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Experimental Study of Arachnoiditis from Iohexol, an Investigational Nonionic Aqueous Contrast Medium

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Myelography was performed in 16 monkeys using either metrizamide or iohexol, a new nonionic aqueous contrast medium. Eight of the animals received almost five times the recommended clinical dose of contrast medium per unit of body weight; the other eight received the equivalent of a high clinical dose. The severity of resultant arachnoiditis 12 weeks later was evaluated by repeat myelography and by histologic study of the arachnoid. No animals had severe arachnoiditis. Two of the four animals examined with the higher dose of metrizamide had moderate arachnoiditis and one had mild arachnoiditis; with the lower dose of metrizamide, two of four animals had mild arachnoiditis. No significant evidence of arachnoiditis was seen in any of the eight animals examined with iohexol.

For myelography, aqueous contrast media such as metrizamide have significant advantages over gases and oily substances [1–3]. They demonstrate the subarachnoid space more faithfully and leave it physiologically through the arachnoid membrane [4]. Furthermore, metrizamide exceeds all previously used aqueous myelographic contrast media in patient tolerance and low incidence of complications [2]. Postmyelographic arachnoiditis, although not detected after clinical myelography [1], has been reported after experimental myelography if sufficiently high concentrations of contrast medium were used [5, 6]. The major disadvantages of metrizamide are cost, side effects such as nausea and vomiting, and risk of seizures. Iohexol, a new nonionic aqueous material, has been developed for myelography. We compared iohexol and metrizamide with respect to the likelihood of postmyelographic arachnoiditis. To determine if iohexol was potentially safer than metrizamide, both contrast media were used in larger concentrations per unit of body weight than should be used clinically.

Materials and Methods

We have previously used monkeys for experimental myelography [5–10]. For the present study, 16 bonnet monkeys (5–7 kg) were divided into four groups after they had completed a 40 day quarantine and a series of mycobacterial and intestinal parasite testing. The types and amounts of contrast media used for myelography in the four groups are shown in table 1. Groups 1 and 2 received, per unit of body weight, almost five times the recommended clinical dose of the contrast medium. Groups 3 and 4 received roughly the equivalent of a high clinical dose.

The animals were fasted overnight prior to the myelogram, but were given fluids ad lib. Phencycladine hydrochloride (2 mg/kg) and atropine (0.12 mg) were given intramuscularly for sedation before the procedure. The animals' lower backs were shaved and disinfected. The animals were then placed prone on a tilting myelographic table, the head end of which was tilted 15° above horizontal. Lumbar puncture was performed with a 22 gauge disposable spinal needle at the L3–L4 interspace. A 1.2 ml quantity of cerebrospinal fluid was withdrawn and then the contrast medium was injected under fluoroscopic monitoring. Radiographs were obtained at 1 and 5 min after the intrathecal injection of contrast

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TABLE 1: **Arachnoiditis from Experimental Myelography with Iohexol or Metrizamide**

Group: Animal No.	Weight (kg)	Myelographic Evidence of Arachnoiditis	Histologic Arachnoiditis Score*
1 (Iohexol 3.6 ml, 370 mg I/ml):			
290	10.5	No	8
299	6.9	No	5
300	5.9	No	0
301	6.2	No	0
2 (Metrizamide 3.6 ml, 370 mg I/ml):			
287	7.2	Block, L5–L6	17
288	8.7	No	9
289	8.3	Partial block	19
291	7.1	No	4
3 (Iohexol 1.2 ml, 300 mg I/ml):			
334	4.2	No	3
335	4.1	No	6
336	3.8	No	6
337	3.5	No	4
4 (Metrizamide 1.2 ml, 300 mg I/ml):			
340	3.7	No	9
343	3.3	No	5
344	3.2	No	10
346	3.5	No	8

* Severity of arachnoiditis based on scores in previous studies: 0–8, no arachnoiditis; 9–16, mild arachnoiditis; 17–24 moderate arachnoiditis; and 25–36, severe arachnoiditis.

medium. The animals were placed in a sitting position in primate restraint chairs 15 min after injection. The animals were returned to their cages 16 hr later.

Repeat myelography and euthanasia were performed 12 weeks later. The dural sac and its contents were removed, fixed in formalin, sectioned, and stained in routine manner [10]. Sections at L5, L6, and L7 were examined for evidence of arachnoid fibrosis, inflammatory cell inflammation, nerve root sheath narrowing, and hemorrhage. Nine regions were each scored on a scale of 0–4 for arachnoiditis. These nine regions included the subarachnoid space, the arachnoid membrane, and the subdural space at L5, L6, and L7. The regions were scored 0 for no evidence of fibrosis, 1 for questionable evidence, 2 for mild fibrosis, 3 for moderate fibrosis, and 4 for severe fibrosis. The scoring was performed by the neuropathologist (K. C. H.) without knowledge of the treatment protocol or the myelographic results. The maximal possible score was 36. On the basis of control and treated animals in previous studies, 0–8 were considered normal scores, 9–16 mild arachnoiditis, 17–24 moderate arachnoiditis, and 25–36 severe arachnoiditis.

Results

All myelograms were technically satisfactory with respect to subarachnoid placement of the contrast medium and excellent opacification of the subarachnoid space and root sheaths. In groups 3 and 4, iohexol or metrizamide effectively demonstrated the subarachnoid space from about L2 to L6. In groups 1 and 2 animals, the entire lumbar space and much of the thoracic subarachnoid space were opacified by the larger volume of contrast medium. In group 1 animals given the larger dose of iohexol, neither the second myelogram nor the postmortem examination of the arachnoid revealed significant evidence of arachnoid scarring or inflammation (table 1). In some anatomic sections, slight thickening or fibrosis was noted in the arachnoid, the subdural space, or the nerve root sheath. In one animal, slight narrowing of a root sheath secondary to fibrosis was noted, and, in another animal, there was some epidural hemorrhage attributable to the myelogram just before sacrifice. No inflammatory cell inflammation was seen. The scores for arachnoiditis ranging from 0 to 8 (table 1) are indistinguishable from normal or control animals in previous studies [5–10].

In two group 2 animals given the larger dose of metrizamide, the myelogram 12 weeks after the test myelogram revealed a complete or partial block of the subarachnoid space due to arachnoid scarring (table 1). Histologic examination of the arachnoid in the four animals showed slight to moderate fibrosis in the arachnoid, subdural space, or nerve roots. Some of the root sheaths appeared significantly narrowed. Slight inflammatory cell inflammation with lymphocytes and polymorphonuclear cells was noted in some animals. Epidural hemorrhage secondary to the recent myelogram was also noted in one animal. With moderate arachnoiditis in two animals and mild arachnoiditis in one, the scores in this group were 4–19. The chance that the scores in groups 1 and 2 differed fortuitously was slightly greater than 10% ($t = 24$, Wilcoxan rank sum test).

The second myelograms in group 3 animals showed no changes of arachnoiditis. Histologic study revealed few abnormalities. A few fibrotic changes were detected in this group but no nerve root sheath narrowing or inflammatory cell inflammation. The arachnoiditis scores were 3–6 (average of 5). These scores do not suggest arachnoiditis.

In group 4 animals, no important differences were observed between the first and the second myelograms. Some fibrotic changes were detected in the subarachnoid or subdural spaces or root sheaths. In some sections, the arachnoid or the dura appeared thickened and infiltrated with

lymphocytes and polymorphonuclear cells. Some nerve root sheaths were narrowed slightly because of fibrosis. The scores were 5–10 (average, 8). These scores signified mild arachnoiditis in two animals. The differences between scores in Groups 1, 3, and 4 were not statistically significant (Wilcoxan rank sum tests).

Discussion

Results from experimental myelography on primates have correlated very well with clinical observations. In monkeys, iocarmate produced arachnoiditis [5–8] as it did in clinical practice [1, 6, 9, 10], while metrizamide did not unless used in excessive amounts [6, 9, 10].

In this study, metrizamide produced arachnoiditis as in previous studies of experimental metrizamide myelography. The concentrations of metrizamide used both in groups 2 and 4 exceeded prudent clinical practice. As in previous studies, the severity of arachnoiditis increased as larger concentrations of metrizamide were used.

In the present studies, iohexol, even in very large concentrations, did not produce arachnoiditis. Although the number of subjects was small, these experimental studies suggest that iohexol used in concentrations under 300 mg I/ml should not produce arachnoiditis in clinical myelography.

Minimizing the intrathecal concentrations of aqueous contrast media, promoting hydration of patients, and selecting patients without block of the lumbar execretory roots for contrast media probably decrease the risk of postmyelographic arachnoiditis [11–15]. With equally good selection of patients and performance of myelography, iohexol should have at least the same margin of safety as metrizamide with regard to postmyelographic arachnoiditis.

The radiographic properties of iohexol are comparable to metrizamide. Excellent demonstration of the subarachnoid space was obtained routinely. The elimination of the contrast medium does not take place with noticeably greater rapidity than metrizamide.

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