Product Monograph

Cholografin for Infusion
(iodipamide meglumine injection (52%), U.S.P.)

A radiopaque medium for intravenous cholangiography
and
cholecystography

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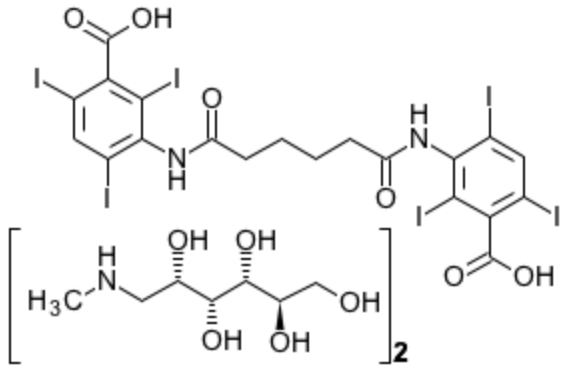
CHOLOGRAFIN™ MEGLUMINE
IODIPAMIDE MEGLUMINE INJECTION USP 52%

THERAPEUTIC CLASSIFICATION
Radiopaque Contrast Agent for Intravenous Cholangiography and Cholecystography

STRUCTURAL FORMULA AND CHEMISTRY
Cholografin Meglumine is a sterile, aqueous solution containing 51.6% of the meglumine salt of iodipamic acid (3,3'-(adipoyldiamino) bis [2,4,6-triiodo benzoic acid]).
The bound iodine content of the base is 66.9% and that of the solution about 26% (5.1 g per 20 mL). The preparation also contains 0.364% sodium citrate as a buffer and 0.04% disodium edetate as a sequestering agent. The solution contains approximately 0.91 mg (0.039 mEq) sodium per mL (18.2 mg/ 20 mL). At the time of manufacture, the air in the container is replaced by nitrogen. Sufficient excess for sensitivity testing is included in the vials.

STRUCTURAL FORMULA:



Molecular Formula: $C_{34}H_{48}I_6N_4O_{16}$ Molecular Weight: 1530.21

ACTION
Following intravenous administration of Cholografin Meglumine, iodipamide is carried to the liver, where it is rapidly excreted. The contrast medium appears in the bile within 10 to 15 minutes after injection, thus permitting visualization of the hepatic and common bile ducts, even in cholecystectomized patients. The biliary ducts are readily visualized within about 25 minutes after administration, except in patients with impaired liver function or biliary tract obstruction. The gallbladder begins to fill within an hour after injection; maximum filling is reached after 2 to 2½ hours. Most of the contrast medium is finally eliminated in the feces without undergoing enterohepatic circulation. Approximately 10% of the dose is excreted through the kidneys.

INDICATIONS
Cholografin Meglumine is indicated for intravenous cholangiography and cholecystography.

CONTRAINDICATIONS
Iodipamide meglumine is contraindicated in patients with a history of hypersensitivity to salts of iodipamide. Sensitivity to iodine per se or to other contrast media is not an absolute contraindication but calls for extreme caution in administration. It is also contraindicated in

patients with concomitant severe impairment of renal and hepatic function, advanced uremia or anuria, and hyperthyroidism.

Contrast media have been shown to promote the phenomenon of sickling in individuals who are homozygous for sickle cell disease when the material is injected intravenously or intra-arterially.

The intravenous use of this product in patients with multiple myeloma is contraindicated (see WARNINGS).

WARNINGS

Acute renal failure has been reported following intravenous administration of contrast media in several patients with multiple myeloma (plasma cell myeloma), possibly because of the proteinuria associated with the disease and dehydration, that must be avoided in such patients. No form of therapy, including dialysis has been successful in reversing this effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before intravenous administration of Cholografin Meglumine.

Patients with pheochromocytoma may be prone to a severe reaction to contrast agents. Administration to these patients should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to the absolute minimum. The blood pressure should be assessed throughout the procedure and measures for treatment of a hypertensive crisis should be available.

Thyroid Dyfunction

Cholografin Meglumine, like all other iodinated contrast media, may induce changes in thyroid function in some patients. Transient hyperthyroidism or hypothyroidism has been reported following iodinated contrast media administration to adult and pediatric patients. Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased Level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or even more than a month (see ADVERSE REACTIONS). Some patients were treated for hypothyroidism (See PRECAUTIONS - Special Populations - Pediatrics – Infant).

Usage in pregnancy:

The safety of iodipamide meglumine for use during pregnancy has not been established; therefore, it should be used in pregnant patients only when, in the judgement of the physician, its use is deemed essential to the welfare of the patient. Exposure of the abdomen to ionizing radiation during pregnancy, especially during the first trimester should be avoided.

PRECAUTIONS

Diagnostic procedures which involve the use of radiopaque contrast agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with situations which may arise as a result of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself.

After intravascular administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have been known to occur.

These severe, life-threatening reactions suggest hypersensitivity to the radiopaque agent. This has prompted the use of several pretesting methods, none of which can be relied upon to predict severe reactions. Many authorities question the value of any pretest. A history of bronchial asthma or allergy, a family history of allergy, or a previous reaction to a contrast agent warrant special attention. Such a history, by suggesting histamine sensitivity and a consequent proneness to reactions may be more accurate than pretesting in predicting the likelihood of a reaction, although not necessarily the severity or type of reaction in the individual case.

The sensitivity test most often performed is the slow injection of 0.5 to 1.0 mL of the radiopaque medium, administered intravenously, prior to injection of the full diagnostic dose. If no reaction occurs within 15 minutes, the full dose may be given; however, this does not preclude the possibility of a reaction. Successive small increments are used over several minutes if the patient has a history of allergy.

An impending reaction is often indicated by respiratory difficulty, faintness, sneezing, itching, vomiting, or urticaria. In some instances, reactions to the test dose may be delayed, and in a few cases have been extremely severe in themselves; therefore, close observation of the patient, and facilities for emergency treatment are indicated.

If an untoward response to the test dose (or to subsequent diagnostic injections) should occur, the examination should be terminated. Antiallergic drugs may be used to advantage. The admixture of Benadryl (Diphenhydramine Hydrochloride Injection) or Chlortripolon (Chlorpheniramine Maleate, U.S.P.) with Cholografin Meglumine (lodipamide Meglumine Injection U.S.P.) may cause a precipitate which may form in the syringe or tubing. If antihistamines are administered concomitantly, they should not be mixed with the contrast agent but administered at another site.

As with any intravenous drug, the more serious reactions require immediate treatment. In particular, anaphylactoid reaction may occur despite a negative sensitivity test. Since such reactions occur without warning, close observation of the patient should be maintained, and facilities for emergency treatment should be readily available when radiopaque media are injected.

The Barnhards have cautioned that emergencies other than sensitivity reactions to the contrast agent may occur during or after these diagnostic procedures. Examples include myocardial infarction, pulmonary embolus, acute pulmonary edema and hypoglycemia. Awareness of their possible occurrence should not, however, prevent the initiation of intensive treatment for an allergic response, if any doubt exists.

Several possible steps may be taken to counteract a severe reaction to this type of product. The more important features are revealed under TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA.

Caution should be exercised in the use of radiopaque media in severely debilitated patients and in those with marked hypertension. The possibility of thrombosis should be borne in mind when percutaneous techniques are employed. If extravasation occurs, the injection should be stopped and physiological saline administered through the needle to dilute the medium.
Since iodine-containing contrast agents may alter the results of thyroid function tests, such tests, if indicated, should be performed prior to the administration of this preparation.
A history of sensitivity to iodine per se or to other contrast agents is not an absolute contraindication to the use of Cholografin Meglumine, but calls for extreme caution in administration.

Contrast agents may interfere with some chemical determination made on urine specimens; therefore urine for these tests should be collected before administration of the contrast medium or two or more days afterwards.

Note: In the presence of liver disease (BSP retention greater than 30%-40%), the contrast medium is not excreted efficiently by the liver and visualization is usually not achieved. In the presence of a serum bilirubin of 3.0 mg/100 mL caused by mechanical obstruction or hepatocellular damage, visualization is rarely achieved. In the presence of severe liver damage, the contrast agent is excreted by the kidneys. If liver function is severely impaired, adequate renal function must be ascertained before injecting this contrast material. Because of the increased risk of hepatic and renal damage, the examination should not be repeated for at least 24 hours.

Special Populations

Pediatrics
Use in Children - Infants
Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased Level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month (see ADVERSE REACTIONS). Hypothyroidism in infants may be harmful for growth and development, including mental development and may require treatment. Thyroid function in infants exposed to ICM should therefore be evaluated and monitored until thyroid function is normalized.

ADVERSE REACTIONS
The following adverse reactions have occured with Cholografin Meglumine: transient symptoms such as restlessness, sensations of warmth, sneezing, perspiration, salivation, flushing, pressure in the upper abdomen, dizziness, nausea, vomiting, chills, fever, headache, pallor, tremors, sweating, weakness, severe retching and choking, wheezing, rise and fall in blood pressure, facial or conjunctival petechiae, urticaria, pruritus, rash and other eruptions, edema, cramps, itching, lacrimation, etc.Antihistaminic agents may be of benefit; such reactions may be severe enough to require discontinuation of dosage. Swollen eyelids, laryngospasm, respiratory difficulties, hypotension, cardiac reactions and cyanosis have been reported. Severe reactions are a possibility. Such reactions, which may require emergency measures (see TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA), may take the form of a cardiovascular reaction characterized by peripheral vasodilatation with resultant hypotension and reflex tachycardia, dyspnea, agitation and confusion and cyanosis progressing to unconsciousness. Ventricular fibrillation or cardiac arrest may also occur. The histamine-liberating effect of contrast agents may induce an allergic-like reaction which may range in severity from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactic shock. Renal function tests may be altered, and temporary renal shutdown may occur. Hepatotoxicity has also been reported.

Post-Market adverse Drug Reactions
Endocrine Disorders
Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to adult and pediatric patients, including infants. Some patients were treated for hypothyroidism.

TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA

Contrast media should be injected only by physicians thoroughly familiar with the emergency treatment of all adverse reactions to contrast media. The assistance of other trained personnel such as cardiologists, internists and anesthetists, etc., is required in the management of severe reactions.

A guideline for the treatment of adverse reactions is presented below. This outline is not intended to be a complete manual on the treatment of adverse reactions to contrast media or on cardiopulmonary resuscitation. The physician should refer to the appropriate texts on the subject.

It is also realized that institutions or individual practitioners will already have appropriate systems in effect and that circumstances may dictate the use of additional or different measures.

FOR MINOR ALLERGIC REACTIONS: (if considered necessary)
The intravenous or intramuscular administration of an antihistaminic such as Diphenhydramine HCI (Benadryl) 25-50 mg is generally sufficient (contraindicated in epileptics). The resulting drowsiness makes it imperative to ensure that outpatients do not drive nor go home unaccompanied.

MAJOR OR LIFE THREATENING REACTIONS:
A major reaction may be manifested by signs and symptoms of cardiovascular collapse, severe respiratory difficulty and nervous system dysfunction. Convulsions, coma and cardiorespiratory arrest may ensue. The following measures should be considered:

1. Start emergency therapy immediately - carefully monitoring vital signs.
2. Have emergency resuscitation team summoned - do not leave patient unattended.
3. Ensure patent airway - guard against aspiration.
4. Commence artificial respiration if patient is not breathing.
5. Administer oxygen if necessary.
6. Start external cardiac massage in the event of cardiac arrest.
7. Establish route for i.v. medication by starting infusion of appropriate solution (e.g. 5% Dextrose in Water).
8. Judiciously administer specific drug therapy as indicated by the type and severity of the reaction. Careful monitoring is mandatory to detect adverse reactions of all drugs administered:

Acute Allergic-Anaphylactic Reactions:
Soluble Hydrocortisone 500-1000 mg i.v. and/or Epinephrine Injection U.S.P. (Adrenalin) 1:1000 solution, 0.2-0.4 mL subcutaneously (in the presence of anoxia this may cause ventricular fibrillation). In extreme emergency 0.1 mL per minute, appropriately diluted, may be given intravenously until desired effect is obtained.
Do not exceed 0.4 mL.

Cardiac Arrest:
Epinephrine Injection U.S.P. (Adrenalin) 1:1000 solution, 0.1-0.2 mL, appropriately diluted, may be given intracardially.

Hypotension:
Monitor blood pressure carefully. Phenylephrine HCI (Neo-Synephrine) 0.1-0.5 mg appropriately diluted slowly i.v. or by slow infusion.
OR

Levarterenol Bitartrate (Levophed) 4 ml of 0.2% solution in 1000 mL of 5% Dextrose by slow drip infusion.

Acidosis:
Sodium bicarbonate 5%; 50 mL i.v. every 10 minutes as needed to combat post-arrest acidosis.

Sinus Bradycardia:
Atropine 0.4-0.6 mg i.v. May also reverse 2nd or 3rd degree block.

Convulsions:
Pentobarbital Sodium (Nembutal) 50 mg in fractional doses slowly i.v. (contraindicated if cyanosis is present).

OR

Diazepam (Valium) 5-10 mg slowly i.v., titrating the dose to the response of the patient.
9. Defibrillation, administration of antiarrhythmics and additional emergency measures and drugs may be required.
10. Transfer patient to intensive care unit when feasible for further monitoring and treatment.

DOSAGE AND ADMINISTRATION
Cholografin Meglumine (Iodipamide Meglumine Injection U.S.P.) is for intravenous use only.

Preparation of the Patient:
For best results, the usual preliminary measures for cholecystography are recommended, particularly in cholecystectomized patients, i.e., a low residue diet on the day before examination and administration of castor oil the night before or neostigmine at the time of examination to dispel excess intestinal gas, unless contraindicated. Cholecystography is preferably carried out in the morning with the patient fasting.

Dosage:
The usual adult dose is 20 mL. For infants and children, the suggested dose is 0.3 to 0.6 mL/kg of body weight, but not exceeding 20 mL. **Note:** The dose should not be repeated for 24 hours.

Administration:
After warming to body temperature, Cholografin Meglumine should be given by slow intravenous injection, following the usual precautions of intravenous administration. IT IS IMPORTANT THAT THE PREPARATION BE INJECTED SLOWLY OVER A PERIOD OF 10 MINUTES. Use of a narrow bore hypodermic needle will ensure a slow rate of injection. During the injection, the patient should be watched for untoward reactions such as a feeling of warmth, flushing and occasionally nausea. Nausea usually indicates that the injection rate is too rapid.

Radiography:
A scout film should be exposed routinely before the intravenous injection is made.

Position of the patient:
With the patient prone and right side elevated, radiographs are made in the posterior-anterior projection. Some radiologists prefer the supine position with the left side elevated. Serial 10 minutes exposures should begin 10 minutes after the injection is made, and continued until optimal visualization of the biliary ducts is obtained. Wet films should be examined immediately

by the radiologist. In some cases a 15 degree rotation or the upright position may prove helpful. Depending on the situation revealed by the roentgenograms in which the duct is first seen, the position of the subject should be changed to displace the shadow of the common bile duct from that of the spine. Tomography is a useful technique for enhancing bile duct visualization after administration of the radiopaque medium. Examination of the gallbladder should be started about two hours after administration. The standard positions in routine examination of the gallbladder should be used unless otherwise indicated. There is no need for the patient to remain quiet awaiting the time for the gallbladder film to be exposed. Moderate activity on the part of the patient will, in most cases, preclude "stratification" of the contrast agent in the gallbladder. If the contrast medium should stratify in the gallbladder, decibitus as well as upright films should be obtained. Additional exposures may be made after the ingestion of a fatty meal. If visualization is not achieved after two and one half hours, the patient should be returned for a 24 hours film whenever possible. Occasionally, delayed opacification of the gallbladder will occur in 24 hours. In infants and children, gallbladder visualization may be expected to occur 30 minutes to four hours after administration.

Interpretation:
The following is an interpretation of some reasons for visualization or nonvisualization of the gallbladder, although other interpretations are possible. When intravenous cholecystography and cholangiography are used as an aid in the differential diagnosis of acute abdominal conditions, visualization of the gallbladder is considered strong evidence against a diagnosis of acute cholecystitis, whereas nonvisualization of the gallbladder two and one half hours after administration with visualization of the bile ducts is considered strong evidence in favour of a diagnosis of acute cholecystitis or cystic duct obstruction (if the bile ducts are only faintly visualized, gallbladder films four hours after administration may occasionally show visualization of the gallbladder). When neither the bile ducts nor the gallbladder is visualized, the study provides no definite information with regard to determining the presence or absence of acute cholecystitis.

DOSAGE FORMS
Cholografin Meglumine is available in single dose vials of 20 mL.

STORAGE
Cholografin Meglumine should be stored at room temperature, and protected from strong light. Avoid excessive heat. The appearance of the solution may vary from essentially colourless to light amber. Solutions which have become substantially darker, however, should not be used. If precipitation or solidification has occurred due to storage in the cold, immerse the container in hot water and shake intermittently to re-dissolve any solids. Discard unused portion.

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