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Iohexol versus Metrizamide for Lumbar Myelography: Double-Blind Trial

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Lumbar myelography was performed in 50 patients; 25 received iohexol (an investigational aqueous contrast agent) and 25 received metrizamide. The two media produced radiographs of equal quality. However, iohexol is stable in solution, while metrizamide is not. Further, markedly less morbidity resulted from iohexol. These features indicate that iohexol may be superior to metrizamide as a contrast agent for lumbar myelography.

Aqueous contrast materials have several well known advantages over oily and gaseous agents for lumbar myelography [1], and metrizamide is the best of the water-soluble contrast agents licensed by the Food and Drug Administration for lumbar myelography [2–6]. The development of this agent represented an important advance, but it is not ideal. Troublesome qualities of metrizamide include high cost; an unwieldy stable state (lyophilized powder); and transient side effects such as headache, nausea, vomiting, dizziness, meningeal irritation, fever, painful paresthesias in the legs, myoclonic leg spasms, seizures, confusion or other abnormal psychic states including hallucinations, affective lability, agitation, impaired memory, asterixis, global aphasia, and cortical blindness [1–5].

Iohexol (N,N′-bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide) is another water-soluble, nonionic, isotonic contrast medium also developed by Nyegaard, Oslo, Norway, and tested and distributed in the United States by Winthrop Labs., New York, NY. Extensive laboratory investigations and early clinical trials have indicated that iohexol appears to be superior to metrizamide for intrathecal application [7–9]. Furthermore, the projected cost of iohexol may well be lower than the current cost of metrizamide. We report the results of a double-blind trial of iohexol versus metrizamide for clinical lumbar myelography.

Subjects and Methods

Fifty patients with appropriate clinical indications (mostly lumbar radicular symptoms) for lumbar myelography participated in this study. Exclusion criteria were age less than 18 years, pregnancy or lactation, clinical emergency, prior myelography, spinal operation or intrathecal chemotherapy within the preceding 1 month, spinal puncture during the preceding 48 hr, sensitivity to contrast media, concurrent participation in any other protocol for clinical investigation, and bloody cerebrospinal fluid (CSF). Medications known to lower the seizure threshold were not permitted 48 hr before and after myelography [4]. Examples include phenothiazine (prochlorperazine, chlorpromazine, etc.) and antidepressant drugs (amitriptyline, doxepin, etc.).

Written informed consent was obtained from all patients; 25 received metrizamide and 25 received iohexol. Premyelographic medications (meperidine, secobarbital, and atropine) were administered intramuscularly to all patients, with doses varying according to body weight. Atropine was omitted if clinically contraindicated. While solid food was not permitted 8 hr before the myelogram, clear fluid oral hydration was encouraged. The strict "npo" status was specifically not permitted. All of the myelograms were obtained by or under the supervision of a single neuroradiologist (S. S. G.). All lumbar punctures were made with the patient prone,

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using a 22 gauge spinal needle, intradermal and subcutaneous 2% xylocaine anesthesia, and fluoroscopic guidance.

Either metrizamide or iohexol was administered intrathecally in a concentration of 180 mg I/ml. Whereas metrizamide must be stored in a lyophilized form and prepared as a solution shortly before its use, iohexol is stable in solution and can be autoclaved, distributed, and stored in a convenient, aseptic liquid state ready for immediate use. All of the solutions were prepared blindly according to a computer-randomized code and handed to the radiologist in an unlabeled syringe containing 17 ml of contrast material. After removal of 3–5 ml of CSF for laboratory analysis, 14–17 ml of contrast material was injected during a strictly timed period of 3 min.

Routine lumbosacral myelography films were obtained, including frontal, oblique, lateral, and lateral decubitus films, followed by filming of the conus medullaris and mid–lower thoracic regions with the patient supine. The contrast material was permitted to flow at least as far cephalad as the midthoracic area but was never deliberately directed to flow into the cervical or intracranial regions. At the completion of the examination, the contrast material was returned to the caudal sac by positioning the patient in a nearly upright position for 5 min.

After myelography the patient was instructed to remain in a position of at least 20°–30° head elevation for 8 hr, and thereafter head elevation was maintained at 15°–20° for another 8–10 hr. The patient was permitted to have bathroom privileges 8 hr after the examination but was instructed to remain as inactive as possible in bed otherwise. Fluid intake was actively encouraged postmyelography.

In 17 patients, high-resolution lumbosacral computed tomography (CT) was carried out at times varying from 6 to 24 hr postmyelography, as clinically indicated. CT was specifically not permitted earlier than 6 hr after myelography. Strict flexion of the head on the chest was maintained during CT scanning in order to minimize intracranial flow of contrast material.

All films were evaluated for technical and diagnostic quality by a neuroradiologist (T. O. G.). Evaluation included visualization of the cauda equina, root sleeves, and the individual nerve roots in the sleeves; each was scored as excellent, good, poor, or no visualization. Excellent visualization provided more than sufficient information to make a myelographic diagnosis, good visualization provided sufficient information, and poor visualization did not provide sufficient information to make a myelographic diagnosis.

All the clinical histories and extensive neurologic examinations with particular reference to vision, reflexes, and motor function were obtained by a single physician (S. S. G.). Clinical histories and neurologic examinations were obtained within 24 hr before myelography and 4–6 hr as well as 24 hr after myelography. In cases of postmyelography morbidity or alteration in neurologic findings compared with the premyelography status, further follow-up examinations and histories at 48 and (if necessary) at 72 hr were obtained. The temperature, pulse, and blood pressure were monitored before, during, and after the procedure.

Extensive serum chemistry and hematology parameters were examined within 4 hr before myelography and about 24 hr after myelography. The serum chemistry determinations were creatinine, BUN, albumin, total protein, alkaline phosphatase, LDH, SGOT, SGPT, glucose, and serum electrolytes (sodium, potassium, chloride). The hematology values obtained were hematocrit, hemoglobin, red blood cell, white blood cell, differential white blood cell (neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands), Westergren sedimentation rate, prothrombin time, and platelet count.

A person who was not one of the investigators knew the secret code specifying the sequential order for administering metrizamide and iohexol. All clinical, laboratory, and myelographic findings were recorded before this code was broken to analyze the results.

Results

All 25 myelograms obtained with iohexol were judged to be of excellent technical quality. Of the metrizamide group, 24 were judged to be excellent and one good, due to a partial subdural injection of metrizamide in that one patient. Post-myelography CT was done 6–12 hr later in 12 patients in the iohexol group. There was sufficient density of the subarachnoid contrast material to define the intrathecal structures to at least a satisfactory degree in all 12 patients. Five patients in the metrizamide group had CT after myelography.

One patient in the iohexol group (13 males, 12 females) developed a moderate headache after the myelogram. In the metrizamide group (15 males, 10 females), seven patients had headaches after myelography; two were mild and five were moderate. The moderate headaches were treated successfully with analgesics. Two of the patients who developed headache also experienced moderate nausea without vomiting. A third patient with moderate nausea did not have associated headache. The moderate nausea in a fourth patient and the severe nausea with vomiting in a fifth patient were not associated with headache and can be attributed to cancer chemotherapy in both cases, since the symptoms were as pronounced before myelography as afterward.

Applying the chi-square test, the statistical significance for the difference in the incidence of headache in the iohexol and metrizamide groups showed a p value of less than 0.025. Regarding the significance of the different incidence of nausea in the two groups, the p value was less than 0.06.

No additional morbidity after myelography occurred in any of the patients in either the metrizamide or iohexol group. Specifically, no patient developed seizures or neurobehavioral abnormalities. No patient had any detectable change in the neurologic examination after myelography as compared with before myelography. There was also no significant change in vital signs during and after myelography as compared with before myelography.

No significant change in the serum chemistry or hematology parameters was noted when comparing the values obtained before and after myelography in either the iohexol or metrizamide group. Two patients who had normal myelography with iohexol and did not undergo any subsequent operation returned for additional clinical evaluations of possible metastatic neoplasm. One of these patients had a lumbar puncture 65 days and the other one 110 days after myelography. No pleocytosis or elevated protein concentration in the CSF was found, and there was no significant change in these values compared with the determinations made on the CSF removed immediately before intrathecal administration of iohexol for the previous myelography.

No formal protocol was developed for clinical follow-up beyond 72 hr postmyelography, and there was no case of early postmyelography morbidity or complication lasting more than 48 hr. Further, no case of late complication attributable to myelography in terms of clinical complaints, physical findings, or hematology and serum chemistry parameters in either the metrizamide or iohexol groups has been brought to our attention since the study patients were examined at 72 hr postmyelography.

Discussion

The types and incidence of postmyelographic morbidity in the metrizamide group in the present study were considerably less than could be expected on the basis of previously reported clinical trials [2, 5]. In fact, a significant incidence of morbidity, especially headache, may be expected after lumbar puncture, even without intrathecal administration of any contrast material [5, 10, 11]. There are several possible explanations for the low incidence of morbidity in *both* the iohexol and metrizamide groups in the present investigation: (1) good hydration before and after myelography; (2) strict attention to protracted head elevation, including marked head elevation with flexion on the chest for CT after myelography; (3) CT not permitted during the first 6 hr after myelography; and (4) possible reluctance on the part of the patients to report feelings of discomfort, since many patients participated in the study hoping to receive iohexol, which was described to them as being potentially advantageous. After the examination, many patients seemed to believe that they had received iohexol. Although such factors may have been responsible for the low morbidity in *both* the iohexol and metrizamide groups, the incidence of morbidity in the iohexol and metrizamide groups was strikingly different.

The results of the present double-blind clinical trial confirm the findings of previous laboratory and clinical investigations [7–9] that a significant decrease in postmyelography morbidity may be expected with the use of iohexol as compared with metrizamide for lumbar myelography.

Editor's Note

As of January 1984, the Food and Drug Administration had still not approved iohexol for clinical myelography.

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