



Bracco Diagnostics

Experience with iopamidol suggests there is much less discomfort (e.g. pain and/or warmth) with peripheral arteriography. Fewer changes are noted in ventricular function after ventriculography and coronary arteriography.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of drug injected, the speed of injection, the mode of injection, and the radiographic procedure.

Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that for the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations. Most adverse reactions to intravascular contrast agents appear within one to three minutes after the start of injection, but delayed reactions may occur. Delayed reactions, usually involving the skin, may uncommonly occur within 2-3 days (range 1-7 days) after the administration of contrast (see **PRECAUTIONS-General**). Delayed allergic reactions are more frequent in patients treated with immunostimulants, such as interleukin-2.

In addition to the adverse drug reactions reported for iopamidol, the following additional adverse reactions have been reported with the use of other intravascular contrast agents and are possible with the use of any water-soluble iodinated contrast agent:

Cardiovascular: cerebral hematomas, petechiae; **Hematologic:** neutropenia; **Skin and Appendages:** skin necrosis; **Urogenital:** osmotic nephrosis of proximal tubular cells, renal failure; **Special Senses:** conjunctival chemosis with infection.

OVERDOSAGE

Treatment of an overdose of an injectable radiopaque contrast medium is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

DOSAGE AND ADMINISTRATION

General

It is desirable that solutions of radiopaque diagnostic agents for intravascular use be at body temperature when injected. Discard the container if crystallization of the medium has occurred.

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile syringes. Sterile techniques must be used with any intravascular injection, and with catheters and guidewires.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range.

Patients should be well hydrated prior to and following ISOVUE (iopamidol Injection) administration.

As with all radiopaque contrast agents, only the lowest dose of ISOVUE necessary to obtain adequate visualization should be used. A lower dose reduces the possibility of an adverse reaction. Most procedures do not require use of either a maximum dose or the highest available concentration of ISOVUE; the combination of dose and ISOVUE concentration to be used should be carefully individualized, and factors such as age, body size, size of the vessel and its blood flow rate, anticipated pathology and degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed should be considered.

Cerebral Arteriography

ISOVUE-300 (Iopamidol Injection, 300 mg/ml) should be used. The usual individual injection by carotid puncture or transfemoral catheterization is 8 to 12 mL, with total multiple doses ranging to 90 mL.

Peripheral Arteriography

ISOVUE-300 usually provides adequate visualization. For injection into the femoral artery or subclavian artery, 5 to 40 mL may be used; for injection into the aorta for a distal runoff, 25 to 50 mL may be used. Doses up to a total of 250 mL of ISOVUE-300 have been administered during peripheral arteriography.

Peripheral Venography (Phlebography)

ISOVUE-200 (Iopamidol Injection, 200 mg/ml) should be used. The usual dose is 25 to 150 mL per lower extremity. The combined total dose for multiple injections has not exceeded 350 mL.

Selective Visceral Arteriography and Aortography

ISOVUE-370 (Iopamidol Injection, 370 mg/ml) should be used. Doses up to 50 mL may be required for injection into the larger vessels such as the aorta or celiac artery; doses up to 10 mL may be required for injection into the renal arteries. Often, lower doses will be sufficient. The combined total dose for multiple injections has not exceeded 225 mL.

Pediatric Angiocardiography

ISOVUE-370 should be used. Pediatric angiocardiography may be performed by injection into a large peripheral vein or by direct catheterization of the heart.

The usual dose range for single injections is provided in the following table: The usual recommended dose for cumulative injections is provided in the following table:

Single Injection Usual Dose Range		Cumulative Injection Usual Recommended Dose	
Age	mL	Age	mL
<2 years	10-15	< 2 years	40
2-9 years	15-30	2-4 years	50
10-18 years	20-50	5-9 years	100
		10-18 years	125

Coronary Arteriography and Ventriculography

ISOVUE-370 should be used. The usual dose for selective coronary artery injections is 2 to 10 mL. The usual dose for ventriculography, or for nonselective opacification of multiple coronary arteries following injection at the aortic root is 25 to 50 mL. The total dose for combined procedures has not exceeded 200 mL. EKG monitoring is essential.

Excretory Urography

ISOVUE-250 ISOVUE-300 or ISOVUE-370 may be used. The usual adult dose for ISOVUE-250 is 50 to 100 mL, for ISOVUE-300 is 50 mL and for ISOVUE-370 is 40 mL administered by rapid intravenous injection.

Pediatric Excretory Urography

ISOVUE-250 or ISOVUE-300 may be used. The dosage recommended for use in children for excretory urography is 1.2 mL/kg to 3.6 mL/kg for ISOVUE-250 and 1.0 mL/kg to 3.0 mL/kg for ISOVUE-300. It should not be necessary to exceed a total dose of 30 grams of iodine.

Computed Tomography

ISOVUE-250 or ISOVUE-300 may be used.

CECT OF THE HEAD: The suggested dose for ISOVUE-250 is 130 to 240 mL and for ISOVUE-300 is 100 to 200 mL by intravenous administration. Imaging may be performed immediately after completion of administration.

CECT OF THE BODY: The usual adult dose range for ISOVUE-250 is 130 to 240 mL and for ISOVUE-300 is 100 to 200 mL administered by rapid intravenous infusion or bolus injection. Equivalent doses of ISOVUE-370 based on organically bound iodine content may also be used. The total dose for either CECT procedure should not exceed 60 grams of iodine.

Pediatric Computed Tomography

ISOVUE-250 or ISOVUE-300 may be used. The dosage recommended for use in children for contrast enhanced computed tomography is 1.2 mL/kg to 3.6 mL/kg for ISOVUE-250 and 1.0 mL/kg to 3.0 mL/kg for ISOVUE-300. It should not be necessary to exceed a total dose of 30 grams of iodine.

Drug Incompatibilities

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

HOW SUPPLIED

ISOVUE-200 (Iopamidol Injection 41%)

Ten 50 mL single dose vials (NDC 0270-1314-30)

Ten 200 mL single dose bottles (NDC 0270-1314-15)

ISOVUE-250 (Iopamidol Injection 51%)

Ten 50 mL single dose vials (NDC 0270-1317-05)

Ten 100 mL single dose bottles (NDC 0270-1317-02)

Ten 150 mL single dose bottles (NDC 0270-1317-09)

ISOVUE-300 (Iopamidol Injection 61%)

Ten 30 mL single dose vials (NDC 0270-1315-25)

Ten 50 mL single dose vials (NDC 0270-1315-30)

Ten 75 mL single dose bottles (NDC 0270-1315-47)

Ten 100 mL single dose bottles (NDC 0270-1315-35)

Ten 150 mL single dose bottles (NDC 0270-1315-50)

ISOVUE-370 (Iopamidol Injection 76%)

Ten 50 mL single dose bottles (NDC 0270-1316-01)

Ten 75 mL single dose bottles (NDC 0270-1316-52)

Ten 100 mL single dose bottles (NDC 0270-1316-35)

Ten 125 mL single dose bottles (NDC 0270-1316-04)

Ten 150 mL single dose bottles (NDC 0270-1316-37)

Storage

Store at 20-25° C (68-77° F). [See USP]. Protect from light.

Also Available

Iopamidol Injection is also available as ISOVUE-M[®] for intrathecal administration.

ISOVUE[®]-200 Iopamidol Injection 41%

ISOVUE[®]-250 Iopamidol Injection 51%

ISOVUE[®]-300 Iopamidol Injection 61%

ISOVUE[®]-370 Iopamidol Injection 76%

NOT FOR INTRATHECAL USE

ISOVUE 200, 250, 300 and 370 are NOT FOR INTRATHECAL USE. See Indications, and Dosage and Administration sections for further details on proper use

DIAGNOSTIC NONIONIC RADIOPAQUE CONTRAST MEDIA For Angiography Throughout the Cardiovascular System, Including Cerebral and Peripheral Arteriography, Coronary Arteriography and Ventriculography, Pediatric Angiocardiography, Selective Visceral Arteriography and Aortography, Peripheral Venography (Phlebography), and Adult and Pediatric Intravenous Excretory Urography and Intravenous Adult and Pediatric Contrast Enhancement of Computed Tomographic (CECT) Head and Body Imaging

DESCRIPTION

ISOVUE (Iopamidol Injection) formulations are stable, aqueous, sterile, and nonpyrogenic solutions for intravascular administration.

Each mL of ISOVUE-200 (Iopamidol Injection 41%) provides 408 mg Iopamidol with 1 mg tromethamine and 0.26 mg edetate calcium disodium. The solution contains approximately 0.029 mg (0.001 mEq) sodium and 200 mg organically bound iodine per mL.

Each mL of ISOVUE-250 (Iopamidol Injection 51%) provides 510 mg Iopamidol with 1 mg tromethamine and 0.33 mg edetate calcium disodium. The solution contains approximately 0.036 mg (0.002 mEq) sodium and 250 mg organically bound iodine per mL.

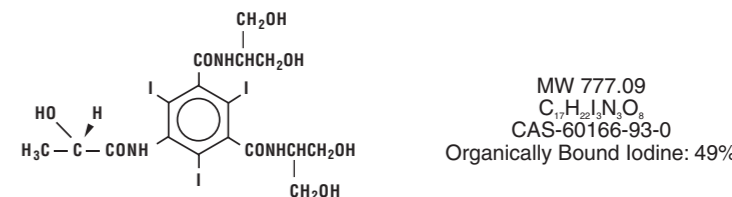
Each mL of ISOVUE-300 (Iopamidol Injection 61%) provides 612 mg Iopamidol with 1 mg tromethamine and 0.39 mg edetate calcium disodium. The solution contains approximately 0.043 mg (0.002 mEq) sodium and 300 mg organically bound iodine per mL.

Each mL of ISOVUE-370 (Iopamidol Injection 76%) provides 755 mg Iopamidol with 1 mg tromethamine and 0.48 mg edetate calcium disodium. The solution contains approximately 0.053 mg (0.002 mEq) sodium and 370 mg organically bound iodine per mL.

The pH of ISOVUE contrast media has been adjusted to 6.5-7.5 with hydrochloric acid and/or sodium hydroxide. Pertinent physicochemical data are noted below. ISOVUE (Iopamidol Injection) is hypertonically as compared to plasma and cerebrospinal fluid (approximately 285 and 301 mOsm/kg water, respectively).

Parameter	41%	51%	61%	Iopamidol 76%
Concentration (mg/ml)	200	250	300	370
Osmolality @ 37° C (mOsm/kg water)	413	524	616	796
Viscosity (cP) @ 37° C	2.0	3.0	4.7	9.4
@ 20° C	3.3	5.1	8.8	20.9
Specific Gravity @ 37° C	1.227	1.281	1.339	1.405

Iopamidol is designated chemically as (S)-N,N'-bis[2-hydroxy-1-(hydroxymethyl)-ethyl]-2,4,6-triiodo-5-lactamidoisophthalamide. Structural formula:



CLINICAL PHARMACOLOGY

Intravascular injection of a radiopaque diagnostic agent opacifies those vessels in the path of flow of the contrast medium, permitting radiographic visualization of the internal structures of the human body until significant hemodilution occurs.

Following intravascular injection, radiopaque diagnostic agents are immediately diluted in the circulating plasma. Calculations of apparent volume of distribution at steady-state indicate that Iopamidol is distributed between the circulating blood volume and other extracellular fluid; there appears to be no significant deposition of Iopamidol in tissues. Uniform distribution of Iopamidol in extracellular fluid is reflected by its demonstrated utility in contrast enhancement of computed tomographic imaging of the head and body following intravenous administration.

The pharmacokinetics of intravenously administered Iopamidol in normal subjects conform to an open two-compartment model with first order elimination (a rapid alpha phase for drug distribution and a slow beta phase for drug elimination). The elimination serum or plasma half-life is approximately two hours; the half-life is not dose dependent. No significant metabolism, deiodination, or biotransformation occurs.

Iopamidol is excreted mainly through the kidneys following intravascular administration. In patients with impaired renal function, the elimination half-life is prolonged dependent upon the degree of impairment. In the absence of renal dysfunction, the cumulative urinary excretion for Iopamidol, expressed as a percentage of administered intravenous dose is approximately 35 to 40 percent at 60 minutes, 80 to 90 percent at 8 hours, and 90 percent or more in the 72-to 96-hour period after administration. In normal subjects, approximately one percent or less of the administered dose appears in cumulative 72- to 96-hour fecal specimens.

ISOVUE may be visualized in the renal parenchyma within 30-60 seconds following rapid intravenous administration. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1 to 3 minutes, with optimum contrast occurring between 5 and 15 minutes. In patients with renal impairment, contrast visualization may be delayed.

Iopamidol displays little tendency to bind to serum or plasma proteins.

No evidence of in vivo complement activation has been found in normal subjects.

Animal studies indicate that Iopamidol does not cross the blood-brain barrier to any significant extent following intravascular administration.

ISOVUE (Iopamidol Injection) enhances computed tomographic brain imaging through augmentation of radiographic efficiency. The degree of enhancement of visualization of tissue density is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid injection of the dose. These levels fall rapidly within five to ten minutes. This can be accounted for by the dilution in the vascular and extracellular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about ten minutes, thereafter the fall becomes exponential. Maximum contrast enhancement frequently occurs after peak blood iodine levels are reached. The delay in maximum contrast enhancement can range from five to forty minutes depending on the peak iodine levels achieved and the cell type of the lesion. This lag suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine within the lesion and outside the blood pool, although the mechanism by which this occurs is not clear. The radiographic enhancement of nontumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool.

In CECT head imaging, ISOVUE (Iopamidol Injection) does not accumulate in normal brain tissue due to the presence of the blood-brain barrier. The increase in x-ray absorption in normal brain is due to the presence of contrast agent within the blood pool. A break in the blood-brain barrier such as occurs in malignant tumors of the brain allows the accumulation of the contrast medium within the interstitial tissue of the tumor. Adjacent normal brain tissue does not contain the contrast medium.

In nonneural tissues (during computed tomography of the body), Iopamidol diffuses rapidly from the vascular into the extravascular space. Increase in x-ray absorption is related to blood flow, concentration of the contrast medium, and extraction of the contrast medium by interstitial tissue of tumors since no barrier exists. Contrast enhancement is thus due to the relative differences in extravascular diffusion between normal and abnormal tissue, quite different from that in the brain.

The pharmacokinetics of Iopamidol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest soon after administration of the contrast medium, and following intraarterial rather than intravenous administration. Thus, greatest enhancement can be detected by a series of consecutive two- to three-second scans performed just after injection (within 30 to 90 seconds), i.e., dynamic computed tomographic imaging.



