

## PRODUCT MONOGRAPH

### **OMNIPAQUE**

iohexol injection USP

Non-ionic radiographic contrast medium

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**NAME OF DRUG**

**OMNIPAQUE**

(iohexol injection USP)

**OMNIPAQUE 180**

(iohexol injection USP 39%)

**OMNIPAQUE 240**

(iohexol injection USP 52%)

**OMNIPAQUE 300**

(iohexol injection USP 65%)

**OMNIPAQUE 350**

(iohexol injection USP 76%)

**THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION**

Non-ionic radiographic contrast medium.

**ACTION AND CLINICAL PHARMACOLOGY**

**A. GENERAL**

Immediately following rapid intravascular injection, Omnipaque (iohexol) reaches peak plasma concentration and is then rapidly distributed throughout the extracellular fluid compartment. Iohexol does not normally cross the blood-brain barrier to any significant extent. It is excreted unchanged by the kidneys, mainly by glomerular filtration; tubular secretion plays a minor role, and a very small quantity (1-2%) is excreted via the bile. About 80-90% of the injected dose is excreted in the first 24 hours, with peak urine concentrations occurring in the first hour.

Pharmacokinetic studies of iohexol following i.v. injection in healthy male volunteers showed, using a three-compartment open model, that its distribution half-life (alpha phase) is 22 minutes, excretion half-life (beta phase) 2.1 hours, and first-order terminal

elimination half-life (gamma phase) 12.6 hours. The volume of distribution of the central compartment is 165-270 mL/kg, the mean renal clearance 120 mL/min., and the mean total body clearance is 131 mL/min.

In the presence of impaired renal function, the excretion of iohexol by the kidneys will be delayed and the amount excreted in the bile increases.

Iohexol is not known to be appreciably metabolized in humans. No metabolites have been found in urine. The presence or absence of metabolites in human bile has not been ascertained. (Small quantities of two metabolites were detected in rabbit bile and urine).

Following its injection into the subarachnoid space, iohexol mixes readily with the cerebrospinal fluid (CSF) and diffuses into root sleeves and upward in the spinal and intracranial subarachnoid spaces. The time it takes iohexol to reach the cervical and intracranial subarachnoid spaces will depend to a large degree on the patient's position and movements. As it diffuses upward, its concentration decreases. Iohexol is eliminated into the systemic circulation via the subarachnoid granulations in the spine and the skull, and is subsequently excreted by the kidneys. Peak plasma concentration following subarachnoid injection of iohexol is reached in 2 to 6 hours. When fitted to a one compartment open model with first order absorption, the mean plasma elimination half-life (beta phase) is 3.4 hours (2.2 to 7.9 hours) and the mean apparent terminal elimination half-life (gamma phase) is 4.5 hours. The mean volume of distribution is 559 mL/kg, the mean renal clearance 111 mL/min. and the total body clearance 119 mL/min. Within the first 24 hours, about 84% of the injected dose is recovered from the urine.

## **B. SUBARACHNOID**

Omnipaque (iohexol), when injected into the lumbar subarachnoid space, will opacify the lumbar subarachnoid spaces and their associated root sleeves to provide contrast for

these structures.

Following lumbar subarachnoid injection in conventional radiography, Omnipaque will continue to provide good diagnostic contrast for at least 30 minutes. After approximately one hour, contrast of diagnostic quality will not be available for conventional myelography, due to diffusion throughout the CSF as well as transfer into the general circulation. If computerized tomography is to follow, it should be deferred for 2 to 6 hours to allow the degree of contrast to decrease. For computerized tomography without conventional radiography, a smaller dose or lower concentration of Omnipaque would be required.

Computerized tomography shows CSF contrast enhancement in the thoracic region in about one hour, in the cervical region in about 2 hours, in the basal cisterns in 3 to 4 hours, and in the ventricles and sulci in 5 to 6 hours. Between 8 and 12 hours after lumbar injection, CT scans of the brain may demonstrate contrast medium enhancement of brain tissue in contact with the subarachnoid spaces indicating permeation of the cerebral cortex by the contrast medium; this "blush" effect will normally disappear in 24 hours.

In lumbar myelography studies, Omnipaque was injected into the lumbar subarachnoid space of 576 adult patients while an additional 208 adult patients received Amipaque (metrizamide) under similar dosages and conditions.

Clinically significant, transient individual changes in vital signs, serum chemistry, hematology and neurological tests, when observed, were similar in magnitude and frequency with the two contrast agents used.

The electroencephalogram was recorded in 182 patients who received Omnipaque. EEG changes (mostly theta and delta waves) were recorded in approximately 4% of these patients. This compares to approximately 35% of patients exhibiting EEG changes

following myelography with Amipaque, based on historical data. No significant changes were evident in the chemistry of cerebrospinal fluid (CSF) obtained by repuncture at either 6 or 24 hours after injection of Omnipaque. Although a few increases in CSF protein, WBC and other laboratory parameters were reported, no effect on IgG, creatinine kinase (CK) or CK-BB band isoenzyme was observed.

### **C. INTRAVASCULAR**

Following intravascular injection, Omnipaque (iohexol) will opacify those vessels in the path of flow of the contrast medium, permitting radiographic visualization of the vasculature of the internal structures and extremities until significant dilution occurs.

After intravenous injection opacification of the renal parenchyma can begin within one minute. Excretion of the contrast material becomes apparent in about 1 to 3 minutes, with optimal contrast in the calyces and collecting system occurring between 5 to 15 minutes.

In nephropathic conditions, particularly when excretory capacity has been altered, the rate of excretion varies unpredictably, and opacification may be delayed for up to several hours after injection. Severe renal impairment may result in a lack of diagnostic opacification of the urinary tract, and depending on the degree of renal impairment, prolonged plasma iohexol levels may be anticipated in these patients as well as in infants with immature kidneys.

In comparative clinical trials of the vascular procedures of angiocardiology, cerebral arteriography, peripheral arteriography, urography, peripheral venography and intravenous digital subtraction angiography a total of 885 consenting adult patients received Omnipaque (523 by arterial injection and 362 by intravenous route) while 724 patients received conventional **ionic** media, such as metrizoate, diatrizoate and iothalamate, (444 intra-arterially and 280 intravenously) for their radiographic examinations.

Statistically significant reductions in patient discomfort, during or shortly after injection, were generally observed with Omnipaque when compared to the above noted conventional ionic contrast media. Injection of Omnipaque was also associated with statistically significant reduction of changes in mean values of some physiological parameters (heart rate, Q-T interval, S-T segment, and systemic pressures), compared to those associated with the use of conventional ionic media in some procedures, especially in angiocardiology. Clinically significant, transient individual changes noted in vital signs and laboratory parameters (increased serum creatinine CK, LDH, SGOT, SGPT, K, decreased creatinine clearance; increased urinary protein, WBC and RBC; and variations in hematology parameters) after administration of Omnipaque were similar in scope to those caused by the conventional ionic control contrast agents.

In-vitro studies done on human basophils from nonallergic, nonatopic, nonreactor subjects showed that iohexol caused a lesser degree of histamine release than diatrizoate, an ionic contrast agent.

As with any iodinated contrast agent, administration of Omnipaque may lead to changes in thyroid function in some patients, and elevation of thyroxine and/or TSH may be observed.

Since iohexol does not ionize in solution, there is less dilution through hyperosmolar fluid shifts within the renal tubules and hence less osmotic diuresis, compared to conventional ionized contrast media, and a higher iodine concentration in the tubular urine is obtained.

Several studies have shown that conventional ionic contrast media caused significantly greater increases in proteinuria, urinary  $\beta$ -hexosaminidase and serum creatinine than did

nonionic media at comparable doses. One study, on the other hand, involving 20 pediatric patients, showed that the significant increase in urinary excretion of other renal enzymes (N-acetyl glucosaminidase, gamma glutamyl transpeptidase and muramidase) following the intravascular administration of Omnipaque was approximately the same as that caused by conventional ionic contrast media. The clinical relevance of these findings is unclear at the present time.

The lower osmolality of Omnipaque compared to conventional ionic media of similar iodine concentration can be expected to cause fewer and less severe osmolality-related disturbances. At 350 mg I/mL, the highest concentration used clinically, Omnipaque has less than half the osmolality of monomeric ionic media of equi-iodine concentration (i.e. approximately 844 mOsm/kg H<sub>2</sub>O vs 1800 mOsm/kg H<sub>2</sub>O).

### **CT SCANNING OF THE HEAD**

In intravenous contrast enhanced computed tomographic head imaging, Omnipaque (iohexol) does not accumulate in normal brain tissue due to the presence of the normal blood-brain barrier. The increase in x-ray absorption in normal brain is due to the presence of Omnipaque within the blood pool. A break in the blood-brain barrier, such as occurs in malignant tumors of the brain, abscesses, vascular accidents, etc. allows for the accumulation of contrast medium within the interstitial tissue of the tumor, and some other lesions. Adjacent normal brain tissue does not contain the contrast medium.

The degree of density enhancement is directly related to the iodine content in an

administered dose; peak iodine blood levels occur immediately following rapid intravenous injection. Blood levels fall rapidly within 5 to 10 minutes and the vascular compartment half-life is approximately 20 minutes. Maximum contrast enhancement in tissue frequently occurs after peak blood iodine levels are reached. Diagnostic contrast enhancement images of the brain have been obtained up to 1 hour after intravenous bolus administration.

### **CT SCANNING OF THE BODY**

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

Contrast enhancement appears to be greatest immediately after bolus administration (15 seconds to 120 seconds).

Utilization of a continuous scanning technique (ie, dynamic CT scanning) may improve enhancement and diagnostic assessment of tumor and other lesions such as abscess, occasionally revealing unsuspected or more extensive disease.

OMNIPAQUE may be useful for enhancement of computed tomographic images for detection and evaluation of lesions in the liver, pancreas, kidneys, aorta, mediastinum,

pelvis, abdominal cavity, and retroperitoneal space.

## **INDICATIONS AND CLINICAL USE**

### **A. SUBARACHNOID**

#### **Adults**

Omnipaque 180 (iohexol 180 mg I/mL), Omnipaque 240 (iohexol 240 mg I/mL) and Omnipaque 300 (iohexol 300 mg I/mL) are indicated for subarachnoid administration in adults for lumbar, thoracic, cervical and total columnar myelography.

#### **Pediatric**

Omnipaque 180 (iohexol 180 mg I/mL) is indicated for subarachnoid administration in children, by lumbar injection, for lumbar, thoracic, cervical and total columnar myelography and for contrast enhancement in computerized tomography (myelography, cisternography and ventriculography).

Delayed CT scans of the spinal subarachnoid space and of the intracranial CSF spaces may be obtained at the appropriate time following myelography, taking advantage of delayed opacification by the physiological cephalad circulation of the opacified CSF.

### **B. INTRAVASCULAR**

Omnipaque 350 (iohexol 350 mg I/mL) is indicated in adults for left ventriculography, coronary arteriography, intravenous contrast enhancement for computed tomographic head and body imaging, peripheral arteriography, excretory urography, and intravenous

digital subtraction arteriography.

Omnipaque 350 (iohexol 350 mg I/mL) is indicated in children for angiocardiology.

Omnipaque 300 (iohexol 300 mg I/mL) is indicated in adults for cerebral arteriography, intravenous contrast enhancement for computed tomographic head and body imaging, peripheral arteriography, peripheral venography, and excretory urography.

Omnipaque 300 (iohexol 300 mg I/mL) is indicated in children for excretory urography and may be used in infants for angiocardiology.

Omnipaque 240 (iohexol 240 mg I/mL) is indicated in adults for intravenous contrast enhancement in computed tomographic head imaging, and for peripheral venography.

### **C. ARTHROGRAPHY**

Omnipaque 300 (iohexol 300 mg I/mL) or Omnipaque 240 (iohexol 240 mg I/mL) is recommended in adults for arthrography of the knee joint. Omnipaque 300 (iohexol 300 mg I/mL) is recommended for arthrography of the shoulder joint in adults.

### **CONTRAINDICATIONS**

Omnipaque (iohexol) should not be administered to patients with known or suspected hypersensitivity to iohexol or in cases of clinically significant impairment of both hepatic and renal function.

## **WARNINGS**

**USE THE RECOMMENDED OMNIPAQUE (iohexol) CONCENTRATION FOR THE PARTICULAR PROCEDURE TO BE UNDERTAKEN.**

### **A. GENERAL**

Serious or fatal reactions have been associated with the administration of water-soluble contrast media. It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate facilities and appropriate personnel be readily available in case a severe reaction should occur.

Diagnostic procedures which involve the use of radiopaque contrast agents should be carried out only by physicians with the prerequisite training and with a thorough knowledge of the particular procedure to be performed and who are thoroughly familiar with the emergency treatment of all adverse reactions to contrast media.

In addition to the following information, generally accepted contraindications, warnings, precautions and adverse reactions commonly related to the use of radiopaque contrast media should be kept in mind during administration of Omnipaque.

Administration of radiopaque media to patients known or suspected to have pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risk, the amount of radiopaque material injected should be kept to a minimum. The blood pressure should be assessed throughout the procedure and measures for treatment of a hypertensive crisis should be available.

Ionic contrast media have been shown to promote the phenomenon of sickling in individuals who are homozygous for sickle cell disease when the material is injected intravenously or intraarterially. Fluid restriction is not advised in these patients.

Some clinicians consider multiple myeloma a contraindication to the use of contrast media because of the possibility of producing transient to fatal renal failure. If a decision to use Omnipaque is made, the patient should be well hydrated beforehand, since dehydration favours protein precipitation in the renal tubules. A minimal diagnostic dose should be used and renal function and extent of urinary precipitation of the myeloma protein checked for a few days afterwards.

Caution is advised in patients with severe cardiovascular disease, hyperthyroidism, and in patients with a history of bronchial asthma or other allergic manifestations or of sensitivity to iodine. Patients with significant hepatorenal disease should not be examined unless the possibility of benefit clearly outweighs the additional risk. As with other iodinated contrast media, the use of Omnipaque is not recommended in patients with anuria or severe oliguria.

Elderly patients may present a greater risk. (See also Precautions General). Special attention must be paid to dose and concentration of the medium, hydration and technique used.

## **B. SUBARACHNOID USE**

Myelography should not be performed when lumbar puncture is contraindicated as in the presence of local or systemic infection where bacteremia is likely.

Myelography should be performed only in hospitalized patients under close medical observation, which is to be continued for 24 hours following the procedure.

**Patients receiving anticonvulsants** should be maintained on this therapy. Should a seizure occur, intravenous diazepam or phenobarbital is recommended. In patients with a history of seizure activity who are not on anticonvulsant therapy, premedication with barbiturates should be considered. Omnipaque (iohexol) should be used in epileptics only if a water soluble contrast medium is considered essential.

Prophylactic anticonvulsant treatment with barbiturates should be considered in patients with evidence of inadvertent intracranial entry of a large bolus of contrast medium, since there may be increased risk of seizure in such cases.

Gravitational displacement of a concentrated bolus of Omnipaque above the level of C<sub>1</sub> and especially into the intracranial subarachnoid spaces is to be avoided.

### **C. VASCULAR USE**

Non-ionic iodinated contrast media inhibit blood coagulation less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes, catheters or tubes containing non-ionic contrast media. Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with non-ionic and also with ionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, number of injections, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic

techniques are recommended including close attention to keeping guidewires, catheters and all angiographic equipment free of blood, use of manifold systems and/or three way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure. Non-ionic iodinated contrast media are not recommended as flush solutions. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of clotting.

Patients with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk.

Extreme caution is advised should the injection of a contrast medium be indicated following the administration of vasopressors since they may strongly potentiate neurologic effects.

General anesthesia may be indicated in some procedures; however, one should be aware of possible increased incidence of adverse reactions in such circumstances.

Also see Dosage and Administration Section for special warnings and precautions.

## **PRECAUTIONS**

### **A. GENERAL**

Before any contrast medium is injected, the patient should be questioned for a history of allergy or bronchial asthma. Although a history of allergy may imply a greater than usual risk, it does not arbitrarily contraindicate the use of the medium, but does warrant special precaution. A previous reaction to a contrast medium or a history of iodine sensitivity is not an absolute contraindication to the use of iohexol, however, extreme caution should be exercised in injecting these patients and prophylactic therapy should be considered. Additionally, the possibility of an idiosyncratic reaction in patients who have previously

received a contrast medium without ill effect should always be considered.

The intravenous injection of a test dose of 0.5 to 1 mL of the contrast agent, before injection of the full dose, has been employed in an attempt to predict severe or fatal adverse reactions. The preponderance of recent scientific literature, however, now demonstrates that this provocative test procedure is not reliably predictive of serious or fatal reactions. Severe reactions and fatalities have occurred with the full dose after a non-reactive test dose, and with or without a history of allergy. No conclusive relationship between severe or fatal reactions and antigen-antibody reactions or other manifestations of allergy has been established. A history of allergy may be more useful in predicting reactions, and warrants special attention when administering the drug. Since delayed severe reactions may occur the patient should be kept under close observation following injection. (See also Patient Management under **DOSAGE AND ADMINISTRATION**).

It is expected that the results of thyroid function tests will not reflect true function for several weeks following radiopaque examination. Such tests, if indicated, should be performed prior to the administration of Omnipaque (iohexol). Tests which directly determine thyroxine levels are less likely to be affected.

Reports of thyroid storm occurring following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients prior to the use of Omnipaque.

Preparatory dehydration is unnecessary and usually contraindicated with the use of Omnipaque for all indications.

Administration of water soluble contrast media should be deferred for 48 hours in patients

with hepatic or biliary disorders who have recently been administered cholecystographic agents, as renal toxicity has been reported in the literature in such patients who received conventional contrast agents.

Caution should be exercised in performing contrast medium examination in patients with endotoxemia and in those with elevated body temperature.

There have been reports in the literature indicating that patients on adrenergic beta-blockers may be more prone to severe adverse reaction to contrast media. At the same time treatment of allergic-anaphylactoid reactions in these patients is more difficult. Epinephrine should be administered with caution since it may not exhibit its usual effects. On the one hand larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart-block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

Special precaution is advised in patients with increased intracranial pressure, cerebral thrombosis or embolism, primary or metastatic cerebral lesions, subarachnoid hemorrhage, arterial spasm, transient ischemic attacks, and in any condition when the blood brain barrier is breached or the transit time of the contrast material through the cerebral vasculature is prolonged, since clinical deterioration, convulsions, and serious temporary or permanent neurological complications (including stroke, aphasia, cortical blindness, etc.) may occur following intravenous or intraarterial injection of relatively large doses of contrast media. Such patients, and patients in clinically unstable or critical condition should undergo examinations with intravascular contrast media only if in the

opinion of the physician the expected benefits outweigh the potential risks, and the dose should be kept to the absolute minimum.

Caution should be exercised in the administration of contrast media to severely debilitated patients, particularly those with severe hypertension and impaired renal function. Acute renal failure has been reported in patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-existing renal disease) following administration of iodinated contrast agents. Careful consideration should be given to the potential risks before performing radiographic procedures in these patients.

### **Usage in pregnancy**

There are no studies on the use of Omnipaque (iohexol) in pregnant women. Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or definite harm to the fetus has been demonstrated due to iohexol.

Animal reproduction studies are not always predictive of human response, therefore, Omnipaque should be used during pregnancy only if the benefit to the mother clearly outweighs the risk to the fetus.

### **Usage in Lactation**

It is not known to what extent iohexol is excreted in human milk.

If use of Omnipaque is considered necessary, it is suggested that breast feeding be discontinued for at least 48 hours following administration of Omnipaque.

### **Pediatric Use**

Pediatric patients at higher risk of experiencing adverse events during administration of Omnipaque may include those having asthma, a sensitivity to medication and/or

allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

## **B. SUBARACHNOID USE**

Elderly patients may present a greater risk following myelography. The need for the procedure in these patients should be evaluated carefully. Special attention must be given not to exceed the recommended dose of the contrast medium, to see that the patient is sufficiently hydrated and to ensure proper and sterile radiographic technique.

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

Any intrathecally administered medication including non-ionic contrast media such as Omnipaque (iohexol) can enter the brain substance which may increase the risk of adverse effects associated with the procedure. Such adverse reactions may be delayed and, in extremely rare cases, may be life-threatening (see Adverse Reactions). Careful patient and dose selection and proper patient management before, during and after the procedure are therefore imperative. Care is required in patient management to prevent inadvertent intracranial entry of a large bolus of contrast medium. Also, effort should be directed to avoid rapid dispersion of the medium (i.e., by active patient movement).

Experience with the use of water-soluble contrast media in myelography indicates that in most cases of major motor seizure one or more of the following factors were present, and should therefore, be avoided:

- . Deviations from recommended procedure on myelographic management
- . Use in patients with a history of epilepsy
- . Inadvertent overdosage
- . Intracranial entry of a bolus or premature diffusion of a high

- concentration of the medium
- . Medication with neuroleptic drugs or phenothiazine antinauseants
- . Failure to maintain elevation of the head during and after the procedure
- . Active patient movement or straining

**Repeat procedures:** If in the clinical judgment of the physician a repeat examination is required, an interval of 5 days between procedures is recommended.

### **Drug Interactions**

**Drugs which lower seizure threshold**, especially phenothiazine derivatives including those used for their antihistaminic or antinauseant properties, should not be used with Omnipaque. Others include monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers or antipsychotic drugs. Such medications should be discontinued at least 48 hours before myelography, should not be used for the control of nausea or vomiting during or after myelography and should not be resumed for at least 24 hours post-procedure. In nonelective procedures in patients on these drugs, prophylactic use of anticonvulsants should be considered.

### **C. INTRAVASCULAR USE**

Preparatory dehydration may be dangerous in infants, young children, the elderly, in the presence of multiple myeloma and azotemic patients (especially those with polyuria, oliguria, diabetes, advanced vascular disease or pre-existing dehydration). The undesirable dehydration in these patients may be accentuated by the osmotic diuretic action of the medium.

When high doses of contrast media are used, caution should be exercised in patients with congestive heart failure because of the transitory increase in circulatory osmotic

load, and such patients should be observed for several hours to detect delayed hemodynamic disturbances.

When considering aortic injections the presence of a vigorous pulsatile flow should be established before using a catheter or pressure injection technique. A small "pilot" dose (about 2 mL) should be administered to locate the exact site of the needle or catheter tip to help prevent injection of the main dose into a branch of the aorta or intramurally.

Entry of a large concentrated bolus into an aortic branch should be avoided.

Mesenteric necrosis, acute pancreatitis, renal shut-down, serious neurologic complications including spinal cord damage and hemiplegia or quadriplegia have been reported following inadvertent injection of a large part of the aortic dose of contrast media into an aortic branch or arterial trunks providing spinal or cerebral artery branches.

Pulsation must be present in the artery to be injected. Extreme caution is advised in considering peripheral angiography in patients suspected of having thromboangiitis obliterans (Buerger's disease) since any procedure (even insertion of a needle or catheter) may induce a severe arterial or venous spasm. Caution is also advisable in patients with severe ischemia associated with ascending infection. Special care is required in patients with suspected thrombosis, ischemic disease, local infection or a significantly obstructed vascular system. Occasional serious neurologic complications, including paraplegia have been reported in patients with aorto-iliac or femoral artery bed obstruction, abdominal compression, hypotension, hypertension and following injection of vasopressors.

When large individual doses are administered, an appropriate time interval should be

permitted to elapse between injections to allow for subsidence of hemodynamic disturbances.

Following catheter procedures gentle pressure hemostasis is advised followed by immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

**Special precautions** to be observed when performing specific diagnostic procedures are listed in the "Dosage and Administration" section, under individual paragraphs pertaining to said specific procedures.

## **ADVERSE REACTIONS**

### **A. GENERAL**

Since the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any non-ionic agent, the same degree of careful patient observation for adverse reactions as with the use of conventional ionic contrast media, should be strictly followed. Adequate equipment and appropriate personnel should be readily available in case a severe reaction should occur.

Adverse reactions following the use of Omnipaque are usually of mild to moderate severity. However, serious, life-threatening and fatal adverse reactions have been associated with both the intravascular and subarachnoid use of iodinated contrast media, including Omnipaque (iohexol).

It should be kept in mind that, although most adverse reactions occur soon after the administration of the contrast medium, some adverse reactions may be delayed and could be of a long-lasting nature.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

**Reactions related to technique** - Adverse reactions to specific procedures are dealt with under Dosage and Administration. General reactions attributed to technique and/or procedure may include extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, vascular spasm thrombosis, thrombophlebitis, bleeding, perforation, rupture and dissection of blood vessels, dislodgement of atheromatous plaques or thrombi with embolization, subintimal injection, injury to nerves and other structures and general trauma during the procedure.

## **B. SUBARACHNOID**

Following subarachnoid administration of Omnipaque (iohexol), as with other currently used non-ionic contrast media, the most important adverse reactions involve the central nervous system and the incidence of such adverse reactions increases when the more cephalad segments of the spinal cord are exposed to the contrast material. The amount and concentration of the contrast material also appear to have a direct relationship to the frequency and severity of such adverse effects.

**Adverse reactions known to occur with the subarachnoid use of other non-ionic iodinated contrast media may also follow the use of Omnipaque. Most adverse reactions occur several hours following the procedure necessitating close and prolonged observation.**

The most frequently reported adverse reactions with Omnipaque are headache, mild to moderate pain including backache, neckache and stiffness, nausea, and vomiting. These

reactions usually occur 1 to 10 hours after injection, and almost all occur within 24 hours. They are usually mild to moderate in degree, lasting for a few hours, and usually disappearing within 24 hours. Rarely, headaches may be severe or persist for days. Headache is often accompanied by nausea and vomiting and tends to be more frequent and persistent in patients not optimally hydrated.

Transient alterations in vital signs may occur.

Those reactions reported in clinical studies with Omnipaque are listed below in decreasing order of occurrence, based on clinical studies of 1,531 patients:

**Headache** - The most frequently occurring adverse reaction following myelography with Omnipaque has been headache, with an incidence of approximately 18%. Rarely, headaches may be severe, lasting in some cases for several days. In managing the patient, it is considered very important to prevent intracranial entry of contrast medium by postural management (see PATIENT MANAGEMENT).

**Pain** - Pain in the back, leg, neck, stiffness and neuralgia occurred following injection with a total incidence of about 8%.

**Nausea and vomiting** - Mild to severe nausea and vomiting was reported with an incidence of approximately 6% and 3% respectively (see **PATIENT MANAGEMENT**). Maintaining normal hydration is very important. The use of phenothiazine antinauseants should be avoided.

**Dizziness** - Transient dizziness was reported in about 2% of the patients.

**The following serious adverse reactions** involving the CNS, have been reported with

the myelographic use of Omnipaque (in approximately <0.1%): convulsions, aseptic meningitis syndrome (see below), toxic encephalopathy, myelitis with transient or persistent sensory and motor disturbances of the central and peripheral nervous system; transient or persistent cortical blindness, unilateral or bilateral loss of vision, amblyopia, diplopia, oculomotor weakness, 6th nerve palsy, photophobia, nystagmus, hearing loss, dysphasia, dysarthria, quadriplegia, hemiplegia, spastic paraparesis, paralysis, areflexia, flaccidity, muscle weakness, hyperreflexia, hypertonia, myoclonus, fasciculation, general spasm, muscle

spasm, spinal convulsion, cauda equina syndrome, urinary retention, nerve root disturbances, sensory loss, meningismus, neck stiffness, fever, fainting, cerebral edema, cerebral hemorrhage, hydrocephalus, somnolence, stupor, coma, confusion, disorientation, hallucination, decreased concentration, memory dysfunction, amnesia, depersonalization, psychosis, anxiety, agitation, depression, nightmares, elevated WBC and protein in spinal fluid as well as EEG changes.

An aseptic meningitis syndrome has been reported rarely (less than 0.01%). It was usually preceded by pronounced headaches, nausea and vomiting. Onset usually occurred about 12 to 18 hours postprocedure. Prominent features were meningismus, fever, sometimes with oculomotor signs and mental confusion. Lumbar puncture revealed a high white cell count, high protein content often with a low glucose level and with absence of organisms. The condition usually clears spontaneously within a few days.

Profound mental disturbances have also rarely been reported. They have usually consisted of various forms and degrees of aphasia, mental confusion, or disorientation. The onset is usually at 8 to 10 hours and lasts for about 24 hours or more. However, occasionally they have been manifest as apprehension, agitation, or progressive withdrawal in several instances to the point of somnolence, stupor, and coma. In a few cases these have been accompanied by transitory hearing loss or other auditory

symptoms and visual disturbances, including unilateral or bilateral loss of vision which may last for hours. In one case, persistent cortical loss of vision has been reported in association with convulsions. Ventricular block has been reported; amnesia of varying degrees may be present.

Although not previously reported with Omnipaque, as with the injection of any foreign substance into the subarachnoid space, the possibility of the potential of Omnipaque to produce adhesive arachnoiditis cannot be excluded.

**Other reactions** occurring with an individual incidence of less than 0.1% included: feeling of heaviness, severe hypotension, vasovagal reactions, bradycardia, cardio-respiratory arrest, sensation of heat, sweating and loss of appetite, chills, fever, profuse diaphoresis, pruritus, rash, erythema, periorbital edema, nasal congestion, dyspnea, and a case of Guillain-Barre syndrome.

### **Pediatrics**

In controlled clinical trials involving 152 patients for pediatric myelography by lumbar puncture, adverse events following the use of Omnipaque 180 and Omnipaque 210 were as follows:

Headache: 9%

Vomiting: 6%

Backache: 1.3%

**Other Reactions:** Other reactions occurring with an individual incidence of less than 0.7% (single occurrence in 152 patients) included: fever, hives, stomach ache and visual hallucination.

### **C. INTRAVASCULAR**

Adverse reactions following the intravascular use of Omnipaque (iohexol) are usually of

mild to moderate severity. However, as with other iodine-containing contrast media, serious, life-threatening and fatal reactions have been associated with the intravascular administration of Omnipaque.

The injection of contrast media is frequently associated with the sensation of warmth and pain, burning sensation, flushing, nausea, vomiting and taste alterations. These relatively minor adverse effects are generally less frequent and less severe with Omnipaque than with conventional ionic contrast media.

Adverse reactions following the intravascular use of Omnipaque include:

**Cardiovascular System:** Arrhythmias including PVC's and PAC's (2%), angina/chest pain (1%) and severe hypotension (0.8%). Others including cardiac failure, asystole, bradycardia, tachycardia, atrial and ventricular fibrillation, premature beats, bundle branch block, vasovagal reaction, chest pain, coronary thrombosis, dyspnea, pulmonary edema, cyanosis, severe hypertension, hypertensive crisis, hypotension, peripheral vasodilatation, acute vascular insufficiency, circulatory collapse, hypotensive and cardiogenic shock, cardiac arrest, and cardio-respiratory arrest were reported with an individual incidence of less than 0.4%.

**Central Nervous System:** Vertigo including dizziness and lightheadedness (0.7%), pain (3%), photomas (2%), headache (2%) and taste perversion (1%). Others including anxiety, blurred vision, transient or persistent blindness, impairment of memory and coordination, tinnitus, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, confusion, dizziness, loss of consciousness, coma, apnea, psychotic reaction, stroke, stiff neck, hemiparesis, hemiplegia, nystagmus, restlessness and tremors were reported with an individual incidence of less than 0.4%.

**Renal System:** Occasionally transient proteinuria, hematuria and rarely oliguria, anuria

and renal failure.

**Allergic - anaphylactoid reactions:** Urticaria (0.3%) and purpura (0.1%). Occasionally asthmatic attacks, nasal and conjunctival symptoms (such as nasal congestion, sneezing, rhinitis, conjunctivitis, lacrimation), dermal reactions (such as urticaria with or without pruritus, erythematous, bullous and pleomorphic rashes), laryngospasm, bronchospasm, wheezing, laryngeal edema, angioneurotic edema, edema of glottis with signs of airway obstruction and rarely, anaphylactic shock leading to cardio-respiratory failure and death.

**Other reactions:** Nausea (2%) and vomiting (0.7%), diarrhea, dyspepsia, and dry mouth were reported with an individual incidence of less than 0.1%, pallor, weakness, sweating, localized areas of edema, especially facial, vein cramps and thrombophlebitis following i.v. injection, rare cases of disseminated intravascular coagulation, neutropenia. Immediate or delayed rigors can occur and do so rarely, accompanied sometimes by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears two days after exposure and subsides by the sixth day.

Transient changes in some laboratory parameters are not uncommon.

The occurrence of thyroid storm in patients with hyperthyroidism or with autonomously functioning thyroid nodule have been reported following the use of iodinated contrast media.

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are also listed under Dosage and Administration for that procedure.

#### **TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA**

Contrast media should be injected only by physicians thoroughly familiar with the emergency treatment of all adverse reactions to contrast media. The assistance of other trained personnel such as cardiologists, internists and anesthesiologists 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.

**For Minor Allergic Reactions:** (If considered necessary).

The intravenous or intramuscular administration of an antihistaminic such as diphenhydramine hydrochloride 25-50 mg is generally sufficient (contraindicated in epileptics). The resulting drowsiness makes it imperative to ensure that out-patients do not drive or 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 cardio-respiratory arrest may ensue.

The following measures should be considered:

1. Start emergency therapy immediately - carefully monitoring vital signs.

2. Have emergency resuscitation team summoned - do not leave patient unattended.
  3. Ensure patent airway - guard against aspiration.
  4. Commence artificial respiration if patient is not breathing.
  5. Administer oxygen if necessary.
  6. Start external cardiac massage in the event of cardiac arrest.
  7. Establish route for i.v. medication by starting infusion of appropriate solution (5% dextrose in water).
  8. Judiciously administer specific drug therapy as indicated by the type and severity of the reaction. Careful monitoring is mandatory to detect adverse reactions to all drugs administered.
- Soluble hydrocortisone 500-1000 mg i.v., for all acute allergic-anaphylactic reactions.
  - Epinephrine 1:1000 solution (in the presence of anoxia it may cause ventricular fibrillation - CAUTION in patients on adrenergic  $\beta$ -blockers - See Precautions):
    - 0.2-0.4 mL subcutaneously for severe allergic reactions.
    - in extreme emergency 0.1 mL per minute, appropriately diluted, may be given intravenously until desired effect is obtained. Do not exceed 0.4 mL.
    - in case of cardiac arrest 0.1-0.2 mL appropriately diluted, may be given intracardially.
  - In hypotension (carefully monitoring blood pressure):
    - phenylephrine hydrochloride 0.1-0.5 mg appropriately diluted, by slow intravenous injection or infusion.
- or
- norepinephrine bitartrate 4 mL of 0.2% solution in 1,000 mL of 5% dextrose by slow drip infusion.

- Sodium bicarbonate 5%: 50 mL i.v., every 10 minutes as needed to combat post-arrest acidosis.
- Atropine 0.4-0.6 mg i.v., to increase heart rate in sinus bradycardia. May reverse 2nd or 3rd degree block.

**- TO CONTROL CONVULSIONS:**

- DIAZEPAM 5-10 mg SLOWLY I.V., TITRATING THE DOSE TO THE RESPONSE OF THE PATIENT

OR

- PHENOBARBITAL SODIUM may be injected i.v., or i.m., at a rate not in excess of 30 to 60 mg/ minute. Depending on the patient's response a total dose of 200-300 mg may be required. The dose may be repeated in 6 hours if necessary.

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

**DOSAGE AND ADMINISTRATION**

BEFORE USE, OMNIPAQUE (iohexol) VIALS SHOULD BE INSPECTED VISUALLY FOR PARTICULATE MATTER AND/OR DISCOLORATION. IF EITHER IS PRESENT, THE VIALS SHOULD BE DISCARDED. OMNIPAQUE SHOULD BE INJECTED AT OR CLOSE TO BODY TEMPERATURE AND SHOULD BE USED IMMEDIATELY ONCE THE VIAL SEAL HAS BEEN PUNCTURED. OMNIPAQUE SHOULD NOT BE

TRANSFERRED FROM THE VIAL TO OTHER DELIVERY SYSTEMS EXCEPT IMMEDIATELY PRIOR TO USE; NOR SHOULD IT BE MIXED WITH OTHER DRUGS. ANY UNUSED PORTION SHOULD BE DISCARDED. OMNIPAQUE VIALS SHOULD BE PROTECTED FROM EXPOSURE TO LIGHT. SYRINGES, NEEDLES AND CATHETER TIPS MUST BE KEPT FREE OF ASPIRATED BLOOD TO PREVENT CLOTTING FROM PROLONGED CONTACT.

#### **A. SUBARACHNOID DOSAGE AND ADMINISTRATION**

Omnipaque 180 (iohexol 180 mg I/mL), Omnipaque 240 (iohexol 240 mg I/mL) or Omnipaque 300 (iohexol 300 mg I/mL) is recommended for the examination of lumbar, thoracic and cervical regions in adults by lumbar or direct cervical injection. Omnipaque 180 (iohexol 180 mg I/mL) is recommended for the examination of the lumbar, thoracic and cervical regions in children by lumbar injection. Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely or when lumbar or cervical puncture is contraindicated.

The volume and concentration of Omnipaque 180, Omnipaque 240 or Omnipaque 300 to be administered will depend on the degree and extent of contrast required within the recommended dose range in the area under examination, and on the equipment and technique employed. Omnipaque solutions are slightly hypertonic to CSF.

**A total dose of 3,060 mg iodine or a concentration of 300 mg I/mL should not be exceeded in adults and a total dose of 2,700 mg iodine or a concentration of 180 mg I/mL should not be exceeded in children in a single myelographic examination.**

As in all diagnostic procedures, the minimum volume and dose to produce adequate visualization should be used. Most procedures do not require the total maximum dose.

Anesthesia is not necessary. Patients should be well hydrated. Seizure-prone patients

should be maintained on anticonvulsant medication.

**Rate of injection:** To avoid excessive mixing with CSF and consequent dilution of contrast, injection should be made slowly, over 1 - 2 minutes.

Depending on the estimated volume of Omnipaque which may be required for the procedure, a small amount of CSF may be removed to minimize distension of the subarachnoid spaces, unless contraindicated.

The spinal puncture needle may be removed immediately following injection since, usually it is not necessary to remove Omnipaque after injection into the subarachnoid space.

If, in the clinical judgment of the physician, a repeat examination is required, an interval of 5 days between procedures is recommended.

**Adults:**

The usual recommended total dosages of Omnipaque 180, 240 or 300 for use in lumbar, thoracic, cervical and total columnar myelography are as follows and must not exceed a maximum total dose of 3.06 g I:

<b><u>Procedure</u></b>	<b><u>OMNIPAQUE FORMULATIONS</u></b>	<b><u>Concentration (mg I/mL)</u></b>	<b><u>Volume (mL)</u></b>
Lumbar Myelography (via Lumbar Injection)	OMNIPAQUE 180	180	10-17
	OMNIPAQUE 240	240	7-12
Thoracic Myelography (via Lumbar or Cervical	OMNIPAQUE 240	240	6-12
	OMNIPAQUE 300	300	6-10

Injection)

Cervical Myelography (via Lumbar Injection)	OMNIPAQUE 240	240	6-12
	OMNIPAQUE 300	300	6-10
Cervical Myelography (via C1-2 Injection)	OMNIPAQUE 180	180	7-10
	OMNIPAQUE 240	240	6-10
	OMNIPAQUE 300	300	4-10
Total Columnar Myelography (via Lumbar Injection)	OMNIPAQUE 240	240	6-12
	OMNIPAQUE 300	300	6-10

If computerized tomography is to follow, it should be deferred for 2 to 6 hours to allow the degree of contrast to decrease. Computerized tomography shows CSF contrast enhancement in the thoracic region in about one hour, in the cervical region in about 2 hours, in the basal cisterns in 3 to 4 hours, and in the ventricles and sulci in 5 to 6 hours.

### **Pediatrics:**

The usual recommended total doses for lumbar, thoracic, cervical and/or total columnar myelography by lumbar puncture in children range from 0.36 to 2.70 g I. Actual volumes administered depend largely on patient age and the following guidelines are recommended.

<b><u>Age</u></b>	<b><u>Conc. (mg I/mL)</u></b>	<b><u>Dose (g I)</u></b>	<b><u>Volume (mL)</u></b>
3 to <36 mos.	180	0.72 - 1.8	4-10
3 to <7 yrs.	180	0.9 - 2.16	5-12
7 - <13 yrs.	180	0.9 - 2.34	5-13
13 to 18 yrs.	180	1.08 - 2.7	6-15

### **PATIENT MANAGEMENT - SUBARACHNOID ADMINISTRATION**

Good patient management should be exercised at all times to minimize the potential for complications.

### **Preprocedure**

- . Discontinue neuroleptic drugs (including phenothiazines, eg, chlorpromazine, prochlorperazine, and promethazine) at least 48 hours beforehand.
- . Maintain normal diet up to 2 hours before procedure.
- . Ensure hydration -- fluids up to procedure.
- . Premedication is not usually considered necessary.
- . Should myelography be necessary in patients with a history of seizures, such patients should be maintained on their anticonvulsant medication.

### **During Procedure**

- . Use minimum dose required for satisfactory contrast (See DOSAGE AND ADMINISTRATION).
- . In all positioning techniques keep the patient's head elevated above highest level of spine.
- . Do not lower head of table more than 15° during examination.
- . In patients with excessive lordosis consider lateral position for injection.
- . Inject slowly (over 1 to 2 minutes) to avoid excessive mixing.
- . Move medium within the spinal subarachnoid space under fluoroscopic monitoring.
- . Avoid intracranial entry of a bolus.
- . Avoid early and high cephalad dispersion of the medium.
- . Avoid abrupt or active patient movement to minimize excessive mixing with CSF. Instruct patient to remain passive. Move patient slowly and

only as necessary.

### **Post-Procedure**

- . Following myelography move contrast medium to low lumbosacral area by upright positioning of the patient, for a few minutes.
- . Raise head of stretcher to at least 30° before moving patient onto it.
- . Movement onto and off the stretcher should be done slowly with patient completely passive, maintaining head up position.
  
- . Before moving patient onto bed, raise head of bed 30<sup>N</sup> to 45<sup>N</sup>.
- . Some clinicians advise patients to remain still in bed, in head up position or in the semi-sitting position, especially in the first few hours. Others have encouraged their patients to be fully ambulatory and have noted a reduction in the incidence of headache, nausea and vomiting.
- . Maintain close observation and head-up position for at least 24 hours after myelogram.
- . Obtain visitors' cooperation in keeping the patient quiet and in head up position, especially in first few hours.
- . Encourage oral fluids. Diet as tolerated.
- . If nausea or vomiting occur do not use phenothiazine antinauseants. Persistent nausea and vomiting will result in dehydration. Therefore prompt consideration of replacement by intravenous fluids is recommended.

### **B. INTRAVASCULAR DOSAGE AND ADMINISTRATION**

Also see Dosage Tables for recommended indications and dosage for intravascular

administration.

**1. ADULT LEFT VENTRICULOGRAPHY AND CORONARY ARTERIOGRAPHY**  
**PEDIATRIC ANGIOCARDIOGRAPHY**

Omnipaque 350 (iohexol 350 mg I/mL) is recommended in adults for left ventriculography, selective coronary arteriography and aortic root injections.

Omnipaque 350 (iohexol 350 mg I/mL) is recommended in children for angiocardiology.

Omnipaque 300 (iohexol 300 mg I/mL) may be used in infants for angiocardiology.

**Specific Precautions**

During administration of Omnipaque 300 and Omnipaque 350, continuous monitoring of vital signs is desirable and adequate facilities for immediate resuscitation and cardioversion are mandatory. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the preexisting condition. Hypotension should be corrected promptly since it may induce serious arrhythmias.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension or stenotic pulmonary vascular beds because of the hemodynamic changes which may occur.

Injection of contrast media into the cardiac chambers or great vessels causes significant hemodynamic disturbances, especially in right sided injections. Depending on the injection site and the time of recording, significant changes include a drop in cardiac output, elevation or decrease in ventricular pressures

(RVSP, LVSP, LVEDP, RVEDP), systemic pressure, peripheral hypotension, brady- or tachycardia, ectopic beats and other arrhythmias.

The hemodynamic changes which occur during and after ventricular and coronary injections are, in general, less pronounced with the low-osmolality Omnipaque than those seen with similar concentrations of conventional ionic contrast media, but serious and life threatening hemodynamic disturbances can occur with the administration of all iodinated contrast media, including Omnipaque.

If repeat injections are made in rapid succession, all these changes are likely to be more pronounced.

After an initial rise, plasma volume may decrease and continue to fall below control levels, even beyond 30 minutes, probably due to diuresis.

The volume of each individual injection is a more important consideration than the total dose used. When large individual volumes are administered, as in ventriculography, sufficient time should be permitted to elapse between each injection to allow for subsidence of hemodynamic disturbances.

Due to increased risk of adverse reactions following recent acute myocardial infarction, careful patient selection is necessary, and the timing and performance of the examination should be carried out with extreme caution, if invasive radiographic procedures are considered necessary.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration include those having asthma, sensitivity to medication and/or allergens, congestive heart failure, pre-existent right heart strain, narrowed pulmonary vascular bed, a serum creatinine >1.5 mg/dL or those

less than 12 months of age.

### **Specific Adverse Effects**

Transient electrocardiographic changes occur frequently during the procedure. The following adverse effects have also occurred following administration of Omnipaque for this procedure: cardiac arrhythmias (bradycardia, ventricular tachycardia, atrial and ventricular fibrillation, heart block), anginal pain, coronary thrombosis, cardiac arrest, hypotensive shock and death. Apnea, arrhythmias, cerebral effects, convulsions, electrolyte and hemodynamic disturbances are more likely to occur in cyanotic infants.

Procedural complications include dissection of coronary arteries, dislodgement of atheromatous plaques, perforation of heart chambers or coronary arteries, hemorrhage and thrombosis.

### **Dosage and Administration:**

#### **ADULTS:**

The usual single injection volume of Omnipaque 350 (iohexol 350 mg I/mL) for adult left ventriculography and coronary arteriography is as follows:

**Left Ventriculography:** The usual adult volume of Omnipaque 350 for a single injection is 40 mL with a range of 30-60 mL. These doses may be repeated if necessary, but the total procedural dose should be limited to the minimum volume required to achieve a diagnostic examination.

**Selective Coronary Arteriography:** The usual adult volume for right or left coronary arteriography is 5 mL (range 3 to 10 mL) per injection.

**Aortic Root Injection When Used Alone:** The usual adult single injection

volume is 35 mL, with a range of 20 to 50 mL.

### **CHILDREN:**

Weight, a minor consideration in adults, must be considered in infants and young children during the administration of radiographic contrast media.

The usual recommended single injection volume of Omnipaque 350 (iohexol 350 mg I/mL) and Omnipaque 300 (iohexol 300 mg I/mL) for angiographic procedures in children are as follows:

### **Angiocardiography:**

The usual single injection dose range is 0.5 - 1.5 mL/kg for Omnipaque 300 and 0.5 - 1.2 mL/kg for Omnipaque 350. When multiple injections are given, the total administered dose should not exceed 4 mL/kg or 100 mL, whichever is less.

The inherent risk of angiocardiography in cyanotic infants must be weighed against the necessity for performing this procedure. A dose of 10-20 mL may be particularly hazardous in infants weighing less than 7 kg. This risk is probably significantly increased if these infants have pre-existing right heart strain, heart failure and effectively decreased or obliterated pulmonary vascular beds.

Apnea, bradycardia and other arrhythmias, cerebral effects, electrolyte and hemodynamic disturbances are more likely to occur in cyanotic infants. Infants are more likely than adults to respond with convulsions, particularly after repeated injections.

## **2. CEREBRAL ARTERIOGRAPHY**

Omnipaque 300 (iohexol 300 mg I/mL) is recommended in adults for use in

cerebral arteriography.

In cerebral arteriography, appropriate patient preparation is indicated. This may include suitable premedication.

### **Specific Precautions**

Cerebral arteriography should be undertaken with extreme care with special caution in elderly patients, patients in poor clinical condition, advanced arteriosclerosis, severe arterial hypertension, recent cerebral embolism or thrombosis, cardiac decompensation, subarachnoid hemorrhage and following a recent attack of migraine, if the examination is considered to be essential for the welfare of the patient, and the patient should be watched for possible untoward reactions.

### **Specific Adverse Effects**

Repeated injections of contrast material, administration of doses in excess of those recommended, the presence of occlusive atherosclerotic vascular disease and technique and method of injection appear to contribute to the majority of adverse effects attributable to cerebral arteriography.

Normally, adverse effects are mild and transient such as a frequent feeling of warmth in the face and neck and infrequently a more severe burning discomfort is experienced.

Although the degree of pain, flushing and patient movement as the result of the use of Omnipaque in cerebral arteriography is generally less than that seen with comparable injections of monomeric ionic contrast media, cerebral arteriography has been associated with neurologic complications such as seizures, drowsiness, paresthesia, TIA, cerebral infarct, transient or persistent hemiparesis, and

disturbances in speech and vision (slurred speech, blurred vision, nystagmus, photomas). Other adverse effects include hypotension, bradycardia, arrhythmia, vertigo, syncope and electrocardiographic and EEG changes. Permanent defects are possible. ALSO, SEE ADVERSE REACTIONS, INTRAVASCULAR.

**Usual Adult Dose:**

The recommended single dose of Omnipaque 300 (iohexol 300 mg I/mL) for conventional cerebral arteriography is as follows: common carotid artery 6 - 12 mL; internal carotid artery 5 - 10 mL; external carotid artery 4 - 8 mL and vertebral artery 6 - 10 mL.

It is advisable to inject at rates approximately equal to the flow rate of the vessel being injected.

**3. CONTRAST ENHANCED COMPUTED TOMOGRAPHY**

OMNIPAQUE 240 (iohexol 240 mg I/mL) may be used for intravenous contrast enhanced computed tomography of the head; OMNIPAQUE 300 (iohexol 300 mg I/mL) and OMNIPAQUE 350 (iohexol 350 mg I/mL) are indicated in adults for use in intravenous contrast enhanced computed tomographic head and body imaging by rapid injection or infusion technique.

**Specific Warnings**

In patients where the blood-brain barrier is known or suspected to be disrupted, the use of any radiographic contrast medium must be assessed on an individual risk to benefit basis, since neurological complications are more likely to occur. Caution is advised in patients with impaired renal function and with congestive heart failure.

**Specific Precautions**

The decision to employ contrast enhancement should be based upon a careful

evaluation of clinical, other radiological and unenhanced CT findings, because unenhanced scanning may provide adequate diagnostic information in the individual patient, and because contrast enhancement may be associated with risk, may obscure certain lesions and increases radiation exposure. Intravenous CT scans of the head performed within 24 hours following myelography may yield false results due to the permeation of the brain by the contrast medium from adjacent CSF spaces. Therefore, if indicated, intravenous CT scan of the brain should be performed either before, or after a period of at least 24 hours following myelography.

#### **Specific Adverse Effects**

Following intravascular injection of large doses, transient or persistent neurological changes have been reported.

#### **Usual adult dose**

The concentration and volume required is influenced by the equipment and imaging technique used. The total procedural dose should be limited to the minimum volume required to achieve a diagnostic examination.

The usual adult dose range is:

Omnipaque 240: - 85 to 150 mL

Omnipaque 300: - 60 to 120 mL

Omnipaque 350: - 50 to 80 mL

#### **4. PERIPHERAL ARTERIOGRAPHY**

Omnipaque 350 (iohexol 350 mg I/mL) or Omnipaque 300 (iohexol 300 mg I/mL) is recommended in adults for use in peripheral arteriography by aortic (bifurcation) or by femoral artery injection.

Sedative premedication may be employed prior to the use of Omnipaque. General anesthesia is not considered necessary.

### **Specific Precautions - Peripheral Arteriography (by aortic injection)**

Under conditions of slowed aortic circulation there is an increased likelihood for aortic injection to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aorto-iliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, injection of vasopressors to increase contrast,

and low injection sites (L2-3). Especially in these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, elevated creatinine and urea nitrogen and possible renal damage.

### **Specific Precautions - Peripheral Arteriography (by femoral injection)**

Patient discomfort during and immediately following injection is generally less than that following injection of conventional ionic media . The incidence of discomfort for the second and subsequent injection may be somewhat higher than with the first injection.

Pulsation must be present in the artery to be injected. In thromboangiitis obliterans, severe ischemia with or without ascending infection, severe atherosclerosis or obstruction, arteriography should be performed with extreme caution, if at all.

### **Specific Adverse Effects**

Adverse reactions observed during peripheral arteriography may sometimes be

due to trauma during the procedure. Adverse reactions reported with the use of iodinated contrast media include hypotension, soreness in extremities, transient arterial spasm, gangrene, perforation of vessels, extravasation, hemorrhage, hematoma formation with tamponade, injury to nerves and other structures in close proximity to the artery, thrombosis, dissecting aneurysm, arteriovenous fistula, dislodgment of atheromatous plaques, subintimal injection and transient leg pain from contraction of calf muscles in femoral arteriography.

**Usual Adult Dose:**

The volume required will depend on the size, flow rate and disease state of the injected vessel and on the size and condition of the patient, as well as the technique used.

Omnipaque dosage recommendations for use in peripheral arteriography are as follows:

Aorto-femoral runoffs (aortic injection)	20-60 mL of Omnipaque 350 (iohexol 350 mg I/mL)
or	
	30-70 mL of Omnipaque 300 (iohexol 300 mg I/mL)
Selective Arteriograms (femoral/iliac injection)	10-30 mL Omnipaque 350 (iohexol 350 mg I/mL)
or	
	10-40 mL Omnipaque 300 (iohexol 300 mg I/mL)

**5. INTRAVENOUS DIGITAL SUBTRACTION ARTERIOGRAPHY**

Omnipaque 350 (iohexol 350 mg I/mL) is recommended in adults for use in intravenous digital subtraction arteriography.

It has been demonstrated that arteriograms of diagnostic quality can be obtained

following the intravenous administration of contrast media employing digital subtraction and computer imaging enhancement techniques. The intravenous route of administration using these techniques has the advantage of being less invasive than the corresponding selective catheter placement of medium.

The dose is administered into a peripheral vein or the superior vena cava usually by mechanical injection although sometimes by rapid manual injection. Omnipaque with this technique has been used to visualize the vessels of the head and neck. Radiographic visualization of these structures is dependent on timing (synchronizing with circulation time).

Omnipaque solution can be injected intravenously as a rapid bolus to provide arterial visualization using digital subtraction radiography. Preprocedural medications are not considered necessary. Omnipaque has provided diagnostic carotid arterial radiographs by intravenous injection in about 92% of patients. In some cases poor arterial visualization has been attributed to patient movement. There is generally less subjective or objective evidence of patient discomfort (general sensation of heat or pain) following injection compared with monomeric ionic media. In about 65% of patients discomfort is either absent or is mild, and is severe in about 2% of patients.

**Specific Precautions related to procedure:**

Since the dose is usually administered mechanically under high pressure, rupture of venous structures has occurred with extravasation of contrast media into the

tissues of extremities or the mediastinum. It has been suggested that this is less likely to occur if an intravenous catheter is threaded proximally beyond larger tributaries, in the case of the antecubital vein into the superior vena cava, or if the femoral vein is used. However with high pressure injection the catheter tip initially placed in larger venous structures may still recoil into a small tributary resulting in rupture of a small vein with extravasation into the neighbouring tissues. In case of mediastinal extravasation severe pain and hypotensive shock have been reported.

**Usual Adult Dose:**

The usual injection volume of Omnipaque 350 (iohexol 350 mg I/mL) for the intravenous digital technique is 30 to 50 mL. This is administered as a bolus at 10-30mL/second either by hand or using a pressure injector. The volume and rate of injection will depend primarily on the type of equipment and technique used, with first exposure made on calculated circulation time.

A dextrose solution may be layered over the contrast medium in the injector with the purpose of delivering the remnant of the bolus forward into the main circulation, and to flush the vein.

The patient is urged not to move or swallow during or immediately after the injection.

**6. PERIPHERAL VENOGRAPHY**

Omnipaque 300 (iohexol 300 mg I/mL) or Omnipaque 240 (iohexol 240 mg I/mL) is recommended in adults for peripheral venography.

### **Specific Precautions**

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, ischemic disease, local infection or a significantly obstructed venous system. In the presence of venous stasis, vein irrigation with normal saline should be considered following the procedure.

### **Specific Adverse Effects**

Following venography with iodinated contrast media, especially in the presence of venous stasis, inflammatory changes, thrombosis and gangrene may occur. Thrombosis is rare if the vein is irrigated following the injection.

### **Usual Adult Dose:**

The recommended single dose of Omnipaque for use in peripheral lower extremity venography is:

20-100 mL of Omnipaque 240 (iohexol 240 mg I/mL)

or

20-100 mL of Omnipaque 300 (iohexol 300 mg I/mL)

## **7. EXCRETORY UROGRAPHY**

Omnipaque 350 (iohexol 350 mg I/mL) or Omnipaque 300 (iohexol 300 mg I/mL) is recommended in adults for excretory urography.

Omnipaque 300 (iohexol 300 mg I/mL) is recommended in children for excretory

urography.

For pharmacodynamics of excretion in adults: See CLINICAL PHARMACOLOGY, INTRAVASCULAR. For adverse effects see ADVERSE REACTIONS, GENERAL AND INTRAVASCULAR.

### **Patient Preparation**

Appropriate preparation of the patient is desirable for optimal results. A laxative the night before the examination, unless contraindicated and a low residue diet the day before the examination are recommended.

### **Specific Precautions**

Preparatory dehydration is not recommended, especially in the elderly, infants, young children, diabetic or azotemic patients, or in patients with suspected myelomatosis.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine >1.5 mg/dL or those less than 12 months of age.

Some clinicians consider multiple myeloma a contraindication to the use of contrast media because of the possibility of producing transient to fatal renal failure. If a decision to use Omnipaque is made, the patient should be well hydrated beforehand, since dehydration favors protein precipitation in the renal

tubules, a minimal diagnostic dose used, and renal function and extent of urinary precipitation of the myeloma protein checked for a few days afterwards.

Caution is advised in patients with congestive heart failure and in cases of impaired renal function. In these patients the individual's clinical status and renal function should be carefully monitored.

Since there is a possibility of temporary suppression of urine formation, it is recommended that an interval of at least 48 hours elapse before excretory urography is repeated in patients with unilateral or bilateral reduction in renal function.

### **Dosage and Administration:**

#### **Adults:**

The usual recommended adult dose range for use in excretory urography is 25-50 mL intravenously of either Omnipaque 350 (iohexol 350 mg I/mL) or Omnipaque 300 (iohexol 300 mg I/mL).

#### **Children:**

#### **Excretory Urography**

The usual dose of Omnipaque 300 for children is 0.7 to 1.5 mL/kg.

Dosage for infants and children should be administered in proportion to age and body weight. The total administered dose in infants should not exceed 3.0 mL/kg.

In older children the maximum dose should not exceed 1.5 mL/kg or 50 mL, whichever is less.

**ADULT INTRAVASCULAR DOSAGE TABLE**

<b>PROCEDURE</b>	<b>CONC. OF SOLUTION (mg I/mL)</b>	<b>USUAL RECOMMENDED SINGLE DOSE (mL)</b>
Left Ventriculography	350	30 - 60
Selective Coronary Arteriography (right or left coronary artery)	350	3 - 10
Aortic Root	350	20 - 50
Cerebral Arteriography		
Common Carotid	300	6 - 12
Internal Carotid	300	5 - 10
External Carotid	300	4 - 8
Vertebral	300	6 - 10
Contrast enhanced CT		
Head imaging by infusion	240	85 - 150
Head or body imaging by injection	300 350	60 - 120 50 - 80
Intravenous Digital Subtraction Arteriography	350	30 - 50
Peripheral Arteriography		
Aorto-femoral runoffs (aortic injection)	350 300	20 - 60 30 - 70
Selective Arteriograms (femoral/iliac injection)	350 300	10 - 30 10 - 40
Peripheral Venography	300 240	20 - 100 20 - 100
Excretory Urography	350 300	25 - 50 25 - 50

**PEDIATRIC INTRAVASCULAR DOSAGE TABLE**

PROCEDURE	CONC. OF SOLUTION (mg I/mL)	USUAL RECOMMENDED SINGLE DOSE (mL/kg body weight)
Angiocardiology	300	0.5-1.5
	350	0.5-1.2
Excretory Urography	300	0.7-1.5

**C. ARTHROGRAPHY**

Omnipaque 300 (iohexol 300 mg I/mL) or Omnipaque 240 (iohexol 240 mg I/mL) is recommended in adults for arthrography of the knee joint. Omnipaque 300 (iohexol 300 mg I/mL) is recommended for arthrography of the shoulder joint in adults.

**Specific Precautions related to procedure**

Strict aseptic technique is required to prevent infection. Fluoroscopic control should be used to ensure proper needle placement, prevent extracapsular injection and prevent dilution of contrast medium. Undue pressure should not be exerted during injection.

**Specific Adverse Effects related to procedure**

Injection of Omnipaque into the joint is associated with transient discomfort, i.e. pain, swelling. However, delayed severe or persistent discomfort may occur occasionally.

Severe pain may often result from undue use of pressure or the injection of large volumes. Joint swelling and effusion may occur. These adverse effects are partly procedurally dependent and of greater frequency when double-contrast technique is employed.

Adverse effects during arthrography included pain (36%), swelling sensation (58%),

heat sensation (8%), muscle weakness (0.4%) and hematoma at the injection site (1%). Occasionally, muscle twitching, rash, itching, fatigue, and dry lips, were also observed during clinical studies involving 429 patients who had received iohexol by injection to the knee or shoulder joints. A single case of allergic synovitis associated with the use of Omnipaque has been reported in the literature.

### **Usual Adult Dose**

Arthrography is usually performed under local anesthesia. As much fluid as possible should be aspirated from the joint. Passive or active manipulation is used to disperse the medium throughout the joint space. The amount of Omnipaque injected is largely dependent on the size of the joint to be examined and the technique employed. Contrast is good during the first 5-10 minutes following injection and begins to fade at 15-20 minutes.

The following concentrations and volumes are recommended for normal adult knee and shoulder joints but should only serve as guidelines since joints may require more or less contrast medium for optimal visualization.

#### Knee

Omnipaque 300 or Omnipaque 240	5 - 15 mL
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#### Shoulder

Omnipaque 300	5 - 10 mL
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Lower volumes of contrast medium are usually injected when performing double-contrast examinations of the knee.

## **PHARMACEUTICAL INFORMATION**

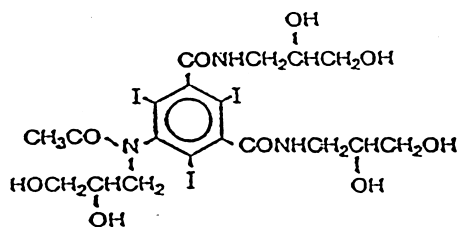
Common Name: Iohexol

Chemical Name: N,N'-Bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodoisophthalamide

Molecular Formula:  $C_{19}H_{26}I_3N_3O_9$

Molecular Weight: 821.14 (iodine content 46.36%).

Structural Formula:



Physical Form: White to off-white odourless powder

Solubility: Very soluble in water and methanol, practically insoluble or insoluble in ether and in chloroform.

Melting Point: 174 - 180°

Composition:

Omnipaque (iohexol) is provided as a sterile, pyrogen-free, colorless to pale yellow solution, in the following iodine concentrations:

180, 240, 300, and 350 mg I/mL. Each milliliter of iohexol solution contains 1.21 mg of tromethamine and 0.1 mg of edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid. All solutions are sterilized by autoclaving and contain no preservatives.

The four available concentrations have the following physical properties:

Name	Iohexol conc. mg/mL	Iodine conc. mg I/mL	Osmolality mosm/kg H <sub>2</sub> O	Absolute Viscosity (cps)		Specific Gravity (g/mL) (37 <sup>B</sup> C)
				20 <sup>N</sup> C	37 <sup>N</sup> C	
Omnipaque 180	388.3	180	408	3.1	2.0	1.205
Omnipaque 240	517.7	240	520	5.8	3.4	1.276
Omnipaque 300	647.1	300	672	11.8	6.3	1.345
Omnipaque 350	755.0	350	844	20.4	10.4	1.404

Omnipaque at recommended concentrations is hypertonic to cerebrospinal fluid (CSF) and blood (300 mosm/kg).

Normal range for the specific gravity of CSF is 1.005 to 1.009 and for blood, 1.050 to 1.064.

#### **Stability and Storage Recommendations:**

Solutions must be protected from light. Unused portions must be discarded. Do not use if solution is discolored or contains a precipitate.

#### **Directions for Dispensing from Pharmacy Bulk Vial**

The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing.

### **AVAILABLE DOSAGE FORMS**

#### Omnipaque 180

Vials of 20 mL, 180 mg I/mL, boxes of 10

#### Omnipaque 240

Vials of 20mL, 240 mg I/mL, boxes of 10

Bottles of 50 mL, 240 mg I/mL, boxes of 10

Bottles of 100 mL, 240 mg I/mL, boxes of 10

Bottles of 250 mL (containing a 200 mL fill),  
240 mg I/mL, boxes of 10

#### Omnipaque 300

Vials of 20 mL, 300 mg I/mL, boxes of 10

Bottles of 50 mL, 300 mg I/mL, boxes of 10

Bottles of 100 mL, 300 mg I/mL, boxes of 10

Bottles of 250 mL (containing a 150 mL fill),  
300 mg I/mL, boxes of 10

Bottles of 250 mL (containing a 200 mL fill),  
300 mg I/mL, boxes of 10

Bottles of 500 mL, 300 mg I/mL, boxes of 6

#### Omnipaque 350

Bottles of 50 mL, 350 mg I/mL, boxes of 10

Bottles of 100 mL, 350 mg I/mL, boxes of 10

Bottles of 250 mL (containing a 150 mL fill),  
350 mg I/mL, boxes of 10

Bottles of 250 mL (containing a 200 mL fill),  
350 mg I/mL, boxes of 10

Bottles of 500 mL, 350 mg I/mL, boxes of 6

## **ANIMAL PHARMACOLOGY**

### **Absorption, Elimination and Metabolism**

About 87% of a dose of  $^{125}\text{I}$ -labelled iohexol was excreted via the kidneys within 3 h after intravenous injection of 60 mg I/kg body weight to 10 male Wistar rats. Within 24 hours following administration,  $91.5 \pm 3.6\%$  of this dose was recovered in urine and  $6.8 \pm 2.7\%$  in feces. Of the remaining 3% of the initial dose, the highest accumulation ( $1,270 \pm 275$   $\mu\text{g I/g}$  wet tissue) after 24 hours was found in the thyroid gland, with no specific accumulation in any other organ examined. The elimination half-life of iohexol in the blood and urine of rats was about 20 minutes.

Urinary and fecal excretion rates were also determined in 3 female beagle dogs following administration of a single intravenous dose of 600 mg I/kg body weight of  $^{125}\text{I}$ -labelled iohexol. During the 3 hours following injection,  $81 \pm 9\%$  of this dose was excreted via the kidneys. Total urinary excretion during the 7 days after injection amounted to  $98 \pm 4\%$  of the initial dose, with total fecal excretion of  $0.95 \pm 0.45\%$ . The elimination half-life of iohexol in the blood and urine of these dogs was about 80 minutes. Total clearance of iohexol from plasma ( $4.2 \pm 0.4$  mL/min/kg) and the renal excretion rates indicate that the compound is excreted via the kidneys without significant tubular reabsorption, mainly by a process of glomerular filtration.

Renal impairment (i.e. removal of the right kidney and part of the left kidney) in five adult beagle dogs resulted in increasing the elimination half-life of iohexol to 5.8 h following single intravenous administration of 3 mL/kg of an aqueous solution of iohexol containing 300 mg I/mL.

Following single intracisternal injections of iohexol to 13 albino rabbits (median dose: 79 mg I/kg) and to 3 female rhesus monkeys (450 mg I/ monkey), over 75% of the administered dose was excreted in the urine within 24 hours (rabbits) or within 71 hours (monkeys) with total recovery of 96% over a 7-day observation period in rabbits (monkeys were not observed beyond 71 hrs following injection). In monkeys the mean renal clearance was 994 mL/hr and the average half life was 5.3 hours.

Biotransformation studies in 10 male rats (60 mg I/kg I.V. dose), 3 female beagle dogs (600 mg I/kg I.V. dose) and 13 albino rabbits (I.V. doses ranging from 100 to 1000 mg I/kg), revealed no metabolites in the urine specimens of rats and dogs and less than 1% metabolites in the urine and bile of rabbits.

### **Cardiovascular effects**

In five coronary arteriography studies involving a total of 37 dogs, iohexol was shown to exert significantly ( $p < 0.05$ ) less myocardial depressant action than diatrizoate ionic contrast media. In one experiment with 14 dogs studied under both normal and coronary artery stenosis conditions, the effects of iohexol and metrizamide (3 mL of 370 mg I/mL solutions of both media injected sequentially to each animal) were seen as mild, transient increases in contractile function of both the normal and ischemic myocardium, whereas diatrizoate contrast media caused profound and more prolonged myocardial depression under similar conditions.

The superior safety of iohexol vs diatrizoate during coronary arteriography was also demonstrated by examining the effect of injecting 1370 mg I or 740 mg I doses of the respective contrast media on the ventricular fibrillation threshold (VFT) in 115 paired experiments in 25 anesthetized dogs. The VFT, expressed in terms of percentage of control VFT, was significantly ( $p < 0.05$ ) lower for the ionic contrast medium than for iohexol, the difference being even more significant ( $p < 0.001$ ) at the higher dose level.

The effects on ECG parameters of injecting 8 mL or 9 mL doses of iohexol or diatrizoate, both at 370 mg I/mL concentration, into respectively, the right or left coronary arteries of 8 anesthetized dogs have shown that iohexol produced significantly ( $p < 0.05$ ) less prolongation (mean 9%) of the PQ interval than diatrizoate (mean 19%) during left-sided injections and significantly ( $p < 0.01$ ) less prolongation (mean 11%) of

the QT interval than diatrizoate (mean 23%) during right-sided injections, leading to the suggestion that iohexol may cause fewer incidences of heart block and ventricular fibrillation than conventional ionic contrast media.

In another study with 8 anesthetized dogs, left coronary artery injections (6 mL of 370 mg I/mL at 0.8 mL/sec.) of iohexol, metrizamide and an experimental non-ionic agent

711 were compared with ionic metrizoate and diatrizoate contrast agents, for effects on cardiac contractility, as measured by aortic flow rate, stroke volume, left ventricular pressure and work. Initially, within 8 seconds following the start of the injection, diatrizoate caused significantly ( $p < 0.01$  or  $p < 0.05$ ) greater reductions in the parameters measured than did the other media, however, after the initial reduction, all of the media produced similar increases in the parameters measured, exceeding their preinjection levels. The increases reached maxima at 15 to 45 seconds after the start of the injection before returning to pre-injection values within 5 minutes.

The cardiac response to intracoronary injections of iohexol, metrizamide and diatrizoate was also evaluated in isolated perfused rabbit hearts by recording continuously the resting tension, contractile force, coronary flow and heart rates. A total of 3 consecutive applications of 1, 2 and 4 mL of each of the respective contrast media, at 370 mg I/mL concentration, were examined on each heart preparation. All three media were well tolerated at the lower doses in terms of changes in the measured parameters. At the 4 mL dose iohexol and metrizamide caused a rise in contractile force, while diatrizoate depressed contractility. At the same high dose of 4 mL, (6.5 times the equivalent human dose) iohexol appeared more arrhythmogenic than metrizamide.

### **Cerebrovascular effects**

Right carotid arteriography experiments were performed on five morphine-sedated, pentobarbital-anesthetized female mongrel dogs, comparing iohexol (300 mg I/mL) against diatrizoate (293 mg I/mL), iothalamate (292 mg I/mL) and metrizoate (280 mg I/mL), all media being selectively injected at a volume of 0.5 mL/kg and a rate of 1 mL/second with a maximum total test dose of 10 mL per dog. Physical parameters (carotid artery hemodynamics, right ventricular function, heart rate, systemic pressure) monitored continuously for 5 minutes post-injection showed that iohexol produced significantly less hemodynamic and cardiovascular effects than the conventional ionic contrast media, with iohexol producing the smallest change at peak response (26 seconds) and returning to pre-injection values more quickly than the other test agents.

Iohexol caused less damage to the blood-brain barrier than ioxaglate or metrizamide when doses of 0.8 mL/kg to 3.3 mL/kg of contrast media (280 mg I/mL) were injected into the internal carotid arteries of 50 albino rabbits. Damage was evaluated quantitatively using the  $^{197}\text{Hg}$ -index after injection of radiolabelled mercuric acetate into an ear vein. Iohexol and ioxaglate resulted in significantly ( $p < 0.05$ ) less extravasation into brain tissue than metrizamide. When injury to the blood-brain barrier was measured as a function of the amount of extravasation using the Trypan blue index, the differences between iohexol and either ioxaglate or metrizamide were not found to be statistically significant.

In one study, involving 3 groups of 8 anesthetized rabbits, selective left vertebral angiography was carried out, using either iohexol (280 mg I/mL and 350 mg I/mL concentrations) or metrizamide (350 mg I/mL). Injections were continued until a convulsion occurred or until a maximum volume of 10 mL was injected. Convulsions were seen more frequently with the highest concentration of iohexol and cardiovascular reactions were also more marked with iohexol than with metrizamide in this study. However, as mentioned below, other animal experiments have shown that iohexol is less toxic than metrizamide when injected into the subarachnoid space.

### **Renovascular effects**

After intravenous injection of 500 mg I/kg dose of contrast media to 13 rabbits via an ear vein, iohexol produced significantly ( $p < 0.05$ ) higher urinary iodine concentration than diatrizoate in the 5-15 minute interval following injection. Diuresis was significantly ( $p < 0.01$ ) less with iohexol in the first half hour following injection when compared with diatrizoate, and estimated x-ray attenuation capacity, measured in  $\text{mol I/m}^2$ , was consistently higher with iohexol than with diatrizoate. These results were consistent with those obtained during periods of ureteric stasis induced experimentally in order to evaluate possible use of iohexol in clinical urography with ureteric

compression.

Two experiments performed using isolated, perfused canine kidneys involved injection of 300 mg I/mL contrast media in doses of 0.25 mL/kg and 0.50 mL/kg. Renal vein blood samples taken were measured for osmolality, iodine concentration and hematocrit. In both experiments, iohexol showed a significantly ( $p < 0.01$ ) smaller change in hematocrit and osmolality than diatrizoate while reaching a higher renal vein iodine concentration, although this difference was not statistically significant.

Nephrotoxicity was measured in nephroangiography experiments using rats (dose=370 mg I/kg) and dogs (dose=185 mg I/kg). In examining 43 dogs and 63 rats, urinary albumin concentration following injection of diatrizoate was significantly ( $p < 0.01$ ) higher than with iohexol.

The effects of high doses (10.5g I/kg) of iohexol on selected blood (urea, creatinine, Na, P, GOT, GPT, AP, bilirubin) and urine (iodine concentration) parameters were determined after intravenous injection in 9 albino rabbits. At this dose, the concentration of GOT, GPT and AT all showed an increase at 2 hours post-injection. In 2 rabbits, the serum GOT concentration rose to 50 times the pre-injection level. All values returned to normal within 24 hours.

### **CNS effects**

The effects of pericerebral injection of iohexol, ioserinate (Schering), metrizamide, iopamidol, iogluclide (Guerbet), and MP 8000 (Mallinckrodt) on electrical brain activity were compared using sequential EEG spectral analysis in guinea pigs. Injections of 0.2 mL iohexol solutions (400 mg I/mL) produced early (within 5 minutes) but

transient increases in the 5-10 Hz band. After injections of 0.3 mL, these early changes were more pronounced but were always short-lived. High voltage discharges or epileptic seizures were never observed. Iopamidol produced typical epileptic discharges within 30 minutes after injection of 0.2 mL of 400 mg I/mL solutions; while the normal EEG pattern was rapidly restored, delayed epileptic seizures were observed after 6 or 8 hours following injection. Injections of 0.2 mL metrizamide (400 mg I/mL) did not produce any immediate changes. Delayed high voltage slow waves were sometimes observed and low amplitude hypersynchronous activities occurred in some animals.

The convulsive effect of iohexol was compared with metrizamide in a study using rhesus monkeys who were restrained but awake. Production of convulsions was measured as well as the corresponding EEG changes after intrathecal injection. The study consisted of five different experiments employed to determine the maximum tolerable dose of contrast media. At iohexol doses of 950 mg I per animal all four study animals experienced convulsions, but using doses of 750 mg I/monkey iohexol produced no seizures or EEG changes in any of the six monkeys studied, while the same dose of metrizamide produced convulsions in seven out of nine monkeys and pronounced EEG changes in six out of nine. Lowering the dose of metrizamide to 425 mg I/monkey still produced convulsions and EEG changes in three out of four monkeys. It was estimated that iohexol had approximately half the convulsive effect of metrizamide.

Direct neurotoxicity of iohexol in comparison with that of sodium diatrizoate, meglumine iothalamate and metrizamide was evaluated using in vitro rat hippocampal

slices maintained by perfusion with oxygenated artificial CSF. Each of the contrast media was perfused in concentrations of 15.0 to 30 mg I/mL and extracellular field potential recordings were made with electrodes. All test media, except for iohexol, produced excitatory changes in field potentials, which are indicative of the epileptogenic potential. Within 5-10 minutes, all agents caused inhibition of electrical activity.

Neurotoxicity was also evaluated using exposed cat spinal cord preparation following thoracic aortography. Ventral root reflexes were evaluated in terms of threshold, monosynaptic amplitude, polysynaptic amplitude and duration of polysynaptic rate measurements. Media in doses of 5 mL/kg and concentrations of 300 mg I/mL were injected three times at five minute intervals. Iohexol and metrizamide, caused no consistent alteration in any of the electrical parameters measured. The lack of depression of electrical activity seen with the nonionic agents indicates that there is less effect on the CNS associated with metrizamide and iohexol than with the above mentioned conventional ionic agents, even at concentrations which were approximately five times the concentration that would be clinically used.

**TOXICOLOGY  
ACUTE TOXICITY**

Route of Administration	Species (Total No., Sex)	Dose/range (g I/kg)	LD <sub>50</sub>		Toxic signs
			g Iohexol/kg	g Iodine/kg	
Intravenous	mouse (405 m, 180 f)	18-26	>40	>20	Common: ataxia, decrease in motor activity, dyspnea, spastic body movements, loss of righting reflex (all resolving by second day following administration).
Intravenous	rat (85 m, 30 f)	8.9-17.8	>20	>10	Occasionally, clonic convulsions
Pericerebral	rat (10/dose, m, f)	0.03-2.0	2	0.97	Lack of motor coordination, hyperexcitability
Intracisternal	mouse (40 m)	1.26-2.0	>4	>2	Ataxia, dyspnea, decrease in motor activity. No death at 2 mg I/kg, the highest dose tested.
Intracisternal	rabbit (n = 24, sex: N/A)	0.185, 0.37	n. d.		No excitation observed at 370 mg I/kg dose with iohexol.
Intracisternal	cynomolgus monkey  (n = 6, sex: N/A)	0.45	n. d.		Increases in total protein and white blood cell counts in CSF, observed with injection of iohexol (450 mg I/ monkey), were not different from changes observed with saline or vehicle controls.

SUBACUTE TOXICITY

Route of administration	Species (no. and sex per group)	Daily doses g Iohexol/kg	g Iodine/kg	Duration of study (days)	Toxic signs
Intravenous	rat  (5 m, 5 f)	2.0, 8.0	1.0, 4.0	7	No gross changes in organ weights, appearance, behaviour, body weight gain or hematology parameters. Microscopically, mild to moderate disseminated vacuolation of kidney tubular epithelium and minimal focal vacuolation of hepatocytes was observed at the higher dosage only.
Intravenous	beagle dog  (3m, 3 f)	7.4	3.7	7	Slight increases in total serum $\alpha$ -globulin, in serum calcium, in relative weights of liver and kidney, slight swelling and vacuolation of hepatocytes in liver, moderate vacuolar degeneration of proximal tubular epithelium in kidney.
Intravenous	cynomolgus monkey  (3, m, f)	2.0, 8.0	1.0, 4.0	7	Changes in hematology and blood chemistry parameters were seen in one of three monkeys in the high-dose group only. These consisted of marked elevations in urea nitrogen and creatinine and marked decreases in sodium, chloride and glucose blood levels. Microscopically, marked vacuolation of renal tubular epithelium and of hepatocytes was seen at the high dose level.
Intravenous	rat  (15 m, 15 f)	2.0, 4.0, 8.0	1.0, 2.0, 4.0	28	No clinical evidence of systemic toxicity. Body weight gain was suppressed and hemoglobin concentrations were slightly increased in male animals at two higher dose levels. Histopathological examination showed cytoplasmic vacuoles in renal cortical tubular cells. This change was minimal in animals receiving the two lower dosages.

SUBACUTE TOXICITY (Cont' d)

Route of administration	Species (no. and sex per group)	Daily doses g Iohexol/kg      g Iodine/kg  (unless otherwise specified)		Duration of study (days)	Toxic signs
Intravenous	cynomolgus monkey  (3 m, 3 f)	0.66, 2.0 6.0	0.33, 1.0, 3.0	28	No overt clinical signs of toxicity. Slight elevation of serum leucine arylamidase and increase in kidney weights were seen at the high dose level only. Histopathologically, minor vacuolation of the hepatocytes at 3.0 g I/kg/day and vacuolation of the tubular epithelial cells at 1.0 and 3.0 g I/kg/day were observed. 0.3 g I/kg/day induced no toxicity.
Intracisternal	mouse  (15 m, 15 f)	0.4, 1.0, 2.0	0.2, 0.5, 1.0	14	Ataxia and decreased motor activity were observed in the high dose and, occasionally, in the middle dose groups. Dyspnea was also observed in the high dose males. No gross or microscopic tissue changes, directly attributable to iohexol, were observed.
		(single injections on days 1, 4, 7 and 10 only)			
Intracisternal	cynomolgus monkey  (6, m, f)	0.90 g Iohexol/monkey	0.45 g I/monkey	32	No gross or microscopic changes attributable to iohexol were observed. Subarachnoiditis, characterized by infiltration of eosinophils, was considered to be related to the vehicle and/or the repeated injections, since it occurred both in control and in medicated groups.
		(single injections on days 1, 8, 15, 22 and 29 only)			

### **Carcinogenesis, mutagenesis, teratogenesis, impairment of fertility**

No long term animal studies have been performed to evaluate the carcinogenic potential of iohexol. No evidence of mutagenicity was seen in standard tests, including the Ames Salmonella/Microsome plate test, the mouse lymphoma forward mutation assay and the micronucleus test.

Iohexol was neither embryotoxic nor teratogenic in either rats or rabbits at the following dose levels tested: 1.0, 2.0, 4.0 g I/kg in rats, administered I.V. to 3 groups of 25 dams once daily during days 6 through 15 of pregnancy; 0.3, 1.0, 2.5 g I/kg in rabbits, administered I.V. to 3 groups of 18 does once a day during days 6 through 18 of pregnancy.

One malformed fetus was observed in the middle-dose group rabbit study. Due to the low incidence and because this did not occur at the next higher dose level, the malformation was not considered drug related.

Intravenous administration of iohexol to 3 groups of 12 male albino rats at 1.0, 2.0 or 4.0 g I/kg dose levels three times weekly for 10 weeks prior to mating and once daily during a 14-day mating period with non-medicated females did not result in any adverse effects on gonadal function, fertility or general reproductive performance.

Intravenous administration of iohexol to 3 groups of 30 female Charles River COBS CD rats, at 1.0, 2.0 or 4.0 g I/kg dose levels every other day beginning 14 days prior to mating, once daily on gestation days 0 to 6 and on alternate days thereafter until weaning of the pups (lactation day 21), produced no biologically meaningful effects on F<sub>0</sub> female estrous cycles, female fertility, parturition or mean gestation length. Treatment of dams did not affect the behaviour, appearance, litter size, number of stillborn pups or body weights of the F<sub>1</sub> generation on day 1 of lactation.

During examination of the litters, a statistically significant decrease in pup survival index was seen in the high-dose group only, during the day 1-4 lactation interval. Thereafter, pup survival indices for this same group were comparable to control. At days 4, 14 and 21, a dose-related trend in decreasing mean pup weights was seen in the treated groups compared to controls. These differences reached statistical significance for the high-dose group at day 14 only.

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