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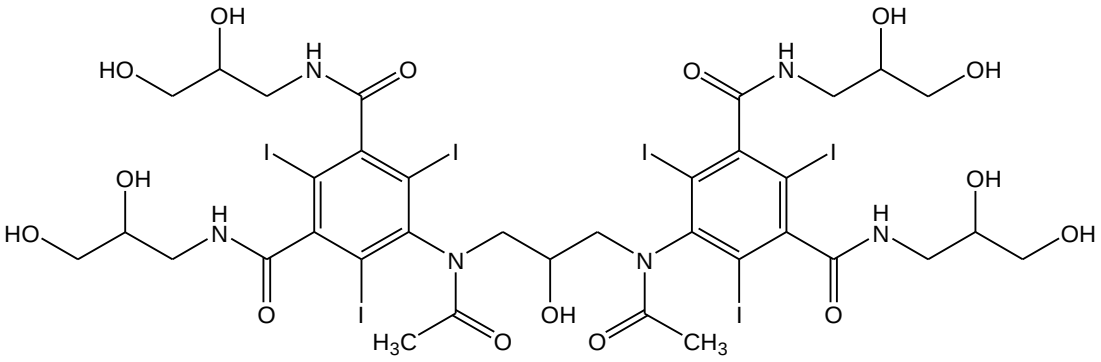
Package Insert for Iodixanol Injection

Please carefully read the package insert and use under the guidance of a physician.

[Drug Name]
Generic name: Iodixanol Injection
English name: Iodixanol Injection
Chinese pinyin: Diankeshachun Zhusheye
[Ingredients]
The active ingredient of the product is iodixanol.
Chemical name: 5,5'-((2-hydroxy-1,3-propanediyl)-bis(acetylimino))-bis(N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide
Chemical structural formula:



Molecular formula: $C_{35}H_{44}I_6N_6O_{15}$
Molecular weight: 1550.20
Excipients: Tromethamine, sodium chloride, calcium chloride, calcium sodium EDTA, hydrochloric acid to adjust pH, water for injection
[Description]
The product is a colorless or light yellow clear liquid.
Iodixanol is a non-ionic, dimeric, hexaiodine, water-soluble X-ray contrast agent. Compared with whole blood and other non-ionic monomer contrast agents of corresponding specifications, pure iodixanol aqueous solutions of all clinical concentrations have lower osmotic pressure. With the addition of electrolytes, this product is isotonic with

normal body fluids. The osmotic pressure and viscosity values of this product are as follows:

Concentration	Osmotic pressure mOsm/kg H_2O	Viscosity (mPa · s)	
	37℃	20℃	37℃
270 mgI/ml	290	11.3	5.8
320 mgI/ml	290	25.4	11.4

*Method: Vapor pressure osmotic pressure determination method.

The pH of this product is 6.8-7.6.

[Indication]

X-ray contrast agent for adult angiocardiography, cerebral angiography (conventional and i.a.DSA), peripheral arteriography (conventional and i.a.DSA), abdominal angiography (conventional and i.a.DSA), urography, venography and enhanced CT examination; angiocardiography, urography and enhanced CT examination in children.

[Specification]

(1)50 ml:16 g(I) (2)100 ml:32 g(I) (3)100 ml:27 g(I)

[Dosage and Administration]

The dose to be administered depends on the type of examination, age, weight, cardiac output, the patient's general condition and the technology used. The commonly used iodine concentration and dosage are similar to other iodine-containing X-ray contrast agents used nowadays, but in some studies, iodixanol injection with a lower iodine concentration has also been used to obtain sufficient diagnostic information. As with other contrast agents, patients should be given adequate water before and after administration.

The following recommended doses can be used as guidance. A single dose for intra-arterial injection can be used repeatedly.

Indications/examinations	Concentration	Dosage
Intra-arterial use		
Arteriography		
Selective cerebral arteriography	270/320[1] mgI/ml	Single injection 5～10 ml
Selective brain i.a.DSA	150 mgI/ml	Single injection 5～10 ml
Aortography	270/320 mgI/ml	Single injection 40～60 ml
Peripheral arteriography	270/320 mgI/ml	Single injection 30～60 ml
Peripheral i.a.DSA	150 mgI/ml	Single injection 30～60 ml
Selective visceral i.a.DSA	270 mgI/ml	Single injection 10～40 ml
Angiocardiography		
Left ventrical and aortic root injection	320 mgI/ml	Single injection 30～60 ml
Selective coronary angiography	320 mgI/ml	Single injection 4～8 ml

Children	270/320 mgI/ml	According to age, weight and pathological conditions (the recommended maximum total dose is 10 ml/kg based on body weight)
Intravenous use		
Urography		
Adults	270/320 mgI/ml	40～80 ml[2]
Children< 7 kg	270/320 mgI/ml	According to body weight 2~4 ml/kg
Children>7 kg	270/320 mgI/ml	According to body weight 2~3 ml/kg All doses are based on age, weight and pathological conditions (the maximum dose is 50 ml)
Venography	270 mgI/ml	50-150 ml per leg
Enhanced CT		
Adult: Head CT	270/320 mgI/ml	50-150 ml
Adult: Body CT	270/320 mgI/ml	75-150 ml
Children: Head and body CT	270/320 mgI/ml	According to body weight 2-3 ml/kg, the dose can be up to 50 ml (150 ml in a few cases)

[1] Both specifications have been documented in the literature, but 270mgI/ml is recommended in most cases.

[2] Higher doses can be used for high-dose urography.

Elderly: Same dosage as other adults.

[Adverse Reactions]

The following is a list of adverse reactions that may occur during the use of Iodixanol Injection for radiological examinations.

The adverse reactions related to iodine-containing contrast agents are generally mild to moderate and transient in nature. Non-ionic contrast agents (this product is one of them) have fewer adverse reactions than ionic contrast agents. Severe and fatal reactions are very rare.

Common adverse reactions are mild paresthesias, such as heat or cold sensation. Peripheral angiography often causes heat sensation (incidence > 1:10), and distal pain occasionally occurs (incidence <1:10, but> 1:100).

Abdominal discomfort/pain is very rare (incidence <1:1000), and gastrointestinal reactions such as nausea and vomiting are also rare (incidence <1:100, but >1:1000).

Allergic reactions occur occasionally, which usually manifest as mild respiratory and skin reactions, such as dyspnea, rash, erythema, urticaria, itching, and angioedema, and can occur immediately after the injection or a few days later. Hypotension or fever may occur. There have been reports of severe and even toxic skin reactions. Severe reactions such as laryngeal oedema, bronchospasm or pulmonary oedema and anaphylactic shock are very rare. The occurrence of anaphylactoid reactions may have nothing to do with the dose and route of administration. The initial symptoms of a severe reaction may only be mild allergic symptoms. The use of the contrast agent must be stopped immediately, and corresponding treatment should be given immediately by intravenous administration if necessary. The symptoms of allergic reactions in patients using β-blockers may be atypical

and may be easily mistaken for vagal reactions.
Vagal reactions can cause hypotension and bradycardia, which is rare.
Iodism or "iodine poisoning mumps" is a rare complication related to the use of iodine contrast agents, which may manifest as swelling and tenderness of the parotid glands, and can persist for up to 10 days after examination.
A transient elevation in serum creatinine is also common, but it is usually not clinically significant. Renal failure is very rare, but fatal cases have been reported in the high-risk patient group.
Coronary, cerebral or renal artery injections can cause arterial spasm and result in ischemia.
Nervous system reactions are very rare, which can be headaches, vertigo, seizures, or transient motor or sensory disturbances. Occasionally on follow-up CT scans, the contrast agent can be seen to be taken up by the cerebral cortex through the blood-brain barrier, which may be sometimes accompanied by transient confusion or cortical blindness.
Cardiac complications such as arrhythmia, hypofunction, or myocardial ischemia are rare. Hypertension may occur.
Thrombophlebitis and intravenous thrombosis after venography are very rare. Very few cases of arthralgia have been reported.
Serious respiratory symptoms and signs (including dyspnea, bronchospasm, laryngospasm, non-cardiogenic pulmonary oedema) and cough may occur.
[Contraindications]
Iodixanol Injection is contraindicated in patients with uncontrolled symptoms of hyperthyroidism and patients with a history of serious adverse reactions to this product.
[Precautions]
General precautions for using non-ionic contrast agents
Particular care should be exercised for people with allergies, asthma, and adverse reactions to iodine-containing preparations. For these cases, preventive medications such as steroids, $H_1$and H_2 histamine receptor antagonists can be considered.
There is a very low risk of serious reactions after using this product. However, iodine-containing contrast agents can trigger anaphylactoid reactions or other manifestations of allergic reactions. Therefore, training on first-aid measures should be given in advance and the necessary rescue drugs and equipment should be prepared to cope with possible serious reactions. The built-in cannula or catheter should always be used throughout the X-ray examination to keep the intravenous infusion channel open.
Given that pre-test has extremely low accuracy in predicting allergic reactions caused by non-ionic contrast agents, and may cause serious allergic reactions itself, it is not recommended to use pre-test to predict iodine allergic reactions.
During in vitro tests, non-ionic contrast agents have milder effects on the coagulation system than ionic contrast agents. During angiography, extreme caution should be exercised with the technical operation in the blood vessel, and the catheter should be rinsed

with heparinized saline from time to time to reduce thrombosis and embolism related to the operation technique.

Before and after using the contrast agent, it is necessary to ensure that the patient has enough water in the body. This is especially suitable for patients suffering from multiple myeloma, diabetes, renal insufficiency, infants and young children, and the elderly. Babies less than 1 year old, especially newborns, are prone to electrolyte disturbances and hemodynamic disorders.

Special attention should be paid to patients with severe heart disease and pulmonary arterial hypertension, because they are prone to hemodynamic disorders and cardiac arrhythmia.

Patients with a history of acute encephalopathy, brain tumors, or epilepsy should prevent seizures and require special attention. In addition, the risk of seizures and neuropathological changes is greatly increased in alcoholics and drug addicts.

In order to prevent acute renal failure after the use of contrast agents, special attention should be paid to patients with renal impairment and diabetes, because they are at high risk. Patients with atypoglobulinemia (multiple myeloma and Waldenstrom macroglobulinemia) are also at greater risk.

Preventive measures include:

− Identify patients with high-risk factors.

− Ensure that there is sufficient water in the body. If necessary, the intravenous infusion can be maintained before the examination until the contrast agent is cleared from the kidney.

− Avoid any nephrotoxic drugs that increase the burden on the kidneys, oral gallbladder contrast agents, arterial clamp surgery, renal angioplasty, or other major surgery before the contrast agent is cleared.

− Postpone another contrast examination until the renal function returns to the level before the examination.

In order to prevent lactic acidosis, the serum creatinine level must be determined before intravascular injection of iodine-containing contrast medium in diabetic patients using metformin. For patients with normal serum creatinine/renal function: Metformin must be stopped when the contrast agent is injected and the medication cannot be resumed within 48 hours, or until the renal function/serum creatinine reaches a normal value. For patients with abnormal serum creatinine/renal function: Metformin must be stopped and the contrast agent examination must be postponed until 48 hours later. The medication of metformin can be resumed only if the renal function/serum creatinine level is constant. For some emergency cases with abnormal or unknown renal function, doctors must assess the pros and cons of using contrast agents and take preventive measures: stop metformin, give the patient adequate water, monitor their renal function, and carefully observe the symptoms of lactic acidosis.

Special attention should be paid to patients with severe hepatic or renal insufficiency,

because the time required to clear the contrast agent is significantly prolonged in these patients. Patients receiving hemodialysis may receive contrast agent examinations. It is not mandatory to perform hemodialysis immediately after injection of the contrast agent, **because there is no evidence suggesting that hemodialysis can protect patients with renal impairment from contrast agent-induced nephropathy.**

Iodine-containing contrast agents can aggravate the symptoms of myasthenia gravis. Patients with pheochromocytoma should be given α blockers to prevent hypertensive crisis during interventional therapy. Special attention should also be paid to patients with hyperthyroidism. Patients with multiple nodular goiter may develop hyperthyroidism after using iodine contrast agents. It should be clearly recognized that premature baby may develop transient hypothyroidism after using contrast agents.

So far, there has been no report of extravasation of this product. However, as this product is isotonic, once it is extravasated, the local pain and oedemacaused thereby is milder than that of hypertonic contrast agents. The conventional treatment method is to raise the affected limb and apply local cold compress. In case of compartment syndrome, surgical decompression is required.

Observation time:

Patients after using contrast agents should be observed for at least 30 minutes, because most serious adverse reactions occur during this period. However, experience has shown that allergic reactions may occur after hours or even days.

[Use in Pregnant and Lactating Women]

The safety of using this product during human pregnancy has not been established. The results of animal experiments have not directly or indirectly indicated any damage caused by this product to human reproduction, embryonic or fetal development, pregnancy process, perinatal period and postpartum period.

Because radiation exposure should be avoided at any time during pregnancy, the pros and cons must be carefully weighed before X-ray examinations are performed on pregnant women, regardless of whether contrast agents are used. This product should not be used in pregnant women, unless the advantages outweigh the disadvantages and the clinician considers it necessary.

The amount of contrast agent excreted in human milk is unknown. Although it is estimated to be very little, breastfeeding should be stopped before and for at least 24 hours after using this product.

[Pediatric Use]

See the content under [Dosage and Administration]

[Geriatric Use]

Same dosage as other adults.

[Drug Interactions]

The use of contrast agents may cause transient renal insufficiency, which can cause lactic acidosis in diabetic patients taking metformin (see the content under [Precautions] for

details).
Patients treated with interleukin-2 within two weeks have an increased risk of developing delayed reactions (cold-like symptoms and skin reactions).
All iodine-containing contrast agents will affect the determination of thyroid function, and the decline in thyroid iodine binding capacity will last for several weeks.
High concentrations of contrast agents in serum and urine can affect laboratory test results of bilirubin, protein, or inorganic substances (e.g., iron, copper, calcium, and phosphate). These examinations should not be performed on the day of use of the contrast agent.
Incompatibility
No incompatibility has been found. However, this product cannot be directly mixed with other drugs. A separate syringe must be used.

[Overdose]

Patients with normal renal function are not prone to overdose. The duration of the examination is important because the kidneys have a limited ability to tolerate high-dose contrast agents ($t_{½}$ is about 2 hours). In case of overdose, the imbalance of water and electrolyte must be corrected by infusion, and renal function must be continuously monitored for at least 3 days. If necessary, hemodialysis can be performed for iodixanol clearance. There are no special antagonists.

[Pharmacology and Toxicology]

Pharmacological effects:
During injection, organically bound iodine absorbs rays in blood vessels/tissues.
Examinations of healthy volunteers after intravenous injection of iodixanol showed no significant deviations in most of the hemodynamic, clinical chemistry and blood coagulation parameters compared with the values before the injection. The observed changes in a small number of laboratory parameters were minimal and not clinically significant.
Iodixanol injection had only a slight effect on the patient's renal function. Only 3% of diabetic patients with a serum creatinine level of 1.3-3.5 mg/dl had an increase of ≥0.5 mg/dl in creatinine levels after using this product, and no patient had an increase of ≥1.0 mg/dl in creatinine levels. The enzymes released from adjacent tubular cells (alkaline phosphatase and N-acetyl-β-glucamidase) were less than those treated with injection of non-ionic monomeric contrast agents, and showed the same trend as ionic monomeric contrast agents. Iodixanol injection is also well tolerated by the kidneys.
Compared with other contrast agents, iodixanol injection has fewer effects on cardiovascular parameters, such as LVEDP, LVSP, heart rate and QT interval, as well as femoral blood flow.
Toxicology studies:
In rat and rabbit reproductive toxicology studies, no evidence suggested that iodixanol would cause fertility damage or teratogenicity.

[Pharmacokinetics]

Iodixanol was rapidly distributed in the body, with an average half-life of approximately 21 minutes. The apparent volume of distribution was the same as the amount of extracellular fluid (0.26 l/kg body weight), indicating that iodixanol was only distributed in the extracellular fluid.

No metabolites were detected. The protein binding rate was less than 2%.

The average excretion half-life was about 2 hours. Iodixanol was mainly filtered by the glomerulus and excreted by the kidneys. After intravenous injection in healthy volunteers, about 80% of the injected volume was excreted in the urine within 4 hours, and 97% was excreted within 24 hours. Only about 1.2% of the injected volume was excreted in the feces within 72 hours. The maximum urine concentration appeared within about 1 hour after injection.

No dose-dependent kinetic characteristics were observed in the recommended dose range.

[Storage] Store at room temperature, protected from light. This product can be stored for up to 1 month at 37℃ before use.

[Packaging] Glass bottles. 1 bottle/box; 10 bottles/box; 30 bottles/box.

[Shelf Life] 24 months.

[Executive Standard] YBH04502011, YBH00672017

[Approval Number]

(1) 50 ml: 16 g (I) GYZZ No. H20113465

(2) 100 ml: 32 g (I) GYZZ No. H20153001

(3) 100 ml: 27 g (I) GYZZ No. H20173077

[Use and Operation Guide]

As with all parenteral drugs, visual inspection should be carried out before using this product to check if there is particles, discoloration and container damage.

The product should be drawn into the syringe only before injection. Each bottle is for one person only. Discard the remaining drug liquid.

The product can be heated to body temperature (37℃) before use.

[Manufacturer]

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