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*AJNR Am J Neuroradiol* 1985, 6 (6) 927-930

http://www.ajnr.org/content/6/6/927

This information is current as of October 23, 2023.
Iohexol for Cervical Myelography via C1–C2 Puncture: Study of Efficacy and Adverse Reactions

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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 psychological 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

Received October 18, 1984; accepted after revision March 20, 1985.

Presented at the annual meeting of the American Society of Neuroradiology, Boston, June 1984.

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myelography.
CT was judged to be
missed egression of contrast
material
Any investigational drugs
Use of any other investigational drugs
Pregnancy
Emergencies
Outpatients
Use of any intrathecal or epidural drugs in the preceding month
Spinal cord surgery in the preceding month
Use of drugs that lower the seizure threshold (e.g., phenothiazine
derivatives)
Exclusionary after cervical puncture:
Blood in the cerebrospinal fluid

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 post-
myelography. 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) immedi-
ately 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 auxiliary 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 reac-
tions 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, night-
mares), 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 injec-
tion, but enough subarachnoid contrast material was present
in the cervical subarachnoid space 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 proce-
dure, 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 neuro-
logic examinations. One patient had mild drowsiness 6 hr
after the myelogram, most likely from the Valium premedica-
tion. 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>
<th>Inclusionary:</th>
<th>Exclusionary before cervical puncture:</th>
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<tbody>
<tr>
<td></td>
<td>Symptoms requiring myelography with a direct cervical puncture</td>
<td>Known or suspected hypersensitivity to iodine-containing contrast media</td>
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<td>Age: 18 years or older</td>
<td>Childbearing potential if the risk is greater than the potential benefit</td>
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<td>Either gender</td>
<td>Pregnancy or lactation</td>
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<td></td>
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<td>Intrathecal or subarachnoid puncture within previous 48 hr</td>
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<td>Use of any other investigational drugs</td>
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<td>Emergencies</td>
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<td>Outpatients</td>
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<td>Use of any intrathecal or epidural drugs in the preceding month</td>
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<td>Spinal cord surgery in the preceding month</td>
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<td>Use of drugs that lower the seizure threshold (e.g., phenothiazine derivatives)</td>
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<td>Blood in the cerebrospinal fluid</td>
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**TABLE 2: Laboratory Studies before and after Cervical Myelography with Iohexol**

| Studies                                                                 | 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* Hematologic: red blood cell count,* white blood cell count,* sedimentation rate,* hematocrit, hemoglobin, platelet count, differential,* prothrombin time Cerebrospinal fluid: red blood cell count,* white blood cell count with differential,* total protein,* and glucose* |

* Also performed in [3].
For hematologic changes in experience, evaluation.

There was no incidence of seizure activity. There was no change in the chemistry or 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 Liesenborghs [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].

ACKNOWLEDGMENTS

We thank Carol Diehl for help in performing this study and Joan Roberge for help in manuscript production.

REFERENCES