Experimental Pantopaque ventriculography

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The injection of Pantopaque into the ventricles of normal and hydrocephalic dogs produced a variety of acute and chronic pathological changes. Multiple granulomatous lesions developed in the ventricular wall and the surrounding brain parenchyma, choroid plexus, cranial nerves, and arachnoid membrane. Adhesions formed in several areas of the ventricles, and Pantopaque became encysted in the third ventricle and tips of the temporal horns. In general there were more serious changes in the animals that had a greater degree of hydrocephalus. Relatively mild lesions were noted in normal animals.

KEY WORDS - dog - hydrocephalus - Pantopaque - ventriculography - tissue reaction - pathological changes

In 1946 Bull introduced iodophendylate (Pantopaque, Myodil) ventriculography and during the next 4 years used this neuroradiologic technique on 80 patients without adverse effects. Microscopic examination of the brains from four of these patients, who subsequently died from other causes, revealed no evidence of ependymitis. Thus, from its inception, Pantopaque ventriculography has been regarded as a safe technique.

During the early 1950's only a few reports concerning this technique appeared in the literature. Starting in the late 1950's, however, a new interest developed in the use of Pantopaque as a contrast medium for the diagnosis of intracranial lesions. In the 1960's Pantopaque intracranial examination, particularly for the study of the posterior fossa, became more and more accepted. In fact, many centers now consider Pantopaque the contrast medium of choice for the demonstration of cerebellopontine pathology, particularly the acoustic neuromas.

Positive contrast ventriculography, Pantopaque ventriculography, posterior fossa myelography, myelonecephalography, and cerebellopontine cisternography represent different variations of the use of iodophendylate radiography in the clinical study of the intracranial cerebrospinal fluid (CSF) spaces. These procedures are becoming quite popular, in spite of reports of damage caused by this contrast medium.

Experimental Pantopaque toxicity studies have been remarkably few. In the original report, autopsy studies of dogs that had been injected intrathecially with Pantopaque showed, in an unspecified number of animals, cystic formations around and within the spinal cord. These lesions were apparently less severe than the comparable lesions caused by the more viscous iodinated poppy

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seed oil (Lipiodol). Fisher\textsuperscript{8} in 1965 showed uniform histological evidence of acute and chronic meningeal irritation after Pantopaque myelography in cats. We have been able to find only three reports concerning experimental Pantopaque ventriculography.\textsuperscript{10,12,13}

Because of this paucity of available information, we have undertaken an extensive study of experimental Pantopaque ventriculography. For one part of this study, we have purposely chosen to use beagles, a strain of dogs that normally has a particularly high incidence of communicating hydrocephalus. In these animals we anticipated a longer than usual retention of the contrast medium within the ventricular system. This offers some obvious advantages if compared to a model in which free-flowing CSF conditions are present. In this report we present evidence that the injection of Pantopaque into the ventricles of purebred beagle dogs can produce devastating results.

**Materials and Methods**

We used 31 apparently healthy, purebred beagle dogs, ranging in age from 7 days to 3 years. With the exception of five animals, all of the dogs were procured from one commercial colony; in a previous study of over 200 dogs from this colony, it had been noted at necropsy that a high percentage of the animals had a communicating type of hydrocephalus apparently resulting from inflammatory infiltrates in the subarachnoid spaces of the brain.\textsuperscript{5,16} Ventriculograms of the animals in the current study revealed that 26 of the 31 dogs actually had communicating hydrocephalus.

Each of the 31 dogs was inoculated with 0.5 to 2.0 ml of Pantopaque into the frontal horn of one lateral ventricle. The animals were sacrificed at intervals varying from 1 hour to 7 months after Pantopaque ventriculography. In addition, the brains of 10 uninoculated litter mates of these dogs were examined grossly and microscopically. Except for five animals that died, each animal was anesthetized with an overdose of sodium pentobarbital and then perfused through the heart with 10% formolsaline containing 1% acetic acid. The brains were removed, sec-

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**Fig. 1.** *Left:* Transverse section of the frontal horn from an animal 7 months after Pantopaque ventriculography. Note the severe inflammatory response that extends into the neighboring brain parenchyma in both the medial and lateral walls. No normal ependyma remains. SP = septum pellucidum; CN = caudate nucleus. H & E, x 20. *Right:* Transverse section of the inferior angle of the frontal horn from another animal 7 months after Pantopaque ventriculography. Note the severe inflammatory lesions in the ventricular wall and surrounding brain parenchyma. No normal ependyma remains. H & E, x 20.
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Fig. 2. Transverse sections at the level of the lateral recess of the 4th ventricle from two animals 6 and 7 months after Pantopaque ventriculography. **Left:** Granulomatous lesions and perivascular infiltrates in the choroid plexus, cerebellum (CB), and dorsal cochlear nucleus (DCN). H & E, ×11. **Right:** Granulomatous lesions and perivascular infiltrates are seen in the 8th nerve (N8) and choroid plexus (CP). H & E, ×36.

**Results**

*Animals with Communicating Hydrocephalus (26 dogs)*

**Ventricular Wall Changes.** Inflammatory lesions were found in various parts of the ventricular wall in all animals, being most severe in the animals having a greater degree of hydrocephalus. During the first few days following the injection of Pantopaque, the lesions consisted primarily of polymorphonuclear leucocytes with a few macrophages and lymphocytes. The infiltrates were located in the ventricular wall in areas that apparently were subjected, because of gravity, to the greatest degree of Pantopaque exposure, namely: 1) the inferior aspect of the frontal horn, 2) the temporal horn, 3) the inferior aspect of the third ventricle, and 4) the floor of the fourth ventricle. The ependyma in many of these areas was completely eroded.
Fig. 3. Transverse section of the choroid plexus in the body of the lateral ventricle from an animal 1 day after Pantopaque ventriculography. Note the large number of polymorphonuclear leucocytes invading the ependyma and underlying stroma. H & E, × 60.

Away. In those animals sacrificed at later times, extensive granulomatous lesions eroding through the ventricular wall and into the brain parenchyma were observed in these same areas (Fig. 1). The granulomatous lesions consisted primarily of large numbers of macrophages and lymphocytes. In addition, the Pantopaque had caused the formation of adhesions in the frontal and temporal horns in several animals. In three animals there were inflammatory infiltrates and fibrosis in the dorsal cochlear nucleus and eighth nerve beneath the lateral recess of the floor of the fourth ventricle (Fig. 2).

Choroid Plexus Changes. Inflammatory lesions were found in the choroid plexus of all animals (Figs. 2, 3, and 4). All ventricles were involved but the most severe lesions were seen in the inferior aspect of the choroid plexus in the temporal horn and in the choroid plexus of the fourth ventricle. During the first few days following Pantopaque ventriculography, the infiltrates in the choroid plexus consisted primarily of polymorphonuclear leucocytes invading the ependymal lining and stroma (Fig. 3). Later, multiple granulomatous lesions with large numbers of macrophages and lymphocytes were observed (Figs. 2 and 4). In those animals sacrificed from 3 to 7 months following the injection of Pantopaque, a considerable amount of fibrosis was noted in the choroid plexus.

Arachnoid Membrane Changes. Although inflammatory lesions were observed in the arachnoid of most animals, the extent of involvement of this structure varied considerably. Cellular infiltrates were most frequently seen in the trabecular meshwork of the basal cisterns (Fig. 5). The lesions were similar to those described previously in other areas and varied from the acute inflammatory type observed in the animals sacrificed during the first few days following ventriculography to a more chronic granulomatous type seen in animals sacrificed at later times. Small inflammatory foci were also seen frequently in various locations of the arachnoid over the hemispheric convexity and sometimes in the arachnoid surrounding the lower brain stem. Perivascular infiltrates and granulomatous lesions were often present in the cranial nerves passing through the subarachnoid spaces.

Severe Complications. Of particular interest were the severe changes that occurred in nine out of 13 animals that survived from 4 to 7 months following Pantopaque ventriculography. Four of the nine animals died suddenly. These four as well as two others had severe hydrocephalus that was of a much greater magnitude than that noted at the time of Pantopaque ventriculography (Figs. 6 and 7). Microscopic examination revealed that the aqueduct of Sylvius was considerably stenosed in three of these animals and the intraventricular foramina in two (Fig. 8). The stenosis was presumably caused by inflammatory reactions to the Pantopaque. Pantopaque-filled cysts of the third ventricle were present in six animals (Figs. 7 and 9), and large granulomatous masses were found in three of the cysts (Fig. 9). Pantopaque-filled cysts were also observed at the tips of the temporal horns in five of the animals (Fig. 7).

Areas of necroses and cellular infiltration
were found adjacent to the needle track in nearly all animals inoculated with Pantopaque; thus in some animals a substantial amount of brain parenchyma was destroyed (Fig. 10).

Animals without Communicating Hydrocephalus (5 dogs)

As previously mentioned, five of the animals had normal ventricles at the time of Pantopaque ventriculography. These animals were individually sacrificed 1, 2, 3, 5, and 7 months later. Microscopic examination revealed that granulomatous lesions, of a mild degree, were present in the ventricular wall, choroid plexus, and arachnoid membrane.

Uninoculated Hydrocephalic Litter Mates (10 dogs)

Ten litter mates of the dogs that received Pantopaque were used as controls. At autopsy it was observed that these animals had communicating hydrocephalus varying in degree from mild to moderate. Four of the dogs had no lesions and the lesions in the other six were quite different from those found in the Pantopaque-treated animals,
Fig. 6. *Left:* X-ray of Dog D-31 at the time of Pantopaque ventriculography. The animal had a moderate degree of dilation of the ventricular system. *Right:* Gross brain section of Dog D-31 necropsied 7 months after Pantopaque ventriculography. The animal had hydrocephalus that was of a much greater magnitude than that indicated at the time of ventriculography.

rather being characteristic of changes previously described in hydrocephalic beagles. Diffuse monocytic infiltrates were frequently present in the leptomeninges and sometimes in the choroid plexus and were particularly prominent in the basal cisterns; they were probably responsible for the hydrocephalus. Neither granulomatous lesions nor cysts were observed in these animals. Significantly, the hydrocephalus in these animals was of a mild to moderate degree and never as severe as that seen in the dogs subjected to Pantopaque ventriculography.

**Discussion**

This study clearly demonstrates that the injection of Pantopaque into the ventricles of an animal whose normal flow of cerebrospinal fluid is compromised can produce very serious complications. At the time of Pantopaque ventriculography 26 of the 31 dogs in this investigation had a communicating type
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of hydrocephalus varying from a mild to moderate degree. Within 5 months following the ventriculograms, four animals died suddenly. These animals as well as two others that were sacrificed at 7 months had severe hydrocephalus that was of a much greater magnitude than that noted at the time of Pantopaque ventriculography. The hydrocephalus was also more severe than that observed in any of the control animals or that found in a previous study of over 200 dogs from this colony. Cellular reactions to the contrast medium were so severe that multiple granulomatous lesions were observed in several areas including the ventricular wall and the surrounding brain parenchyma, choroid plexus, and arachnoid membrane. Adhesions had formed in several areas of the ventricles, and Pantopaque had become encysted in the third ventricle and tips of the temporal horns.

Encysted Pantopaque was not observed in those animals that either did not have hydrocephalus or were mildly hydrocephalic at the time of Pantopaque ventriculography. However, all of these animals had some degree of fibrosis of the choroid plexus and granulomatous lesions present in the ventricular wall, choroid plexus, and leptomeninges. This, of course, suggests that in the presence of a nearly normal rate of cerebrospinal flow the Pantopaque is more readily cleared from the ventricular system and causes less damage. Factors other than stagnation may also contribute to the degree of damage caused by Pantopaque. Studies of experimental hydrocephalus in the monkey and dog indicate that structural and permeability changes oc-

Fig. 8. Transverse section of the aqueduct of Sylvius from an animal 7 months after Pantopaque ventriculography. Note the severe stenosis caused by the inflammatory reaction to the Pantopaque. Very little normal ependyma is left. H & E, ×35.

Fig. 9. Left: Gross brain section of an animal 6 months after Pantopaque ventriculography. Note the cyst in the third ventricle in which there is a large granulomatous mass (arrow). Right: Gross brain section of an animal 4 months after Pantopaque ventriculography. Note the cyst in the third ventricle in which there is a large granulomatous mass protruding ventrally through the ventricular wall (arrow).
cur in the ventricular wall soon after the onset of hydrocephalus. Such changes, accompanied by an increased intraventricular pressure, could possibly enable the Pantopaque to penetrate more readily through the ependyma into the underlying brain parenchyma.

It must be emphasized that during the past 2 years the brains of over 200 apparently normal dogs from this same colony have been examined and lesions like the ones present after Pantopaque ventriculography have never been observed. A high percentage of the control animals had monocytic subarachnoid infiltrates, but cysts and granulomatous lesions were never observed.

What is the relevance of this study to the clinical application of Pantopaque ventriculography? Obviously there are pitfalls involved in predicting the potential danger of a compound for humans based upon its toxic effect in a given species of animal. The lack of research on Pantopaque toxicity is alarming, however. Only three experimental studies of the use of Pantopaque ventriculography are cited in the literature. All were performed with dogs. One of these investigations involved an emulsified form of Pantopaque that is not used clinically. Another is a brief report of a study in 15 dogs in which the authors state that no significant changes were observed in the ependyma, choroid plexus, and brain parenchyma. They concluded that the ependyma and pia mater acted as barriers which prevented injury to the adjacent brain parenchyma. In the third study, which tested several contrast media, only two dogs were inoculated intraventricularly with Pantopaque. Microscopic examinations were not performed on the brains of these animals. The authors did not investigate this medium extensively because they considered that the low toxicity of intraventricular Pantopaque had been well documented.

Conclusions

The fact that Pantopaque has been used for 24 years in ventriculography and for 26 years in myelography, with only a relatively small number of reported unfavorable reactions, may be imparting a false sense of security. We have demonstrated the devastating effects of Pantopaque in an animal species whose CSF system is relatively stagnant. Since it is under comparable conditions (hydrocephalus) that Pantopaque ventriculography is most often employed in man, we feel it important to emphasize the potential dangers of its clinical use. In summary, we have presented experimental evidence that Pantopaque can cause damage to the ependyma, choroid plexus, brain parenchyma, arachnoid membrane, and cranial nerves of hydrocephalic dogs (beagles).

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References

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