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Iohexol in Lumbar Myelography: Preliminary Results from an Open, Noncomparative Multicenter Clinical Study

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This is a preliminary report of the first clinical trials using iohexol as a contrast agent in lumbar myelography. The study was noncomparative and involved 82 adult patients in four centers. Iohexol doses of 10–15 ml (180 mg I/ml) were administered and clinical and laboratory tests were performed before and at intervals during 48 hr after myelography. Side effects were noted in 29 (35%) of 82 patients. Spinal repuncture 6 or 24 hr after myelography was performed in 51 patients. No significant increases in cerebrospinal fluid parameters were seen. No seizures or spikes on electroencephalography were seen.

Preclinical studies of the effects of injection of iohexol* into the subarachnoid space of rats and rabbits showed iohexol caused less excitation than other media examined [1, 2]. Mice and monkeys showed good tolerance of iohexol injected intrathecally in single-dose studies as well as in multiple-dose studies. Promising was the observation that iohexol seemed to have less depressive and less convulsive effect than metrizamide after suboccipital injection in animals [3–8]. Nearly the total dose was excreted in the urine 3–4 days after intracisternal injection of iohexol in rabbits [9].

This preliminary report summarizes the results of initial clinical trials using iohexol as a contrast agent in lumbar myelography. A complete report from each participating center will be published separately.

Subjects and Methods

Study subjects were 82 adult patients undergoing lumbar iohexol myelography in four centers (Ullevål Hospital, Oslo: 27 patients; Rikshospitalet, Oslo: 26 patients; The National Hospital/Middlesex Hospital, London: 18 patients; Karolinska Sjukhuset, Stockholm: 11 patients). Patients not accepted for the study were: emergency cases, patients with pathological electroencephalograms (EEG) (spikes), uncooperative patients, epileptics, patients with a history of lumbar spinal surgery or lumbar puncture within 3 months prior to the study, patients with contrast-media hypersensitivity, and drug addicts.

The clinical trials were conducted as an open, noncomparative study in accordance with a phase II protocol approved by local and national health authorities. The myelographies were performed in the period from November 1981 to June 1982. Adverse reactions, laboratory parameters for cerebrospinal fluid (CSF), blood, and urine, heart rate, blood pressure, and EEG were monitored.

Lumbar puncture was performed with a 22 gauge disposable spinal needle, 10 ml of CSF was removed, and 10–15 ml iohexol (180 mg I/ml) was injected into the subarachnoid space. The patients were confined to bed for 20 hr after myelography with the head end elevated 10–15° for the first 6–8 hr. Clinical examination and questioning took place before and at 6, 24, and 48 hr after myelography. Blood samples were drawn before and at 24 hr after myelography. Spinal repuncture (51 patients) and EEG (all patients) were performed 6 or 24 hr after myelography. Patients with side effects or changes in EEG were followed until normalization.

Ten patients were selected for a pharmacokinetic study. These patients had the same procedures as the others, but also had serial blood samples drawn during the first 24 hr after myelography.

Results

Eight patients were excluded from the study after iohexol myelography because CSF protein prior to myelography was higher than 0.9 g/l (exclusion criterion according to the protocol). One of these patients experienced moderate headache and moderate back pain after myelography and one patient had mild headache. Otherwise no side effects or significant laboratory changes were recorded in the excluded patients.

The type and frequency of clinical side effects are listed in table 1. No side effects were recorded in 53 (65%) of 82 patients. One or more symptoms possibly related to iohexol myelography and/or spinal repuncture were recorded in 29 patients (35%). Side effects

TABLE 1: **Side Effects Reported after Lumbar Myelography with Iohexol**

	No. Reports (% of total) (n = 82)	Degree of Severity		
		Mild	Moderate	Severe
Headache	20 (24)	15	5	0
Back pain	11 (13)	4	7	0
Nausea	5 (6)	2	2	1
Dizziness	3 (4)	3	0	0
Vomiting	2 (2)	0	2	0
Mild mental symptoms	1 (1)	0	1	0
Seizures	0 (0)	0	0	0

Note.—51 of 82 patients underwent spinal repuncture 6 or 24 hr after myelography.

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* N, N′-bis (2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide (Nyegaard, Oslo, Norway).

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TABLE 2: **CSF Parameters before and after Lumbar Myelography with Iohexol**

CSF Parameter	Mean Value (range)		
	Before (n = 51)	6 hr Post (n = 14)	24 hr Post (n = 37)
White blood cells/μl	1 (0–2)	1 (0–2)	2 (0–4)
Red blood cells/μl	0 (0–2)	4 (0–14)	5 (0–45)
Total protein (g/l)	0.46 (0.32–0.60)	0.45 (0.34–0.60)	0.54 (0.38–0.70)
Albumin (g/l)	0.19 (0.13–0.32)	0.15 (0.11–0.23)	0.22 (0.17–0.31)
IgG (mg/l)	26 (14–40)	17 (14–31)	21 (14–56)
Glucose (mmol/l)	3.5 (3.3–3.7)	3.2 (3.0–3.4)	3.5 (3.2–4.2)

TABLE 3: **EEG Registration before and after Lumbar Myelography with Iohexol**

Type of Activity	Before (n = 82)	6 hr Post (n = 60)	24 hr Post (n = 74)
Normal	76	56	66
Slow waves	3	1	4
Spikes	0	0	0
Other nonspecific changes	3	3	4

were judged mild or moderate in all patients, except one who experienced relatively severe nausea. One other patient had recurrent symptoms over a 10 day period with moderate headache and nausea, a feeling of tension in the head and neck, disturbances ("sounds have changed"), one nightmare, and a feeling of depression on the third day after myelography. There were no neurological signs or significant laboratory changes in this patient and EEG was normal. Audiometric examination showed no significant pathology. The patient had previously experienced attacks of headache and nausea two to three times a year.

Spinal repuncture 6 or 24 hr after myelography was performed in 51 of the 82 patients. CSF parameters for these patients are given in table 2.

EEG was performed in all 82 patients before myelography. In addition, all patients had one or more EEG after iohexol myelography: 45 patients after 1 hr, 60 patients after 6 hr, and 74 patients after 24 hr. Results are given in table 3. No spike activity was recorded.

No clinically significant changes were recorded in the laboratory parameters for blood, blood pressure, pulse rate, or CSF pressure.

Detailed results of the pharmacokinetic study will be published separately. Maximum serum iohexol concentrations were observed at 2.19 (range, 1.95–2.74) hr after administration in six patients with a regular serum iohexol pattern. The half-life of the slower phase after peak serum concentrations was calculated at 3.39 (range: 2.21–7.94) hr.

The image quality of the iohexol myelograms was similar to that of metrizamide myelograms: good or excellent root-pocket filling, root visualization, and conus medullaris visualization.

Discussion

The number of lumbar iohexol myelographies in this multicenter study has been increased from 82 to 90 since June 1982. Data from the additional patients will appear in the detailed reports from participating centers. A total of 260 lumbar iohexol myelographies and 10 cervical iohexol myelographies have been performed as of October 1, 1982. The type and frequency of side effects seem to be similar to the present results.

Patients in this study were questioned specifically about possible side effects. In similar prospective studies of metrizamide myelography [10, 11], side effects were recorded in 60%–70% of the subjects, in contrast to the overall incidence of side effects in 35% of subjects in the present study. It is remarkable that only one patient experienced severe discomfort after iohexol myelography.

The high frequency of spinal repunctures performed 6 or 24 hr after myelography (51 of 82 patients) may have increased the number of patients who reported headache and back pain. Spinal repunctures were considered necessary for detection of possible damage to the central nervous system. Enzyme measurements in blood and CSF have been considered a sensitive indicator of cell membrane leakage [12]. Creatine kinase was measured in 22 of the 27 patients from Ullevål Hospital in this study. All CSF measurements of creatine kinase (both the muscular and the brain type) were within the lower normal range. There was, however, a minor increase in creatine kinase values within the lower normal range 6 and 24 hr after myelography as compared with levels measured before contrast medium injection. The implication of this finding is uncertain. Further investigations are planned to compare enzyme values in CSF before and after myelography using various water-soluble contrast media.

Investigation of the side effects of intrathecal iohexol is being continued in several phase III studies. The preliminary results of clinical trials using iohexol in lumbar myelography are promising. Iohexol is easy to administer (ready in solution), well tolerated, and is less expensive than metrizamide.

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