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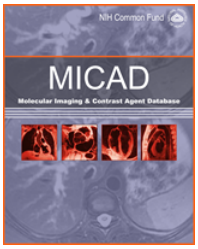

N,N′-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl-3-methoxypropyl)-acetamidol]-2,4,6-triiodoisophthalamide

Iopentol

Kenneth T. Cheng, PhD[1]

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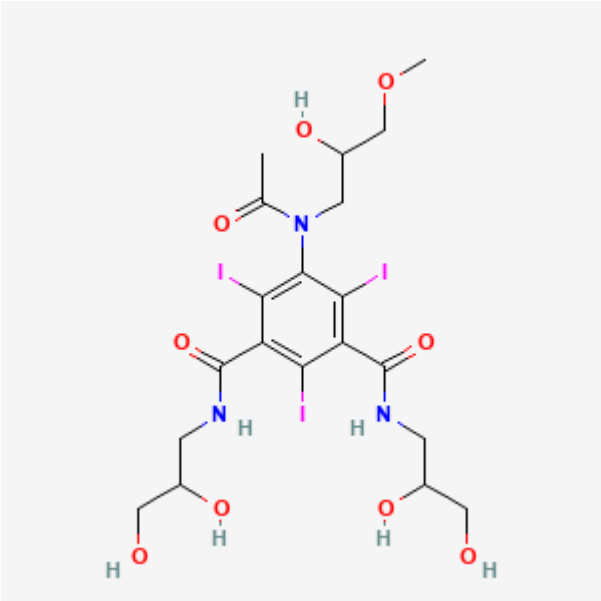
Chemical name:	*N,N′*-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl-3-methoxypropyl)-acetamidol]-2,4,6-triiodoisophthalamide
Abbreviated name:	Iopentol
Synonym:	Imagopaque®, Ivepaque, Compound-5411, 5-[Acetyl(2-hydroxy-3-methoxypropyl)amino]-*N,N′*-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide
Agent Category:	Compound
Target:	Non-targeted agent, accumulation in the blood pool and extracellular space
Target Category:	Nonspecific filling of blood vessels and tissues
Method of detection:	X-ray, CT
Source of signal / contrast:	Iodine
Activation:	No



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Studies:

- *In vitro*
- Rodents
- Non-primate non-rodent mammals
- Non-human primates
- Humans

Author Affiliation: 1 National Center for Biotechnology Information, NLM, NIH, Bethesda, MD; Email: micad@ncbi.nlm.nih.gov.

Background

[PubMed]

N,*N*′-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl-3-methoxypropyl)-acetamidol]-2,4,6-triiodoisophthalamide (iopentol) is a nonionic X-ray contrast agent used in various radiologic procedures to aid the radiographic visualization of selected tissues or organs.

X-Ray imaging (planar and tomographic) techniques depend on tissue density differences that provide the image contrast produced by X-ray attenuation between the area of interest and surrounding tissues (1, 2). 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 intravenous injectable forms have been developed for clinical applications (3, 4).

Water-soluble, intravenous X-ray contrast agents are generally organic iodine compounds that contain one or more tri-iodinated benzene rings (5, 6). When injected intravenously, they are largely distributed in the extracellular fluid space and excreted unchanged by the kidneys (7). 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 (3). 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 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 but maintain the iodine concentration (8). This was generally achieved by conversion of the carboxyl groups to hydroxyalkylamide groups (9). Further improvement was made by replacing the amino sugar with aminoalcohols to produce heat-stable hydroxyalkylamides to allow product sterilization (10).

As a low-osmolar nonionic monomer, iopentol was developed in an effort to increase the safety and tolerance of X-ray contrast agents. Chemically, it is a *m*-carboxamido-*O*-iodo-*N*-(β-hydroxyalkyl)aniline derivative and a water-soluble ratio 3.0 (3 iodine atoms to 1 osmotic particle) compound (11, 12). Iopentol is not commercially available in the United States. It has been used in Europe for arteriography, urography, phlebography and computed tomography enhancement, arthrography, endoscopic retrograde cholangiopancreatography, hysterosalpingography, and gastrointestinal studies. The commercial preparations were available in iodine concentrations ranging from 150 to 350 mg/ml (13).

Synthesis

[PubMed]

The synthesis steps involved in the production of X-ray contrast agents are well-established organic reactions (5). Hoey et al. (14) described the basic approach of synthesizing derivatives of isophthalamic acid as contrast agents. Berg and Fagervoll (15) and Haavaldsen et al. (16) reported the synthesis of iopentol by treating dimethyl 5-nitroisophthalate with 3-amino-1,2-propanediol in boiling methanol and refluxing for 24 h to produce the corresponding isophthalamide. This product was hydrogenated in the presence of 10% palladium/charcoal in a Parr apparatus for 1 day at room temperature to give the aminoisophthalamide. Iodination followed by acetylation gave the acetamido derivative, which was alkylated with 1-chloro-3-methoxy-2-propanol in a

suitable solvent, such as methanol or propylene glycol, under basic conditions. This final step yielded ~70% iopentol. Because of the use of racemic mixtures of chiral reagents during synthesis, the final product consisted of several diastereomers. In another report, Berg et al. (17) identified, synthesized, and characterized several potential impurities for quality control purposes.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Skinnemoen (18) studied the *in vitro* physicochemical properties of iopentol and determined that the osmolality and viscosity of iopentol ranged from 0.31 osmoles/kg H_2O and 2.7 mPa·s at 37 °C for the150 mg iodine/ml concentration to 0.81 osmoles/kg H_2O and 26.6 mPa·s at 37 °C for the 350 mg iodine/ml concentration. In comparison, for iohexol (a nonionic contrast agent) at a concentration of 350 mg iodine/ml, the values were 0.78 osmoles/kg H_2O and 23.3 mPa·s. The 1-octanol:water partition coefficients for iopentol and iohexol were 0.007 and 0.001, respectively.

Krause et al. (19) investigated the biochemical properties of 11 ionic and nonionic contrast agents. The lowest protein binding values were obtained for iopentol and iomeprol. In a histamine release study using rat mast cells, iopentol and other nonionic contrast agents released less than 12% of histamine at the 100 mg iodine/ml concentration. At the same concentration, diatrizoate, an ionic contrast agent, released 77.5% of histamine. Iopentol and iotetrol showed the highest influence on complement activation (77 and 71% inhibition, respectively, at 100 mg iodine/ml). The lowest effect was observed for iopamidol (0%) and diatrizoate.

In a series of *in vitro* studies (20-22), the effects of iopentol and other nonionic contrast agents (iohexol, iodixanol, and iopamidol) on red blood cells were investigated. A microscopy study revealed that all contrast agents induced morphologic changes with small differences among the agents. The changes appeared to be related to the osmolality of the tested solution. The authors of the study suggested that the changes were most likely of small clinical importance. All contrast agents decreased red blood cell aggregation with no differences among the various agents. The authors suggested that the chemotoxic effect had more impact than the osmolality on red blood cell aggregation. No difference was found among the agents in the effect on red blood cell rigidification. Diatrizoate did induce significantly more red blood cell rigidity when compared with the nonionic agents.

Animal Studies

Rodents

[PubMed]

Michelet and Skinnemoen (23) examined the pharmacokinetics of iopentol in rats by injecting [^{125}I]iopentol (specific activity = 2 kBq (0.05 µCi)/kg) at a dose of 200 mg iodine/kg into the caudal vein. After injection, the blood radioactivity level decreased rapidly with time and approached zero after 1-2 h. The blood elimination half-life ($t_{½}$) was 24.4 ± 6.3 min (n = 5). About 86.8 ± 3.8% (n = 10) of the injected dose (ID) and 12.7 ± 2.0% ID were found in urine and feces at 24 h, respectively. Most organs did not contain any detectable activity. The concentration in the thyroid was 31.6 ± 10.0 iodine/g wet tissue. The highest tissue concentrations were 89.2 ± 40.8 and 314.3 ± 163.7 µg iodine/g wet tissue in the gastrointestinal tract at 24 h and 7 days, respectively. High-performance liquid chromatography (HPLC) analysis of the urine (pooled samples from 0 to 48 h) did not detect any possible metabolites from deiodination. At a higher dose of 10 g iodine/kg, the level of deiodination products was estimated to be 0.1% ID. HPLC analysis of the bile (pooled samples from 0 to 180 min) showed that a minimum of 4.6% ID was excreted unchanged.

In a study of acute toxicity at the 350 mg iodine/ml concentration of iopentol, Michelet et al. (24) reported an acute i.v. median lethal dose (LD_{50}) of 19.5 g iodine/kg for doses between 17.5 and 24.5 g iodine/kg in male mice and an LD_{50} of 119.4 g iodine/kg for doses between 17.5 and 24.5 g iodine/kg in female mice. The acute i.v. LD_{50} of iopentol in rats was 10.3-11.7 g iodine/kg for doses between 8.75 and 15.75 g iodine/kg. For the same concentration and doses, the LD_{50}s were 11.7-12.1 and 10.3-10.8 g iodine/kg for iohexol and iopamidol, respectively. Heywood et al. (25) reported a summary of the toxicologic profile of iopentol and found that the only significant finding in the repeat-dose studies in rats was cytoplasmic vacuolation in the kidney proximal tubules at the highest dose level (4 g iodine/kg/day) for 4 weeks. This effect was reversible within 14 days. The battery of mutagenic tests showed no genotoxic or clastogenic potential for iopentol. No teratogenic effects and other adverse effects of importance were observed on any of the measured characteristics of reproduction.

Luzzani et al. (26) reported the LD_{50} values of intracisternal injection in rats and intracerebroventricular injection in mice for nonionic monomers (iomeprol, iopamidol, iohexol, iopentol, and iopromide) and dimers (iofratol, iotrolan, and iodixanol). For iopentol, the intracerebroventricular LD_{50} in mice was 1.11-1.24 g iodine/kg, and the intracisternal LD_{50} in rats was 0.15-0.34 g iodine/kg. In comparison, iohexol had values of 0.69-1.00 and >1.50 g iodine/kg, respectively. Iodixanol had values of 0.88-1.06 and >1.60 g iodine/kg, respectively.

Other Non-Primate Mammals

[PubMed]

Leunbach et al. (27) studied the metabolism and excretion of iopentol (350 mg iodine/ml concentration and 1 g iodine/kg dose) in pigs. The iodine concentration in the urine increased from 46-113 mg iodine/ml at 0-2 h to 64-118 mg iodine/ml at 2-4 h and then decreased to 2-33 mg iodine/ml at 10-12 h. The iodine concentration in bile increased from 2.4-3.0 to 2.2-3.4 mg iodine/ml and then decreased to 0.1-0.7 mg iodine/ml at 10-12 h. Most of the compound appeared to be excreted in urine during the first 12 h. The amounts of metabolites in the 24 h urine and bile samples were 0.2-0.8 and 0.02-4.7 mg iodine/ml, respectively.

Michelet (28) studied the effect of intravascular contrast media on the rabbit blood-brain barrier (BBB) after intracarotid injection of iopentol, iohexol, iothalamate, and iodixanol. BBB injuries were demonstrated by the extravasation of ^{99m}Tc-pentetate (^{99m}Tc-DTPA; reversible changes), ^{125}I-labeled human serum albumin (^{125}I-HSA; severe permeability disturbances), and Trypsin blue. The results were expressed as percentage of increased radioactivity in the injected hemisphere over the amount in the non-injected hemisphere. All contrast agents had increased mean values of ^{99m}Tc-DTPA extravasation in the injected hemisphere compared with the contralateral hemisphere. For iopentol, the extravasation of ^{99m}Tc-DTPA and ^{125}I-HSA was 137 ± 75 and 9 ± 16%, respectively. In comparison, the values for iohexol were 128 ± 39 and 32 ± 15%, respectively. The values for iothalamate (ionic monomer) were 475 ± 118 and 215 ± 68%, respectively.

Sunnegardh et al. (29) reported that both iopentol and iohexol (at 300 mg iodine/ml concentration and 4 ml/kg dose) had similar pulmonary and renal hemodynamic effects in pigs. Renal venous blood flow and vascular resistance were not significantly changed. Both induced a significant increase in pulmonary arterial occlusion pressure and cardiac output.

Non-Human Primates

[PubMed]

Heywood et al. (25) performed a toxicity study of iopentol at dosage levels of 0.5, 1.5, and 3.0 g iodine/kg in 24 cynomolgus monkeys for 28 days. There were no deaths and no overt signs of toxicity. Hematology, biochemistry, and urinalysis did not show any significant differences of toxicologic importance. Cytoplasmic

vacuolations were found in kidney proximal tubules. Coarse vacuolation of centrilobular hepatocytes and islet cells were observed in animals that received the highest dose (3 g iodine/kg).

Human Studies

[PubMed]

Waaler et al. (30) conducted a pharmacokinetic study of 3 dose levels of iopentol in 24 healthy volunteers. Iopentol was given in the concentration of 350 mg iodine/ml. No significant dose effect was observed on the iopentol pharmacokinetics. The serum concentration of iopentol decreased biexponentially. The volume of distribution corresponded approximately to that of the extracellular fluid. Unmetabolized iopentol was excreted almost entirely in urine during the first 24 h. The authors observed that this was different from rat studies in that a high fraction of iopentol was excreted in the feces by rats. The overall mean values (95% confidence interval; n =24) of the initial distribution half-life ($t_{½\alpha}$), elimination half-life ($t_{½\beta}$), the apparent volumes of distribution, and renal clearances were 23 (21.1-25.5) min, 121 (115.9-125.8) min, 18.4 (17.3-19.5) liters, and 104 (97-111) ml/min, respectively. After 24 h, 98% of the dose was accumulated in the urine and no metabolites were detected. On the basis of ^{51}Cr-EDTA studies, the authors indicated that the mechanism of iopentol excretion was glomerular filtration.

The pharmacologic effects of iopentol were studied by Aakhus et al. (31) in 24 healthy volunteers. Iopentol was well tolerated when injected i.v. in doses of 300 to 1,200 mg iodine/kg. No changes were observed in blood pressure and electrocardiograms with a clinically insignificant increase in heart rate. Five subjects reported headache, and a mild sensation of warmth was reported by 13 subjects. The majority of the clinical-chemical observations did not show any statistically significant changes. A slight increase was demonstrated in the serum thyrotropin level. In phase I and II clinical trials, Jakobsen et al. (32) and Andrew et al. (12) reported no severe or unexpected adverse events. Jakobsen et al. (33) studied the renal effects of iopentol and iohexol (350 mg iodine/ml concentration and dose of 700 mg iodine/kg) in 64 patients and found no significant difference between iopentol and iohexol. Both agents had no significant effects on creatinine clearance and the mean serum values of creatinine, urea, and β_2-microglobulin.

In a randomized, double-blind, parallel phase III clinical trial, 149 patients received iopentol (300 mg iodine/ml) and 150 patients received iohexol (300 mg iodine/ml) for urography, Rasmussen et al. (34) reported that there was no significant difference between the two agents. There appeared to be a trend for iopentol to increase the heart rate and iohexol to decrease the heart rate, but no significant difference in the heart rate was observed between the two groups. No change in blood pressure was observed in both groups. Seven patients (5%) in the iohexol group and 12 patients (8%) in the iopentol group experienced mild adverse effects other than a sensation of warmth. Only 1 patient in the iopentol group complained of a severe headache. In the diagnostic efficacy study, 86% of the iopentol group and 81% of the iohexol group received an excellent grade in the overall quality of visualization. Only 3% and 2% received a poor grade for the iopentol and iohexol group, respectively.

Various other studies [PubMed] have indicated that iopentol has safety and efficacy profiles similar those for other nonionic contrast agents.

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