N-(2,3-Dihydroxypropyl)-*N*′-(2-hydroxyethyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide

Ioxilan

The MICAD Research Team

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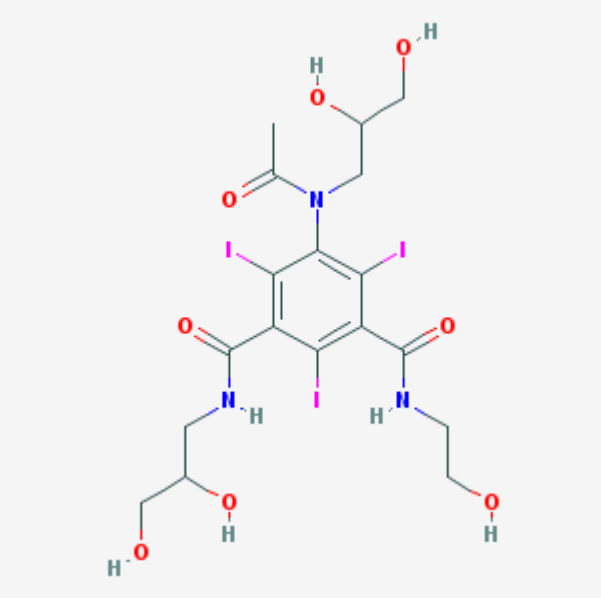
Chemical name:	*N*-(2,3-dihydroxypropyl)-*N*′-(2-hydroxyethyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide
Abbreviated name:	Ioxilan
Synonym:	Oxilan®, 5-(*N*-2,3-dihydroxypropylacetamido)-2,4,6-triiodo-*N*-(2-hydroxyethyl)-*N*′-(2,3-dihydroxypropyl)-isophthalamide, ioxitol
Agent Category:	Compound
Target:	None
Target Category:	Nontargeted filling of blood vessels and tissues
Method of detection:	X-ray, CT
Source of signal:	Iodine
Activation:	No
Studies:	• *In vitro* • Rodents • Other non-primate mammals • Humans



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Background

[PubMed]

N-(2,3-dihydroxypropyl)-*N′*-(2-hydroxyethyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide (ioxilan) is a nonionic X-ray contrast agent approved by the United States Food and Drug Administration for X-ray imaging contrast enhancement (1, 2). Ioxilan can be administered intravenously for excretory urography and contrast-enhanced computed tomography (CT) imaging of the head and body (3). Ioxilan can also be given intraarterially for cerebral arteriograpy, coronary arteriography and left ventriculography, visceral angiography, aortography, and peripheral arteriography.

Techniques for X-ray imaging (planar and tomographic) depend on tissue density differences that provide the image contrast produced by X-ray attenuation between the area of interest and its surrounding tissues (4, 5). Contrast enhancement (opacification) with use of contrast agents increases the degree of contrast and improves the differentiation of pathologic processes from normal tissues. Because iodine, an element of high atomic density, causes high attenuation of X-rays within the diagnostic energy spectrum, water-soluble and reasonably safe iodinated contrast agents in intravenously injectable forms have been developed for clinical applications (6, 7).

Water-soluble, intravenous X-ray contrast agents are generally organic iodine compounds that contain one or more tri-iodinated benzene rings (8, 9). When injected intravenously, they are largely distributed in the extracellular fluid space and excreted unchanged by the kidneys (10). Contrast enhancement of a region of interest depends on the route of 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 2,4,6-triiodobenzene acetrizoic acid, was synthesized by Wallingford (6). 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-triiodobenzene-1,3,5-tricarbonic acid. In addition to monoacidic ionic dimers, nonionic compounds have also been developed to improve the tolerance 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 but maintain the iodine concentration (11). This is generally achieved by conversion of the carboxyl groups to hydroxyalkylamide groups (12).

As a low-osmolar nonionic monomer, ioxilan was developed in an effort to increase the safety and tolerance of X-ray contrast agents. The development of ioxilan was based on the belief that the introduction of a double methylene as a hydrophobic region and masking it with a hydrophilic hydroxyl group could lower the osmolality without adversely affecting the biological tolerance (13). Ioxilan is available commercially in

preparations of 300 mg I/ml (632 mg ioxilan) and 350 mg I/ml (727 mg ioxilan). Their measured osmolality values (mOsm/kg water) at 37°C are 585 and 695, respectively. The viscosity values (cP) at 37°C are 5.1 and 8.1, respectively.

Synthesis

[PubMed]

Ioxilan can be synthesized in a variety of ways (13). Sovak and Ranganathan (14, 15) reported the eight-step conversion of ioxithalamic acid into ioxilan. Briefly, ioxithalamic acid was alkylated and acetylated into 5-(*N*-2,3-diacetoxypropylacetamido)-2,4,6-triiodo-*N*-(2-acetoxyethyl)-isophthalamic acid. The yield was 97%. This was reacted with thionyl chloride and heated at 60-65°C for 1 h to form an acyl-chloride with a yield of 96%. The *N*-alkylated, acetylated, ioxithalamic acid chloride was amidated with trans-dioxepane and then deprotected to produce an aminothreitol derivative. The resulting product was further amidated with 1-amino-2,3-propanediol in triethylamine at room temperature for 8 h with a 87.9% yield. The amidated compound was then deacetylated in methanol at pH 13 for 30 min to yield (80%) the final product of ioxilan.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Violon studied the *in vitro* osmolality of ioxilan and seven other monomeric nonionic agents (16). The author concluded that both the hydrophilic and hydrophobic characteristics of a molecule are important in the determination of the osmolality. Parvez and Patel (17) studied the *in vitro* effect of ioxilan on human erythrocytes. Ioxilan (7, 14, and 35 mg I/ml) was incubated with freely drawn and ethylenediaminetetraacetic acid-anticoagulated human blood, heparinized whole human blood, or platelet-rich plasma at 37°C for 60 min, 30 min, or 3 min, respectively. No change was observed in the red cell morphology study. Ioxilan inhibited adenosine diphosphate–induced platelet aggregation in a manner similar as iopamidol. It did not activate the serum complement system.

Rabbit thoracic aortas (aortic rings) were used to study the functional and morphologic effects of ioxilan on endothelial cells *in vitro* (18). The ability of the endothelial cells to release an endothelium-derived relaxing factor was tested by measuring the dilator response to acetylcholine. After incubation with ioxilan (350 mg I/ml), the percentages (%) of retained dilator activity to acetylcholine (0.2 μmol/L) were 95.1 ± 15.2 and 114.5 ± 29.8 (n = 3) for incubation times of 15 min and 60 min, respectively. In comparison, sodium meglumine diatrizoate (370 mg I/ml0, a high-osmolar ionic contrast agent, had values of 48.6 ± 6.9% and 0 ± 0%, respectively. Scanning and transmission electron micrographs showed that ioxilan produced irregularities in the cell borders and in some vesicles. Similar effects were produced by another nonionic monomer, iohexol (350 mg I/ml). Schneider and Rand (19) showed that ioxilan, iohexol, and diatrizoate all caused a direct chemotoxic effect on smooth muscle cells in isolated rabbit aortas. The study suggested that the effects were caused by activating the production of a cyclic nucleotide.

Lasser and Lyon (20) studied the *in vitro* inhibition of angiotensin-converting enzyme (ACE) by ioxilan. In a pattern similar to six other commercial ionic and nonionic contrast agents, ioxilan (30% iodine) showed an inhibitory effect on ACE under the studied condition.

Animal Studies

Rodents

[PubMed]

Thomsen et al. (21, 22) studied the effects of ioxilan on urine profiles in rats. Ioxilan (350 mg I/kg) was given by i.v. administration. Ioxilan caused albuminuria, higher excretion of both glucose and L-γ-glutamyltransferase, and tubular dysfunction. Similar effects were observed with iohexol. In comparison, diatrizoate caused significantly greater effects on the kidneys. These renal effects were confirmed in a rat model of nephropathy induced by intramuscularly administered glycerol (23). Ioxilan did not appear to aggravate Fanconi's syndrome (tubulointerstitial nephropathies) in rats induced by i.v. injection of sodium maleate in rats (24).

Harnish et al. (25) investigated the effects of ioxilan on the blood-brain barrier (BBB) in hypertensive rats. Ioxilan in doses of 350 mg I/ml and 175 mg I/ml were injected into the carotid artery. No significant BBB damage assessed by ^{14}C-labeled inulin was found in normal and hypertensive rats with elevated blood pressure of 165-190 mm Hg.

Sovak et al. (2) used a psychopharmacological method, conditioned taste aversion (CTA), to quantify the vascular pain caused by ioxilan in rats. The percentage of CTA to ioxilan was -9.99 ± 22.31 (n = 15). In comparison, iohexol and iopamidol had values of -56.33 ± 20.81 and -33.08 ± 24.37, respectively.

Other Non-Primate Mammals

[PubMed]

The effects of ioxilan on renal size, renal profiles and blood profiles were studied in rabbits (26). Ioxilan (350 mg I/ml; 5 ml/kg) did not cause significant changes in any of the studied profile components. Moore et al. (27) reported that ioxilan (300 mg I/ml) produced no pathologic response in the rabbit fallopian tube or peritoneal cavity. Thurmond et al. (28) showed that ioxilan (350 mg I/ml) administration by direct intratubular injection caused 0.9 (average inflammation number) fallopian tube inflammation in 10 rabbits 24 h after injection. The average inflammation numbers were 0 (n = 3) and 0.7 (n = 5) for 4 days and 2 weeks, respectively. In comparison, the average inflammation numbers for diatrizoate (52%) were 1.4 (n = 5), 0 (n = 3), and 0.7 (n = 3), respectively. The authors suggested that ioxilan could be clinically acceptable for direct injection into the human fallopian tube.

Eisenberg et al. (29) evaluated the early and delayed inflammatory response of the peritoneal surfaces to ioxilan in guinea pigs. Animals given intraperitoneally injections of

ioxilan (300 mg I/ml) showed only two inflammatory responses (n = 5) at 7 days and no inflammation at 1 day or 30 days after injections. In comparison, diatrizoate sodium (300 mg I/ml) showed two, three, and one inflammatory responses at 1, 7, and 30 days, respectively.

In a dog study (n = 6), Katzberg et al. (1) demonstrated that i.v. ioxilan administration (350 mg I/ml; 2 m/kg) produced satisfactory nephrograms and pyelograms. The effects of ioxilan on systemic and renal hemodynamics were minimal and similar to those of iohexol (350 mg I/ml). Izci et al. (30) reported that no adverse clinical signs were observed in dogs (n = 6) that received i.v. ioxilan (350 mg I/ml or 700 mg I/kg). Blood samples were collected to evaluate acid-base, venous blood gas status (pH, PCO_2, PO_2, HCO_3–, BE, O_2) and electrolytes (Na^+, Ca^{++}, K^+). No long-lasting or major effects of any of these studied parameters were found. Nakamura et al. (31) found that ioxilan radiographic images (cerebral angiography, aortofemoral angiography, and left ventriculography) and cardiovascular changes in dogs (n = 4-5) after administration of ioxilan (350 mg I/ml) were similar to radiographic images after administration of iohexol (350 mg I/ml) and iopamidol (370 mg I/ml). In comparison, diatrizoate (76%) had a greater effect on studied cardiovascular parameters. Misumi et al. (32) reported that ioxilan (350 mg I/ml) had low incidence of ventricular fibrillation in dogs, and they suggested that this property might be attributable to its optimal sodium concentration of 9 mmol/L.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Callantine et al. (33) conducted a phase I study of ioxilan (300 and 350 mg I/ml) at four dose levels (100, 300, 500, and 700 mg I/kg) in 24 human volunteers. After i.v. administration, there were no clinically significant changes in the physical examination findings (ophthalmic and neurologic evaluations), vital signs, or electrocardiograms. A mild and transient increase in blood pressure and heart rate was observed at 3 min after injection in some patients. No significant changes were found in serum chemistries, hematologic values, or renal functions. Pharmacokinetic data revealed no significant differences in plasma concentrations over time with either ioxilan concentrations. There was an initial rapid distribution phase ($t_{½\alpha}$ = 18.01 ± 3.12 min) which was followed by a slower elimination phase ($t_{½\beta}$ = 107.43 ± 3.92 min). Ioxilan was excreted primarily by the kidneys with a volume of distribution of 19.5 L and renal clearance of 116.5 ml/min. About 93% of the dose was excreted unchanged in the urine within 24 h.

McIntosh and Reed (34) reported the results of a phase III clinical studies for ioxilan. There were 835 patients who received ioxilan (300 or 350 mg I/ml). The results were

compared with those of iohexol in 523 patients. Overall clinical adverse events showed that 2 patients experienced a total of four adverse events. In comparison, the iohexol group had 3 patients who experienced five adverse events. The hepatic, hematologic, and renal safety profiles, as well as patient tolerance for pain and warmth of ioxilan were similar to those of iohexol. There was no evidence of *in vitro* or *in vivo* activation of blood coagulation. Images (aortofemoral and visceral arteriography, coronary and left ventricular angiography, cerebral arteriography, excretory urography, and body and head CT) were reviewed by two blinded independent readers reported that 97% of 358 ioxilan images were of diagnostic quality. In comparison, iohexol had 98% of 375 iohexol images were of diagnostic quality.

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