Letters to the Editor

CEREBRAL ABSORPTION OF METRIZAMIDE

SIR,—Metrizamide ('Amipaque', Winthrop Laboratories) was released in Australasia for general use in the lumbar spine in August, 1979, and for use, in some centres only, for examinations of the thoracic and cervical spine in November, 1980. Because there seem to have been no reports of adhesive arachnoiditis following intrathecal insertion, the water-soluble compound has been considered to have great potential. However, neurotoxicity has been reported.[1-4] The passage of metrizamide between CSF and brain has been studied in the rabbit[5] and in man.[6] It has been suggested that metrizamide passes through grey-matter by simple diffusion and that it is largely distributed in the extracellular fluid. No changes had been found in the white-matter. However, with the introduction of metrizamide into this hospital it was immediately apparent that patients were having very severe delayed headaches and, in some cases, distressing nausea and vomiting. For this reason, the passage of metrizamide was monitored in eight patients for a period of 24 hours.

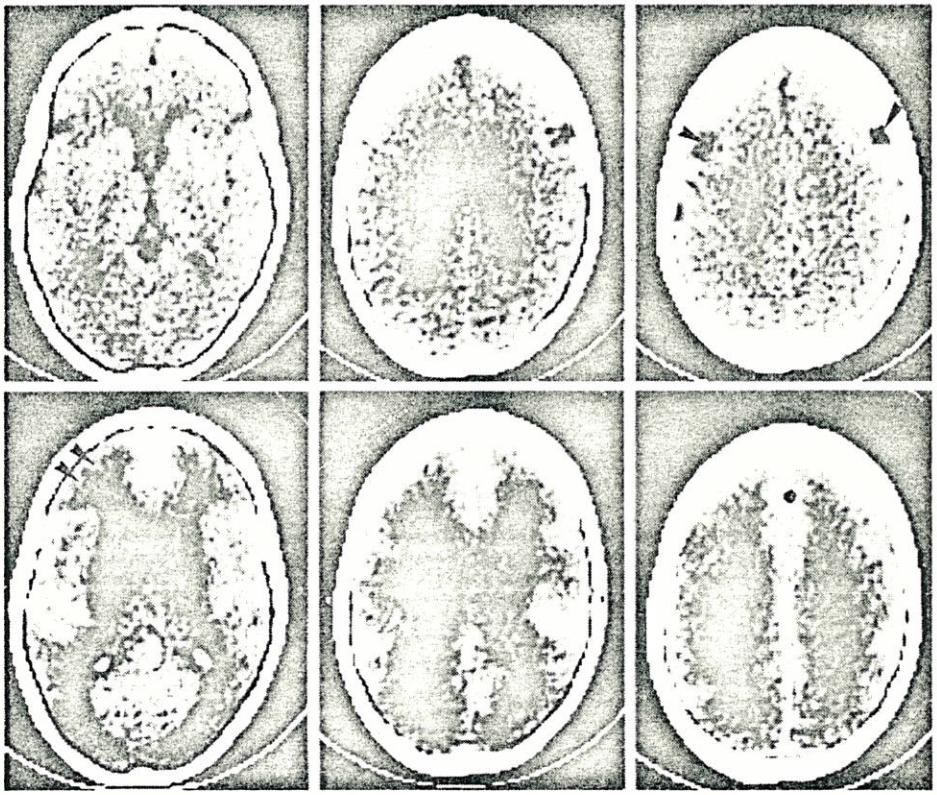
A non-contrast computerised tomographic scan on an EMI CT1010 head scanner was done 24 h before and 24 h after a spinal metrizamide study in the eight patients. A computer printout was prepared of the horizontal section at the level of the caudate nucleus to analyse the density of the frontal white-matter and the deep grey-matter of the caudate nucleus.[7] A pictorial display was also obtained (figure). Control studies were performed by examination of one patient 24 h before and 24 h after an iophendylate ('Myodil', 'Pantopaque') myelogram and of three patients 24 h before and 24 h after a diagnostic lumbar puncture.

Metrizamide was inserted into the lumbar theca and tilted only as far cranially as T12 (four patients) or it was inserted into the lumbar theca but later tilted into the cervical region (one patient) or it was inserted by lateral cervical puncture at C1/C2 (three patients).

Our study is not dissimilar to that of Caillé et al.[6] but those workers did not do baseline scans before the insertion of metrizamide, they did not have controls, and they did not find changes in white-matter.

As the changes we observed in both white and grey matter (see table) may have been due to the lumbar puncture itself or to the changes in intracranial pressure during tilting of the patient, we also studied three patients booked for diagnostic lumbar puncture for suspected multiple sclerosis and in one patient undergoing iophendylate myelography of the entire spine. Changes occurred in

1. Picard L, Vespignani H, Vieux-Rochar P, Moret CH, L'Esperance G, Montaut J, Weber M, Roland J. Serious neurological complications of metrizamide myelography. *J Neuroradiol* 1979; **6**: 3–14.
2. Rubin B, Horowitz G, Katz RI. Asterixis following metrizamide myelography. *Arch Neurol* 1980; **37**: 522.
3. Schmidt RC. Mental disorders after myelography with metrizamide and other water-soluble contrast media. *Neuroradiology* 1980; **19**: 153–57.
4. Bertoni JM, Schwartzman RJ, Van Horn G, Partin J. Asterixis and encephalopathy following metrizamide myelography: investigations into possible mechanisms and review of the literature. *Ann Neurol* 1981; **9**: 366–70.
5. Fenstermacher JD, Bradbury MWB, du Boulay G, Kendall BE, Radu EW. The distribution of ^{123}I-metrizamide and ^{125}I-diatrizoate between blood, brain and cerebrospinal fluid in the rabbit. *Neuroradiology* 1980; **19**: 171–80.
6. Caillé JM, Guibert-Trainer F, Howa JM, Billerey J, Calabet A, Piton J, Cerebral penetration following metrizamide myelography. *J Neuroradiol* 1980; **7**: 3–12.
7. Cala LA, Thickbroom GW, Black JL, Collins DWK, Mastaglia FL. Brain density and cerebrospinal fluid space size: CT of normal volunteers. *Am J Neuroradiol* 1981; **2**: 41–47.



CT scans before and after metrizamide.

63-year-old woman given 300 mg iodine/ml for a study of cervical as well as lumbar region.

Upper row: pre-metrizamide CT scan demonstrating three representative levels. Arrows show small peripheral cortical infarcts, top right.

Lower row: post-metrizamide CT scan comparable levels. Cortical infarcts no longer visible. Ventricular system almost obliterated. Frontal white-matter increased 10 Hounsfield units (arrows bottom left).

CHANGES IN DENSITY OF WHITE AND GREY MATTER AFTER METRIZAMIDE, DIAGNOSTIC LUMBAR PUNCTURE, OR IOPHENDYLATE

Sex, age	Iodine conc. (mg/ml)	Change in density (Hounsfield units) of:	
		White-matter	Grey-matter
Metrizamide: Lumbar:			
F, 63	203	−3 ($p<0.01$)	−2 ($p<0.05$)
M, 30	203	NS	+4 ($p<0.01$)
M, 58	170	+7 ($p<0.001$)	NS
M, 62	300	NS	NS
Metrizamide: Lumbar tilted to cervical:			
F, 63	300	+10 ($p<0.001$)	+3 ($p<0.01$)
Metrizamide: Lateral cervical puncture			
M, 38	220	NS	+7 ($p<0.001$)
F, 22	220	NS	+2·5 ($p<0.01$)
F, 58	220	+3 ($p<0.01$)	+4 ($p<0.01$)
Diagnostic lumbar puncture:			
F, 32	..	+3 ($p<0.01$)	NS
F, 33	..	+4 ($p<0.01$)	NS
F, 21	..	NS	+3 ($p<0.01$)
Iophendylate myelogram:			
M, 59	..	NS	NS

NS = not significant

white and grey matter after diagnostic lumbar puncture and after insertion of metrizamide but not after the iophendylate myelographic study. Possibly this reflects fluid shift from one compartment to another, but in any event changes in value similar to those seen in controls cannot be attributed solely to metrizamide. However, one lumbar metrizamide study increased the density of white-matter by 7 Hounsfield units; when metrizamide was introduced into the lumbar theca and tilted to the cervical region white-matter density increased by 10 units; and in one patient lateral cervical puncture increased grey-matter density by 7 units. These cases may show additional insult from the metrizamide itself. Curiously, the single iophendylate case did not even show the degree of change found with diagnostic lumbar puncture. This may relate to the manner in which this contrast medium is introduced under television control but the oily medium necessitates a 19 gauge needle whereas in the diagnostic cases a 22 gauge needle was used which should cause a smaller CSF leak.

Considerable reduction was noted in ventricular size and the subarachnoid spaces were obliterated (figure). This feature was noted in two of the fourteen cases examined by Caillé et al.[6] It may indicate cerebral swelling. All patients having metrizamide felt sufficiently well to either walk or travel in a wheelchair back to the ward, but 15 h later they complained of severe headache, nausea, and vomiting, so the postulate of cerebral swelling may well be substantiated by these clinical features. Metrizamide may become bound to cerebral tissue.[5] Certainly the severity of the delayed symptoms seemed directly related to the iodine concentration used. The possibility of the existence of cerebral swelling may have an important bearing on the choice of anaesthesia for patients requiring lumbar laminectomy within 24 h of a metrizamide study.

The long-term effects on cerebral and spinal cord tissue (e.g., scarring) can only be speculated upon at this stage as the longest follow-up is only of the order of eleven years. Toxic effects from other materials used in medicine have had a latent period of 20–30 years in some instances.

This small study suggests that patients for whom a rise in intracranial pressure due to swelling may be harmful, should have the spinal theca examined with iophendylate rather than metrizamide.

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