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Clinical Trial of Iopamidol for Lumbosacral Myelography

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The results of the initial North American trial of the nonionic, water-soluble contrast medium Iopamidol for lumbosacral myelography are reported. The Iopamidol was easily visualized by fluoroscopy during introduction, and the radiographic quality of all 12 conventional myelographic examinations was excellent. The diagnoses were herniated nucleus pulposus (seven), traumatic dislocation (one), metastasis (one), and normal (three). One patient had a repeat myelogram with a different hydrosoluble contrast medium 2 months after his Iopamidol examination and surgery and showed no radiographic evidence of arachnoiditis. The adverse reactions were all mild and transient: headache (four cases), nausea (two), and leg pain (one). There were no diaphoresis, fever, seizures, hallucinations, agitation, or vital sign changes. Electrocardiography, hematology, and blood chemistries were all normal. In two patients, electroencephalogram changes, three to four bursts of diffuse intermittent rhythmic delta activity with no spiking, were present at 6 hr with return to normal at 24 hr.

Myelography with water-soluble contrast media has two major advantages: (1) improved anatomic specificity due to more complete filling of nerve root sheaths and (2) shorter procedure time and decreased patient discomfort with elimination of the need to remove the contrast medium. Relatively recent development of low toxicity intrathecal contrast agents has resulted in widespread acceptance of nonionic, hydrosoluble materials [1–5].

Although adverse reactions to nonionic, water-soluble contrast media are generally tolerable and fairly short-lived, the patient may become very uncomfortable with headache, nausea, vomiting, diaphoresis, meningism, fever, lethargy, and leg pain [6, 7]. More severe adverse reactions, such as seizures, asterixis, encephalopathy, vertigo, and transient aphasia, have been reported infrequently [8–12]. Behavioral aberrations and agitation may occur in a few individuals. Therefore, an active search has continued for even less toxic, nonionic, hydrosoluble contrast media [13–15]. We report the results of the initial North American trial for lumbosacral myelography of a potentially safer contrast medium, Iopamidol [14–16].

Subjects and Methods

This clinical trial comprised 12 patients referred for lumbosacral myelography. Criteria for exclusion included previous myelography or surgery, age below 18 or above 60 years, contrast medium allergy, seizure disorder, pregnancy, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and certain medications (e.g., phenothiazines, butyrophenones, and tricyclic antidepressants). These medications were excluded to match the protocols of clinical trials with other water-soluble contrast media. There is no evidence they will increase the incidence of seizure or other adverse reaction when used in combination with Iopamidol.

The new nonionic, water-soluble iodinated material was developed by Bracco (Milan, Italy) and will be distributed in the United States by Squibb (Princeton, N.J.). Iopamidol (SQ

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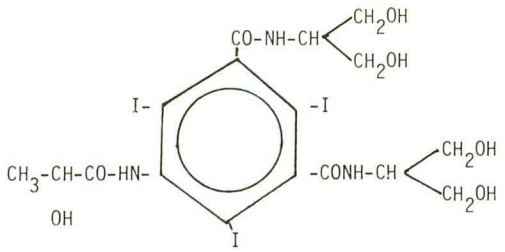


Fig. 1.—Structural formula of Iopamidol. Molecular weight is 777.1; iodine content is 49.08%.

13,396) has a triiodinated benzene ring (fig. 1) with a molecular weight of 777.1 and an iodine content of 49.08%. The compound appears stable both in solution and in the cerebrospinal fluid (CSF). At the concentration used for this study (200 mg I/ml), the specific gravity at 37°C is 1.216 and the osmolality is 0.413 mol/kg.

Standard myelographic technique was used with no premedication. After insertion of a 22 gauge lumbar puncture needle under fluoroscopic control, 10 ml of 200 mg I/ml Iopamidol were introduced after removing about 5 ml of CSF for laboratory analysis of cells, glucose, and protein., Myelographic imaging was performed in the posteroanterior (PA), lateral, and oblique (both vertical and horizontal beam) projections and concluded with PA prone and anteroposterior (AP) supine views of the region of the conus medullaris. After myelography, the patient was kept in bed for 24 hr with the head elevated 30°. Oral liquids were encouraged both before and after the procedure.

A complete general and neurologic examination was performed before and after myelography. Vital signs were obtained every 15 min for 1 hr and then every hour for 8 hr. Electroencephalography (EEG), electrocardiography (ECG), blood chemistries (total bilirubin, SGOT, alkaline phosphatase, LDH, cholesterol, creatinine, SGPT, G6PD, calcium, phosphorus, blood urea nitrogen [BUN], uric acid, glucose, total protein, albumin, sodium, and potassium), complete urinalysis, and hematology (total white blood cell [WBC] count and differential, total red blood cell [RBC] count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelets, and RBC morphology) were done before myelography as well as 24 hr after the procedure. Standard montages, a 16 channel recorder, and about 30 min study time were used for all three EEG tracings (baseline, 6 hr, 24 hr). On interviewing the patient and observing for adverse reactions, emphasis was placed on certain symptoms, headache, nausea, vomiting, dizziness, hallucinations, agitation, anxiety, restlessness, and leg pain, that have been reported following intrathecal use of other nonionic, hydrosoluble iodinated contrast media.

Results

Image Quality

Fluoroscopic visualization of the Iopamidol during introduction was quite good. The radiographs were of high quality in all 12 patients, providing excellent visualization of the Iopamidol-filled nerve root sheaths and the course of the nerve roots (figs. 2 and 3). Abnormalities were readily defined. The conus medullaris was seen in all cases and better delineated with the patient supine.

Pathology

In seven of the 12 studies, ventrolateral extradural defects (figs. 4 and 5) consistent with herniated nucleus pulposus (HNP) were observed; all were confirmed surgically. An extradural defect was detected in a patient with cancer of the colon and known metastasis. In another patient, a ventral defect at the site of previous injury with mild vertebral body dislocation and compression fracture was noted. The other three patients had normal lumbosacral myelograms.

Adverse Reactions

A summary of side effects is presented in table 1. The major feature of the adverse reactions was their mildness. Most patients commented on the benignity of the procedure. In the one individual with moderate leg pain requiring Demerol analgesia, repeat myelography 9 weeks later for recurrent symptoms with the same technique used a different intrathecal iodinated contrast medium (metrizamide). This second myelogram produced more symptoms including severe leg pains from the umbilicus downward (requiring Demerol and morphine) as well as moderate to severe headache with nausea, vomiting, diaphoresis, and mild agitation. This repeat study, after Iopamidol myelography and surgical resection of a herniated disk, showed no evidence of arachnoiditis.

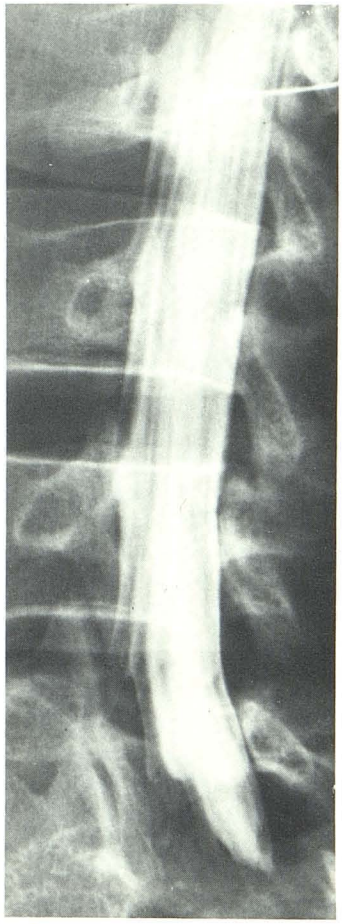
The headaches reported by four of 12 patients were all mild and transient. Only two required analgesia (aspirin) and they never lasted more than 3 hr. Minimal nausea was reported by two patients. A single episode of vomiting occurred once. Very mild and transient leg pain was noted by one patient a few minutes after completion of the myelogram and was gone within 20 min. A second patient with leg pain is described above.

No seizure or focal neurologic deficit occurred. The patients did not report nor did observers find any evidence for hallucinations, abnormal anxiety, or agitation. The baseline EEGs were normal in all as were the 24 hr EEG examinations. Three to four bursts of diffuse intermittent rhythmic delta activity (DIRDA) were seen interspersed on an otherwise minimally slow background in two of 12 patients on the EEG at 6 hr after myelography (fig. 6). No patient had a subsequent neurologic deficit. The blood pressure, heart rate, respiratory rate, and temperature as well as the hematologic and chemical bloodwork were all within the range of normal on pre- and postmyelographic examinations.

Discussion

From this study of 12 patients, Iopamidol appears to be a safe and extremely well tolerated intrathecal contrast medium. The image quality for lumbosacral myelography is excellent and its stability in solution should prove advantageous. Further clinical trials for thoracic and cervical conventional and CT myelography as well as CT cisternography and ventriculography definitely seem warranted.

A previous study reported a similar incidence of adverse



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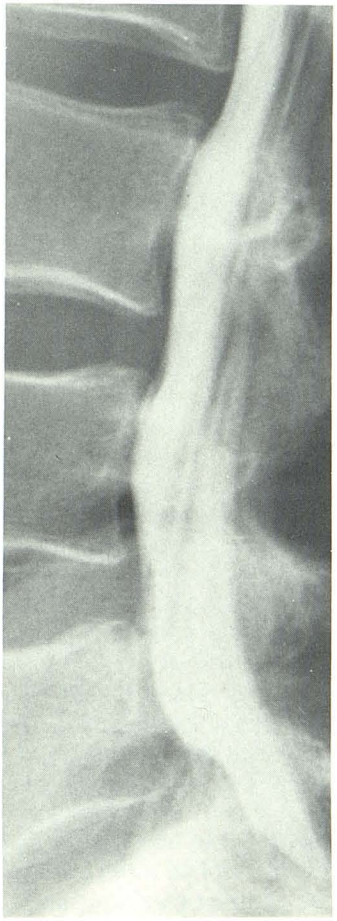

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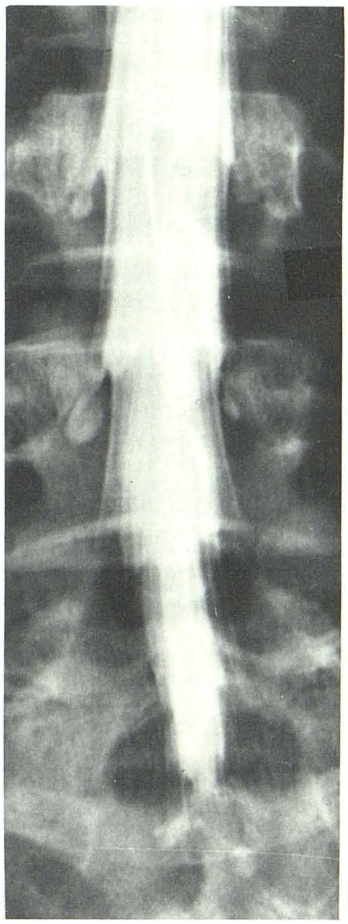

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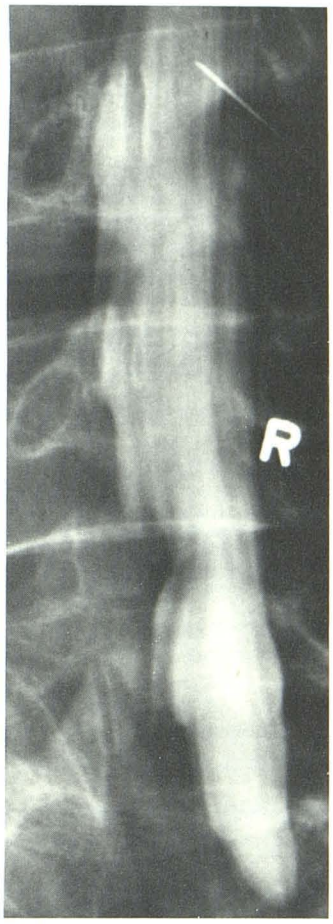

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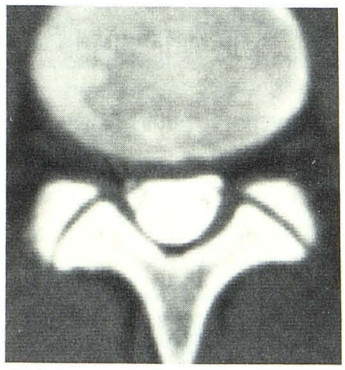

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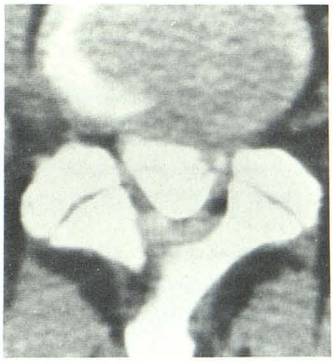


5B

Fig. 2.—Normal Iopamidol myelogram. **A**, Excellent visualization of normal lumbosacral nerve root sheaths and nerve roots. **B**, Normal CT myelogram.

Fig. 3.—Normal lateral lumbosacral myelogram.

Fig. 4.—Herniated nucleus pulposus, surgical confirmation. Iopamidol myelogram. Ventrolateral extradural defect at L4–L5 disk space level.

Fig. 5.—Herniated nucleus pulposus, surgical confirmation. **A**, Ventrolateral extradural defect on Iopamidol myelogram effacing nerve root sheath. **B**, Same herniated disk on CT myelogram causing eccentric soft-tissue bulge, obliteration of epidural fat space, and compression of Iopamidol-filled thecal sac.

reactions with metrizamide and Iopamidol [17]. Although five of the 12 individuals in our study had some side effect, the striking feature was the mildness of the reactions and good patient acceptance of the procedure. Severe headache, nausea, or vomiting did not occur nor did any of the patients have seizures, focal neurological deficit, hallucinations, or agitation. This may relate to the relatively low dose (10 ml of 200 mg I/ml) or good patient hydration, although subsequent patients studied with a larger dose have had a similar benign experience.

The Iopamidol entered the intracranial subarachnoid spaces in all patients, even though only lumbosacral myelography was performed (fig. 7). This occurred even though our patients were turned supine with the myelographic table at 0° for visualization of the conus. Using conventional imaging, a reasonable view of the Iopamidol in the thoracic

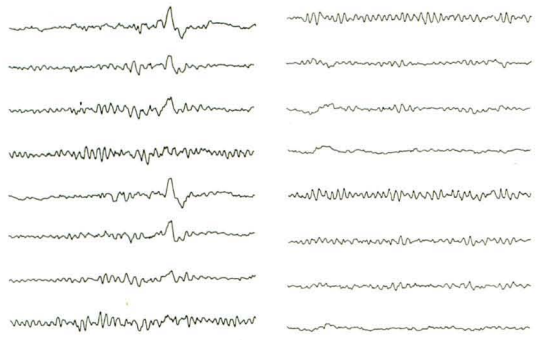
region was obtained (fig. 8). CT imaging permitted analysis of the thoracic and cervical spinal cord as well as the brain stem (fig. 7).

The fact that the contrast medium entered the intracranial region is also confirmed by the changes in the EEG. Diffuse or frontally prominent bilaterally synchronous intermittent delta activity is a fairly nonspecific EEG change being seen with posterior fossa lesions, midline supratentorial abnormalities, diffuse cortical or subcortical gray matter encephalopathies, metabolic encephalopathies, and even rarely with a localized lesion to one cerebral hemisphere [18–21]. A similar EEG pattern, yet somewhat more common with a greater number of paroxysms, was described following myelography and cisternography with metrizamide [22–26]. The time course of EEG alterations correlates closely with the maximal concentration of the Iopamidol or metrizamide in the extracellular or intracellular brain space as even complex hydrophilic macromolecules may readily cross the cerebrospinal fluid–brain barrier [25]. Within 24 hr, most of the iodinated contrast medium has cleared from the subarachnoid spaces and adjacent brain.

TABLE 1: **Iopamidol Myelography: Adverse Reactions (Mild)**

	No. Patients (n = 12)
Headache	4
Nausea, vomiting	2
Leg pain	1

Note.—There were no moderate or severe adverse reactions (except for one patient who had moderate leg pain). No diaphoresis, hallucinations, agitation or confusion, seizures, fever, or changes in vital signs were encountered in any patients. The only adverse laboratory findings were two patients with abnormal EEGs (DIRDA) at 6 hr.

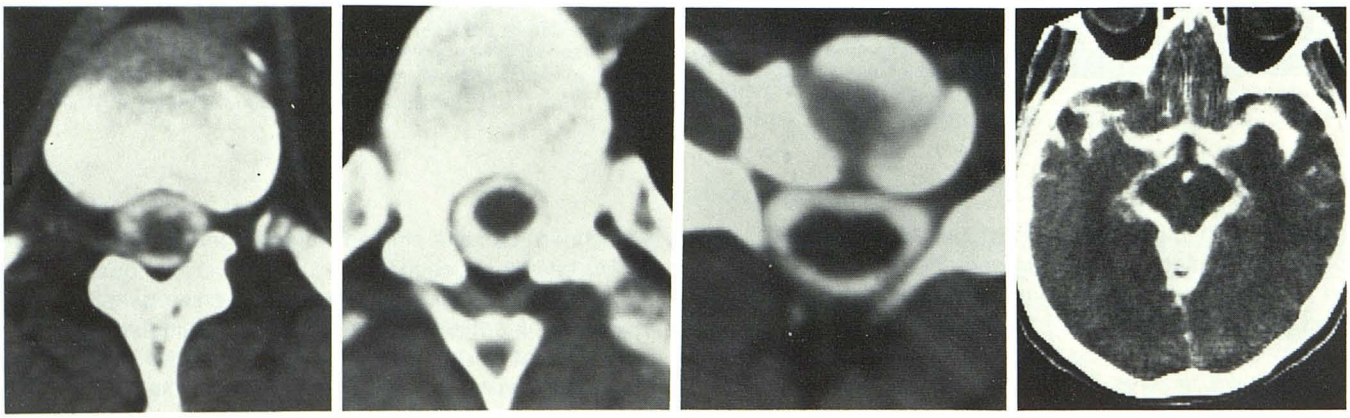


A B

Fig. 6.—Electroencephalographic findings. **A**, Tracing 6 hr after lumbar installation of Iopamidol. Short burst of diffuse intermittent rhythmic delta activity. **B**, At 24 hr. Normal baseline alpha activity.

The normal background activity in association with the DIRDA may reflect sparing of the reticulocortical and thalamocortical pathways that regulate background cortical activity [20]. Epileptiform spiking activity was never seen in our series nor were any seizures or disturbance in normal consciousness. In animal studies, some controversy exists concerning the potential for provoking EEG abnormalities of Iopamidol as opposed to metrizamide [27, 28].

The issue arises as to whether it is worthwhile to develop new intrathecal contrast media when spinal CT imaging is rapidly improving [29, 30]. Spinal CT is extremely useful in the unoperated patient with a well localized disorder in the lumbar or sacral region. However, previous surgery often obliterates the epidural fat planes that assist in diagnosing herniated disks and residual Pantopaque may produce major artifacts on the CT scan that preclude a diagnostic evaluation. The regions of the conus medullaris and thoracic and cervical spinal cord and nerve root sheaths are not readily defined using spinal CT [31]. Intrathecal hydrosoluble contrast media enhance diagnostic accuracy in these regions using either conventional radiographic or CT imaging [31–33]. In addition, the diagnostic evaluation of the unoperated individual with suspected lumbosacral radiculopathy using conventional myelography is a time-honored and accurate technique that will continue to be used by many if not most physicians, particularly if ready access to CT scanners is not available.



A B C D

Fig. 7.—Normal Iopamidol CT myelography and cisternography. Normal conus medullaris (**A**), thoracic cord (**B**), cervical cord (**C**), and midbrain (**D**), which is highlighted by Iopamidol in interpeduncular, crural, and ambient cisterns. These scans were obtained after lumbosacral myelography with no deliberate attempt to fill thoracic, cervical, or intracranial subarachnoid spaces.

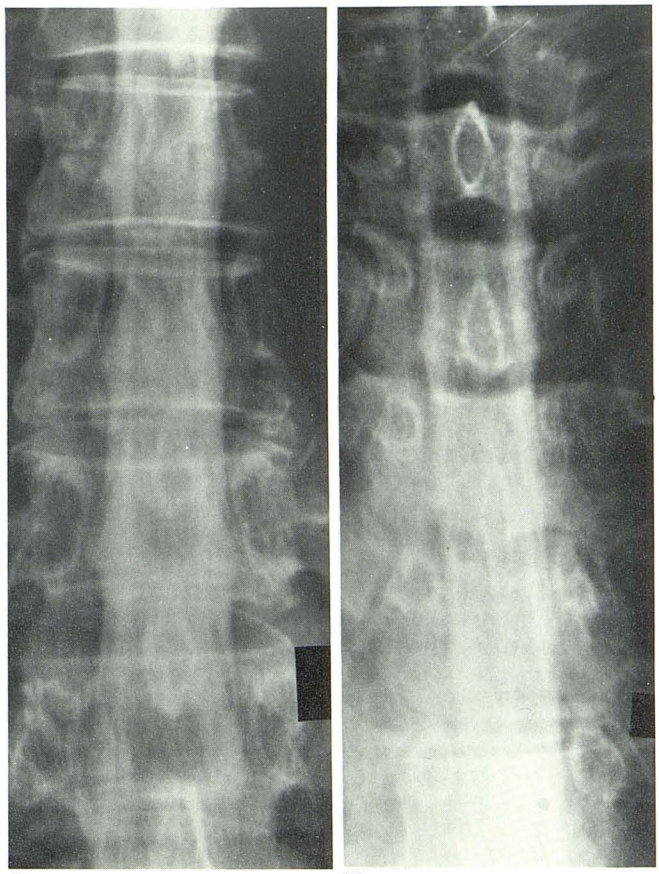


Fig. 8.—Normal thoracic myelogram. Reasonably well visualized conus and lower thoracic (**A**) and middle and upper thoracic regions (**B**) in supine patient at end of lumbosacral examination. Only 10 ml of 200 mg I/ml Iopamidol were used.

Therefore, it seems important to test new contrast substances to determine whether the toxicity can be decreased without sacrificing image quality. Stability in solution in vitro, providing for a long shelf life, is also an important characteristic, as are decreased cost and ease of production. Our initial studies suggest that Iopamidol has definite advantages in terms of these requirements.

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