PRODUCT MONOGRAPH

OSMOVIST®

Iotrolan Injection

OSMOVIST® 240

Iotrolan Injection 240 mg I/mL

OSMOVIST® 300

Iotrolan Injection 300 mg I/mL

Dimeric Non-ionic Radiographic Contrast Medium

For Myelography

Bayer Inc.
77 Belfield Road
Toronto, Ontario
M9W 1G6
Canada
www.bayer.ca

Date of Preparation:
April 11, 2007

Submission Control No.: 113334

PRODUCT MONOGRAPH

OSMOVIST®

Iotrolan injection

OSMOVIST® 240

Iotrolan injection 240 mg I/mL

OSMOVIST® 300

Iotrolan injection 300 mg I/mL

THERAPEUTIC CLASSIFICATION

A Dimeric Non-ionic Radiographic Contrast Medium For Myelography

ACTION and CLINICAL PHARMACOLOGY

OSMOVIST (iotrolan) is a dimeric, non-ionic, hexaiodinated radiocontrast medium. The contrast-giving substance, iotrolan, is a dimer of triiodinated isophthalic acid derivatives, in which the firmly bound iodine absorbs the X-rays. Solutions of OSMOVIST 240 mg I/mL and 300 mg I/mL are isotonic to plasma and cerebrospinal fluid at radiologically useful iodine levels.

After intrathecal administration, iotrolan is absorbed from cerebrospinal fluid (CSF) into the blood stream. The mean half-life of the transfer of iotrolan from the spinal fluid to the blood plasma was found to be 5.7 ± 6.0 hours in adults. The highest concentration of iodine in plasma occurred 3.5 ± 3.1 hours after intrathecal administration. Plasma protein binding at a concentration of 1.2 mg I/mL is 2.4%. The mean elimination half-

life of iotrolan in the plasma is 13.6 ± 13.9 hours (median of 9 hours). Approximately 50-80% of the administered dose is excreted unmetabolized by the kidneys within 24 hours after administration, and approximately 90% within 72 hours. Only 0.6% of the dose was found in the feces collected up to 72 hours after dosing.

Total and renal clearance following intravenous injection is 93.5 ± 5 mL/min and 90 ± 4 mL/min, respectively.

In patients with renal impairment, depending on the degree of impairment, decreased renal elimination may cause prolonged iotrolan levels in plasma.

After i.v. administration, the blood-chemical parameters — including those in renally impaired patients (creatinine more than 1.5 mg/dL) — did not display any statistically significant changes compared to the baseline values. The fluctuations lay within the circadian range.

There is no evidence of metabolism, deiodination or biotransformation in rats and humans.

Generally, acceptable diagnostic contrast by conventional radiographic techniques can be achieved for at least 30 minutes following intrathecal injection. Computerized tomography may be performed up to 3 to 5 hours after iotrolan administration depending on the level of injection (cervical, thoracic or lumbar).

Contrast enhancement is directly related to the initial dosage of iotrolan administered and patient positioning.

INDICATIONS and CLINICAL USE

OSMOVIST 240/300 (iotrolan) is indicated in adults for:

Lumbar Myelography

Cervical Myelography

Total Columnar Myelography

Computerized Tomography of spinal and subarachnoid spaces.

CONTRAINDICATIONS

OSMOVIST 240/300 (iotrolan) should not be administered to patients with known hypersensitivity to the drug or to patients with manifest hyperthyroidism.

Intrathecal administration of corticosteroids with OSMOVIST 240/300 is contraindicated.

Lumbar and cervical puncture should not be performed in the presence of significant local or systemic infection where bacteremia is likely.

WARNINGS

Contrast media which are related chemically to triiodinated benzoic acid derivatives have been associated with serious and fatal reactions. Therefore, clear indication and evaluation of the risk/benefit ratio for every patient should precede each examination with contrast media. Also, it is of utmost importance that adequate facilities and appropriate personnel be readily available and a course of action be planned in advance for the immediate treatment of any serious untoward reaction. Diagnostic procedures utilizing a radiopaque contrast medium should be conducted only by a physician with the requisite training and a thorough knowledge of the particular procedure to be performed.

The physician must also be thoroughly familiar with the emergency treatment of all adverse events.

If grossly bloody CSF is encountered, the possible benefits of a myelographic procedure should be compared in terms of risk to the patient.

Direct intracisternal or ventricular administration for standard radiography is not recommended. Although seizures were not seen in clinical trials of iotrolan, caution should be observed in patients with epilepsy. Patients who are receiving anticonvulsants should be maintained on that therapy. In patients with a history of seizure activity who are not on anticonvulsant therapy, premedication with barbiturates or phenytoin should be considered.

Caution must be exercised in patients with a reduced seizure threshold. Neuroleptics or antidepressants should be discontinued 48 hours before the examination because they reduce the seizure threshold.

Use in Pregnancy

The safe use of OSMOVIST 240/300 during pregnancy has not been established. Therefore, it should not be used unless the benefits outweigh the risks.

Use in Lactation

If the use of OSMOVIST 240/300 is considered necessary in a nursing mother, it is suggested to discontinue breast feeding for 48 hours.

Use in Children

The safety and effectiveness of OSMOVIST 240/300 in myelography for children has not been established.

Use in the Elderly

Elderly patients may present a special risk in the use of radiographic contrast media. These patients may have compromised renal and cardiac function and may be taking medication (e.g. ß-blockers) which may make them more susceptible to the potentially harmful effects of procedures involving the use of contrast media.

Repeat Procedure

A minimal interval of 72 hours should be allowed before repeat examinations with OSMOVIST 240/300; however, a 5 to 7 day interval is recommended (See **Dosage and Administration**).

PRECAUTIONS

Before any contrast medium is injected, the patient should be questioned for **a history of previous reaction to a contrast medium, a known sensitivity to iodine or known clinical hypersensitivity (bronchial asthma, hay fever and food allergies**). The reported incidence of adverse reactions to contrast media is higher in patients with these conditions. Most adverse reactions to contrast agents appear within 30 minutes after the start of the injection, but a delayed reaction may occur. Premedication with antihistamines (except phenothiazine derivatives: see **Drug Interactions**) or corticoids may be considered in order to avoid or minimize possible allergic adverse reactions. However, antihistamines or corticosteroids should not be mixed in the same syringe with any contrast medium because of potential chemical incompatibility.

Caution must be exercised in the case of hypersensitivity to iodinated contrast media, latent hyperthyroidism, severe cardiovascular disease and bland nodular goitre. Experience shows that patients with an allergic disposition suffer more frequently from hypersensitivity reactions.

Hypersensitivity reactions to contrast media including shock cannot be ruled out, but are expected to be rare in the proposed indications. The susceptible population includes especially patients with a history of a previous reaction to contrast media, with a known sensitivity to iodine, or with known clinical hypersensitivity.

The use of a test dose of the contrast medium before injection of the full dose has been employed to predict severe or fatal reactions. These provocative tests may themselves cause severe, even fatal, reactions and are unreliable in predicting patients at special risk.

Care in patient management should be taken to prevent inadvertent intracranial entry of a large or concentrated bolus of contrast medium, which increases the risk of neurotoxicity. Also, effort should be directed to avoid rapid dispersion of the medium causing inadvertent rise to intracranial levels (e.g. by active patient movement).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients and susceptible nondiabetic patients (often elderly patients with pre-existing renal disease). Patients should be well hydrated before and after iotrolan administration.

Assessment of thyroid function may be obscured for several weeks following the administration of OSMOVIST 240/300.

Drug Interactions

Intrathecal administration of corticosteroids with OSMOVIST 240/300 (iotrolan) is contraindicated.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, concurrent drugs should not be physically admixed with contrast agents.

Drugs which lower the seizure threshold, especially phenothiazine derivatives, including those used for their antihistamine properties, should not be used with OSMOVIST 240/300. Other drugs lowering the seizure threshold to be avoided include MAO inhibitors, tricyclic antidepressants, CNS stimulants and psychoactive drugs described as analeptics, or antipsychotic drugs. Such medication should be discontinued at least 48 hours before myelography, should not be used for the control of nausea and vomiting, and should not be resumed for at least 24 hours after the procedure.

Hypersensitivity reactions can be aggravated in patients on ß-blockers.

The prevalence of delayed reactions (e.g. fever, rash, flu-like symptoms, joint pain and pruritus) to contrast media is higher in patients who have received interleukin.

ADVERSE REACTIONS

General

Careful patient observation for adverse reactions is recommended in the use of all contrast media. Reactions accompanying use may vary with the dosage, the technique of administration, the procedure and the underlying condition of the patient. Adverse reactions generally occur within 30 minutes after injection and some may be of long-lasting nature. These reactions include: laryngospasm, bronchospasm, wheezing, dyspnea, and status asthmaticus; angioedema, subglottic edema and signs of airway obstruction; anaphylactic shock; cardiovascular collapse with peripheral vasodilation, hypotension, tachycardia, dyspnea, cyanosis, sweating, pallor, ventricular fibrillation and cardiac arrest; CNS stimulation or depression with agitation, convulsions, coma and death. Severe life-threatening reactions to iodinated contrast media require appropriate emergency measures. Temporary renal failure may occur in rare cases. Delayed reactions can occasionally occur.

Many life-threatening reactions begin with only mild symptoms such as nasal congestion, sneezing, watery eyes, skin erythema, or a vague sense of discomfort. It is therefore extremely important that all patients be watched closely until their symptoms have abated. The symptoms, which occur regardless of the amount of contrast medium administered and the mode of administration, can indicate incipient shock. Administration of the contrast medium must then be interrupted immediately and - if necessary - specific therapy initiated intravenously. In the case of intravenous administration, use of a flexible indwelling catheter is therefore recommended.

Hypersensitivity reactions to the contrast medium including shock cannot be ruled out, but are expected to be rare in the proposed indications.

As after the use of other myelographic agents, cell count increases can be expected after administration of OSMOVIST 240/300 (iotrolan) into the cerebrospinal fluid. No cases of arachnoiditis have been reported.

The most frequent subjective complaints are headaches, nausea and vomiting; however, experience shows that their incidence is no higher than after the loss of pressure in the subarachnoid space resulting from puncture of the spinal canal. In view of this, an effort should be made to remove only as much fluid as is being replaced by the contrast medium solution. On the other hand, a volume of contrast medium in excess of the amount of fluid removed does not lead to an increase of pressure in the subarachnoid space.

Severe headaches lasting several days may occur.

There have been very rare cases of aseptic meningitis with fever, stiff neck, headaches and an increased cell count in the cerebrospinal fluid following administration of hydrosoluble non-ionic contrast media for myelography. In most cases, all the symptoms disappeared within a week.

Severe side effects are extremely rare when the contrast medium is administered in the proper manner.

The safety of OSMOVIST 240/300 was evaluated in 2000 patients during clinical trials for myelography. OSMOVIST 240/300 was generally well tolerated. The most frequently reported adverse events were headache (27.5%), neck pain (13.5%), nausea (6.7%), vomiting (3.3%), stiff neck (2.8%), circulatory dysregulation (2.5%), giddiness (2.3%), back pain (2.2%), pain - localized (2.1%), dizziness (1.9%), sweats (1.9%) and tinnitus (1.1%).

Spontaneous Adverse Events having an incidence of <1% :

Allergic/Cutaneous Reactions: allergoid reaction, cellulitis.

CNS Reactions: root pain/radicular symptoms, pain - radiating, paresthesia, clouding of sensorium, hyperesthesia, sensation of warmth, disturbed vision, anxiety, sensation of cold, shivering, chills, nystagmus, somnolence, transient change neurobehaviour, very brief non-specific EEG changes, speech disorder.

Post-marketing surveillance revealed two cases of adverse events not recorded during the clinical trials. They included psychotic syndrome with confusion and hallucinations, and retrograde amnesia that developed 36 hours and 8 hours, respectively after the administration of Osmovist. These adverse events were considered non-serious and both patients recovered completely. A contributory role of Osmovist could not be ruled out in these two cases.

Gastrointestinal Reactions: constipation, abdominal cramps, indigestion, diarrhea, dry mouth.

Musculoskeletal Reactions: myoclonia, dystonia/hypertonia, myasthenia.

Other Reactions: fever, urinary tract disorder, viral syndrome/URI, hepatitis, crying, bleeding from gums and nose, dyspnea, ear ache, sub-xyphoid pressure.

Treatment of Adverse Effects: Contrast media should be injected only by physicians thoroughly familiar with emergency treatment of all adverse reactions to contrast media.

The assistance of other trained personnel such as cardiologists, internists and anesthetists is required in the management of severe reactions.

A guideline for the treatment of adverse reactions is presented below. This outline is not intended to be a complete manual on the treatment of adverse reactions to contrast media or on cardiopulmonary resuscitation. The physician should refer to the appropriate texts on the subject.

It is also realized that institutions or individual practitioners will already have appropriate systems in effect and that circumstances may dictate the use of additional or different measures.

Minor allergic reactions: When treatment is considered necessary, the intravenous or intramuscular administration of an antihistamine such as diphenhydramine HCl 25 to 50 mg is generally sufficient (contraindicated in epileptics). The resulting drowsiness makes it imperative to ensure that outpatients neither drive nor go home unaccompanied.

Major or life-threatening reactions: A major reaction may be manifested by signs and symptoms of cardiovascular collapse, severe respiratory difficulty and nervous system dysfunction. Convulsions, coma and cardiorespiratory arrest may ensue. The following measures should be considered:

- Start emergency therapy immediately - carefully monitoring vital signs.
- Have emergency resuscitation team summoned - do not leave patient unattended.
- Ensure airway is patent - guard against aspiration.
- Commence artificial respiration if patient is not breathing.
- Administer oxygen if necessary.

- Start external cardiac massage in the event of cardiac arrest.
- Establish route for intravenous medication by starting infusion of appropriate solution (i.e., 5% dextrose in water).
- Judiciously administer specific drug therapy as indicated by the type and severity of the reaction. Careful monitoring is mandatory to detect adverse reactions of all drugs administered:

  Acute allergic-anaphylactoid reactions: Soluble hydrocortisone 500 to 1000 mg intravenously and/or epinephrine injection USP 1:1000 solution, 0.2 to 0.4 mL subcutaneously. In the presence of anoxia, this may cause ventricular fibrillation. Caution is required in patients on adrenergic ß-blockers. In extreme emergency, 0.1 mL/minute, appropriately diluted, may be given intravenously until the desired effect is obtained. Do not exceed 0.4 mL.

  Cardiac arrest: epinephrine injection USP 1:1000 solution, 0.1 to 0.2 mL, appropriately diluted, may be given intracardially.

  Hypotension: Monitor blood pressure carefully. Phenylephrine HCl 0.1 to 0.5 mg appropriately diluted by slow intravenous injection or by slow infusion, or norepinephrine 4 mL of 0.2% solution in 1000 mL of 5% dextrose by slow drip infusion.

  Acidosis: Sodium bicarbonate 5%; 50 mL intravenously every 10 minutes as needed to combat post-arrest acidosis.

  Sinus bradycardia: Atropine 0.4 to 0.6 mg intravenously. May also reverse 2nd or 3rd degree block.

  Convulsions: Phenobarbital sodium 50 mg in fractional doses by slow intravenous injection (contraindicated if cyanosis is present) or diazepam 5 to 10 mg by slow intravenous injection, titrating the dose to the response of the patient.

- Defibrillation, administration of antiarrhythmics and additional emergency measures and drugs may be required.
- Transfer patient to intensive care unit when feasible for further monitoring and treatment.

SYMPTOMS and TREATMENT OF ACUTE OVERDOSAGE

An overdose of OSMOVIST 240/300 (iotrolan) should be treated by support of vital functions and prompt institution of symptomatic therapy. On inadvertent overdosage or in greatly limited renal function, OSMOVIST 240/300 can be removed from the body by extracorporeal dialysis.

DOSAGE and ADMINISTRATION

OSMOVIST 240/300 (iotrolan) is indicated for intrathecal use only.

General information

As with all radiopaque contrast agents, the minimum concentration and volume to produce adequate visualization should be used. Factors such as age, body size, anticipated pathology and degree and extent of opacification required, structure(s) or area to be examined, disease process, equipment and technique to be employed should be considered. If the equipment available allows films in all necessary projections without having to move the patient and allows instillation under fluoroscopic control, the iodine concentrations and volumes at the lower limit of each specified range are sufficient. Higher concentrations are indicated if it is necessary to reposition the patient since the contrast medium dilutes more quickly due to turbulence.

The dose and concentration used in the spinal area influence the ultimate intracranial concentrations.

After every examination of the subarachnoid space - particularly thoracic/cervical sections - the contrast medium should be drained as far as possible into the lumbar region by sitting the patient up for a few minutes. Then the patient should rest in bed for at least 24 hours, the first 6 hours of which should be spent with the trunk horizontal and the head raised 15°.

Recent evidence suggests that maintaining the patient in an upright position (wheelchair or ambulation) after the myelographic procedure may help minimize adverse effects. The upright position may help to delay dispersion of the medium and to maximize the spinal arachnoid absorption.

Anesthesia is not necessary if thin puncture needles are used, and premedication with sedatives is usually not needed.

The patient should be fasting but adequately hydrated on the day of the examination. Disorders of water and electrolyte balance must be corrected.

Experience has shown that pronounced states of excitement, anxiety and pain can be the cause of side effects or intensified contrast medium-related reactions. They can be counteracted by calm management of the patient and the use of suitable medication.

Solutions of OSMOVIST 240/300, like those of other radiopaque contrast media, should be at or close to body temperature when injected. As with other sterile parenteral products, OSMOVIST 240/300 should not be transferred from the vial to other delivery systems except immediately prior to use.

Withdrawal of contrast media from their containers should be accomplished under aseptic conditions with sterile syringes. Spinal puncture must always be performed under sterile conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. OSMOVIST 240/300 should be used only if particulate free and within the normal colourless to pale yellow range.

OSMOVIST 240/300 should not be drawn into the syringe until immediately before use. Any unused portion should be discarded.

Vials containing contrast medium solutions are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. The use of cannulas with a long tip and a maximum diameter of 18 G is recommended for piercing the stopper and drawing up the contrast medium.

Recommended Dosages

The following dosage recommendations for conventional radiography or computed tomography are intended as general guidelines.

	OSMOVIST 240	OSMOVIST 300
Radiculography excluding the medullary cone	7 - 10 mL	7 - 10 mL
Lumbar Myelography	7 - 10 mL	7 - 10 mL
Lumbar Myelography with thoracic transition	7 - 12 mL	7 - 12 mL
Thoracic Myelography	10 - 15 mL	8 - 12 mL
Total Columnar Myelography	10 - 15 mL	10 - 15 mL

Cervical Myelography		
Direct (lateral access between C1/C2)	8 - 12 mL	7 - 10 mL
Indirect (instillation in the lumbar region)	15 mL	8 - 15 mL
Ventriculography		
Indirect (instillation in the lumbar region)	3 - 5 mL	3 - 5 mL
Cisternography		
Indirect (instillation in the lumbar region)	4 - 12 mL	4 - 10 mL

Rate of Injection: To avoid excessive mixing with CSF and consequent loss of contrast, as well as premature dispersion, injection must be made slowly over 1 to 2 minutes.

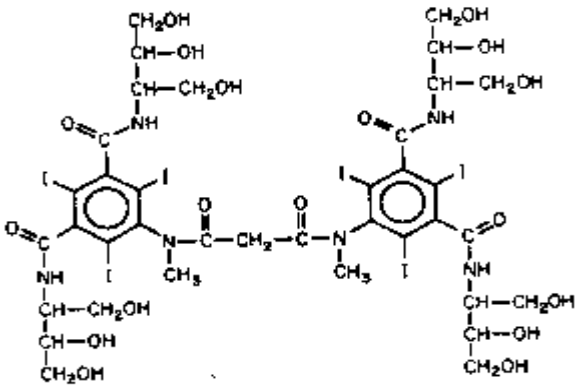
Repeat Procedure: A minimal interval of 72 hours should be allowed before repeat examinations with OSMOVIST 240/300; however, a 5 to 7 day interval is recommended.

N.B.: Higher concentrations are indicated if it will be necessary to reposition the patient during myelographic examination, since the medium becomes diluted more quickly as a result of turbulence, and the clarity of detail deteriorates.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Structural Formula:



Molecular Formula: $C_{37}H_{48}I_6N_6O_{18}$

Molecular Weight: 1626.24

Iodine Content (%): 46.82

Chemical Name: (USAN)

(1) 1,3-Benzenedicarboxamide, 5,5'-[(1,3-dioxo-1,3-propanediyl)bis(methylimino)] bis[*N,N*'-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodoisophthalamide]

(2) 5,5'-[Malonyl-bis(methylimino)]bis[*N,N*'-bis[2,3-dihydroxy-1-(hydroxymethyl)propyl]-2,4,6-triiodoisophthalamide]

Other Name: 5,5'-(N,N'-Dimethylmalonyldiimino)-bis{N,N'-bis[(1RS,2SR)-2,3-dihydroxy-1-hydroxymethylpropyl]-2,4,6-triiodo iosphthalamide}

(IUPAC)

Physical Properties:	OSMOVIST 240	OSMOVIST 300
Iodine concentration (mg/mL)	240	300
Iotrolan concentration (mg/mL)	513	641
Viscosity (mPa·s or cp)		
at 20°C	6.8	17.4
at 37°C	3.9	8.4
Osmolarity at 37°C (mOsm/L)	220	208
Osmolality at 37°C (mOsm/kg H_2O)	270	290
pH	6.4 – 8	6.4 - 8

Composition

Each mL of OSMOVIST 240 solution contains 513 mg of iotrolan (active ingredient). Also contains: Water for Injection as vehicle, 0.1 mg edetate calcium disodium, 0.4 mg sodium bicarbonate, 0.6 mg sodium chloride and sodium hydroxide to adjust the pH.

Each mL of OSMOVIST 300 solution contains 641 mg of iotrolan (active ingredient). Also contains: Water for Injection as vehicle, 0.1 mg edetate calcium disodium, 0.4 mg sodium bicarbonate and sodium hydroxide to adjust the pH.

Stability and Storage Recommendations

OSMOVIST 240/300 should be stored between 15°C and 30°C. Protect from light. Do not freeze. It should be visually inspected and used only if clear and colourless to slightly yellow and free of particulate matter. Discard unused portions.

AVAILABILITY OF DOSAGE FORMS

OSMOVIST 240 mg I/mL and OSMOVIST 300 mg I/mL are sterile, colorless to slightly yellow, odorless, pyrogen-free, aqueous solutions of iotrolan.

OSMOVIST 240 provides 513 mg of iotrolan per mL equivalent to 240 mg of organically bound iodine per mL. Each mL also contains 0.6 mg sodium chloride to adjust the osmolality of the formulation to that of blood plasma. The pH is adjusted to between 6.4 and 8.0. OSMOVIST 240 contains no preservative. It is supplied in units of 10 shrink-wrapped individually boxed 10 mL vials.

OSMOVIST 300 provides 641 mg of iotrolan per mL equivalent to 300 mg of organically bound iodine per mL. . The pH is adjusted to between 6.4 and 8.0. OSMOVIST 300 contains no preservative. It is supplied in units of 10 shrink-wrapped individually boxed 10 mL vials.

PHARMACOLOGY

General Pharmacodynamics

No hemodynamic changes attributable to the contrast medium were observed after intraarterial administration of iotrolan. On intravenous injection and on injection into the coronary artery of dogs, iotrolan was found to have very slight and short-lasting effects (fibrillation, arrhythmia and RR prolongation) which were less pronounced than after administration of other non-ionic contrast media.

Neuropharmacology

The neuropharmacology of iotrolan was evaluated in rats, rabbits and monkeys following intracisternal, intracerebral, subarachnoid and intraarterial injection.

The effects of iotrolan on the central nervous system of the rat were compared with those of ionic comparators following intracisternal administration of 0.2 mL of contrast media (370 mg I/mL). Iotrolan caused significantly fewer movement abnormalities than did the comparators tested. There were no significant differences among these agents with respect to their ability to induce seizures.

The impact of various contrast media on the blood-brain barrier was investigated in rabbits. Contrast media were injected into one internal carotid artery at doses ranging from 4 to 8 mL/kg of 280 mg I/mL, with technetium-99m-pertechnate and Evans' blue marker solution injected immediately after. Based upon the degree of uptake of these markers, it was found that the degree of damage to the blood-brain barrier was lower for iotrolan than for all other comparators tested. Administration of iotrolan resulted in a very small uptake of the marker into the brain, which was comparable to that of the saline control solution.

One study was performed to assess the relative contributions of contrast media osmolality and chemotoxicity to blood-brain barrier damage. Experimental carotid angiography was carried out in rabbits with mannitol at an osmolality of 714 mOsm/kg and with nonionic dimeric contrast media at osmolalities half that of mannitol. Mannitol caused no detectable blood-brain barrier damage. However, blood-brain barrier damage was caused by all contrast media tested. It was concluded that the blood-brain barrier damage was not attributable to osmolality, but to other physical and/or chemical effects of these media.

Cardiovascular Pharmacology

The cardiovascular tolerance of iotrolan and other contrast media was studied in anesthetized rats. Following intravenous injections of 320 mg I/mL (1 or 5 mL/kg), femoral arterial blood pressure, left ventricular end-diastolic pressure and contractility, heart rate, cardiac output and total peripheral resistance were measured. Of all contrast agents investigated, iotrolan produced the least changes to these parameters.

Intravital microscopic studies in rats were performed to assess the impact of intracardially-administered contrast media with different osmolalities on the perfusion of myocardial capillaries. Of all contrast agents investigated, iotrolan induced the least disturbance in capillary perfusion.

The coronary hemodynamics were investigated in the perfused rat heart model, where 0.3 mL of various contrast media were injected at a rate of 3 seconds. Iotrolan caused the least changes in coronary blood flow, coronary vascular resistance and myocardial blood flow, while the high-osmolar contrast agents induced the greatest change.

In a dog model, following the insertion of a catheter into the coronary right artery, 300 to 370 mgI/mL of various contrast agents were infused for 25 seconds. Iotrolan was found

to be totally inert, causing neither arrhythmia nor ventricular fibrillation. The safety of iotrolan may be related to its isotonicity to blood and that a sufficient quantity of sodium ions is provided by the $NaHCO_3$-buffer in the iotrolan formulation (i.e., 8 mEq/L).

Renal Tolerance

The tolerance and renal retention in mice (in two experiments) and rats of single intravenous doses of iotrolan, iohexol and iopamidol were evaluated. The mice were somewhat less tolerant to iotrolan than to the other contrast media, but the rats tolerated iotrolan better than the other contrast media. The renal retention of iotrolan in the mouse and in the rat was significantly longer than that of iohexol or iopamidol.

The renal tolerance of iotrolan in the rat was assessed by ascertaining urine albumin levels following simultaneous flooding of both kidneys (400 mg I/kg) via the renal arteries with iotrolan, iopamidol, iotriside and iopromide (300 mg I/mL). Albumin excretion rates were only slightly higher after the administration of iopromide (1.5 mg) or iotrolan (2.9 mg) than after the saline (1.0 mg). Maximum albumin excretion occurred in the first 30 minutes post-administration. Creatinine excretion levels after contrast medium administration were similar to those obtained after saline administration. Iotrolan was found to have good renal tolerance in the rat.

Pharmacokinetics

Iotrolan was administered by the oral, intravenous, intraduodenal, intracisternal, subarachnoid or suboccipital routes to rats, rabbits and dogs to investigate absorption, excretion and pharmacokinetics. Iotrolan was not absorbed following oral or intraduodenal administration in the rat (<1% of the dose). In all species studied, within 24 hours following intravenous, intracisternal or suboccipital injection, the contrast medium was excreted mainly by the kidneys (88%-98%), with only small amounts excreted in the feces (1%-3%). The apparent elimination half-life from blood was the same as the renal excretion half-life indicating that elimination was by glomerular

filtration without secretion or reabsorption. The excretion pathways did not show a dose dependency in the rat at doses of 60 mg I/kg and 1000 mg of I/kg.

The transfer of iotrolan from the cerebral spinal fluid to the blood indicated an invasion half-life of 0.91 ± 0.51 hours in the dog. After intravenous administration in the rat, the plasma and urinary half-lives were 18 and 16 minutes, respectively. In the rabbit, the plasma half-life was 60 minutes. After suboccipital administration, in the rabbit, the plasma and urinary half-lives were 9.7 hours and 6.3 hours and in the dog 1.47 and 1.57 hours.

In Cynomolgus monkeys, a subarachnoid dose of 0.5 mL of iotrolan 300 mg I/mL had a clearance half-life from the third ventricle of 11.5 hours similar to iohexol (14 hours), iopamidol (14 hours) and metrizamide (13.5 hours). Iotrolan showed approximately the same amount of accumulation in the neural parenchyma as iohexol and iopamidol and significantly less than metrizamide ($p<0.05$).

Passage across the placental barrier was determined quantitatively in the rabbit. Only a maximum of 0.2% of the administered dose could be detected in the fetus after i.v. injection of 60 mg I/kg to pregnant animals. These results were supported by a study in the rat, where no iotrolan was found in the fetuses.

Excretion of iotrolan in breast milk was extremely low. In the rat, less than 0.4% of the administered dose passed into the milk and was subsequently ingested by the neonate. However, because of the low enteric absorption of iotrolan, less than 1% of this amount would be absorbed from the intestine.

TOXICOLOGY

The formulation containing 300 mg I/mL (OSMOVIST 300) was used for the toxicological characterization of iotrolan, and is considered to be representative of the lower concentration (OSMOVIST 240) as well.

Single Dose Toxicity

The LD_{50} values of iotrolan could not be determined for the intravenous route of administration in either the rat or the mouse: the maximum administration volume (rat – 12 g I/kg and mouse – 15 g I/kg) was reached without lethal effects and were tolerated by both species without symptoms. No difference in the tolerance between young rats and older animals was observed.

In mice, intracisternal injections of both iotrolan 300 mg I/mL and Ringer's solution produced deaths in a non-dose-related manner, presumably due to the application technique. A median lethal dose could not be calculated. In rats, intracisternal injections of iotrolan 300 mg I/mL, diluted in Ringer's solution, caused death in half of the animals at 1.141 mg of iodine/kg.

The median effective dose (ED_{50}) by intracisternal injections in the rat and in the guinea pig was found to be approximately 0.16 g I/kg and approximately 0.5 g I/kg, respectively. In dogs, a subarachnoid injection of iotrolan 300 mg I/mL in the lumbar region at a dose level of 249 mg of iodine/kg elicited no local, systemic or neurological effects.

Local Tolerance

A single or repeated subarachnoidal application in the lumbar region of dogs or repeated intracisternal application in rats gave no indication that local intolerance reactions should be expected at the leptomeninges of humans.

The local tolerance of iotrolan in muscle and paravenous tissue was as good as that of physiological saline. No local irritation was observed in the eye. On the peritoneum of the rat, iotrolan was as well-tolerated as the non-ionic contrast media. In the muscle tissue of the rabbit, iotrolan was better tolerated than all other contrast media tested.

Special Toxicity Studies

Iotrolan produced no contact-sensitizing effect in the guinea-pig (optimisation and maximisation test).

Repeated Dose Toxicity

Iotrolan was administered intravenously to rats and dogs for 3–4 weeks. Slight, toxicologically insignificant, changes in clinico-chemical and hematological parameters were observed in the rat, only. No organ toxicity was seen in either species.

As with other X-ray contrast media, proximal renal tubular epithelium vacuolisation occurred in both rat and dog kidneys after intravenous administration. After single doses of 3.0 g I/kg the vacuolisation was reversible within 5 weeks. No alteration of cell organelles was observed even after the extremely high dose of 6 g I/kg. In rabbits, no vacuolisation occurred in doses up to 7.5 g I/kg.

Combined systemic and local tolerance studies with single (249 mg I/kg) or repeated (39; 90; 249 mg I/kg) subarachnoidal applications in the lumbar region of dogs or

repeated intracisternal (2.4; 12; 60 mg I/animal) applications in the rat revealed no compound-related effects either systemically or locally.

Iotrolan was administered by the subarachnoid route once weekly for four weeks at doses of 39, 90 and 249 mg of iodine/kg to beagle dogs. Except for one death in the high-dose group, iotrolan had no effect on animal body weight, food or water consumption or physical well being. Inflammation of the meninges was evident in the dog that died, but the cause of death was not determined. The pyrogen content of this preparation of iotrolan, discovered after the study was initiated, could have been responsible for this effect. No toxicological or histopathological effects were seen in the other animals that could be attributed to iotrolan.

Multiple-dose studies were also performed by the intracisternal route of administration. Doses were limited by the capacity of the cerebrovascular space. In the rat, 200 µL of iotrolan 300 mg I/mL represented the high dose in a study in which one injection was administered into the cisterna magna of each animal weekly for four weeks. No iotrolan-related pathology was detected in brain or spinal tissues following histopathological examination.

A second study was performed in which iotrolan (300 mg I/mL) doses of 8, 40 or 200 µL/injection were administered intracisternally once every four days for two weeks to male and female rats. Again, there was no significant, dose-related histopathological evidence of irritation or effect on the brain, spinal cord or their associated membranes.

Reproduction and Teratology

Reproduction investigations were performed in the rat and rabbit; 0.3, 0.9 and 3.0 g I/kg was administered by intravenous or intraperitoneal injection. The embryo toxicity studies in the rat and the rabbit gave no indication of a teratogenic effect at high doses.

In the rabbit, marginal and moderate increases in embryo mortality were observed after i.v. injection of 0.9 and 3.0 g I/kg. A special study was performed in rabbits with a single dose of 3.0 g I/kg administered on different days (6, 8, 10, 12 or 14) of gestation; no compound-related effects on embryo mortality or teratogenicity were observed.

Mutagenicity

No mutagenic action was demonstrated in the Ames test with *Salmonella typhimurium*; nor with a tryptophan-dependant strain of *E. coli* in the reverse mutation assay. No mutagenic effect was detected in the mouse during the micronucleus and dominant-lethal test.

Iotrolan did not show any genotoxic potential in the UDS test on rat hepatocytes, and did not display any cell-transforming effect in mouse embryo fibroblasts.

BIBLIOGRAPHY

Behrends B, Albrecht A, Bingas B, Becker H, et al. Neural tolerance of iotrolan 300 in ascending cervical myelography: results of a multicenter study. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:171-5; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 171-175.

Bien S, Schumacher M, Berger W, Wenzel-Hora BI. Iotrolan, a nonionic dimeric contrast medium in myelography. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:158-60; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 158-160.

Coutinho C, McGeorge A, Macpherson P, Teasdale E. Iotrolan versus iopamidol for cervical myelography: a randomized double-blind trial. Br J Radiol 1988; 61(730):965-967.

Goldstein HA, Pfennig D. Clinical trials with iotrolan in myelographic and computed tomography applications in the United States. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:167-170; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 167-170.

Hoffmann B, Becker H, Wenzel-Hora BI. Influence of the spread and period of retention of Iotrolan in the subarachnoid space on the side effects rate in myelography. Neuroradiology 1987; 29(4):380-384.

Inoue S, Watanabe T, Yamamura H. Comparative clinical study with iotrolan versus metrizamide in lumbar myelography. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:161-166; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 161-166.

Lamb J, McAllister V, Nelson M, Bartlett R, et al. A prospective comparison of iotrolan, iohexol and iopamidol for lumbar myelography. Acta Radiol Suppl (Stockh) 1986: 369:524-7.

Mützel W, Press WR, Weinmann HJ. Physicochemical properties and general pharmacology of the nonionic dimer iotrolan. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:28-32; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 28-32.

Ringel K, Klotz E, Wenzel-Hora BI. Iotrolan versus iopamidol: a controlled, multicenter, double-blind study of lumbar and direct cervical myelography. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:153-7; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 153-157.

Scholz P, Weinmann HJ, Mützel W, Staks T. Pharmacokinetics of iotrolan after intravenous injection into healthy volunteers. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:211-4; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 211-214.

Weinmann HJ, Vogelsang H, Mützel W, Speck U. Plasma level and renal excretion of iotrolan after lumbar injection in patients. Fortschr Geb Rontgenstr Nuklearmed Erganzungsbd 1989; 128:224-227; also in Taenzer V, Wende S (eds). Recent developments in nonionic contrast media, Georg Thieme Verlag Stuttgart, New York 1989: 224-227.