(S)-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)-ethyl-2,4,6-triiodo-5-lactamidoisophthalamide

Iopamidol

The MICAD Research Team

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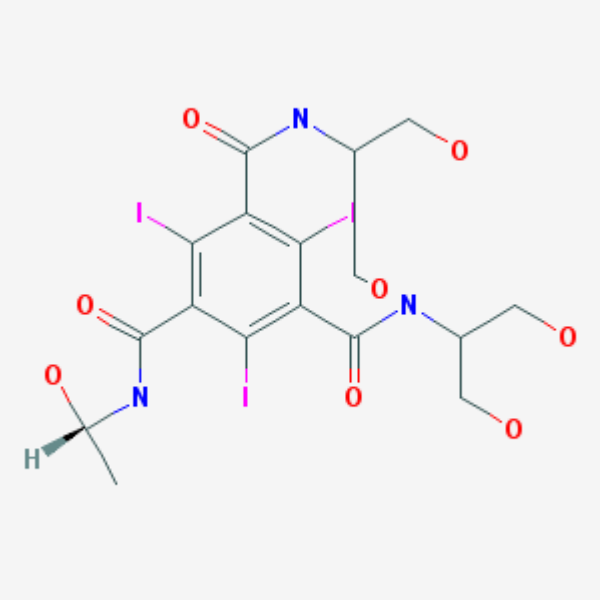
Chemical name:	(*S*)-*N*,*N*'-bis[2-hydroxy-1-(hydroxymethyl)-ethyl-2,4,6-triiodo-5-lactamidoisophthalamide
Abbreviated name:	
Synonym:	Iopamidol, Isovue
Agent Category:	Compound
Target:	Blood pool, extracellular fluid space
Target Category:	Nonspecific filling of extracellular fluid space
Method of detection:	CT and X-ray
Source of signal:	Iodine
Activation:	No
Studies:	• *In vitro* • Rodents • Non-primate non-rodent mammals • Non-human primates • Humans



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Background

[PubMed]

Computed tomography (CT) is a diagnostic imaging procedure that uses a combination of x-rays and computer technology to produce cross-sectional images used to diagnose or evaluate treatment of a variety of the cardiovascular system diseases, peripheral angiography, and cancer. This is a noninvasive technique and may require the administration of a contrast media (CM) before the procedure is performed. The CMs used for these procedures are usually iodinated compounds and are classified as ionic or nonionic on the basis of their chemistry. Both CM varieties are either high- or low-osmolality and are available in monomeric or dimeric forms (1). The CM preparations are usually available at various iodine concentrations and have different physiochemical properties such as pH, hydrophilicity, and viscosity. Although CMs are considered safe to use, some patients may experience a general adverse reaction or nephrotoxicity with these agents (1-4). The management of these reactions has been discussed, and different methods to reduce development of toxicity in the patients have been proposed by some investigators (3-5). The nonionic variety of CMs was developed because the ionic variety had a higher rate of adverse reactions and was particularly unsuitable for severely ill patients or individuals with kidney dysfunction (2, 4).

This chapter is a brief review of (*S*)-*N*,*N*'-bis[2-hydroxy-1-(hydroxymethyl)-ethyl-2,4,6-triiodo-5-lactamidoisophthalamide (generic name: iopamidol), an iodinated, nonionic, low-osmolality CM. Iopamidol was approved for use as a CM by the US Food and Drug Administration and is commercially available in the US. According to the manufacturer (6), this CM may be used for adult and pediatric angiography throughout the cardiovascular system, coronary arteriography and ventriculography, intravenous excretory urography, contrast enhancement of CT (CECT), and head and body imaging.

Synthesis

[PubMed]

The method to synthesize iopamidol has been described in a patent issued to the manufacturer in the US (7).

For this, *N*,*N*'-bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-amino-2,4,6-triiodo-1-,3-benzenedicarboxamide was mixed with dimethylacetamide (DMA). A solution of propanediol and triethylamine in DMA was then added to the mixture. After mixing, the temperature was gradually elevated to 30°C and maintained for 1.5 h. The reaction was then cooled, and 4-dimethylaminopyridine was added to the vessel and followed by slow addition of acetic anhydride. The mixture was stirred for 2 h and quenched by slow addition of water to yield a solid. The solid was isolated by filtration, washed with water, and dried, with a yield of 90%. The solid was dissolved in DMA and 2(*S*)-acetoxypropionyl chloride was slowly added to it. The reaction was stirred at room temperature for ~2 h and quenched by the slow addition of isopropanol to obtain

pentaacetyliopamidol. The pentaacetyliopamidol was collected by filtration, washed with isopropanol, and dried, with a yield of 90%. A solution of pentaacetyliopamidol in methanol was refluxed for ~30 h with aqueous hydrochloric acid. The methanol was removed by distillation and the residue was dissolved in water. The residual acid was neutralized by stirring the solution with an acid-scavenging resin. The resin was removed by filtration and the aqueous solution was passed through a column of Amberlite XDA-16 resin. The eluent was concentrated to obtain an oil and a residue that was crystallized by heating the oil in a mixture of acetonitrile and ethanol. Iopamidol was collected by filtration, washed with ethanol, and dried. The yield was 74%.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Because of the intra-arterial or intravenous application of iopamidol, a variety of studies describing the *in vitro* effects of this agent on cell adhesion molecules (8), platelet aggregation (9), partial thromboplastin time (10), thrombogenicity (11), potassium release rates in blood (12), metabolic functions in renal epithelial cells (13, 14), nephrotoxicity (15), and chemotoxic effects on renal tubules (16) are available.

Animal Studies

Rodents

[PubMed]

The use of iopamidol was compared with a new contrast agent, Fenestra VC, for *in vivo* imaging of cardiac structure and function in mice (17). Fenestra VC is a contrast agent that consists of iodinated triglycerides formulated in a stable, oil-in-water lipid emulsion. One group of mice received a constant infusion of iopamidol while the other group received a single bolus injection of Fenestra VC. The investigators observed and concluded that Fenestra VC was a better contrast agent compared to iopamidol to study cardiac structure and function in these animals because it provided a higher signal-to-noise ratio.

The use of CM diffusion across vascular endothelium to study the magnitude of endothelial defects induced by the endotoxin lipopolysaccharide (LPS) sepsis was evaluated in a rat model (18). LPS was administered to the animals through the intraperitoneal route, and the vascular leakage and volume values were quantified in the various organs (myocardium, kidney, liver, and colonic wall) after the administration of various CMs, including iopamidol. Vascular leakage increased in all the organs and the elimination of iopamidol from the intravascular compartment in LPS-treated animals was reduced compared with controls. The investigators concluded that CMs could be used to study vascular leakage and volume in an animal model of endotoxin toxicity.

Other Non-Primate Mammals

[PubMed]

The use of rabbits to determine nephrotoxicity of several ionic and nonionic CMs, including iopamidol, has been described (19). Nonionic monomer CMs were observed to be nephrotoxic at ~15 times the normal dose used for CT procedures.

Non-Human Primates

[PubMed]

The distribution of therapeutics to specific locations in the central nervous system is often performed by using the convection-enhanced delivery (CED) system (20). The system requires use of surrogate imaging tracers to monitor optimal, real-time, *in vivo* distribution of drugs. Using CED, Croteau et al. (20) used clinical observations and histopathology of the animals to evaluate the safety and toxicity of iopamidol as a surrogate tracer for CT scanning of the central nervous system in primates (*Macaca mulatta*). Distribution of the tracer in the animals was determined by *in vivo* real-time and postinfusion CT scanning along with quantitative autoradiography using ^{14}C sucrose and ^{14}C dextran. The investigators concluded that iopamidol was safe and suitable for monitoring drug delivery using CED and produced no clinical or histopathological toxicity in the animals.

Human Studies

[PubMed]

The use of iopamidol for different techniques has been investigated in various clinical studies [PubMed] designed to diagnose cancer [PubMed], investigate cardiac function [PubMed], vasculature [PubMed], and nephrotoxicity [PubMed].

Iopamidol was used as an alternative to radioactivity for interstitial CT lymphography in superficial esophageal cancer patients (21). Sentinel lymph node (SLN) mapping and biopsy examination was performed on the patients using an experimental endoscopic CT technique after an endoscopic submucosal peritumoral injection of iopamidol. This was followed by radical esophagectomy and regional lymph node dissection with CT lymphography guidance. The draining lymphatic vessels and the SLNs were visualized by CT within 5 min of CM injection and the lymph node metastasis was detected with excellent accuracy and sensitivity. The investigators concluded although this study (21) showed that endoscopic CT lymphography using iopamidol could be clinically applied for esophageal SLN mapping and biopsy examination, a larger investigation would be necessary to establish its accuracy and usefulness.

Murakami et al. (22) investigated the use of iopamidol with a double-phase CT technique for the diagnosis of hepatocellular carcinoma. With results obtained from the study, the

investigators concluded that the technique could improve diagnostic accuracy of cancer detection.

Bone marrow transplantation (BMT) patients are often exposed to a variety of nephrotoxic, antineoplastic, immunosuppressive, and antimicrobial drugs. In addition, BMT patients are also often subjected to CT using low-osmolality CMs to detect any infections or other non-hematological complications. The clinical records of 120 pediatric patients who had undergone allogenic BMT were reviewed to assess the effects of iopamidol and antimicrobial drugs on the renal function of these individuals (23). Serum creatinine and blood urea nitrogen concentrations were measured 24 h before and 72 h after each administration of iopamidol for CT examination performed within 100 days of BMT. The reviewers concluded that iopamidol had negligible nephrotoxicity in the allogenic pediatric BMT patients, even in individuals with elevated renal function prior to the procedure.

An estimated 0.6–2.3% of patients who undergo an angiographic procedure may experience contrast-induced nephropathy (CIN), and the incidence is particularly higher (3.3–14.5%) in patients with cardiovascular problems (24). Patients with impaired renal function, diabetes, or a combination of the two are also a population at high risk for CIN (25). It is believed that CIN is the result of direct CM toxicity to the renal tubular cells and medullary ischemia. Although CM osmolality is generally considered as the main cause of nephrotoxicity, other factors, such as molecular structure differences of the CM (26) and free radical generation (27), also probably contribute to the development of CIN. A review of data obtained from several clinical trials where CMs were used for cardiac or peripheral angiography showed that iopamidol had a lower incidence of CIN compared to other CMs (24, 28). The antioxidant acetylcysteine was shown to reduce renal ischemic failure in animals (29), and Kay et al (30). investigated the prophylactic use of this compound to prevent CIN in patients with moderate renal insufficiency undergoing coronary angiography with iopamidol. From this study the investigators concluded that acetylcysteine was a safe, effective, and inexpensive prophylactic treatment against CIN. In contrast, another study (31) concluded that there was no benefit of the prophylactic treatment with acetylcysteine for patients undergoing peripheral angiography with CMs, including iopamidol. In another study to evaluate the prophylactic treatment of sodium bicarbonate or sodium chloride against CIN caused by iopamidol, it was concluded that sodium bicarbonate was more effective than sodium chloride in reducing the occurrence of CIN (32).

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