Iohexol for cervical myelography via C1-C2 puncture: study of efficacy and adverse reactions.

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Iohexol for Cervical Myelography via C1–C2 Puncture: Study of Efficacy and Adverse Reactions

Cervical myelography with iohexol via C1–C2 puncture was performed in 30 patients in two medical centers using a concentration of 240 mg I/ml. The study demonstrated iohexol to be a safe contrast medium without significant changes in neurologic and physical examination, vital signs, electrocardiogram, or hematologic or blood chemistry parameters. Fifteen patients had electroencephalograms (EEGs); two were abnormal. In one patient the baseline EEG demonstrated nonspecific slow waves in the temporal regions bilaterally that remained unchanged after myelography. In the second patient, transient changes in the left hemisphere during either hyperventilation or photic stimulation on postmyelographic EEG had not been present on the baseline recording. The relation of these changes to the drug remains unclear. Iohexol was found to be an efficacious myelographic contrast agent, with good to excellent myelograms in 93% of cases. Headache occurred in 13% and nausea in 3%.

While the water-soluble, nonionic contrast agent metrizamide has proven to be an extremely valuable myelographic contrast agent, a high incidence of adverse reactions has been encountered. In particular, the incidences of headache, nausea, and vomiting have proven to be high. There are increasing recognition of psychologic disturbances and rare reports of seizures.

Iohexol is a new, nonionic, water-soluble contrast agent that has had extensive use in Europe [1]. Initial investigations in the United States for use in lumbar myelography [2] have demonstrated that iohexol is equally effective in producing high-quality radiographs, but it has significantly fewer side effects as compared with metrizamide. This study was performed as an open trial at two hospital centers to evaluate the efficacy of iohexol for cervical myelography via C1–C2 puncture and the incidence of adverse reactions.

After this study, we performed a double-blind comparison study of iohexol and metrizamide for cervical myelography, and the results are reported in this issue [3]. Because of similarities in the materials and methods between the two studies, techniques common to both studies will be described in detail in this study and reference made to similar techniques when describing the second study.

Subjects and Methods

Thirty adult patients were studied, 15 at each of the two study centers. The indications for myelography and exclusionary criteria for both this open study and the double-blind study [3] were the same and are listed in table 1. The patient population for the open study consisted of 21 men and nine women aged 20–71 years (median age, 44 years).

All patients were encouraged to drink fluids liberally before myelography and to consume at least 2 L of fluid over the 8 hr after the myelogram in addition to eating a regular diet; no intravenous fluids were administered. Seventeen of the 30 patients received some form of mild premyelographic sedation, generally Valium. In both institutions the procedure was performed with the patient prone during subarachnoid placement of either a 22 gauge (20 patients) or 20 gauge (10 patients) needle at the C1–C2 interspace under lateral fluoroscopic

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control. Between 3 and 15 ml of cerebrospinal fluid (CSF) was removed for chemical analysis, after which 3.5–10 ml of iohexol was administered at a concentration of 240 mg I/ml. The total volume was dependent on size of the cervical subarachnoid space and the presence of partial or complete block. The upper level of the contrast material was not allowed to move above the foramen magnum as judged by both fluoroscopy and plain films.

After the procedure, the patient was placed upright for 2–10 min to allow the contrast medium to collect in the lumbar subarachnoid space. The patient was kept 30° upright in bed for at least 8 hr, except for the time during which the patient underwent computed tomographic (CT) scanning, requiring a supine position.

Neurologic examinations were performed by members of the study team within 24 hr before myelography and at 4–6 and 24 hr postmyelography. Vital signs including blood pressure, pulse, and oral temperature were monitored 30 min before, immediately before, and at the completion of myelography and at 30 min, 1 hr, 2 hr, 3 hr, 24 hr, and 48 hr after myelography. Various hematologic and blood chemistry parameters were evaluated on venous samples obtained within 24 hr before and at 24 and 48 hr after myelography. These parameters and the examinations on the CSF are listed in Table 2.

Eleven of the 30 patients had electrocardiograms (ECGs) immediately before, immediately after, and at 30 min after myelography. Electroencephalography (EEG) was performed in 15 of the 30 patients, seven at one study center and eight at the other. EEGs were obtained in all 15 patients within the 24 hr before the myelogram. Eight of the patients at one study center had EEGs both immediately after the myelogram and at 2–4 hr after myelography, while at the second study center the seven patients had EEGs 2–4 hr after myelography. All patients had EEGs 24 hr postmyelography. CT scanning in selected areas of the cervical spine was performed in all 15 patients at one study center and in two of 15 patients at the other study center. CT was performed in the supine position within 5 hr of myelography.

Evaluation of the myelographic quality included assessment of the degree of filling of the cervical root sleeves and the axillary pouches, demonstration of the nerve roots themselves, and overall evaluation of the quality of the myelogram. Individual parameters were judged as excellent, good, poor, or not demonstrated.

The patients were observed for adverse reactions over a 48 hr period. Members of the study team interviewed the patients and attempted to determine the presence and severity of adverse reactions or the augmentation of previous symptomatology. The adverse reactions looked for included headache, nausea, vomiting, pain at the puncture site, radiculopathy, neck pain, psychologic disturbances (decreased ability to concentrate, confusion, disorientation, nightmares), and seizures. Particular attention was given to the interview technique. Initially, each patient was asked for his overall tolerance of the procedure. If specific symptoms could not be elicited, direct questions were asked pertaining to each of the possible adverse reactions.

Results

Myelographic quality was judged to be good to excellent in 28 (93%) of the 30 patients. Two of the patients had poor demonstration. The first patient had a partial subdural injection, but enough subarachnoid contrast material was present to permit an appropriate diagnosis when the plain films were combined with the subsequent CT scan. This patient had no adverse reactions after the partial subdural injection. The second patient had severe pain in his neck before the procedure, which was secondary to a herniated disk. Discomfort led to acute flexion of the neck during the procedure, allowing most of the contrast material to pass into the intracranial subarachnoid spaces. CT subsequently demonstrated the herniated disk, and the patient had no symptoms whatsoever after the movement of this large bolus of contrast material intracranially. CT was judged to be excellent in all patients who underwent this additional procedure.

There were changes in two of the patients’ clinical neurologic examinations. One patient had mild drowsiness 6 hr after the myelogram, most likely from the Valium premedication. The second patient had restricted spinal movement before the myelogram and had a further reduction in spinal mobility 6 hr after the myelogram; however, this returned to the premyelographic state at 24 hr. There were no significant changes in any of the patients’ vital signs, blood chemistry or hematologic parameters, or ECGs. All CSF studies were normal.

Thirteen of the 15 patients had normal EEGs both before and after myelography. Two patients from the study center performing EEGs both immediately after the myelogram and

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**TABLE 1: Inclusionary and Exclusionary Criteria for Cervical Myelography Using Iohexol**

<table>
<thead>
<tr>
<th>Criteria</th>
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<tr>
<td>Inclusionary:</td>
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<tr>
<td>Symptoms requiring myelography with a direct cervical puncture</td>
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<tr>
<td>Age: 18 years or older</td>
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<tr>
<td>Either gender</td>
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<tr>
<td>Exclusionary before cervical puncture:</td>
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<tr>
<td>Known or suspected hypersensitivity to iodine-containing contrast media</td>
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<tr>
<td>Childbearing potential if the risk is greater than the potential benefit</td>
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<tr>
<td>Pregnancy or lactation</td>
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<tr>
<td>Intrathecal or subarachnoid puncture within previous 48 hr</td>
</tr>
<tr>
<td>Use of any other investigational drugs</td>
</tr>
<tr>
<td>Emergencies</td>
</tr>
<tr>
<td>Outpatients</td>
</tr>
<tr>
<td>Use of any intrathecal or epidural drugs in the preceding month</td>
</tr>
<tr>
<td>Spinal cord surgery in the preceding month</td>
</tr>
<tr>
<td>Use of drugs that lower the seizure threshold (e.g., phenothiazine derivatives)</td>
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<tr>
<td>Exclusionary after cervical puncture:</td>
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<td>Blood in the cerebrospinal fluid</td>
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</table>

**TABLE 2: Laboratory Studies before and after Cervical Myelography with Iohexol**

<table>
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<th>Studies</th>
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<tbody>
<tr>
<td>Serum chemistry: albumin,* alkaline phosphatase,* total bilirubin, BUN,* calcium, chloride, cholesterol, creatinine,* glucose, uric acid, globulin, LDH, inorganic phosphorus, potassium, SGOT,* SGPT, sodium, triglycerides, total proteins*</td>
</tr>
<tr>
<td>Hematologic: red blood cell count,* white blood cell count,* sedimentation rate,* hematocrit, hemoglobin, platelet count, differential,* prothrombin time</td>
</tr>
<tr>
<td>Cerebrospinal fluid: red blood cell count,* white blood cell count with differential,* total protein,* and glucose*</td>
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* Also performed in [3].
for hematologic consideration to be good or changes in any of the patients undergoing myelography. In the incidence or severity of side effects and the between the two agents [2].

Two patients, one at each study center, had the injection site changes of short duration were seen over the left hemisphere, predominantly in the left frontal region, on EEGs immediately after myelography, 2½ hr after myelography, and at 24 hr after myelography. These transient changes occurred only during hyperventilation or photic stimulation and were not clearly epileptiform in nature. The overall impression was of mildly abnormal tracings in a patient without objective or subjective clinical abnormality. The patient was discharged the day after myelography, and attempts to contact him for further evaluation were unsuccessful.

A mild degree of headache occurred in four (13%) of the patients, three of whom were women. In the one male patient, the headache began immediately at the end of the procedure and lasted for 8 hr, while in the three female patients the headaches began between ½ and 5 hr after myelography. There was no correlation between the incidence of headache and CT, since only one headache occurred at the study center where all patients underwent CT.

There was only one case (3%) with nausea; it began 24 hr after the procedure in one of the female subjects who had had early onset of a mild headache. The adverse reaction was of a questionable relation to the contrast material in view of its late onset and the fact that it only lasted 1 hr; it was of mild degree and there was no vomiting. One patient who had had neck pain before the procedure appeared to have an exacerbation of the neck pain for 48 hr after the myelogram. Two patients, one at each study center, had localized pain at the injection site lasting 4–8 hr. There were no cases of psychologic disturbances or confusional states, and there was no incidence of seizure activity. There was no correlation in the incidence or severity of side effects and the total dose of contrast medium injected.

Discussion

Iohexol has proven to be an effective contrast agent for myelography. In this study, 93% of the myelograms were considered to be good or excellent in quality, and the two poor myelograms resulted from technical difficulties. In our experience, iohexol appears to be as effective as metrizamide for cervical myelography, although our double-blind comparison of the two agents [3] was necessary for a more complete evaluation. A multicenter double-blind comparison between iohexol and metrizamide in similar concentrations in 350 patients undergoing lumbar myelography demonstrated no difference in the quality of the myelographic examinations between the two agents [2].

Iohexol appears to be a safe contrast agent. There were no significant changes in any of the blood chemistry or hematologic parameters, vital signs, or ECGs. Only minor changes in physical findings were present in two patients; one of these was related to premedication and the other to preexisting disease.

The EEG abnormalities in two of the patients should be scrutinized closely. The first patient had nonspecific temporal lobe EEG abnormalities on the baseline EEG that did not appear to change significantly in the presence of iohexol. The patient may have had a subclinical abnormality that was not worsened by the presence of iohexol. The second patient had transient changes of short duration that were not clearly epileptiform and required either hyperventilation or photic stimulation to produce. While the baseline tracing had been normal, the patient may have had an underlying abnormality. The role of the contrast agent in producing these subclinical EEG findings is uncertain, and unfortunately the patient could not be located to evaluate the possibility of occult disease. Gonsette and Liesenburs [4] studied a large group of patients using spectral analysis of EEG recordings before and after myelography with iohexol and failed to demonstrate disturbances related to the presence of the contrast agent. In three separate studies, metrizamide was shown to produce slow wave activity in 13% [5], 16% [6], and 32% [7], while spike wave changes were present in 4% [5].

The 13% incidence of headache using this high concentration of a water-soluble contrast agent is low and should be put into perspective relative to metrizamide as a contrast agent. The incidence of headache after metrizamide cervical myelography via a C1–C2 puncture is more difficult to assess than is the incidence of headache after metrizamide lumbar myelography. Most reports describe the incidence after lumbar myelography, deal with a patient population in which cervical myelography was performed after injection of contrast material into the lumbar region, or discuss overall incidence of adverse reactions, regardless of the site of administration. Headache with metrizamide, whatever the site of administration and region studied, has a reported incidence of 21%–62% [8–13]. A recent multicenter double-blind comparison of metrizamide and iohexol in 350 patients undergoing lumbar myelography using a concentration of 180 mg I/ml showed an incidence of headache of 38% for metrizamide and 21% for iohexol [2]. Headache after cervical metrizamide myelography has ranged from 32% to 60% [14–17]. While the site of administration has been considered inconsequential by some [14], other studies suggest a higher incidence of headache with lumbar administration than with C1–C2 deposition [15, 17] and an increased incidence with increasing contrast medium concentration. The low incidence of headache in our current study using a high concentration of iohexol, therefore, compares very favorably with previous reports using metrizamide.

Previous comparison studies have demonstrated that patients have fewer adverse reactions if cervical myelography is performed via C1–C2 puncture than via lumbar puncture [15]. In large part, less contrast agent probably enters the head if the contrast material is deposited directly into the cervical region than if the contrast material is moved by gravity after lumbar puncture. In addition, the site of puncture itself may be important. There is an incidence of headache from lumbar puncture alone of 36% if a 22 gauge needle is used and 12% if a 26 gauge needle is used [18]. There have been
no studies of the incidence of headache after C1–C2 puncture alone, since this route is not traditionally used for obtaining CSF. However, there may be less leakage of fluid from the cervical puncture site relative to a lumbar site, because of the greater hydrostatic column of CSF above a lumbar puncture. Whatever the pathophysiology, the incidence of headache after C1–C2 deposition of iohexol is not dissimilar to the incidence of headache after lumbar puncture alone using a 26 gauge needle.

The nausea and vomiting so typical of metrizamide myelography were not present. The incidence of nausea from metrizamide is 13%–39%. [19], and it varies greatly with the concentration of the contrast agent and the state of hydration of the patient; nausea and vomiting are often severe. Psychologic disturbances that have been found in as many as 46% of patients receiving metrizamide [17], including visual and auditory hallucinations, disorientation, and sleep disturbances, were not found with iohexol in our study. Of particular interest is the patient in whom most of the iohexol spilled directly into the head during the examination, with the lack of any symptomatology or EEG changes after the procedure.

In summary, it appears that iohexol is an effective myelographic contrast agent for cervical myelography, particularly via C1–C2 puncture. It appears to be safe, and there is a low incidence of adverse reactions. In order to objectively evaluate the safety and efficacy of iohexol for cervical myelography and to compare the incidence of adverse reactions to that of metrizamide, a double-blind comparison of the two contrast agents was performed and is also reported in this issue of AJNR. [3].

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REFERENCES