Iohexol lumbar myelography: clinical study.

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Iohexol Lumbar Myelography: Clinical Study

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Forty-three patients underwent lumbar myelography with the new, nonionic contrast medium iohexol. Multiple laboratory examinations, neurologic examinations, and electrocardiograms showed no significant alterations after intrathecal injection of the contrast agent. Mild electroencephalographic changes were seen in one patient. Nineteen adverse reactions occurred in 13 patients; only one of them was considered severe. No patient experienced a seizure, auditory or visual hallucination, or similar neuropsychologic reaction. This is a distinct improvement over the side effects described for previous water-soluble contrast agents. The adverse reactions occurring with iohexol myelography are fewer in number and less severe than with metrizamide myelography, and radiographic visualization obtained with iohexol is equal to that obtained with metrizamide. With iohexol, it appears that the most disturbing and disabling neuropsychologic reactions have been reduced to an acceptable minimum.

For more than 35 years Pantopaque (iodophendylate, Lafayette Pharmacal) has been the standard agent for myelography in the United States. However, its high viscosity and low solubility have made it less than ideal. Early attempts to produce a better contrast agent met with mixed success [1–3].

In 1968, Torsten Almen [4], working in conjunction with Nyegaard, produced the first clinically acceptable nonionic contrast medium, Amipaque (metrizamide, Winthrop). Almen reasoned that the high molar concentration of the ionic contrast agents (diatrizoates, iothalamates) was responsible for the undesirable side effects seen with these agents. He produced a nonionic contrast medium by substituting an amide group for a carboxyl group. This exchange reduced the molar concentration by 50% while maintaining the iodine concentration. Because of its excellent visibility and ease of usage, Amipaque has become a most popular contrast agent for myelography, having already been used in more than 2 million examinations. Amipaque is supplied in lyophilized form to ensure long-term stability. Kieffer et al. [5] have shown that Amipaque is comparable to Pantopaque in both diagnostic quality and number of side effects.

In an attempt to further reduce the neurotoxicity of nonionic contrast agents, Nyegaard has produced a second contrast agent, iohexol (Omnipaque, Nyegaard; Winthrop, U.S.A. and Canada). Iohexol has been used successfully in more than 375 myelograms in Europe. In animal studies, iohexol has been found to have significantly less neurotoxicity than metrizamide, sodium diatrizoate, or meglumine iothalamate [6]. In monkeys, no significant evidence of arachnoiditis was seen in any of the animals examined with iohexol, whereas five animals examined with metrizamide had some evidence of at least mild arachnoiditis [7].

Three medical centers were asked to evaluate the safety and effectiveness of iohexol in patients in a clinical trial (phase II study). This was accomplished by evaluating vital signs, changes in blood biochemical parameters, and changes in neurologic status and recording adverse reactions; by evaluating the changes on electroencephalograms (EEGs) and electrocardiograms (ECGs) in a number of patients; and by evaluating the image effectiveness of iohexol.
Subjects and Methods

Iohexol, a water-soluble, nonionic, radiopaque contrast medium, has been given the Chemical Abstracts name 5-facetyl(2,3-dihydroxypropylaminoj-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide. Iohexol has a molecular weight of 821.14, empirical formula of C₁₇H₂₇N₂I₄O₉, and iodine content of 46.36%. It is a white, nonpolymeric, nonsolvated hygroscopic powder.

Iohexol was used in this study at an iodine concentration of 180 mg I/ml and a volume of 10–17 ml (1.80–3.06 g I). To be included in the study, patients had to be 18 years of age and have symptoms requiring a lumbar myelogram. Patients were excluded from the study if they required potent analgesics; had known or suspected hypersensitivity to contrast media; were of childbearing age, pregnant, or lactating; had leg paresis of unknown etiology; had previous lumbar surgery; had an intrathecal or subarachnoid injection within the previous 24 hr; were receiving another investigational drug; had urgent medical problems; had unknown or suspected decreased seizure threshold; were outpatients; had suspected cauda equina or conus syndromes; had received intrathecal or epidural medications in the preceding 3 months; were receiving neuroleptic drugs or phenothiazine derivatives; or had bloody cerebrospinal fluid (CSF) at lumbar puncture.

Once the patient was accepted into the study group, complete history and physical examination were performed. Within 24 hr before myelography each patient underwent a complete neurologic examination including the following parameters: general mental condition, concentration, and orientation tests; visual function, acuity, and field testing; sensory and motor function; and cranial nerve examination and coordination tests.

Changes in the neurologic status were assessed and recorded at 4–6 hr, 24 hr, and 48 hr after iohexol administration.

Vital signs were obtained twice within 30 min before lumbar puncture. Blood pressure and pulse measurements were repeated immediately before contrast injection, at the end of the myelographic procedure, at 30 min, and at 1, 2, 3, 24, and 48 hr after contrast medium injection.

Venous blood for biochemical analysis was obtained within 4 hr before the myelograms and at 2, 24, and 48 hr after contrast medium injection. Hematologic parameters were also measured on these same venous blood samples.

Standard limb lead ECGs were recorded in 28 of the 43 patients just before injection, at the end of the myelogram, and at 30 min postinjection.

Standard EEGs were recorded in 18 of the 43 patients within 24 hr before myelography, at the end, and at 2 and 24 hr after injection. Lumbar puncture was carried out in the usual manner using a 20 or 22 gauge needle. Manometry was performed, and 4–7 ml of CSF was sent to the laboratory where white blood cell count and differential were determined. CSF electrolytes were also measured.

At least 180 mg I/ml seizure was injected into the subarachnoid space at the L2-L3 level in amounts varying from a minimum of 10 ml to a maximum of 17 ml. The patients' heads were kept elevated 25°–30° during the injection. Anteroposterior, oblique, and cross-table horizontal-beam lateral radiographs were exposed. The contrast material was not advanced cephalad beyond the T10 level. After the procedure, the patients were positioned upright to allow iohexol to flow into the sacral region. For up to a period of 6–8 hr after the myelogram, the patients were maintained in a 15°–20° head-elevated position.

All radiographs were reviewed and interpreted by neuroradiologists to obtain a final diagnosis. In addition, each study was graded for the quality of radiologic visualization. Axillary pachy, nerve roots, and cauda equina were graded as not visualized, poorly visualized, well visualized, or excellently visualized in each patient. The overall visualization for each examination was also determined.

Computed tomographic (CT) scans were obtained within 6 hr on many of the patients. Selected exposures were made at multiple levels.

All patients were observed for adverse reactions for up to 48 hr after myelography. The patients were specifically queried about unusual or bizarre behavior, headache, nausea, and vomiting.

Results

Of the 43 patients in this study, 15 were women and 28 were men ranging in age from 20 to 70 (mean age 47.6 years). The opening pressure at lumbar puncture averaged 10 mm Hg and in no patient exceeded 20 mm Hg. In no patient were the baseline CSF laboratory examinations significantly abnormal. In 24 of the 43 patients, 10–14 ml of iohexol (180 mg I/ml) was injected, whereas in 19 others, 15–17 ml of contrast material was used. There were no significant alterations in the vital signs, blood chemistries, or hematologic and electrocardiographic parameters due to or related to the subarachnoid injection of iohexol. No new abnormalities were detected on the postmyelogram neurologic examinations. Specifically, no untoward psychologic or neuropsychologic reactions were observed.

Fifteen of 18 patients had normal EEGs before, immediately after, and at 2 and 24 hr after myelography. Two patients had abnormal baseline EEGs showing either “mild, intermittent, sharp and slow wave activity” or “moderate, slow, sharp wave activity arising diffusely.” In both instances, postmyelogram tracings showed either no change or mild improvement. In only one patient, whose preprocedure EEG was normal, did the two and 24 hr postprocedure tracings show “intermittent, sharp and slow wave activity predominantly in the left hemisphere.”

Thirteen of the 43 myelograms were normal. Twenty-three showed a herniated nucleus pulposus at various lumbar levels. Three demonstrated spinal stenosis. Two had spinal stenosis and a herniated disk. Lumbar spondylosis and a bulging anulus fibrosus were separately present in one case each (figs. 1 and 2).

The overall radiographic visualization was excellent in 79% of the 43 examinations and good in the other 21% (table 1). The nerve roots were seen excellently in 35 instances and seen well in the other eight cases. Both the root sleeves and axillary pachy were seen excellently in 34 examinations, seen well in eight, and seen poorly in only one. The cauda equina was seen excellently in 22 patients, seen well in 18, seen poorly in two, and was not seen in three.

A total of 19 adverse reactions occurred in 13 patients (table 2). Nine patients had headaches; two became nauseated, and one of these vomited. Five instances of pain were recorded, either in the hip, back, or leg. Ringing in the ears and hyperpyrexia to 38.5°C occurred in one patient. Of the nine recorded instances of headache, eight were considered of mild and one of moderate severity. There appeared to be no set pattern in these patients. Headache occurred as soon as 1 hr after myelography and lasted but 1 hr, or was delayed as long as 16 hr and lasted another 36 hr. Seven headache
IOHEXOL LUMBAR MYELOGRAPHY

Fig. 1.—L4–L5 herniated disk in 50-year-old man who had worsening pain in both legs for several years. Iohe xol lumbar myelography shows bulging anulus fibrosus at L4–L5 associated with minimum decrease in AP diameter of spinal canal at this level. Laminectomy at L4 with diskectomy at L4–L5 provided significant relief in leg discomfort.

Fig. 2.—L5–S1 herniated disk in 61-year-old man who had right leg pain radiating from midlumbar area. Iohe xol lumbar myelography shows herniated nucleus pulposus on right at L5–S1 level. Diskectomy on right at L5–S1 provided significant improvement of leg and back pain.

TABLE 1: Quality of Radiologic Visualization with Iohe xol Myelography

<table>
<thead>
<tr>
<th>Area</th>
<th>Excellent</th>
<th>Good</th>
<th>Poor</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve roots</td>
<td>35 (81)</td>
<td>8 (19)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Axillary pouches</td>
<td>34 (79)</td>
<td>8 (19)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Root sleeves</td>
<td>34 (79)</td>
<td>8 (19)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>22 (51)</td>
<td>16 (37)</td>
<td>2 (5)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Overall visualization</td>
<td>34 (79)</td>
<td>9 (21)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 2: Adverse Reactions in Iohe xol Myelography

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Total No.</th>
<th>Degree of Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mid</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pain (hip, leg, back)</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>19*</td>
<td>10</td>
</tr>
</tbody>
</table>

* The 19 adverse reactions were found in 13 of the 43 patients studied.

Discussion

Eldevik et al. [8] first reported the results of 82 iohe xol myelograms obtained at four study centers in Europe. That phase II protocol was similar to the one described in our study. The intrathecal injection of iohe xol did not cause spike activity on any of the postprocedure EEGs obtained by Eldevik and coworkers. In addition, no significant changes were discerned in any of the vital signs or laboratory parameters in their study. These same results were obtained in the 43 patients we examined, except for one instance of postprocedure EEG changes.

Concerning adverse reactions, the studies are likewise comparable. Eldevik et al. reported no side effects in 53 (65%) of 82 patients as compared with 30 (69%) of the 43 patients reported here. The total number of adverse reactions reported here, 19 (44%) in 43 patients, is just slightly lower than that reported by Eldevik et al., 42 (51%) in 82 patients. The types of adverse reactions were comparable.
of adverse reactions were essentially the same for both studies.

Iristam [9] has divided the adverse reactions from myelography into three groups: (1) meningeal irritation, manifested by headache, nausea, vomiting, and dizziness; (2) spinoradicular symptoms such as radicular pain, hypesthesia, hyperreflexia, and urinary retention; and (3) cerebral and spinocerebral symptoms such as convulsions and visual and auditory disturbances. The reactions in category 1, so-called meningeal reactions, are thought to be related to spinal puncture techniques and not to the contrast medium being used. Nevertheless, the number of patients in both the European iohexol study (37%) and our iohexol study (26%) who manifested category 1 reactions was slightly less than that reported in a large series of patients undergoing metrizamide lumbar myelography (42%) as reported by Hauge and Falkenberg [10].

Category 2 reactions (spinoradicular), such as pain, hyperreflexia, etc., occurred in 30% of lumbar metrizamide studies reported by Hauge and Falkenberg. Category 2 reactions occurred in 13.5% and 12% in the phase II European iohexol study and in our phase II North American iohexol study, respectively [8]. The category 3 (so-called cerebral and spinocerebral) reactions occurred in 46% of the lumbar metrizamide study reported by Hauge and Falkenberg [10] and in 1% and 4% of the European and North American iohexol studies, respectively [8].

Most important, only one patient in the European iohexol study and no patients in our North American iohexol trial manifested the more severe and disabling side effects reported previously with metrizamide [11, 12]: auditory or visual hallucinations, confusional states, amnesia, nightmares, or any other profound neuropsychologic symptom complexes. In the European iohexol study, only one patient complained of recurrent symptoms that lasted over a 10 day period and included moderate headaches, nausea, neck and head "tension," auditory disturbance, one nightmare, and depression on the third postprocedure day. Multiple neurologic examinations, laboratory studies, EEGs, and audiometry were normal in that patient.

Of all the adverse reactions in the two iohexol lumbar myelography studies reported to date, only two of 125 were designated as severe. One patient had persistent severe nausea and another patient complained of severe leg pain. Of the total 19 adverse reactions reported in our study, seven were so mild as to not require treatment. The other 12 responded to routine medical management. Most of the adverse reactions in our study were recorded within the first 24 hr after intrathecal injections of iohexol. In only one patient did a reaction occur as late as 39 hr after myelography. In this patient a fever to 38.5°C lasted for 9 hr. Only three patients suffered adverse reactions lasting more than 12 hr, two having headaches that began at 6 and 16 hr postmyelography and lasting 24 and 36 hr, respectively. One other patient remained moderately nauseated for almost 3 days after myelography.

The excellent delineation of intrathecal anatomy with iohexol myelography was predictable with a water-soluble contrast agent. The overall radiographic visualization equaled that of metrizamide, as was to be expected considering their comparable iodine concentrations [5].

REFERENCES