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Iotrol, a New Myelographic Agent: 1. Radiography, CT, CSF Clearance, and Brain Penetration

C. W. Kerber,¹ M. Sovak,² R. S. Ranganathan,² and C. B. Heilman¹

Four new myelographic agents, metrizamide, iopamidol, iothexol, and iotrol, were studied in the subarachnoid space of cynomolgus monkeys. Plain films and computed tomographic scans documented the transport of each material throughout the space and into the brain. At the concentration used (300 mg I/ml), all gave good radiopacity for myelography and delineation of the cerebral subarachnoid space. All four cleared similarly from the ventricular system. Metrizamide, however, penetrated the brain in greater degree and persisted longer than the other three agents. Next in persistence was iopamidol and least, and both statistically equal, iotrol and iothexol.

An ideal myelographic contrast agent should be biologically inert, easily deliverable, and rapidly excretable. It should mix with cerebrospinal fluid (CSF) to outline fine structures and be radiodense enough to be seen even in large patients. Metrizamide has become widely accepted as an improvement over the oily myelographic media, but it is not ideal. Metrizamide is unstable in solution and has neurotoxicity that is disturbing to both patient and clinician. The degree of penetration of metrizamide into the neurologic tissue and its ingress into the cranial subarachnoid space after instillation at the spinal level was found to correlate with the incidence of side effects [1-7]. We wondered whether the new nonionic isotonic dimer, iotrol [8], would penetrate and persist in the neurologic tissue of a nonhuman primate to the same substantial degree as metrizamide. The toxicity of contrast media can be expected to depend not only on the compounds' location, but mainly on their chemotoxicity. The purpose of our study was to evaluate a new dimer isotonic at 300 mg I/ml in experimental myelography. The clearance of four nonionic contrast agents from the cerebral ventricles and the degree of their penetration into the gray and white matter of monkeys was studied.

Materials and Methods

Cynomolgus monkeys weighing 3-3.5 kg were anesthetized with atropine, 0.05 mg/kg, and ketamine, 30 mg/kg. Baseline coronal scans were then obtained on an Ohio Nuclear (Technicare) 2010 computed tomographic (CT) scanner. Additional ketamine was injected as needed. Scanner factors of 130 kVp and 150 mAs were used. Appropriate phantom testing kept baseline values within 5%.

With the monkeys in a small chair, their backs were shaved and prepped, and a short-bevel 22 gauge needle was placed into the lumbar subarachnoid space over the second lumbar vertebral body under fluoroscopic control. One ml of cerebrospinal fluid was removed and 0.5 ml/kg (at 300 mg I/ml) of one of the four contrast

agents was introduced, again with fluoroscopic control. A frontal spine radiograph was obtained. The monkey was then placed head-down for 4 min. A lateral skull film then demonstrated filling of the basal cisterns and subarachnoid space. The monkey was then placed in the scanner and scanned as before. Repeat scans were obtained at 24 and 48 hr.

For each monkey, six densitometric samples using a standardizing mat and a standardized densitometric window were taken from the gray matter, and two samples were taken from the white matter of the brain. One sample was obtained from the area of one of the lateral ventricles. In order to ascertain that the contrast material passed in sufficient quantity into the subarachnoid space of the head, scans and densitometric readings were obtained from the region of the sylvian fissure immediately after the inversion. The minimum density considered useful was 150 Hounsfield units (H).

For the same compound, the density averages in Hounsfield units with standard deviations for the same samples were determined, and increase/decrease of density over the baseline was calculated. The consistency of the baseline densitometric readings over the three areas studied, that is, third ventricle, gray matter, and white matter, was established by analysis of variance of the raw data. Statistical significance of differences among the four studied media, established by the Student *t* test, was at 98% level of confidence.

Results

In the animals in which subarachnoidal injections succeeded, there was no significant difference among those readings. The subarachnoid spaces of the cynomolgus was extremely small in the upper lumbar area, and, as a result, 32% of all injections proved to be subdural, which necessitated repetition of the procedure after a 1 week period.

Analysis of variance of the raw data offered control of the consistency of the baseline densitometric readings over three areas studied (third ventricle, gray matter, and white matter). Each structure showed a statistical equality for the same animals.

The densitometric data obtained from the lateral ventricles immediately after the injection served as baseline, that is, 100%. Percentage of the remaining density with elapsed time is shown in figure 1A. There was no statistical difference among the data for all four components.

Densitometry of the cortical gray matter immediately after the injection was not found helpful inasmuch as the thickness of the CT scan slice would, in an unpredictable manner, encompass some densitometric reading from the subarachnoid space, which at that time contained a high concentration of contrast media. Therefore,

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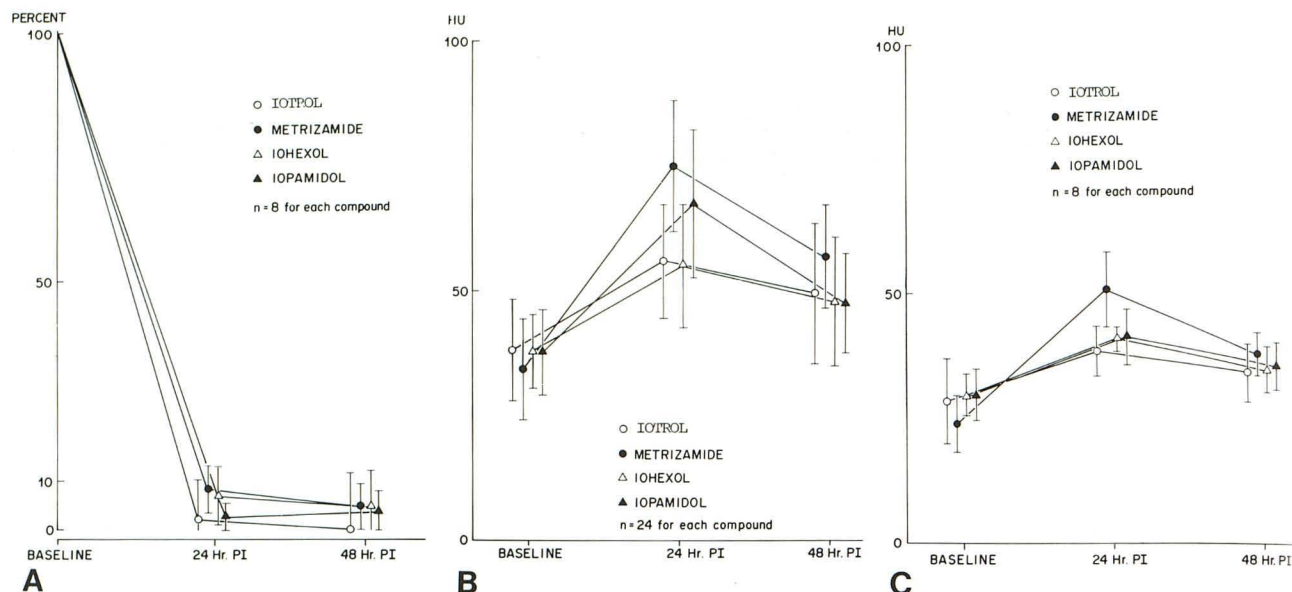


Fig. 1.—Findings after myelography. Percentage density of third ventricle (A) and average densities (with SD) of gray (B) and white (C) matter. PI = postinfusion.

only 24 and 48 hr postinfusion values were used for calculation. In figure 1B, we see that at 24 hr postinfusion densitometric readings showed an increase of 56% for iotrol and 42% for iohexol (these were statistically equal). Iopamidol produced a statistically significant increase of 85.5% and so did metrizamide with a value of 132.7%. At 48 hr after infusion the only statistically significant different value from the other agents was that of metrizamide, which remained increased by 67.6% over the baseline. Iopamidol was 25.3%, iotrol was 35.3%, and iohexol was 27.1%.

Figure 1C shows the results of a density increase in the white matter at 24 and 48 hr after infusion. The density averages of the samples were statistically significantly increased from the baseline. Thus, for metrizamide, the average was 117.6%, while the density for iohexol was 39.9%, for iopamidol 41.4%, and for iotrol 44.9%, all statistically equal. At 48 hr after infusion the density for iotrol was 26.7%, for iopamidol 17.8%, and for iohexol 18.5%, all statistically indistinguishable, while the 64.7% increase for metrizamide was statistically different from those of the other compounds.

Discussion

The extracellular space of brain tissue and the subarachnoid space are continuous. Throughout the aqueous phase of extracellular space, consisting of hydrated mucopolysaccharides, solutes from CSF can migrate freely. This migration is governed mainly by simple diffusion into both the gray and white matter, although the gray matter may be compartmentalized [9, 10]. The latter work [10], using an enzyme (horseradish peroxidase), also demonstrated that large molecular size and osmotic effect do not affect penetration. This was substantiated by our experiments; although we do not know the absolute degree of penetration, iohexol and iotrol persisted in the cortical gray matter to a substantially lesser degree than iopamidol and metrizamide, with metrizamide surpassing iopamidol and also showing greater persistence at 48 hr when all three remaining compounds had decreased their concentrations considerably. The amount of metrizamide in the white matter was about three times higher than those of the other three compounds, both at 24 and 48 hr. The molecular weight of iotrol is roughly twice that of the other contrast media; iotrol is also isotonic. Yet, its persistence did not differ from iohexol, which, in turn, has higher hyperosmolality than the more persisting metrizamide. The degree of persistence, however, seems to correlate with the degree of neurotoxicity. Several studies ranked the four media studied in decreasing order of neurotoxicity as iotrol, iohexol, iopamidol, metrizamide [8, 11]. Since neurotoxicity is determined primarily by

the molecule's chemotoxicity, it can be speculated that a medium's persistence is a result of its effect on the mucopolysaccharides of the extracellular brain tissue space. It is possible that such an interruption changes the gel's physical property, resulting in an impediment of the aqueous phase flow. The persistence of contrast media could hence be considered either a cause or a symptom of neurotoxicity based on this mechanism. Because of the diffusion principle, some penetration of intrathecally injected contrast media into the brain tissue is unavoidable. Therefore, in clinical myelography, only media of the lowest neurotoxicity, that is, iotrol, should be used.

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