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Iohexol vs. Metrizamide: Study of Efficacy and Morbidity in Cervical Myelography

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A double-blind study was conducted in 60 patients undergoing either cervical or more complete myelography via C1–C2 puncture. Patients received either iohexol or metrizamide at a 300 mg I/ml concentration. The contrast media were equally efficacious in the production of high-quality radiographs and CT scans. However, the incidence of adverse reactions differed markedly. Of patients receiving metrizamide, 68% had some type of adverse reaction, whereas only 26% receiving iohexol had symptoms. The incidence of headache (metrizamide, 34%; iohexol, 26%) was not statistically different, but the quality of the headache differed: half of the metrizamide headaches were moderate or severe, whereas all iohexol headaches were mild. Nausea (31%) and vomiting (28%) were common with metrizamide but unusual (3% nausea) with iohexol. Of the metrizamide patients, 21% had overt psychologic changes that did not occur in the iohexol group.

Iohexol is a new, nonionic contrast medium that was developed in hopes of decreasing the morbidity of myelography associated with water-soluble contrast agents. An open trial of iohexol for cervical myelography via a C1–C2 puncture, using a concentration of 240 mg I/ml, was performed in 30 patients and is reported in this issue [1]. That study demonstrated that iohexol is a safe and efficacious contrast agent and is associated with a low degree of morbidity.

To further establish the efficacy of iohexol for cervical myelography via C1–C2 puncture and to further evaluate the incidence of adverse reactions in a larger group of patients, this double-blind comparison of iohexol and metrizamide was undertaken. A high concentration (300 mg I/ml) of each of the contrast agents was chosen because of the inclusion in the study population of patients not only requiring cervical myelography, but patients requiring more extensive myelography such as cervicothoracic, cervicolumbar, or complete myelography. Evaluation of film quality and observations for adverse reactions were performed on all patients.

Subjects and Methods

Many of the methods were identical to those in our preliminary study [1]. Only the differences between the two studies are described here. Sixty adult patients underwent cervical or more extensive myelography via a C1–C2 puncture for a variety of indications. Many of the patients underwent cervicothoracic, cervicolumbar, or complete myelography. The indications for myelography and exclusionary criteria are listed in our other article. Patients were randomized by a computer-generated randomization code to receive either metrizamide or iohexol. Thirty-one patients received iohexol in a concentration of 300 mg I/ml, while 29 patients received metrizamide in the same concentration. The ages of the patients were 21–72 years (median, 43 years). There were 33 men and 27 women. Age and gender distribution were similar in both contrast-agent groups.

Because metrizamide comes as a powder while iohexol is a solution, the contrast agent was prepared in another room by a member of the myelographic team so that the myelographer was unaware of which contrast agent was to be used. Between 4 and 10 ml of the

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300 mg I/ml solution was injected, and routine myelography was performed.

The degree of oral hydration, the type of premedication, the technique of C1-C2 puncture, the position of the patient during and after myelography, the frequency of neurologic examinations, and the frequency and type of vital signs monitored have been described [1]. Analyses of multiple hematologic, cerebrospinal fluid, and blood chemistry parameters were performed and are listed in our other article [1]. We examined fewer parameters in this study than in our other study, and these are indicated appropriately.

All patients underwent CT scanning in the area(s) of interest. Most patients were scanned 4-6 hr after myelography, although some patients had an earlier scan. A number of patients underwent repeat scanning 24 hr after myelography to evaluate the possibility of the uptake of contrast material within the spinal cord.

A single myelographic team member not actually involved in obtaining any of the myelograms independently evaluated all myelograms for degree of demonstration and overall quality. Criteria included the degree of filling of nerve root sleeves and axillary pouches, demonstration of nerve roots, and overall quality of the cervical myelogram. Thoracic and lumbar studies were also evaluated separately when performed.

Each patient was observed for 48 hr to determine the incidence of adverse reactions. Particular attention was given to headache; nausea; vomiting; onset or exacerbation of radicular pain or pain associated with the neck or back; and psychologic disturbances such as confusion, disorientation, decreased ability to concentrate, and sleep disturbance. Close attention was paid to the interview technique used to determine the incidence of adverse reactions. The patient was asked in a general manner for his feelings and reactions after the myelogram. If no symptoms were disclosed spontaneously, more specific questions were asked. A record was kept of the degree of aggressiveness required to elicit symptomatology. In a similar manner, because of methodologic questions revolving around the pre- and postmyelographic care of a patient and his state of hydration, records were kept on all fluid intake.

Results

Good to excellent demonstration of the cervical subarachnoid space, nerve root sleeves, axillary pouches, nerve roots, and spinal cord margins was present in all cases, whether the patient received metrizamide or iohexol. There were no radiographic indications as to which contrast medium had been used. The postmyelographic CT scans were of equal quality.

Incidence of adverse reactions are listed in table 1. Of the 29 patients receiving metrizamide, 20 (68%) had one or more adverse reactions from the myelogram. This is in contradistinction to eight (26%) of 31 patients receiving iohexol who had an adverse reaction. The difference between drugs is highly significant (chi square: $p < 0.0001$).

Headache was the main complaint, with 10 (34%) of 29 metrizamide patients and eight (26%) of 31 iohexol patients complaining of postmyelographic headache. While the differences are not statistically significant, the degree of severity of the headaches was quite different. Of the 10 headaches associated with metrizamide myelography, five were mild but four were of moderate and one of severe degree. All of the eight headaches associated with iohexol myelography were mild.

TABLE 1: Adverse Reactions after Myelography Using Iohexol or Metrizamide

Side Effect	No. of Patients (%)		Chi-square Test
	Iohexol (n = 31)	Metrizamide (n = 29)	
None	23 (74)	9 (32)	$p < 0.0001$
Headache	8 (26)	10 (34)	NS
Nausea	1 (3)	9 (31)	$p < 0.01$
Vomiting	0	8 (28)	$p < 0.01$
Mental changes	0	6 (21)	$p < 0.01$
Seizures	0	0	NS

Note.—NS = not significant.

The group of 29 patients receiving metrizamide comprised 18 men and 11 women. Four (22%) of the 18 men had postmyelographic headache, while six (55%) of the 11 women had headache. Of the 31 patients receiving iohexol, 16 were women, seven (44%) of whom had headache. Of the 15 men receiving iohexol, only one (7%) had headache.

Nine (31%) of 29 patients receiving metrizamide had nausea, which was mild in six cases and moderate or severe in three. Eight (28%) of the metrizamide patients also had vomiting, five to a moderate or severe degree. In contradistinction, only one (3%) of the 31 patients receiving iohexol had nausea, and it was mild; none experienced vomiting. The differences in the incidences of nausea and vomiting between the two contrast agents were statistically significant.

Six (21%) of the patients receiving metrizamide had overt psychologic disturbances and mental changes after the myelogram, consisting of confusion, disorientation, affective and cognitive changes, and nightmares. None of the patients receiving iohexol had overt psychologic changes. Again, these differences between the two contrast agents were statistically significant. There were no seizures in either group.

Discussion

We found no qualitative differences between iohexol and metrizamide in their radiopacity on conventional radiographs and CT scans. Equal concentrations of iodine were used for the two media, and the contrast agents do not differ significantly in their viscosity.

The incidence of adverse reactions was certainly put to the test by using 300 mg I/ml concentration for both contrast media. This is the most concentrated solution recommended for metrizamide. This concentration was selected so that a diverse patient population and a variety of clinical indications could be included for this study. In our institution, routine cervical myelography only is usually performed using a 220-250 mg I/ml concentration. Therefore, one might expect a high percentage of adverse reactions with so concentrated a contrast agent.

The 68% overall incidence of adverse reactions in the metrizamide group is not only in keeping with the high concentration of contrast agent used, but is in keeping with previously published statistics. Baker et al. [2] studied 200

patients with all forms of metrizamide myelography. A concentration of 170–200 mg l/ml metrizamide instilled via lumbar puncture was used for those undergoing lumbar myelography, while cervical examinations were performed via C1–C2 puncture and the instillation of 250 mg l/ml metrizamide. Of the 200 patients, 75% had some form of adverse reaction. Sackett et al. [3] performed a similar study on 215 patients, using both lumbar and cervical approaches, and 67% of the patients had some form of adverse reaction. Gulati et al. [4] studied 189 patients referred for lumbar myelography, with 60% of the patients having some type of side effect. One of the early multinational evaluations of metrizamide for all types of myelography described 1850 examinations performed from the lumbar or cervical route, and 68% of the patients had some type of adverse reaction to metrizamide [5].

The overall incidence of adverse reactions differed markedly between iohexol and metrizamide in our study, even with the high concentration of contrast material used. Whereas 68% of patients receiving metrizamide had some form of adverse reaction, only 26% of the iohexol patients had symptoms. The incidence of headache was marginally lower for iohexol. While 34% of the metrizamide patients complained of headache, 26% of the iohexol group also had headache. While not a statistically significant difference, the severity differed markedly. All of the iohexol headaches were mild, whereas half of the metrizamide headaches were moderate or severe. The 26% of iohexol patients having headache compares with the 21% of iohexol patients having headache after lumbar myelography in a randomized double-blind multicenter study of 350 patients [6]. However, those patients received only 180 mg l/ml of iohexol.

Of interest, the incidence of headache was similar in the female populations of both study groups. Of the women patients receiving metrizamide, 55% had postmyelographic headache, while 44% of the women patients receiving iohexol had headache. Only one of the iohexol patients with headache was a male. A similar preponderance of headache in the female population receiving iohexol was seen in the randomized double-blind study of iohexol and metrizamide in lumbar myelography [6].

Nausea and vomiting can be extremely disturbing to both patient and clinician. In this regard, iohexol appears to be a much better contrast agent. Nine (31%) of the metrizamide patients had nausea, usually of moderate to severe intensity, and all but one of these progressed to vomiting. There was only one case of mild nausea with iohexol. A similar incidence of nausea and vomiting was found in the initial trials of metrizamide [5].

Psychologic disturbances are becoming more recognized with the use of metrizamide. Psychologic disturbances include confusion, disorientation, a decreased ability to concentrate, sleep disturbances, affective disorders, and visual and auditory hallucinations. Such disturbances have been found in as many as 46% of patients undergoing all types of myelography [7]. Of the patients in our current study receiving metrizamide,

21% had overt psychologic problems. None of the patients receiving iohexol manifested overt psychologic disturbances.

The role of postmyelographic CT scanning in the production of headache is controversial. While it has been reported that a horizontal position after metrizamide myelography increases the incidence of side effects [8], ambulation after myelography does not seem to increase side effects as long as the patient does not lie supine for at least 8 hr after myelography [4]. In our other article, we describe 15 patients in one institution who underwent postmyelographic CT scanning and only two of 15 patients in the other institution who underwent postmyelographic CT scanning [1]. There was no significant difference in the incidence of headache between the two institutions. Therefore, the role of the supine position for CT scanning remains controversial but certainly may be a factor that contributes to an overall higher incidence of adverse reactions relative to myelography performed without subsequent CT scanning.

In summary, iohexol has proven to be as efficacious as metrizamide in the production of high-quality radiographs and CT scans. The incidence of adverse reactions to iohexol is substantially lower, particularly of the symptoms most irritating to the patient, including nausea, vomiting, and psychologic disturbances.

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