

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10. Horne HW Jr. and Kundsins RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317.
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