A double-blind clinical trial of iopamidol versus metrizamide for lumbosacral myelography

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A double-blind study was performed to compare metrizamide with the new iodinated water-soluble nonionic contrast medium, iopamidol, for conventional and computerized tomography lumbosacral myelography. Both contrast agents were used in 30 patients, and were equivalent in terms of image quality and clinical accuracy. Headaches and nausea were less severe using iopamidol. The most striking difference was found in adverse neurobehavioral reactions and associated electroencephalographic abnormalities, which were noted in 17% of the metrizamide group but were not seen with the use of iopamidol. Iopamidol appears to be superior to metrizamide for intrathecal applications. An explanation of the differential neurotoxicity is provided.

KEY WORDS: myelography, iopamidol, metrizamide, contrast agent, drug reaction

For more than 30 years, Pantopaque has been the contrast agent of choice in North America. The high viscosity and specific gravity of this iodinated substance relative to cerebrospinal fluid (CSF) enabled the formation of an uninterrupted, easily positioned, complete column of contrast material within the thecal sac. However, Pantopaque has definite shortcomings. Because of its very low solubility and extremely slow clearance from the CSF, Pantopaque should be aspirated from the thecal sac at the conclusion of the examination, prolonging the study and increasing patient discomfort. Also, because of its high viscosity, it does not completely fill root sleeves, particularly in the lumbar region. In addition, there are side effects which patients experience following Pantopaque myelography, including headaches, occasional nausea and vomiting, and rarely leg numbness, paresthesias, mild fever, and (on a long-term basis) arachnoiditis.22,29,30,43

At present, the non-ionic hydrosoluble contrast medium, metrizamide, is the most widely used agent for myelography and cisternography in both adults9,16,24,26,29,36,38,39 and children.1,2,3,4 Because of its high solubility and relatively rapid clearance from the CSF, it is unnecessary to aspirate this agent at the conclusion of a myelographic study. It rapidly became apparent that its delineation of nerve rootlets, including the cauda equina, was far superior to Pantopaque.29 The ability to combine computerized tomography (CT) with metrizamide myelography is an additional advantage of a hydrosoluble substance.7,21,34 However, this newer agent is also far from ideal. Although rapid mixing with CSF is advantageous, this can cause problems. If one is faced with an excessively capacious thecal sac or an uncooperative patient, rapid dilution limits optimal visualization. The dilution factor may also curtail the ability to perform diagnostically superior total myelography, cervical studies via the lumbar route, and highly specific examination such as searching for small arteriovenous malformations.4,13,25,28,38

The major disadvantage of metrizamide myelography has been the relatively high frequency of side effects, sometimes severe, experienced by some patients. The most common complaints include headaches, followed by nausea, vomiting, and dizziness. More severe adverse reactions, including meningeal irritation, transient hypotension, fevers, and grand mal seizures, as well as acute psycho-organic reactions, such as hallucinations, agitation, impaired...
memory, depression, aphasia, asterixis, and cortical blindness, have been reported. These reactions have been reversible within several days without long-term sequelae.

Several clinical trials have been performed using the non-ionic water-soluble contrast medium, iopamidol, for lumbosacral myelography. In the initial North American trial, iopamidol produced excellent image quality, and adverse reactions were strikingly mild and seemingly less frequent as compared to contrast media presently in use. To confirm these impressions, a double-blind trial was instituted comparing the frequency and severity of adverse reactions, image quality, and diagnostic capabilities using iopamidol and metrizamide for lumbosacral myelography.

Clinical Material and Methods

A double-blind clinical trial was performed comparing metrizamide to iopamidol for lumbosacral myelography. Each group included 30 patients. Patients were excluded from the trial due to pregnancy, surgical requirement within 24 hours of radiological examination, hypersensitivity to any form of contrast agent or iodine compounds, spinal puncture within the past month, bloody CSF, and evidence of increased intracranial pressure or mass. Other factors that eliminated patients from this study included the use within 1 week prior to surgery of medications that lowered the seizure threshold, a history of convulsive disorders, or the diagnosis of multiple sclerosis, psychosis, alcoholism, or drug abuse. Written informed consent was obtained from all patients who participated in the study.

Unlike metrizamide, iopamidol is stable in solution and therefore does not need to be reconstituted prior to administration. It derives its radiopaque property from a tri-iodinated benzene ring, and water solubility from three highly hydrophilic groups attached symmetrically to the benzene ring. It has an iodine content of 49.0%, and molecular weight of 777.09 (Fig. 1 and Table 1).

Standard myelographic technique included intradermal and subcutaneous local anesthesia without any premedication, followed by the removal of 5 to 10 ml of CSF for laboratory analysis. A No. 22 spinal needle was used under fluoroscopic control to introduce 12 to 15 ml of 200 mg I/ml iopamidol or metrizamide. Frontal, oblique, and lateral radiographs were obtained, followed by a supine view of the conus in all patients. Patients were then transported on a stretcher with the head elevated 30°, and instructed to remain still in a head-up supine position at least for the first 8 hours. Adequate hydration was stressed both before and after the procedure.

All films were evaluated for technical and diagnostic accuracy by a neuroradiologist who was not involved in performing or witnessing the procedure. This evaluator was not aware of the patients' histories, medical diagnoses, or the particular contrast agent administered. All films were graded on a scale from 0 (no visualization or opacification) to 3 (superior visualization permitting easy diagnosis).

Patients undergoing the study had a complete medical history taken, and a thorough general and neurological examination both prior to and after myelography. Vital signs were obtained immediately before, and at 15 and 30 minutes, and 1, 4, and 8 hours after the procedure. Careful patient follow-up examination to detect adverse reactions was performed for 24 hours after myelography.

Hemoglobin, hematocrit, total leukocyte count, platelet estimation, total serum protein, albumin, cholesterol, blood urea nitrogen, uric acid, total bilirubin, alkaline phosphatase, lactic dehydrogenase, serum glutamic oxaloacetic transaminase, glucose, calcium, and phosphorus levels were obtained routinely both before and after myelography. In addition, a complete urinalysis was carried out and electrocardiography performed. Pre- and postprocedural electroencephalograms (EEG's) were obtained in 22 of the 60 patients (11 in the metrizamide group and 11 in the iopamidol group).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Metrizamide</th>
<th>Iopamidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>supplier</td>
<td>Winthrop</td>
<td>Squibb</td>
</tr>
<tr>
<td>non-ionic</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>water-soluble</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>tri-iodinated benzene ring</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>glucosamide</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>preparation</td>
<td>powder/diluent</td>
<td>solution</td>
</tr>
<tr>
<td>molecular weight</td>
<td>789</td>
<td>777</td>
</tr>
<tr>
<td>iodine content (%)</td>
<td>48.25</td>
<td>49.00</td>
</tr>
<tr>
<td>other characteristics*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>osmolality</td>
<td>0.300</td>
<td>0.413</td>
</tr>
<tr>
<td>specific gravity at 37°C</td>
<td>1.184</td>
<td>1.216</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.5</td>
</tr>
</tbody>
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* At 170 mg I/ml for metrizamide and at 200 mg I/ml for iopamidol.
Iopamidol versus metrizamide for myelography

TABLE 2
Adverse reactions associated with iopamidol and metrizamide*

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Iopamidol</th>
<th>Metrizamide</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>mild headache, nausea</td>
<td>5</td>
<td>6</td>
<td>0.500</td>
</tr>
<tr>
<td>moderate/severe headache,† nausea, vomiting</td>
<td>7</td>
<td>11</td>
<td>0.250</td>
</tr>
<tr>
<td>painful paresthesias (legs)</td>
<td>1</td>
<td>3</td>
<td>0.306</td>
</tr>
<tr>
<td>dizziness</td>
<td>0</td>
<td>1</td>
<td>0.500</td>
</tr>
<tr>
<td>hypotension (transient)</td>
<td>0</td>
<td>1</td>
<td>0.500</td>
</tr>
<tr>
<td>neurobehavioral abnormalities‡</td>
<td>0</td>
<td>6</td>
<td>0.012</td>
</tr>
<tr>
<td>seizure</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>EEG abnormality§</td>
<td>0</td>
<td>4</td>
<td>0.045</td>
</tr>
<tr>
<td>some adverse reaction</td>
<td>13</td>
<td>20</td>
<td>0.059</td>
</tr>
</tbody>
</table>

* All studies included 30 patients in each group except for electroencephalograms (EEG's), which were performed in 11 patients in each group. Significance calculated by Fisher's exact test, one-tailed.
† Moderate to severe headache was a subjective evaluation by the patient's nurse and examiner. Moderate to severe headaches always required analgesia and often anti-emetics.
‡ Neurobehavioral abnormalities included disorientation, affective lability, dysarthria, asterixis, global aphasia, and visual field defect.
§ The EEG abnormalities (background slowing with intermittent bursts of rhythmic delta activity) were noted in the patients with the toxic confusional encephalopathy.

Results

Adverse Reactions

A summary of the side effects associated with intrathecal iopamidol versus metrizamide is presented in Table 2.

Iopamidol. No adverse reaction was experienced by 17 patients in the iopamidol group. In an additional five patients, only mild headache with minimal nausea was noted. A moderately severe headache with associated nausea and vomiting was present in the remaining eight patients. Although these symptoms persisted for up to 24 hours, they were readily controlled with appropriate medications. Of three patients who had had a previous metrizamide myelogram, all commented that the present myelography caused much less discomfort.

A single patient reported mild leg numbness which resolved within 12 hours. Even with careful interrogation over 24 hours, no patient reported any neurobehavioral adverse reaction. Neither seizure nor meningeal adverse reaction was reported by any patient.

Metrizamide. Only 10 of 30 patients experienced no adverse reaction. Mild headache and nausea lasting up to 24 hours was reported by six patients, with one having associated mild dizziness. An additional 11 patients had moderate to severe headache with pronounced gastrointestinal complaints. Three patients reported aching paresthesias in both legs and buttocks, lasting up to 12 hours and requiring narcotic analgesia. Transient hypotension (120/84 to 90/60 mm Hg) occurred in one patient 8 hours after myelography and lasted for 30 minutes.

In addition to the moderate to severe headache and nausea, six patients had significant adverse neurobehavioral reactions, including agitation, hallucinations, affective lability, confusion, memory loss, global aphasia, and asterixis. One patient had a possible visual field defect described as "letters sliding" and lasting approximately 2 hours. Four of these six patients had EEG's performed, all of which showed a normal baseline study and an abnormal examination during the clinical period of diffuse toxic confusional encephalopathy. The EEG abnormality consisted of mild to moderate background slowing with intermittent bursts of delta activity. No patient had a clinical seizure or epileptiform activity on EEG.

Image Quality

The overall diagnostic adequacy of the conventional and CT myelograms using both agents are generally excellent. The visualization of the nerve roots, the thecal sac, and nerve root sleeve was excellent in all 30 iopamidol studies and 28 of 30 metrizamide studies. The other two metrizamide studies were of a quality adequate to make a diagnosis. This was not due to the opacification obtained with the metrizamide, but rather to patient cooperation and radiographic technique.

Visualization of the conus (Fig. 2) using iopamidol was graded as excellent in 17 patients, suboptimal in five, poor in five, and negative in three.
FIG. 4. Typical appearance on prone (left) and supine (right) myelography with iopamidol of a surgically verified low conus (arrowheads) tethered by a lipoma (arrow). Note the horizontal exit of the nerve root sleeves often seen with a low conus.

The widespread use of metrizamide has greatly facilitated the performance of lumbosacral myelography for both the patient and physician. In addition, many CT-related applications have now developed which would not have been possible with Pantopaque. As the development of contrast materials is an evolutionary process, we must continue to strive to find new agents with decreased toxicity, particularly in terms of adverse neurological reactions. This in no way diminishes the seminal role played by metrizamide in popularizing and expanding the applications of hydrosoluble agents for both conventional and CT myelography and cisternography.

Non-ionic water-soluble contrast materials were developed because, on dissolving ionic hydrosolubles in CSF, the cations readily dissociate, with a resultant increase in osmolality and toxicity. The non-ionic materials retain the radiopaque tri-iodinated benzene ring moiety containing stable carbon-iodine bonds, they do not contain dissociable hydrogen or sodium ions, and they contain additional constituents which increase water solubility and decrease toxicity. By decreasing hypertonicity in aqueous solutions, the non-ionic agents are better tolerated by the meninges, nerve rootlets, spinal cord, and brain.

As with any pharmaceutical substance, non-ionic agents are not completely inert in the meninges, neural parenchyma, or other body tissues if used in excessive volumes or concentrations. Although there are no
reported cases of arachnoiditis in man, this inflammatory process has been reported in experimental animals when metrizamide is used in high concentrations. With routine clinical dosage, headache, nausea, and vomiting occurred in 57% of patients in this study. Generalized grand mal seizures did not occur in this study, but are a well known, although uncommon complication with intrathecal injections of metrizamide. Myoclonic leg spasms, presumably related to contrast material entering the spinal cord, may occur with metrizamide but have only been reported once with iopamidol. In this case, an exceptionally high dose (20 ml of 300 mg I/ml) of iopamidol was used in a patient with complete block in the thoracic region. This merely makes the point that even an extremely safe substance will have toxicity if it comes in contact with the spinal cord in excessive volume and concentration.

The most striking feature of this double-blind study was the high incidence of severe adverse neurobehavioral reactions (17%) associated with metrizamide. This toxicity was not seen in any patient in the iopamidol group, even with multiple interviews over the 24 hours following the myelogram. A recent case report has described neurobehavioral changes with iopamidol. Once again the dose was excessive (20 ml of 300 mg I/ml administered by C1–2 puncture). The contact with and entry into the brain substance of such a large volume and concentration of even a relatively inert contrast material would not unexpectedly result in transient neurotoxicity.

The delayed onset of adverse neurobehavioral reactions correlates with maximal brain penetration of metrizamide rather than with maximal concentration in the subarachnoid spaces. This suggests that this passage across the CSF-brain barrier into the extracellular or intracellular brain space is closely related to neurotoxicity. Schmidt suggested a gross correlation between the severity of side effects and the concentration of intraparenchymal metrizamide as quantitated using sequential CT scanning. Richert, et al. equated brain penetrance of metrizamide with behavioral abnormalities, although definite variability was noted. They also suggested a higher incidence of adverse reactions with cisternography and cervical myelography as compared to lumbosacral studies.

The actual mechanism underlying neurotoxicity is not as well established as the ready transport of the non-ionc hydrosoluble substances across the CSF-brain barrier. Both metrizamide and iopamidol produce a parenchymal blush of delayed onset, as monitored by sequential CT scanning (Fig. 5).
graded staining of the more superficial brain substance adjacent to the subarachnoid spaces is routinely seen after lumbosacral, thoracic, or cervical myelography as well as after cisternography. The question thus arises as to why metrizamide is so much more neurotoxic in terms of clinical and EEG parameters.

When metrizamide is introduced into the subarachnoid space of experimental animals, it produces depressive (encephalopathic) rather than irritative (epileptogenic) adverse effects. The animals become lethargic and recover from anesthesia slowly.\(^2,19\) Diffuse delta and theta activity is more commonly seen on EEG than spiking.\(^9,26,33,41\) These findings are fully consistent with the higher incidence of toxic confusional metabolic encephalopathy as compared to seizure. An additional EEG finding is sometimes noted, consisting of intermittent bursts of frontally predominant rhythmic delta activity (FIRDA) with a normal background rhythm. This abnormality is most often noted from 6 to 18 hours after the intra-arterial introduction of an iodinated non-ionic hydrosoluble contrast material at a time when the brain blush is also maximal, and may be related to the entry of contrast medium into diencephalic structures.\(^6,8,9,11,15,16\)

Bertoni, et al.,\(^3\) have suggested that metrizamide, a glucosamide of metrizoic acid, causes a specific metabolic defect that would not be present if other non-ionic substances were used. As a deoxyglucose analog, metrizamide inhibits hexokinase at the first step in glycolysis through competition with its substrate glucose. To further establish the significance of the proposed competitive inhibition, these authors studied CSF concentrations of metrizamide and glucose in two patients with post-myelography metabolic encephalopathy. The concentration of metrizamide was 50 mM as compared to only 3.6 mM of glucose. This discrepancy of concentration seems sufficient to cause competitive inhibition of glucose metabolism and the resultant clinical picture of a metabolic encephalopathy and diffuse slowing of background rhythms on EEG.

The significantly decreased incidence of adverse reactions associated with iopamidol, particularly in terms of neurotoxicity, with equivalent image quality and diagnostic accuracy, strongly suggests that this is an agent of choice for performing conventional or CT myelography in the lumbosacral region. It is, however, important to remember that any nonionic hydrosoluble contrast material introduced into the subarachnoid space will cross the CSF-brain barrier into the brain substance, and is therefore potentially neurotoxic if given in excessive volume or concentration.

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