Package Insert of Iopamidol Injection

Please read the instructions for use carefully and use it under the guidance of a physician

[DRUG NAME]

Generic Name: Iopamidol Injection

English Name: Iopamidol Injection

Chinese Pinyin: Dianpachun Zhu She Ye

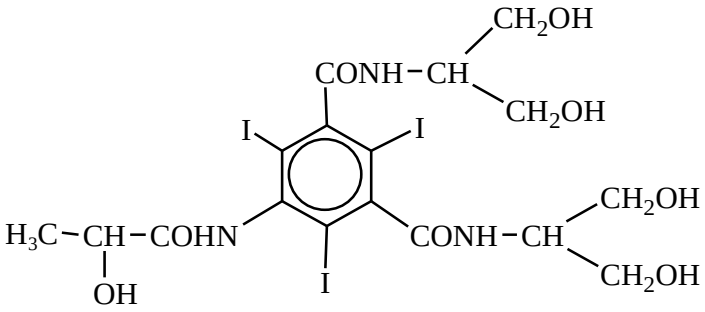
[Ingredients]

Iopamidol is the main ingredient of this product.

Chemical Name: (S) -N, N'-bis [2-hydroxy-1- (hydroxymethyl) ethyl] -5-

[(2-hydroxy-1-oxopropyl) amino] -2,4,6-triiodo-1,3-benzenedicarboxamide.

Chemical structural formula:



Molecular Formula: $C_{17}H_{22}I_3N_3O_8$

Molecular weight: 777.09

Excipients: Calcium disodium edetate, tromethamine, hydrochloric acid (adjust pH) and water for injection.

[Description]

A clear, colorless liquid.

[Indications]

Neuroradiology: Myeloradiculography, cisternography, and ventriculography. **Angiography**: Cerebral angiography, coronary angiography, thoracic aortography, abdominal aortography, cardiac angiography, selective splanchnic arteriography, peripheral arteriography, and venography. **Digital subtraction angiography (D.S.A.):** cerebral artery D.S.A., peripheral artery D.S.A., abdominal artery D.S.A. **Urography**: Intravenous urography. **Enhanced scan during CT examination. Arthrography. Fistulography.**

Note: For the details of specific recommended concentrations and doses for each indication,

please see the section of “Usage and Dosage”.

[Strength] 50 mL: 15 g (I)

[Dosage and Administration]

Please choose different concentrations and doses depending on different X-ray examination needs.

The dose and rate of administration can be varying depending on routes of administration, clinical problems, types of examination, techniques used, body sites examined, equipment used, as well as age, body size, and clinical conditions (renal function, cardiac output, left ventricular function, etc.) of patients.

All iodine concentrations and volumes are generally the same as other radiographic iodine contrast agents currently used in the radiological field.

As with all contrast agents, the lowest dose capable of obtaining adequate imaging should be used.

Doses were expressed as follows: total dose (ml), single injection, or body weight per kilogram (kg) (especially for children).

Neuroradiology

	Concentration (mg I/ml)	Recommended dose (ml)
Myeloradiculography	200-300	5-15
Cisternography and ventriculography	200-300	3-15

Angiography

	Concentration (mg I/ml)	Recommended dose (ml)
Cerebral angiography	300	5-10 (per bolus)
Coronary angiography	370	8-15 (per bolus)
Angiocardiography	370	1.0-1.2/kg
Thoracic aortogram	370	1.0-1.2/kg
Abdominal aortogram	370	1.0-1.2/kg
Selective splanchnic arteriography	300-370	Depending on examination needs
Peripheral arteriography	300-370	40-50
Digital subtraction angiography	150-370	Depending on examination needs
Venogram	300	30-50

Urography

The recommended dose for adults undergoing such tests is 30 to 50 mL.

The iopamidol injection 370 mg iodine / ml is particularly suitable for patients with moderate renal insufficiency and neonates because of its low osmotic diuretic effect. It could even obtain diagnostic renal parenchyma in patients with severe renal insufficiency.

Other Diagnostic Examinations

	Concentration (mg I/ml)	Recommended dose (ml)
Enhanced scan during CT examination	300-370	0.5-2.0/kg
Arthrography	300	Depending on examination needs
Fistulography	300	Depending on examination needs

For enhanced scans in CT examinations, the contrast agents can be administered by intravenous bolus or intravenous infusion. It also could be administered through both the routes.

The administration by Intravenous infusion is limited to older generation CT scanners. For spiral CT and the next-generation multislice CT scanners, rapid bolus administration is preferred, particularly for arterial contrast-enhanced examinations.

Intravenous infusion is preferred for scanners with slow scanning speed, and rapid intravenous bolus is preferred for fast scanners.

In arthrography and fistulography, the total dose administered is depending on the local anatomy, local lesion, and general condition of patients.

Geriatrics: No dose adjustment is required.

[ADVERSE REACTIONS]

Overview

The use of iodinated contrast agents may result in adverse reactions.

Adverse reactions are usually mild to moderate and transient, but there have been rare reports of severe and life-threatening reactions, and sometimes even death.

After intravascular injection of contrast agents, most adverse reactions occur within minutes but delayed reactions (usually involving the skin) may also occur within 2-3 days; very few cases occur within 7 days.

The following table presents adverse reactions reported in 3008 adult subjects and 35 pediatric patients in clinical trials and in postmarketing surveillance by frequency and MedDRA system organ class.

The adverse reactions in each frequency group were listed in decreasing order of severity.

Intravascular Injection

Adult subjects

The clinical trial of intravascular injection of iopamidol involved 2919 adult subjects, of which 1681 were injected intra-arterially and 1238 were injected intravenously.

System organ class (SOC)	Adverse reaction			
	Clinical Trial			Post-marketing surveillance
	Common （≥1/100~＜1/10）	Uncommon （≥1/1,000~＜1/100）	Rare （≥1/10,000~＜1/1,000）	Frequency unknown *
Blood and lymphatic system disorders				Thrombocytopenia
Metabolic and nutritional disorders				Acidosis, Anorexia
Immune system disorders				Allergic reaction, Anaphylactoid reaction
Mental disorders			Confusional state	
Nervous system disorders	Headache	Dizziness, Taste disorder	Paresthesia	Coma, Transient ischemic attack, Syncope, Decreased level of consciousness or loss of consciousness, Convulsion, Amnesia, Paralysis, Somnolence, Tremor
Eye disorders				Transient blindness, Visual impairment, Conjunctivitis, Photophobia, Itchy eyes, Increased lacrimation
Ear and labyrinth disorders				Hearing loss
Cardiac disorders		Arrhythmias such as extrasystoles, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation * *	Bradycardia	Cardiopulmonary arrest, Myocardial ischemia or infarction, Heart failure, Angina, Cyanosis, Tachycardia
Vascular disorders		Hypotension, Hypertension, Redness (skin)		Circulatory failure or shock, Thromboembolism, Arterial thrombosis, Venous thrombosis, Thrombophlebitis, Pallor
Respiratory, thoracic, and mediastinal disorders			Pulmonary oedema, Asthma, Bronchospasm	Respiratory arrest, Apnea, Respiratory failure, Acute respiratory distress syndrome, Laryngeal edema, Dyspnea, Cough, Rhinitis, Sneezing, Respiratory distress
Gastrointestinal disorders	Nausea	Vomiting, Diarrhea, Abdominal pain, Dry mouth		Salivary gland enlargement, Hypersalivation
Disorder of skin and subcutaneous tissue		Rash, Urticaria, Pruritus, Erythema, Hyperhidrosis		Facial swelling, Periorbital edema

Musculoskeletal and connective tissue disorders		Back pain	Muscle spasms	Musculoskeletal pain, Muscle weakness
Renal and urinary system disorders		Acute renal failure		Anuria, Urinary retention, Renal failure (including acute renal failure and renal impairment), Oliguria, Hematuria, Urinary incontinence
General disorders and administration site conditions	Burning sensation	Chest tightness, Injection site pain, Fever, Cold sensation		Chills, Pain, Malaise
Investigation		Elevated creatinine level		Electrocardiogram changes (including ST-segment depression, increased T-wave amplitude, prolonged QT interval), decreased systolic blood pressure, electrolyte imbalance

* The frequency cannot be estimated from available data.
** Arrhythmia may occur primarily after cardiovascular angiography and coronary catheterization.

The most appropriate MedDRA terms were used to describe specific reactions as well as their symptoms and associated diseases.
Coronary artery thrombosis has been reported as a complication of coronary artery catheterization.
Accidents during the examination may result in pseudoaneurysm and/or peripheral embolism or bruising of the injection site.
Brachial plexus injuries may occur as a result of axillary artery injection.
Other cardiac adverse reactions that may occur as a consequence of the examinations include coronary artery dissection.

Anaphylactic reactions (anaphylactoid reactions/ hypersensitivity) may manifest as mild localized or disseminated vascular (neurological) edema, tongue edema, laryngospasm, laryngeal edema, dysphagia, pharyngitis, and throat tightness, sore throat, cough, conjunctivitis, rhinitis, sneezing, burning sensation, hyperhidrosis, weakness (frail) , dizziness, pallor, dyspnea, wheezing (stridor), bronchospasm, and moderate hypotension. Skin reactions may manifest as multiple forms of rash, disseminated (diffuse) erythema, disseminated (diffuse) blisters, urticaria, and pruritus. These reactions do not correlate with the dose or route of administration, but may be the initial symptoms of shock. Dosing must be stopped immediately and, if necessary, appropriate treatment should be administered via intravenous access.
More severe adverse reactions involving the cardiovascular system, such as vasodilation associated with significant hypotension, tachycardia, dyspnea, anxiety, cyanosis, and loss of consciousness (syncope), can lead to respiratory and/or cardiac arrest. These reactions can occur rapidly and require emergency treatment.

Circulatory failure may occur as the sole and/or first manifestation, without respiratory symptoms or other symptoms or signs.

Swelling and pain at the injection site may occur. In rare cases, extravasation of the contrast agent leads to inflammation (manifested as localized erythema, edema, and blistering), skin necrosis, and lacunar syndrome.

Severe dermatosis

As with other iodinated contrast agents, there have been reports of very rare mucocutaneous syndromes after iopamidol injection, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome), and erythema multiforme.

Pediatric patients

The safety profile of iopamidol is similar in pediatric and adult patients.

Intrathecal Injection

Adult subjects

Clinical trials of intrathecal iopamidol involved 132 adult patients.

System organ class (SOC)	**Adverse reaction**			
	Clinical Trial			**Post-marketing surveillance**
	Common （≥1/100~＜ 1/10）	**Uncommon （≥1/1,000~ ＜1/100）**	**Rare （≥1/10,000~ ＜1/1,000）**	**Frequency unknown ***
Infections and parasitic infections				Aseptic meningitis, Bacterial meningitis due to examination procedures
Metabolic and nutritional disorders				Acidosis
Immune system disorders				Allergic reaction, Anaphylactoid reaction
Mental disorders				Hallucination, Unconsciousness, Disorientation, Depression, Mental agitation, Anxiety, Irritability, Restlessness
Nervous system disorders	Headache			Coma, Syncope, Decreased level of consciousness or loss of consciousness, Episode of tremor, Paralysis, Myelitis, Pseudomeningitis, Vertigo, Paresthesia, Hypoaesthesia, Dizziness, Radiculalgia, Somnolence, Tremor, Muscle spasm
Eye disorders				Transient blindness, Conjunctivitis, Photophobia, Increased lacrimation, Itchy eyes
Ear and labyrinth disorders				Hearing impairment, Tinnitus
Cardiac disorders				Arrhythmia, Tachycardia, Cyanosis
Vascular disorders		(Skin) redness		Hypertension
Respiratory, thoracic, and mediastinal			Pulmonary oedema, Asthma,	Respiratory arrest, Apnea, Respiratory failure, Dyspnoea

disorders			Bronchospasm	
Gastrointestinal disorders		Nausea, Vomiting		
Disorder of skin and subcutaneous tissue			Rash, Hyperhidrosis	
Musculoskeletal and connective tissue disorders		Back pain, Neck pain, Acralgia		Muscle weakness
Renal and urinary system disorders				Renal failure (including acute renal failure), Urinary retention, Hematuria, Urinary incontinence
General disorders and administration site conditions		Sensation of heaviness		Pyrexia, Malaise, Chills

* The frequency cannot be estimated from available data.
The most appropriate MedDRA terms were used to describe specific reactions as well as their symptoms and associated diseases.

Anaphylactic reactions (anaphylactoid reactions/hypersensitivity reactions) may occur.
Anaphylactoid reactions with circulatory disturbances following intrathecal injections, such as severe blood pressure reductions leading to syncope or cardiac arrest and life-threatening shock, are much less common than intravascular injection. Respiratory (dyspnea or respiratory distress that manifests as bronchospasm) and mucocutaneous reactions (urticaria, vascular (neurologic) edema, and other skin reactions such as rash) are also less common than intravascular injection.

Pediatric Patients
The safety profile of iopamidol is similar in pediatric and adult patients.

Administration in Body Cavity

Most adverse reactions occur within hours of contrast injection because the contrast media is slowly absorbed from the injection area and distributed to the organs throughout the body.

Extremely rare cases of pancreatitis have been reported.

Adverse reactions in cases of arthrography and fistulography are usually manifested by superimposed irritation of existing tissue inflammation.

Systemic allergic reactions are rare, usually mild, and manifest as skin reactions. However, the possibility of severe anaphylactoid reactions cannot be ruled out.

[CONTRAINDICATIONS]

Iopamidol injections should not be used in patients who are known to be allergic to iopamidol or any of its excipients.

Examination of female reproductive organs is contraindicated when pregnancy is suspected or determined, and during acute inflammation of the female reproductive organs.

Simultaneous intrathecal injection of corticosteroids and iopamidol is prohibited.

To avoid overdose, myelography cannot be repeated immediately in case of technical operational errors.

[WARNINGS AND PRECAUTIONS]

During angiography, nonionic contrast agents should not remain in the syringe or intravascular catheter and come into contact with blood. The syringe or intravascular catheter should be flushed frequently to minimize the risk of coagulation and thromboembolic events.

Factors such as long examination times, catheter and syringe materials, underlying disease status, and concomitant medications can all lead to thromboembolic events.

Therefore, rigorous angiographic techniques are recommended, including paying close attention to guidewire and catheter operation, using connecting plates and/or three-way stopcocks, frequent rinsing the catheter with heparinized saline solution, and minimizing the examination duration.

Iodine allergy tests: Because iodine allergy tests cannot predict serious or fatal contrast agents reactions, it is not recommended to perform iodine allergy tests.

For intravascular or intrathecal injections, the contrast solution is heated to body temperature in order to improve the tolerance.

Before use, the product should be inspected to ensure that the container and seal are not broken.

The contrast solution must be drawn from the vial under sterile conditions using a sterile syringe.

The operations of intravascular injection, intrathecal injection and/or catheterization and guidewire catheter guidance must comply with strict sterile conditions.

Please open the vial before use. Once opened, it should be used immediately. Any unused contrast agents must be discarded.

Occasionally, crystallization of the solution of Iopamidol Injection is observed in the bottle. This phenomenon has been shown to be caused by defects or damage to the container, at which time the solution in the vial could no longer be used.

Iopamidol Injection ®, like other iodine-containing contrast agents, may react with copper-containing metal surfaces (e.g., brass), and therefore instruments with which products come into direct contact with such metal surfaces should be avoided.

The injection product should be visually inspected for particulate matter and discoloration of drug product prior to use, when solutions and containers allow. Do not use if the discoloration or particulates matters in the solution are observed.

The rubber plugs for intravascular and intrathecal solution injections can be punctured only

once.

It is recommended to use a suitable trocar to pierce the rubber plugs and draw contrast agents.

At the end of each examination, all disposable components of the connecting tubing and syringe system should be discarded. Other usage requirements of each device manufacturer must also be followed at the same time.

If disposable equipment is not used, special care must be taken to prevent contamination of trace detergent residuals.

Contrast agents should not be mixed with other drugs.

Organic iodinated contrast agents should be limited to those cases where angiography is definitely needed.

Diagnostic tests that require the use of any radiopaque contrast agents should be performed under the direction of personnel who have received the necessary training and a thorough understanding of the particular examination.

Appropriate facilities should be provided for the management of various complications of the examination, as well as the emergency treatment of severe adverse reactions to the contrast agent itself.

Like all other contrast agents, this product may cause allergic reactions or other allergic manifestations such as nausea, vomiting, dyspnea, erythema, urticaria, and hypotension. Severe adverse reactions leading to death have been reported occasionally.

Special attention should be paid to patients with a history of allergies, asthma, or a history of adverse reactions during similar previous examinations; in such patients, the benefits should clearly outweigh the risks. In such patients, antihistamines or corticosteroids may be considered before examinations to prevent or minimize the possibility of allergic reactions.

The contrast agent has an increased risk of inducing response of bronchospasm in patients with asthma, particularly those who are taking beta-blockers.

An intravenous access is required during the examination for emergency treatment of severe reactions.

Contrast agents must be used with qualified personnel, relevant drugs, and equipment capable of performing emergency resuscitation. All patients should be observed for at least 30 minutes after angiography.

Contrast agents for cardiac angiography can only be used in hospitals and clinics where emergency intensive care facilities and personnel are available.

For other more common diagnostic examinations using iodinated contrast agents, all necessary resuscitation equipment and therapeutic drug facilities (simple artificial respirator

[AMBU], oxygen, antihistamines, vasoconstrictors, cortisone, etc.) should always be available in the radiology department of public or private clinics where such examinations are performed.

Patients with congestive heart failure should be observed for several hours after angiography to detect delayed haemodynamic disturbances that may be associated with transient increases in circulating osmotic load.

Patients should be informed that allergic reactions may occur within a few days of the radiographic examination; if an allergic reaction occurs, prompt medical attention should be sought.

Special care should be taken during contrast injection to avoid extravasation.

Local tissue irritation may occur when perivascular invasion of the contrast agent occurs.

Patients must be adequately hydrated before and after imaging. Dehydration should be avoided in patients with severe hepatic or myocardial impairment, myeloma, diabetes, polyuria or oliguria, hyperuricemia, and infants, elderly patients, and those with severe systemic disorders.

Fluid intake should not be restricted, and disturbances in water and electrolyte balance should be corrected before hyperosmotic solutions are used. For patients with underlying conditions that may worsen due to fluid overload (including congestive heart failure), special attention should be paid to hydration.

In particular, the fluid intake should not be restricted in infants and children, and fluid or electrolyte imbalances should be corrected before hyperosmotic contrast agents are used.

Anticonvulsant therapy should be maintained in patients with known epilepsy or a history of epilepsy. In some cases, anticonvulsant therapy may be intensified 48 hours before the start of the examination.

The risks associated with specific examinations may be increased by certain diseases such as advanced atherosclerosis and hypertension.

Conditions with a greater risk of serious adverse events

In all of the following conditions with an increased risk of serious adverse events, it is recommended to perform a careful assessment of the risk-benefit ratio before contrast administration.

Patients at increased risk include those who are suspected of having a previous allergy reaction to contrast agents or iodinated contrast agents and those with allergic diseases (bronchial asthma, hay fever, or food allergy).

Patients with Waldenstrom's paraproteinemia, multiple myeloma, or severe hepatic or renal

impairment also have particular risks and should be adequately hydrated.

For patients with sickle cell disease, adequate hydration must be ensured.

In patients with moderate to severe renal impairment, specific caution should be used.

In patients with renal impairment, contrast injection may cause acute renal failure.

The key precautions include identifying high-risk patients; ensuring adequate hydration prior to contrast injection, preferably maintaining intravenous fluids before and during the examination until the contrast agent is completely cleared through the kidneys; avoiding administration of nephrotoxic drugs or major surgery or examination (such as renal angioplasty) before the contrast agent is completely cleared; monitoring renal function parameters after examination; postponing new examinations using contrast agents until renal function returns to pre-examination levels.

Patients with severe hepatic insufficiency, renal insufficiency, or hepatic and renal insufficiency should not be examined unless absolutely necessary.

Repeat examination with contrast administration should be postponed for 5 to 7 days.

Patients on dialysis can use contrast agents such as iopamidol injection, because iopamidol injection can be successfully cleared by dialysis.

The concomitant renal impairment in patients with diabetes mellitus is one of the factors predisposed to acute renal impairment after intravascular contrast injection, which may lead to lactic acidosis in patients taking biguanides (see Drug-Drug Interactions).

When performing iodinated contrast enhanced examinations in patients with or suspected of having hyperthyroidism or autonomic thyroid nodules, caution should be used, as thyroid crisis has been reported in such patients after iodinated contrast injection.

Hyperthyroidism may recur in previously treated patients with Graves' disease.

For patients with hyperthyroidism, radiological examinations should be performed only when determined necessary by a physician.

For patients who have been scheduled for a thyroid examination and/or radioactive iodine tracer therapy, the ability of the thyroid to uptake iodine may be reduced for days, sometimes even up to 2 weeks, after injection of iodinated contrast agents cleared by the kidney.

The use of this product will interfere with antithyroid function tests.

Patients with pheochromocytoma may develop severe hypertensive crisis after intravascular injection of iopamidol. It is recommended to use alpha- and beta-blockers under supervision of a physician before arterial injection.

Injection of iodinated contrast may exacerbate signs and symptoms of myasthenia gravis.

Contrast agents should be used with caution in patients with hyperkalemia and

cerebrovascular disease.

Contrast agents should be used with caution in patients with symptomatic cerebrovascular disease, heart attack/recent stroke or transient ischemic attack (TIA), abnormal blood-brain barrier permeability, increased intracranial pressure, suspected intracranial tumor, abscess or hematoma/hemorrhage, previous seizures, and alcoholism.

Precautions for Neuroradiological Examinations

When cerebrospinal fluid circulation is blocked, contrast agents should be cleared as much as possible.

Patients who are taking anticonvulsant drugs should continue to use the drugs before and after angiography.

If seizures occur during the examination, the patients could be given intravenous diazepam or phenobarbital.

Precautions for Intrathecal Injection

An accurate assessment of the risk/benefit ratio is required if the clinical history indicates that the patient has a previous history of epilepsy, blood in the cerebrospinal fluid, or local or systemic infection (possibly bacteremia).

In these cases, the physician should assess whether these patients require the diagnostic examinations based on these possible risks.

After cervical or lumbar and cervical examination:

- raising the head of the bed to a 45 °angle for about 2 minutes to allow the contrast to flow to the patient's partes sacralis;
- Raise the head side of the stretcher by at least 30 ° before moving the patient onto the stretcher;
- Avoid excessive, especially active movement or stretching of the patient;
- Observe the patient closely to keep him or her quiet and in a "head up" position, especially during the first few hours;
-Patients should remain supine and rest in bed during this period;
- Patients should be encouraged to drink and eat when they tolerate.

In case of accidental intrathecal injection of an iodinie strength not approved for intrathecal administration, the patient must be closely monitored for symptoms and signs of central nervous system disorders during the first 12 hours.

Precautions for Angiography

The risks associated with specific examinations may be increased by certain conditions such as advanced atherosclerosis, hypertension, heart failure, severe systemic disorders, embolism,

or recent cerebral thrombosis.

Patients with severe and chronic hypertension are at increased risk of renal impairment and catheterization after contrast administration.

Special attention should be paid to right cardiac function and pulmonary circulation in patients undergoing cardiac angiography. Bradycardia and systemic hypotension can be induced by right heart failure and pulmonary hypertension when organic iodine solution is injected. Right cardiovascular angiography is performed only if absolutely necessary.

Ventricular arrhythmias may occasionally occur during intracardiac and/or coronary angiography.

Special caution should be used when injecting contrast agents into the heart chamber, particularly in neonates with pulmonary hypertension, cardiac impairment and cyanosis.

Intravascular injection of contrast agents in patients with congestive heart failure can cause pulmonary edema.

The possibility of plaque detachment, vessel wall damage or perforation should be considered during catheter manipulation and contrast injection when performing angiography.

Pre-injection is recommended to ensure accurate catheter positioning.

When examining the aortic arch, the catheter tip should be placed carefully to avoid hypotension, bradycardia, and central nervous system injury due to excessive pressure passing from the syringe pump to the aortic brachiocephalic artery branch.

Angiography should be avoided whenever possible in patients with homocystinuria because of an increased risk of thrombosis and embolism.

Intra-arterial injection of contrast agents may cause vasospasm and subsequent cerebral ischemia.

Even in abdominal angiography, excessive pressure from the syringe pump can cause renal infarction, spinal cord injury, retroperitoneal hemorrhage, and myocardial and intestinal necrosis.

During peripheral arteriography, Iopamidol Injection ® 370 mg I/ml injection could elicit a painful response while the Iopamidol Injection ® 300 mg I/ml could not.

Patients undergoing peripheral angiography should be evaluated for pulsation of the contrast-injected arteries. If necessary, angiography should be performed with caution in patients with thromboangiitis obliterans or ascending infection with severe ischemia.

In patients undergoing phlebography, particular caution should be exercised in patients suspected of having phlebitis, severe ischemia, local infection, or complete venous occlusion.

In vitro tests have observed that compared with ionic contrast agents, non-ionic contrast

agents with the same concentration have a weaker inhibitory effect on coagulation activity.

Effects on the ability to drive vehicles and operate machines

No data are available on the effects of Iopamidol Injection on the ability to drive vehicles and operate machines. Before driving a vehicle or operating a machine, consideration should be given at least to possible side effects such as hypotension, dizziness, confusion and tachypnea that may occur during the use of the drug.

Do not drive a vehicle or operate a machine within 6 hours after intrathecal injection.

[Use in Pregnancy and Lactation]

Pregnancy

The safety of iopamidol injections during pregnancy has not been determined.

Given that radiation exposure should be avoided under any circumstances during pregnancy (with or without the use of contrast agents), the benefits of X-ray examinations must be carefully considered. In evaluating the benefit-risk of iodinated contrast examination, fetal thyroid hypersensitivity to iodine should be considered in addition to fetal radiation exposure.

Examination of female reproductive organs is contraindicated when pregnancy is suspected or determined, and during acute inflammation of the female reproductive organs.

Animal studies have not shown direct or indirect effects on pregnancy and embryo/fetal development. Caution should be exercised when prescribing contrast agents to pregnant women.

Lactation

A small amount of iodine-containing X-ray contrast agent can be secreted into the milk. It is unlikely to have a harmful effect on the breastfed infants at the therapeutic dose. Although no adverse effects have been reported, intravascular X-ray contrast should be used with caution in breastfeeding women due to the potential adverse effects and consideration should be given to stop breastfeeding for 24 hours after using contrast agents.

Fertility

[Pediatric Use]

Neonates, children-infants (< 1 yr), especially neonates, are particularly prone to electrolyte imbalances and hemodynamic changes. Attention should be paid to the dosage, examination details, and patient status.

[Elderly]

The elderly are at particular risk of adverse effects due to declining physiological function, particularly when using high-dose contrast agents.

[Drug-Drug Interactions]

In order to prevent lactic acidosis during selective radiography for diabetic patients who are taking oral biguanide antidiabetic drugs and have moderate renal impairment, the use of biguanide should be discontinued 48 hours before the administration of the contrast agent and should not be resumed until renal function has been shown to return to pre-examination values.

In emergency patients with impaired or unknown renal function, physicians should weigh the risks and benefits of examinations using contrast agents. Metformin should be discontinued from the time of contrast administration. After examination, patients should be monitored for signs of lactic acidosis. Metformin can be resumed only 48 hours after contrast administration if the patient's serum creatinine/eGFR is unchanged compared with the pre-examination levels. Patients with normal renal function may continue taking metformin as usual.

Atypical adverse reactions, such as erythema, fever, and influenza symptoms, have been reported after administration of iopamidol in patients treated with interleukin-2 and interferon.

In patients who have been scheduled for thyroid examination and/or radioactive iodine tracer therapy, the ability of the thyroid to uptake iodine could decrease for several days, sometimes even up to two weeks, after injection of a iodinated contrast agent cleared by kidneys.

Cases of arterial thrombosis have been reported following the use of papaverine after injection of iopamidol.

Vasopressors can significantly enhance the neurological effects of intra-arterial administration of contrast agents.

Nephrotoxicity has been reported in patients with hepatic insufficiency using intravascular contrast after oral administration of cholecystography contrast. However, recent studies have found no interaction between the contrast agents cleared by kidneys and the oral contrast agents for cholecystography.

Contrast agents may interfere with laboratory tests for bilirubin, proteins, or inorganic substances (such as iron, copper, calcium, and phosphate). These substances should not be tested and analyzed on the day after administration of contrast agents.

Patients who are taking beta-blockers are at increased risk for more severe anaphylactoid reactions. Beta-blockers may impair the treatment response to contrast-induced bronchospasm.

The medications that lower the seizure threshold should be considered to discontinue and may be reintroduced 24 hours after the end of the examination.

Alcoholism or drug addiction may increase the permeability of the blood-brain barrier, making it easier for iodinated contrast agents to enter brain tissues that may have CNS

disorders. It must be kept in mind that seizure thresholds may be lowered.

[Overdose]

Doses beyond labeling are not recommended because it may cause fatal adverse reactions.

If needed, hemodialysis may be used to remove iopamidol from the body.

Overdose is treated with direct supportive measures for all vital functions and prompt symptomatic treatment.

Intravascular

In case of accidental overdose of intravascular injection, fluid should be infused to supplement lost water and electrolytes. Renal function should be monitored for at least 3 days.

Intrathecal

Signs of intrathecal overdose: Ascending hyperreflexia or tonic paroxysmal spasms, until generalized seizures; hyperthermia, coma, and respiratory depression may occur in severe cases involving the CNS.

[PHARMACOLOGY AND TOXICOLOGY]

Pharmacological Effect

Iopamidol is a nonionic iodinated contrast agent, which contains a hydrophilic substitution group in the molecule and has high solubility. The iopamidol is radiopaque, so the internal structure of the body can be radiographed after intravascular injection, until it is sufficiently diluted by blood. The calculations of the apparent volume of distribution at steady state showed that iopamidol was distributed between the blood circulation and other extracellular fluids, and no significant deposition in tissues was observed. Iopamidol is evenly distributed in the extracellular fluid, thus could enhance the computed tomography of the head and body after intravenous administration.

Toxicology Study

Genotoxicity:

The results of Ames test, Saccharomyces cerevisiae (in vitro) gene mutation test, Schizosaccharomyces pombe (in vitro) test and in vivo micronucleus test in mice for Iopamidol were all negative.

Reproductive Toxicity:

No significant effects on fertility were observed in female and male rats receiving the intravenous doses of 0.6 g (I) kg/day, 1.5 g (I) kg/day, and 4 g (I) kg/day. The intravenous injection of iopamidol 0.3-0.4 g (I)/kg/day in pregnant rats and rabbits continued until the

end of the embryogenesis period, which is 2.7 and 1.4 times of the maximum recommended human dose (body weight 50 kg, 1.48 g (I)/kg) respectively, with induced maternal toxicity (slight increase in body weight) but no observed significant effect on embryo-fetal growth and development. The intravenous administration of iopamidol in pregnant rats from gestation day 15 to postnatal day 21 at the doses of 1 g (I)/kg/day, 2 g (I)/kg/day and 4 g (I)/kg/day did not lead to significant effects on fetal growth and development.

[Pharmacokinetics]

Iopamidol is excreted mainly in an unchanged form through the kidney following injection. After administration in dogs, 93-95% of the dose was excreted by the kidney and 0.5% of the dose was excreted by the gallbladder within 7-10 hours.

In humans, more than 90% of the dose was excreted by the kidneys within 24 hours.

The half-life of blood concentration in the elimination phase is about 60 minutes in dogs and 90-120 minutes in humans.

The peak plasma concentration was reached within 90-150 minutes after intrathecal injection and it was completely excreted within 24 hours.

There is no significant metabolism of iopamidol in animals and humans.

[Storage]

Store belw 30°C and protected from light.

Prevent freezing. Do not freeze.

[Package] Glass vial, 1 vial/box; 10 vials/box; 30 vials/box.

[Shelf life] 36 months

[Marketing Authorization Holder]

Name: Beijing Beilu Pharmaceutical Co., Ltd.

Address: No. 3, Shuiyuan West Road, Miyun District, Beijing

[MANUFACTURER]

Manufacturer Name: Beijing Beilu Pharmaceutical Co., Ltd.

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