Indocyanine Green for Injection USP
Rx Only

Description:
Indocyanine Green for Injection USP is a sterile, lyophilized green powder containing 35 mg of indocyanine green with no more than 5% sodium chloride. Indocyanine Green for Injection USP is dissolved using Sterile Water for Injection and should be administered intravenously.

Indocyanine green is a water-soluble, triarylmethane dye with peak spectral absorption at 800 nm. The chemical name for indocyanine Green is 1,1-[2-((5-(2-(1H-Imidazol-1-yl)phenyl)ethyl)amino)ethyl]indolizino[3,2-a]quinoline-3,6-dione. It is a salt of triphenylmethane, with sodium, in 2-(1H-imidazol-1-yl)phenylalanine. The indocyanine green solution is administered by intravenous infusion. The concentration of indocyanine green is adjusted to 5 mg/mL (approximately 3 mg/mL maximum) using Sterile Water for Injection. The concentration of indocyanine green should be no less than 5 mg/mL when reconstituted. Each vial of Indocyanine Green for Injection USP contains 25 mg of indocyanine green as a sterile lyophilized powder.

Clinical Pharmacology:
Following intravenous injection, Indocyanine Green is rapidly bound to plasma protein, of which albumin is the principle carrier (85%). Indocyanine Green undergoes no significant extravascular or enterohepatic circulation. Simultaneous arterial and venous blood estimations have shown negligible renal, peritoneal, lung, or cerebral-synaptic uptake of the dye. Indocyanine Green is taken up from the circulation by the hepatic parenchymal cells, is conjugated in the liver to indocyanine glycosides, and then excreted in the bile. The metabolism of dyes occurs by conjugation with glucuronides and sulfates. The resulting conjugates are excreted in the bile into the intestinal tract. MICHAELIS-MENTEN analysis of blood samples from patients undergoing liver transplantation or liver disease showed a decrease in the clearance of indocyanine green over time, likely due to impaired hepatic function. The dye is not selectively concentrated in any organ or tissue and is freely filtered by the kidney, with minimal tubular uptake or secretion. The clearance of indocyanine green from the plasma is biphasic, with a rapid initial phase followed by a slower second phase.

The plasma fractional disappearance rate at the recommended 0.5 mg/kg dose has been reported to be significantly greater in women than in men, although there was no significant difference in the calculated value for clearance.

Indications and Usage:
For determining cardiac output, hepatic function and liver blood flow, and for somatic angiocardiography.

Contraindications:
Indocyanine Green for injection USP contains sodium iodide and should be used with caution in patients who have a history of allergy to iodide.

Warnings:
Anaphylactic deaths have been reported following Indocyanine Green for injection USP administration during cardiac catheterization.

Precautions:
General:
Indocyanine Green Powder and Solution: Indocyanine Green is unstable in aqueous solution and must be used within 6 hours. However, the dye is stable in plasma and whole blood. The samples obtained in discontinuous sampling after the use of the dye as a diagnostic test should be analyzed and used within 6 hours of the test.

For the use of the dye as a therapeutic agent, the dye solution as well as the performance of the dye solution curves. Indocyanine Green dye may glow in the dark (a phenomenon of the dye solution) that is measured during the test.

Drug Interactions:
Heparin preparations containing sodium iodide reduce the absorption peak of indocyanine Green in blood, and therefore, should not be used as an anticoagulant for the collection of samples for analysis.

Drug/Laboratory Test Interactions:
Reductive iodine uptake studies should not be performed for at least a week following the use of indocyanine Green.

Carcinogenicity, Mutagenesis, Impairment of Fertility:
No studies have been performed to evaluate the carcinogenicity, mutagenicity, or impairment of fertility.

Pregnancy - Teratogenic Effects: Pregnancy Category C
Animal Reproduction studies have not been conducted with Indocyanine Green. It is not known whether Indocyanine Green can cause fetal harm when administered to pregnant women. Indocyanine Green should be given to a pregnant woman only if clearly indicated.

Nursing Mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Indocyanine Green is administered to a nursing woman.

Pediatric Use:
Safety and effectiveness in pediatric patients have been established.

Geriatric Use:
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Adverse Reactions:
Anaphylactic or urticarial reactions have been reported in patients with or without a history of allergy to iodine. Such reactions occur, treatment with the appropriate agents (e.g., epinephrine, antihistamines, and corticosteroids) should be administered.

Overdose:
There are no data available describing the signs, symptoms, or laboratory findings associated with overdosage of Indocyanine Green. The LD50 is not known. Administration rates between 50 and 80 mg/kg in mice, 50 and 70 mg/kg in rats and 50 and 80 mg/kg in rabbits.

Dosage and Administration:
Indicator-Dilution Studies:
Indocyanine Green permits recording of the indicator-dilution curves for both diagnostic and research purposes independently of fluctuations in cardiac output. The dye is injected as a single bolus as rapidly as possible via cardiac catheter into selected sites in the vascular system. A trapping instrument (skeletal muscle or dermabens) is attached to a needle or catheter for sampling of the dye-blood mixture from a systemic arterial sampling site.

Under sterile conditions, the Indocyanine Green for Injection USP powder should be administered using aseptic technique. After reconstitution, the solution should be used within 6 hours after it is prepared. If a precipitate is present, discard the solution. The concentration of blood samples obtained in discontinuous sampling after the use of the dye as a diagnostic test should be analyzed and used within 6 hours of the test.

This matter of the dye solution with distilled water may not be critical, since it is known that an amount of sodium chloride supplied to make the isotonic concentrations of the dye solution. Under sterile conditions, the indocyanine green solution should be used within 6 hours after it is prepared. If a precipitate is present, discard the solution. The concentration of blood samples obtained in discontinuous sampling after the use of the dye as a diagnostic test should be analyzed and used within 6 hours of the test.

The usual doses of Indocyanine Green which have been used for dilution curves are as follows:

- Adults: 5 mg/kg
- Children: 5 mg/kg
- Infants: 5 mg/kg

These doses of the dye are usually injected in a 1-3 mL volume. An average of five dilution curves is required to perform a diagnostic cardiac catheterization. The total dose of dye injected should be kept below 2 mg/kg.

Calibrating Dye Curves:
To quantify the dilution curves, standard dilutions of indocyanine Green in whole blood are made as follows. It is strongly recommended that the same dye lot be used for each injection. The concentration is roughly the concentration of dye in the dilution curve. A 1 ml of the dye solution is diluted with 1 mL of distilled water. The most concentrated dye solution is made by accurately diluting 1 mL of the 5 mg/mL dye with 7 mL of distilled water. The dye concentration is then determined by diluting 2% of the previously calculated solution with 4 mL of distilled water (if 2% 3% of the dye solution is used for the dilution curve, 1 mL of the 2% solution, 1 mL of the dye is added to 3 mL of distilled water to make the most concentrated ‘dilution’ solution). This concentration is then approximately 3 mg/mL dye in distilled water, and this concentration is used to calibrate the dye dilution curve. The dye concentration is accurately measured by a calibrated instrument to an accuracy of ±0.1% of the total concentration of dye in blood taken from 24 healthy patients (approximately actual concentration depends on the exact volume of dye dilution). The concentration is determined by subtracting the blood hematocrit (corrected for dilution) from the total dye concentration of the blood. The technician then has an opportunity to correct for the presence of indocyanine Green in the blood, and this correction is then subtracted from the total dye concentration of the blood. This dye concentration is then determined by calibrating the dye dilution curve constructed from the deflections recorded.

Hepatic Function Studies:
Due to the absorption spectrum, changes in concentrations of indocyanine green in the blood can be monitored by ear densitometry or by a computerized blood spectrophotometer. The patient should be studied in a fasting, basal state. The patient should be weighed and the dosage calculated on the basis of 0.5 mg/kg of body weight.

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Indicating the indocyanine Green is administered to the ear, giving 3 mg/kg of dye per mL of solution.

Red blood cells are taken from the lumen of an arm vein as rapidly as possible, without allowing the line to escape outside the vein. If the proportion of solution is used, prior to injecting indocyanine Green, whether 3 mg/mL of venous blood from the patient's area for serum bilirubin and standard curve construction, and through the same needle, inject the correct amount of dye.
Phorometric method

Determination Using Percentage Retention of Dye

A typical curve obtained by plotting dye concentration versus optical density is shown opposite. Percent retention can be read from this plot.

Optical Density

805 nm using the patient's normal serum as the blank. Dye concentration is read from the curve above. A single 20-minute sample of serum in healthy subjects should contain no more than 4% of the initial concentration of the dye. This rate of percentage retention is less accurate than percentage disappearance rate but provides reproducible results. Hemolysis does not interfere with a reading.

Determination Using Disappearance Rate of Dye

To calculate the percentage disappearance rate, obtain samples at 5, 10, 15 and 30 minutes after selecting the dye. Prepare the sample as in the previous section.

The concentration of dye is determined as 0% using the sample as the blank. The indocyanine Green concentration in each timed specimen can be determined by using the concentration curve illustrated. Plot values on semilogarithmic paper.

Specimens containing Indocyanine Green should be read at the same temperature since its optical density is influenced by temperature variations.

Normal Values: Percent disappearance rate in healthy subjects is 18-24% per minute. Normal biological half-time is 2.9-3.0 minutes.

Optochromatic Angiography Studies:

The excitation and emission spectra (Figure 1) and the absorption spectra (Figure 2) of Indocyanine Green make it useful in ophtalmic angiography. The peak absorption and emission of Indocyanine Green lies in a region (850-850 nm) where transmission of energy by the pigment epithelium is more efficient than in the region of visible light energy. Indocyanine Green also has the property of being relatively non-toxic, since it is not taken up by the choroidal vasculature and does not leak into the highly blood-stained choroidal vasculature. It is, therefore, useful in both absorption and fluorescence ophtalmic angiography of the choroidal vasculature when using appropriate filters and filters in a luminous camera.

Dissapear up to 40 mg Indocyanine Green dye in 3 mL of Sterile Water for Injection, USP, have been found to give optimal angiograms, depending on the imaging equipment and technique used. The arteriographic venous injection Indocyanine Green dye should be immediately followed by a 5-mL bolus of normal saline.

Clinically, angiograms of uniformly good quality can be assured only after taking care to prevent the contamination of any possible factors, such as patient cooperation and the injection. The following injection regimen is designed to provide delivery of a sharply limited dye bolus of optimal concentration to the choroidal vasculature following intravenous injection.

How Supplied:

Indocyanine Green for Injection USP, is supplied in a kit, (NDC 25431-424-02) containing six 25-mg Indocyanine Green for Injection USP vials and six 15-mL Sterile Water for Injection vials.

NDC 25431-424-01 Indocyanine Green for Injection 25-mg vial in 30-mL vial, 10 mL.

NDC 63323-185-10 Sterile Water for Injection 10-mL vial, 5 mL in 10-mL vial.

Storage:

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

Rx only

Manufactured by:

Pathway Italia S.p.A.
Via G.B. Storchi 110
ITALY

Sterile Water for Injection USP is Manufactured by:

APP Pharmaceutical LLC
Schumertl IL 60193
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