LIPIODOL®
(Ethiodized Oil) Injection

FOR INTRAUTERINE AND INTRALYMPHATIC ADMINISTRATION ONLY

DESCRIPTION: LIPIODOL, ethiodized oil injection, is a sterile injectable radio-opaque diagnostic agent for use in hysterosalpingography and lymphography. Each milliliter contains 480 mg of Iodine organically combined with ethyl esters of fatty acids of poppyseed oil. The precise structure of LIPIODOL is unknown at this time.
LIPIODOL is a sterile, clear, pale yellow to amber colored oil.
LIPIODOL has a viscosity of 34 – 70 mPa.s at 20°C, and a density of 1.28 g/cm^3 at 20°C.

CLINICAL PHARMACOLOGY: There has been little detailed investigation of the metabolic fate of LIPIODOL in either man or animals. However, the fate of LIPIODOL following lymphangiography in dogs has been reported.[1] Koehler et al. employed I^{131}–tagged LIPIODOL for lymphangiography in dogs and analyses of individual organs at various time intervals were done. The investigators reported an average of only 25% of the injected medium was retained in the lymphatics at the end of three days. An average of 50% was recovered from the lungs. They found the remainder of injected activity was fairly uniformly distributed throughout the body. Urinary excretion in the form of inorganic iodine was revealed as the chief mode of iodine loss from the system.

INDICATIONS: LIPIODOL is indicated for use as a radio-opaque medium for hysterosalpingography and lymphography.

IN HYSTEROSALPINGOGRAPHY

CONTRAINDICATIONS: LIPIODOL is contraindicated in patients hypersensitive to it. LIPIODOL should not be injected intrathecally or intravascularly, or used in bronchography. A history of sensitivity to iodine contraindicates the use of LIPIODOL; iodine is split off from fatty compounds and becomes free iodine in the body. Hysterosalpingography is contraindicated in intrauterine pregnancy, acute pelvic inflammatory disease, marked cervical erosion, endocervicitis in the presence of intrauterine bleeding, in the immediate pre-or postmenstrual phase, or within 30 days of curettage or conization.

WARNINGS:
LIPIODOL is not intended for use in bronchography and, therefore, is not to be introduced into the bronchial tree. A history of sensitivity to iodine or to other contrast materials is not an absolute contraindication to LIPIODOL, but calls for extreme caution. All procedures utilizing contrast media carry a definite risk of adverse reactions. While most reactions are minor, life threatening and fatal reactions may occur without warning. The risk/benefit factor should always be carefully evaluated. At all times a fully equipped emergency cart and resuscitation equipment should be readily available, and personnel competent in recognizing and treating reactions of all severity should be on hand.

PRECAUTIONS:

General: Since iodine-containing contrast materials may alter the results of certain thyroid function tests, such tests, if indicated, should be performed prior to the administration of this drug. Pulmonary embolization of the contrast material may occur if hysterosalpingography is performed under conditions which may lead to intravasation of the contrast materials. These conditions include uterine bleeding, recent curettage or conization and injection of the contrast material under excessive pressure.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether LIPIODOL can affect fertility in males or females.

Pregnancy Category C: Animal reproduction studies have not been conducted with LIPIODOL. It is also not known whether LIPIODOL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LIPIODOL should be administered to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from LIPIODOL, 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.

ADVERSE REACTIONS:

Hypersensitivity reactions, foreign body reactions and exacerbation of pelvic inflammatory disease, although infrequent, have been reported. In an occasional patient, abdominal pains may occur. Such pains may be the result of tubal torsion, or possibly due to too rapid a rate of instillation or excessive pressure, or both. The condition is usually only transitory, lasting one or two hours at most, and may be relieved by the administration of any of the commonly used analgesics.

DOSAGE AND ADMINISTRATION:

The hysterosalpingogram is preferably taken during the patient's preovulatory phase (as determined from her basal body temperature record) and not less than two days after cessation of her menstrual flow. It has been frequently observed that some bleeding will occur during or after the onset of pregnancy which cannot be distinguished by the patient from a normal menstrual period. In such cases a basal body temperature record will reveal a sustained high temperature phase, and thus enable an operator to avoid hysterosalpingography when a pregnancy may exist. Salpingography should not be performed if the blood is exuding from the cervical os (which occasionally occurs without the patient being aware of it) or if any gross evidence of endocervicitis exists.

Careful aseptic technique should be employed as for any operative procedure in which the uterus is entered. A self-retaining cannula should be used thereby permitting removal of the vaginal speculum so that the outline of the cervical canal may be seen in the film. The use of a radio-opaque aluminum speculum may be employed in patients where a lacerated or patulous cervix does not permit the use of a retaining cannula.

The radio-opaque agent is introduced under pressure and preferably with fluoroscopic control. A preliminary film is exposed and a skiagram is made after the injection of 5 mL of the agent. The pressure is raised to 80-90 mm Hg. In cases of normal bilateral tubal patency, the pressure falls immediately to below 60 mm Hg. The wet film may be viewed immediately and if both tubes are seen to "fill", the apparatus is removed and the procedure is finished, except for the 24 hour

follow-up to establish whether or not "spill" into the peritoneal cavity has occurred.

Increments of 2 mL of the agent are injected and successive films exposed until tubal patency is established or until the patient's limit of tolerance to discomfort is reached. Few patients will complain of discomfort at pressures under 200 mm Hg.

IN LYMPHOGRAPHY

CONTRAINDICATIONS:
LIPIODOL is contraindicated in patients hypersensitive to it. LIPIODOL should not be injected intrathecally or intravascularly or introduced into the bronchial tree. Patients with known sensitivity to iodine should not have lymphography performed. Iodine is split off from fatty compounds and becomes free iodine in the body. Lymphography is contraindicated in patients with a right to left cardiac shunt, in patients with advanced pulmonary disease, especially those with alveolar-capillary block, and in patients who have had radiotherapy to the lungs.

WARNINGS:
The use of intralymphatic LIPIODOL presents a significant hazard in patients with pre-existing pulmonary disease characterized by a decrease in pulmonary diffusing capacity and/or pulmonary blood flow. A few fatalities have been noted in such patients. With reference to this potential complication, recent studies indicate a significant decrease in both pulmonary diffusing capacity and pulmonary capillary blood flow following LIPIODOL lymphography without appreciable concomitant clinical manifestations. Also, care should be exercised in patients with other types of pulmonary disease in view of the more frequent incidence of overt pulmonary complications such as pulmonary infarction, in these groups. However, it is to be noted that pulmonary infarction, although rare, has occurred in patients without evidence of pre-existing pulmonary disease.

The safety of intralymphatic LIPIODOL has not been established in pregnant women, and accordingly, its use should be restricted to such situations where it is deemed necessary.

PRECAUTIONS:
General: Although subclinical pulmonary embolization occurs in a majority of patients following LIPIODOL lymphography, clinical evidence of such embolization is infrequent and is usually of a transient nature. Such clinical manifestations are usually immediate, but may be delayed from a few hours to days. It would appear that it is advantageous to use the smallest volume of LIPIODOL necessary for radiographic visualization. For this reason, and to prevent inadvertent venous administration, radiographic monitoring of patients is recommended during the injection of LIPIODOL.

The timing and choice of anesthesia following LIPIODOL injection may be influenced by consideration of the above noted decrease in pulmonary and capillary blood flow and diffusing capacity. It should be noted that although an average of 2 to 3 days was required for complete reversibility for such tests, an occasional patient required up to 12 days to return to baseline values.

PBI determination of thyroid uptake studies should be carried out prior to the lymphographic procedure because interference with these tests may be anticipated for as long as one year. In the presence of known iodine sensitivity, LIPIODOL lymphography should be carried out with greatest precaution.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether LIPIODOL can affect fertility in males or females.

Pregnancy Category C: Animal reproduction studies have not been conducted with LIPIODOL. It is also not known whether LIPIODOL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. LIPIODOL should be administered to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from LIPIODOL, 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.

ADVERSE REACTIONS:
The occasional observation of pulmonary LIPIODOL embolization (infarction) several hours after injection has been reported. This was noticed more frequently when excessive amounts of LIPIODOL have been injected, in the presence of marked lymphatic obstruction or through accidental intravenous injection. Radiologic manifestations are fine, granular stippling throughout both lung fields. The clinical symptoms usually noted have been mild, consisting of moderate temperature elevation, dyspnea, and cough. However, severe acute symptoms developed in two patients both of whom were severely ill and required extensive care.[2] Fuchs[3] experienced 1 severe and 3 minor complications in a series of 20 bilateral procedures. Two are described by the author as cardiovascular collapse occurring at two hours respectively following the completion of the procedure. It was postulated that minute emboli may have been causative. Recovery was rapid and complete in both instances.

The occurrence of pulmonary invasion may be minimized if radiographic confirmation of intralymphatic (rather than venous) injection is secured, and the procedure discontinued when the medium becomes visible in the thoracic duct or the presence of lymphatic obstruction is noticed.

While rare, other side effects reported include transient fever, lymphangitis, iodism (headache, soreness of mouth and pharynx, coryza and skin rash), allergic dermatitis, and lipogranuloma formation. Delayed wound healing at the site of incision and secondary infection are occasionally seen, and can be prevented or minimized by adhering to a strict sterile technique.

Transient edema or temporary exacerbation of preexisting lymphedema, as well as thrombophlebitis have also been reported. In the extremely rare presence of concomitant lymphatic and inferior vena cava obstruction the contrast medium may be shunted partially to the liver, resulting in hepatic embolization. Also, when accidental intravenous administration of LIPIODOL results in a considerable amount of this medium entering the circulation, embolization other than pulmonary may occur as reported in 2 cases.[4] Both cases developed a transient, psychotic-like manifestation, which in all probability stemmed from the entrance of fine oil droplets into the cerebral circulation. Recovery was uneventful and complete without evidence of neurological sequelae.

DOSAGE AND ADMINISTRATION:
This method applies for both the upper and lower extremities. A lymphatic vessel is selected for cannulization.

The patient should be comfortably arranged in a supine position on a portable stretcher or an x-ray table. When available, a radiolucent pad will add to the patient's comfort during the one to two

hours required for completion of the examination. It is important that the patient be in a cooperative state. Premedication might be advisable in the unusually apprehensive patient.

In the unusually restless patient, the extremities should be immobilized during the entire procedure to prevent displacement of the needle. Thomas splints have been satisfactorily employed for the legs and simple arm boards for the upper extremities. The cut-down and injection instruments and materials include the following:

Sterile pediatric cut-down set

Sterile towels for draping, sponges, etc.

Local anesthetic, such as procaine hydrochloride, and a syringe

Bactericidal painting solution

20 mL syringe containing 15 mL of LIPIODOL with an 18 inch catheter to which is affixed a 27 or 30 gauge needle. (If bilateral lymphography is scheduled, two syringes should be prepared.)

A manually driven or motorized unit (a pressure regulated pump) to provide for slow injection.

Under local infiltration anesthesia, a transverse, curvilinear or longitudinal small skin incision should be made near the ankle or wrist (just lateral and distal to the first metatarsal head on the dorsum of the foot, or just over the "snuff-box" in the dorsum of the hand).

Upon superficial dissection (but not penetrating the subcutaneous layer of tissue) lymph vessels will be noted in the immediate subcutaneous tissue, while larger lymph vessel trunks are found in the extrafascial plane. The deeper lymph trunks will be easier to cannulate.

One lymph vessel is then exposed, avoiding circumferential dissection. The less manipulation performed, the better the results that will be obtained. The lymphatic, thus isolated, is then cannulated with a 27 or 30 gauge 5/8 inch needle, depending upon the size of the lymphatic selected for injection. It is rarely possible to cannulate with a needle greater than 27 gauge. Insertion of the needle through the skin flap before cannulating the lymphatic serves to reduce the movement of the needle within the vessel. Additional security of the needle in the lymphatic is obtained by strapping, with sterile tape, the polyethylene tubing to the patient's foot.

The injection should be started at a slow rate, i.e., 0.1 mL to 0.2 mL per minute. Radiographic monitoring either by fluoroscopy or serial radiographs after 1 mL to 2 mL has been injected, will confirm the proper intralymphatic placement of the needle, rule out accidental intravenous injection or extravasation of the medium by perforation or rupture of the lymphatic. Monitoring will also permit prompt termination of the procedure in the event that lymphatic blockage is present. In such situations, continuation of the injection will result in unnecessary introduction of contrast material in the venous system via the lymphovenous communication channels. If the injection is satisfactory, approximately 6 to 8 mL, are then injected. However, as soon as it becomes radiographically evident that LIPIODOL has entered the thoracic duct, the procedure should be terminated to minimize entry of the contrast material into the subclavian vein. Two to four mL of LIPIODOL injected into the upper extremity will suffice to demonstrate the axillary and supraclavicular nodes. In penile lymphography approximately 2 to 3 mL of LIPIODOL is required. In infants and children, a minimum of 1 mL to a maximum of 6 mL should be employed.

The rate of speed at which the contrast material may be introduced varies and is dependent upon receptivity of the lymphatics in the individual patient. If the injection is proceeding at too rapid a rate, extravasation will be noted and the patient may refer to pain in the foot, leg or arm.

At the completion of the injection, anteroposterior roentgenograms are obtained of the legs or arms, thighs, pelvis, abdomen and chest (dorsal spine technique). Lateral or oblique views as well as laminograms are obtained when indicated. Follow-up films at 24 or 48 hours provide better demonstration of lymph nodes and permit more concise evaluation of nodal architecture.

As a general rule, the smallest possible amount of LIPIODOL should be employed according to the anatomical area to be visualized. Therefore, and to prevent inadvertent venous administration, fluoroscopic monitoring or serial radiographic guidance of patients is recommended during the injection of LIPIODOL. Average dose in the adult patient for unilateral lymphography of the upper extremities is 2 to 4 mL; of lower extremities, 6 to 8 mL; of penile lymphography, 2 to 3 mL; of cervical lymphography, 1 to 2 mL.

In the pediatric patient, a minimum of 1 mL to a maximum of 6 mL may be employed according to the anatomical area to be visualized.

SUMMARY OF STEPS TO AVOID COMPLICATIONS IN LYMPHOGRAPHY [5]

1. Contraindicate patients:
   A. With a known hypersensitivity to LIPIODOL
   B. With a right to left cardiac shunt
   C. With advanced pulmonary disease, especially those with alveolar-capillary block. Pulmonary gas diffusion studies should be done if in doubt.
   D. Who have had radiation therapy to the lungs

2. Proceed with caution:
   A. Patients having markedly advanced neoplastic disease with expected lymphatic obstruction.
   B. Patients having undergone previous surgery interrupting the lymphatic system.
   C. Patients having had deep radiation therapy to the examined area.

If in those cases in which extreme caution should be exercised, lymphography is still necessary, a smaller dose of oily contrast medium with protracted injection time with less pressure and careful monitoring is required.

3. Skin testing should be done on all patients before submitting them to lymphography. Be aware of possible hypersensitivity to local anesthetics and skin disinfectants. Careful history taking is important.

4. Technique of cannulation: extravasation is to be avoided and/or detected early. The injection site should be included on the "scout film" or observed under image amplification fluoroscopy. The needle tip must remain visible in the incision wound.

5. Oily contrast materials: once opened, ampoules should be discarded. Ampoules of LIPIODOL should not be used if the color has darkened or if particulate matter is present. The average dose for each foot in an adult is 5 to 6 mL; one-half as much for the upper extremity. The amount for children should be determined by careful monitoring. It should stay below 0.25 mL/kg.

6. Injection pressure should be regulated to deliver the average dose in no less than 1 1/4 hours. Continuous monitoring helps to determine the speed most appropriate for each individual. Sensation of pain is a warning of too high pressure.

7. Scout roentgenograms: if scout roentgenograms are used for monitoring, they should be developed and viewed immediately in order to apply corrective measures when needed; e.g.,

discontinuation of the study when one sees intravenous injection or lymphatico-venous anastomosis. Reduction of injection speed is needed if evidence of collateral circulation occurs or if the higher abdomino-aortic nodes do not opacify in spite of the usual injection pressure. This is highly suggestive of lymphatic obstruction. Scout roentgenograms should be taken more frequently in such cases.

8. Surgical technique: strict aseptic surgical technique is followed including the wearing of a face mask. Before suturing the incision wound, the remnants of the lymphatic vessels and loose tissue are removed and the wound well washed with saline to remove any possible oil. In case of reflux type lymphedema, the cannulated large lymphatic vessel may have to be closed by catgut to avoid development of a lymphocyst.

The patient is instructed to elevate the legs as often as possible to promote healing. The sutures are removed from the feet on the 10th day, and on the 5th or 6th from the hands.

HOW SUPPLIED:
LIPIODOL is supplied in a box of one 10 mL ampoule, NDC 67684-1901-1.
Store at controlled room temperature15°- 30°C (59°- 86°F). See USP.
Protect from light. Remove from carton only upon use.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

BIBLIOGRAPHY

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