N,N´-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl)-glycolamidol]-2,4,6-triiodoisophthalamide

Ioversol

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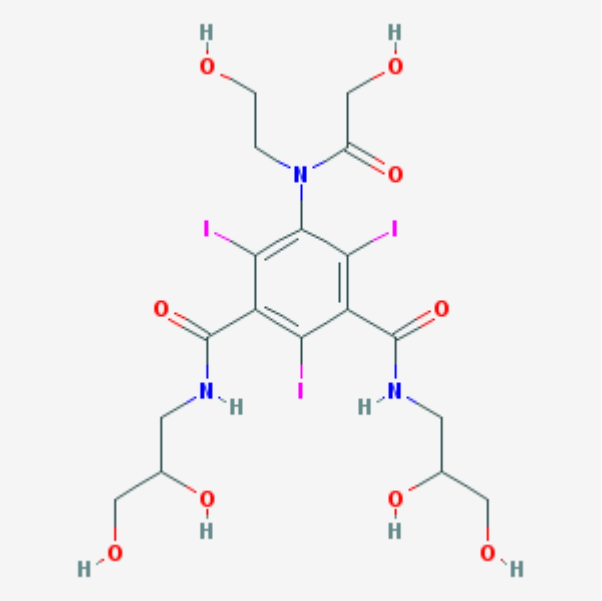
Chemical name:	*N,N´*-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl)-glycolamidol]-2,4,6-triiodoisophthalamide
Abbreviated name:	Ioversol
Synonym:	Optiray® ,MP-328
Agent Category:	Compound
Target:	Non-targeted, blood pool, extracelluar space
Target Category:	Nonspecific filling of blood vessels and tissues
Method of detection:	X-ray, CT
Source of signal/ contrast:	Iodine (I)
Activation:	No



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Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans	Click on the above structure for additional information in PubChem.

Background

[PubMed]

N,*N*′-bis(2,3-dihydroxypropy)-5-[*N*-(2-hydroxyethyl)-glycolamidol]-2,4,6-triiodoisophthalamide (ioversol) is a nonionic X-ray contrast agent used to aid the radiographic visualization of blood vessels, heart, head, and body (1). Ioversol is approved by the United States Food and Drug Administration for contrast enhancement in peripheral and coronary arteriography and left ventriculography and for computed tomographic (CT) imaging of the head and body (2).

X-Ray imaging (planar and tomographic) techniques depend on tissue density differences which provide the image contrast produced by X-ray attenuation between the area of interest and surrounding tissues (3, 4). Contrast enhancement (opacification) with use of contrast agents increases the degree of contrast and improves the differentiation of pathological processes from normal tissues. Because iodine, an element of high atomic density, casuses high attenuation of X-rays within the diagnostic energy spectrum, water-soluble and reasonably safe iodinated contrast agents in intravenous injectable forms have been developed for clinical applications (5, 6).

Water-soluble, intravenous X-ray contrast agents are generally organic iodine compounds that contain one or more tri-iodinated benzene rings (7, 8). When injected intravenously, they are largely distributed in the extracellular fluid space and excreted unchanged by the kidneys (9). Contrast enhancement of a region of interest depends on the route of

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administration, delivery of the agent to the area by blood flow, and the final iodine concentration in the region. There are two basic types of these compounds: ionic and nonionic agents. The first monomeric ionic compound in the form of the 2,4,6-triiodobenzene acetrizoic acid, was synthesized by Wallingford (5). Most ionic contrast agents are derived from the basic structures of 3,5-diamino-2,4,6-triiodobenzoic acid, 5-amino-2,4,5-triiodoisophthalic acid, or 2,4,6-tri-iodobenzene-1,3,5-tricarbonic acid. In addition to developing monoacidic ionic dimers, nonionic compounds have also been developed to improve the tolerability of these agents in patients. The basic strategy of developing nonionic agents is to eliminate the electrical charges in the structure, which will lead to a reduction in osmolality of the compound. Because osmolality is related to the number of particles in solution, the challenge is to reduce the number of particles and maintain the iodine concentration (10). This was generally achieved by conversion of the carboxyl groups to hydroxyalkylamide groups (11). Further improvement was made by replacing the amino sugar with aminoalcohols to produce heat-stable hydroxyalkylamides to allow product sterilization (12).

Ioversol is a monomeric nonionic, tri-iodinated contrast agent that is characterized by relatively high hydrophilicity (13). Bonnemain et al. (14) discussed the concept of evenly distributed facial hydrophilicity, which led to the high hydrophilicity (log P octanol/water = -2.98) of ioversol. The current commercial formulations contain iodine concentrations of 160, 240, 300, 320 and 350 mg of iodine/ml (mg I/ml) with corresponding osmolality values (mOsm/g water) of 355, 502, 651, 702, and 792, respectively (2). The corresponding viscosity values (cps at 37 °C) are 1.9, 3.0, 5.5, 5.8, and 9.0, respectively.

Synthesis

[PubMed]

The synthesis steps involved in the production of X-ray contrast agents are well established organic reactions (7). Hoey et al. (15) described the basic approach of synthesizing derivatives of isophthalamic acid as contrast agents. The synthesis of ioversol involved an S_N2 reaction in which the amine was a nucleophile and an alkyl halide was the substrate. The reaction was carried out at a basic pH to avoid deactivation of the amino group. Lin (16) first described the synthesis that involved the synthesis of *N*,*N*′-bis(2,3-dihydroxypropyl)-5-glycolamido-2,4,6-triiodoisophthalamide from the starting chemical of 5-amino-2,4,6-triiodoisophthalic acid. This compound was then reacted with chloroethanol for 3 days, and 1 N NaOH and 2-chloroethanol were added and reacted for 3 more days. Additional portions of 1 N NaOH and 2-chloroethanol were added and reacted overnight. After trituration with methanol, filtration, and purification by preparative liquid chromatography, the final yield was 47.7%. Bailey et al. (17) reported a synthesis in which they added 2-bromoethylacetate and potassium carbonate to a solution of 5-acetoxyacetamido-*N*,*N*′-bis(2,3-diacetoxypropyl)2,4,6-triiodoisophthalamide in dimethylsulfoxide. The mixture was stirred until the reaction was complete. The resulting compound was then hydrolyzed with water containing sulfuric acid to produce ioversol. Ioversol prepared by this method required extensive purification to remove impurities.

Bosworth et al. (18) reported a high-efficiency reverse osmosis method to remove the low-molecular impurities. Bailey et al. (17) described an additional step involving a selective hydrolysis reaction so that most of the unwanted impurities were reduced and/or eliminated

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Ralston et al. (1) reported the genetic toxicology of ioversol (32% iodine w/v) ioversol in several *in vitro* systems. The mutagenicity of ioversol was evaluated in the *in vitro* microbial reverse mutation assay, mammalian forward mutation assay, and mammalian chromosomal aberration assay. Ioversol was not considered to be mutagenic in any of the three assays.

Heinrich et al. (19) studied the cytotoxic effects of iodinated contrast agents on renal tubular LLC-PK1 cells (porcine origin) *in vitro*. Ioversol in concentrations of 49.25 and 98.5 mM were studied. An ionic agent (ioxithalamate) showed a stronger cytotoxic effect than that of ioversol with cell viability of 4 ± 0.3% and 32± 2%, respectively. The study suggested that both hyperosmolality and direct cytotoxic effects contributed to the overall cytotoxic effects. Oldroyd et al. (20) used the isolated perfused rat kidney model to showed that ioversol (20 mg I/ml) produced endothelin-mediated effects on renal hemodynamics. Krause et al. (21) found that ioversol (*n*-butanol/water partition coefficient = 0.038) had *in vitro* effects similar to those of iopamidol (nonionic agent with *n*-butanol/water partition coefficient = 0.100) on rabbit erythrocyte morphology, lysozyme inhibition, and coagulation time. In a study involving cultured bovine aorta endothelial cells (ECs) and smooth muscle cells (SMCs), Sawmiller et al. (22) found that ECs were more severely affected by iothalamate (ionic agent), but that SMCs were more severely affected by Ioversol and iopamidol (nonionic agents).

Animal Studies

Rodents

[PubMed]

Ralston et al. (1) examined the reproductive, developmental, and genetic toxicology of ioversol in mice and rats. No teratogenic, fertility, or reproductive effects were observed in rats receiving intravenous doses up to 3.2 g of I(iodine)/kg/day. Offspring of dams treated with ioversol developed and reproduced in a normal fashion. A mammalian micronucleus assay was performed in mice that had received single intravenous doses up to 3.2 g I/kg, and it showed that ioversol did not induce a significant increase in micronuclei in mouse bone marrow. In another study (10), the medium lethal dose (LD_{50}) for the acute intravenous toxicity of ioversol (32% iodine (I) w/v) in mice and rats was 17 and 15 g I/kg, respectively. The LD_{50} for acute intracisternal toxicity (43% I w/v) in rats was 1,000 mg of iodine/kg for females and > 1,200 mg I/kg for males. A study of the subacute intravenous

toxicity (32% I w/v) in rats that received daily injections for 4 weeks showed that only significant effect was slight-to-moderate renal tubular cytoplasmic vacuolation at doses of 0.8 and 3.2 g I/kg/day dose levels. Ralston et al. (23) studied the effect of intracarotid injection in rats. Bilateral intracarotid injection of ioversol produced slight but transient changes in heart rate, respiratory rate, and mean arterial pressures. No arrhythmias, respiratory arrests, or alteration in the blood-brain barrier (BBB) were observed.

Wible et al. (24) studied the neurotoxicity of ioversol and other contrast agents after intracisternal administration of doses up to 1000 mg I/kg in rats. Signs of toxicity included tremors, head shaking and vocalization, convulsions, chewing and hypoactivity, and apnea. After performing a comparison with other less-hydrophilic nonionic agents (iopromide, iohexol, and iopamidol), the authors suggested that agents with higher hydrophilicity might produce lesser central nervous sytem toxicity.

Other Non-Primate Mammals

[PubMed]

Ralston et al. (1) assessed the effects of ioversol on the pregnancy and development in rabbits. Treatment with doses of 0.2, 0.8, and 3.2 g I/kg/day from day 6 to day 18 of pregnancy did not adversely affect the incidence of malformations, skeletal and visceral anomalies, or skeletal variants. In another study (10), the acute intravenous toxicity (LD_{50}) values of ioversol (32% I w/v) for rabbits and dogs were ≥25 and >12 g I/kg, respectively. In a study of acute intrathecal toxicity in dogs showed that signs of toxicity were limited to prolonged lethargy within the first few hours after injection of 240 mg I/kg. Ralston et al. (23) studied the intravenous pharmacokinetics in dogs. They reported that regardless of the route of injection, they observed only minimal effects on the heart rate and minimal to moderate decreases in myocardial contractility, left ventricular pressure, mean arterial pressure, pulmonary vascular resistance, and systemic vascular resistance.

Coveney and Robbins (25) used ^{125}I-labeled ioversol to study the biodistribution and excretion of ioversol (0.2 g I/kg and 1 g I /kg) in dogs. Biexponential blood clearance was observed in 3 of 4 dogs. Average distribution $t_{½}$s were 2.5 to 3.5 min, and elimination $t_{½}$s were 51 to 54 min. Volumes of distribution were 25-27% of the body weight which was consistent with extracellular fluid space distribution. Ioversol appeared to be excreted unchanged by the kidneys with ~40% of injected dose recovered in the urine at 2 h after injection. Very little of the radioactivity was found in tissues assayed at 48 h.

Evill et al. (26) studied the chemotoxic effects of ioversol (320 mg I/ml) and other contrast agents in rabbits with use of ^{99m}Tc pertechnetate to measure BBB injury. The ^{99m}Tc uptake (BBB injury) was calculated based on the difference in the blood/brain activity ratio (radioactivity in µg of blood per g of brain) between a BBB region that was exposed to the agent and a control BBB region (no exposure). For ioversol, this ratio was 6.06. In comparison, the values for mannitol (control), iohexol, iodixanol, and iotrolan were 0.15, 12.11, 9.46, and 4.21, respectively.

Non-Human Primates

[PubMed]

Ralston et al. (10) studied the acute neurotoxicity of ioversol (27% I w/v) in cynomolgus monkeys. After lumbar intrathecal injection of ioversol (60 mg of iodine/kg of body weight), transient tremors and muscular fasciculations were observed immediately, but the symptoms were absent at 1 h. No histologic abnormalities were found on the spinal leptomeninges at 12 weeks after injection.

Human Studies

[PubMed]

Wilkins et al. (27) conducted a single-blind randomized study of the safety and pharmacokinetics of ioversol (320 mg of iodine/ml in doses of 50, 100, and 150 ml) in 24 healthy volunteers. No significant changes were observed in physical examination, vital signs, electrocardiography, and biochemical and hematological data. Biphasic blood clearance ($n = 6$) was observed with $t_{½}\alpha$ (min) and $t_{½}\beta$ (h) determined to be 15.5 ± 3.5 and 2.06 ± 0.13 for the 50 ml dose. For the 150-ml dose, $t_{½}\alpha$ and $t_{½}\beta$ were 18.9 ± 3.2 min and 2.04 ± 0.04 h, respectively. The urinary excretion $t_{½}\beta$ for the 50-ml and 150-ml doses were 1.88 ± 0.14 h and 1.73 ± 0.25 h, respectively. The volumes of distribution (ml/kg), $V_{d\beta}$ and V_{dss}, for the 50-ml dose were 394 ± 22 and 353 ± 12, respectively. For the 150-ml dose, the values were 410 ± 25 and 360 ± 19 ml/kg, respectively.

McClennan (28) and Benamor et al. (29) reported on the clinical safety of ioversol based on 23 double-blind, controlled, parallel group studies and 9 open-label studies. A total of 1,186 patients participated in the trials and received a mean contrast dose of 1.6 ml/kg (ioversol, 320 mg I/ml and 240 mg I/ml for venography only), or a mean iodine dose of 470.7 mg/kg. About 91% of patients reported no or mild pain associated with the injection. Whereas about 5.8% of patients had one or more adverse reactions. Nausea (1.0%), headache (0.8%), vomiting (0.5%), blurred vision (0.4%), vertigo (0.4%), and lightheadedness (0.3%) were the most common reactions. In comparison, the reference group that received ionic contrast agents reported an adverse reaction rate of 14.8%. No significant changes of renal function up to 96 h after injection were observed. The diagnostic efficacy of ioversol appeared to be comparable to the efficacies of both ionic and nonionic agents with respect to diagnostic quality. Le Mignon et al. (13) reported the European clinical experience of 472 patients who received ioversol (300 mg I/ml or 350 mg I/ml). About 11% of patients had adverse reactions, and Ioversol was found to be 99% useful in all radiologic applications. In 76% of the cases, image quality was judged to be good or excellent. In 1996, Floriani et al. (30) performed a metaanalysis of data from all available randomized, double-blind trials of ioversol. A total of 1931 patients were included in the analysis which indicated that ioversol was considered diagnostic in 99.3% of examinations, with good to excellent enhancement quality in 89.3% of cases.

Other studies have indicated that ioversol appears to have safety, tolerability, and efficacy profiles comparable to other nonionic contrast agents in various radiographic studies of the brain, heart, blood vessels, kidneys, and whole body [PubMed].

Supplemental Information

[Disclaimers]

Ioversol Package Insert

Ioversol Bulk Pack Package Insert

Ioversol Material Safety Data Sheet

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