An Experimental Evaluation of Pantopaque and Other Recently Developed Myelographic Contrast Media

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Since the original radiographic visualization of the spinal cord in 1919 (6), many different myelographic contrast media have been employed. Unfortunately, none has fulfilled all the requirements of an ideal contrast medium—no toxicity, complete and rapid absorption, good radiographic contrast, and miscibility with the cerebrospinal fluid (3, 8). Of the materials currently used, ethyl iodophenyl-undecylate (Pantopaque) has radiographic shortcomings and has been associated with significant toxicity—intravasation, adhesive arachnoiditis, severe meningeal reaction, and death—as recently summarized by Di Chiro and Fisher (8). Toxic reactions have also been reported from the water-soluble compound, methiodal (Abrodil, Skiodan), which requires the administration of a spinal anesthesia and has thus been employed clinically only in examination of the lumbosacral area (9, 14-17, 22). Gas myelography has found only limited use because of the considerable skill required for its performance and interpretation, the faintness of the gas contrast, and its discomfort to the patient (8).

The search for a more satisfactory contrast medium has recently led to the investigation of three agents—SH 617L (Myographin) (25), Ethiodol emulsion (24), and meglumine iothalamate (Conray) (4, 5). Original reports would indicate that, though these agents differ considerably in their chemical composition, they have been claimed to possess a low toxicity, excellent radiographic contrast, and fairly rapid absorption from the subarachnoid space (Table I).

The present work is an attempt to compare the radiographic and toxicologic properties of these new contrast agents in animals.

**MATERIAL AND METHODS**

Thirty cats weighing 1.0-3.0 kg were divided into five groups to receive subarachnoidal injections of saline (controls), Pantopaque, SH 617L (20 per cent suspension in 5 per cent dextrose solution), Ethiodol emulsion, and Conray (60 per

<table>
<thead>
<tr>
<th>Table I: Properties of Recently Developed Contrast Media</th>
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<tr>
<td>Medium</td>
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<tr>
<td>SH 617L</td>
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<td>Ethiodol emulsion</td>
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<td>Conray</td>
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1 From the Hospital for Special Surgery affiliated with The New York Hospital—Cornell University Medical College, New York, N. Y. Accepted for publication March, 1966.
2 This work was supported by U. S. Public Health Service General Support Grant FR-00495 and Training Grant AM-541, and the Whitaker Foundation.
3 Supplied by E. Fougera and Company, Inc., Hicksville, N. Y.
Partial laminectomies at the lower lumbar spinal level were performed under sterile operating-room conditions with the animals under light Nembutal anesthesia. Injections were then made directly into the subarachnoid space. In each group, 2 animals were to be sacrificed at one week, one month, and three months following injection. A dosage of 0.5 ml/kg of each material was used in the "one week" animals while 0.25 ml/kg was employed in the remainder. Postero-anterior and lateral spine roentgenograms were obtained immediately after injection and

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Figs. 1 and 2. Characteristic myelograms obtained with Pantopaque (A), SH 617L (B), Ethiodol emulsion (C) and Conray (D).

Fig. 1 (upper). Postero-anterior views.

Fig. 2 (lower). Lateral views.

*Supplied by Mallinckrodt Pharmaceuticals, St. Louis, Mo.*
just prior to sacrifice. Complete autopsies were performed in animals which died during the course of the experiment. In all cats the spinal cord and meninges were examined grossly and microscopically at cervical, thoracic, and lumbar levels. In addition, one cat was given a subarachnoidal injection of 20 per cent methiodal (0.5 ml/kg) and sacrificed one week later.

**RESULTS**

1. **Radiographic Characteristics:** Typical myelograms obtained with each of the contrast agents may be seen in Figures 1 and 2. Of the media tested, Pantopaque produced the most radiopaque-contrast column and provided the best definition of the cat subarachnoid space. The contrast densities of Ethiodol emulsion and Conray were somewhat less than that of Pantopaque while only a faint shadow was produced by SH 617L. Pantopaque tended to form droplets while the other contrast agents were freely miscible with the cerebrospinal fluid, thus providing total myelography. Though the caudal extent of the subarachnoidal space was well visualized with all media, the nerve roots and their sheaths were not clearly defined by any of the compounds evaluated.

2. **Toxicity:** The effects of subarachnoid injections of saline and different myelographic contrast media on the experimental animals are summarized in Table II. It may be noted that none of the cats died at the time of subarachnoid injection. During the injection of Conray, however, all the cats became hypopneic and several lost urine and feces. Similar reactions were seen in the one cat receiving methiodal.

Four cats died after administration of SH 617L and one after Pantopaque. Obvious paraplegia was noted in 2 animals receiving SH 617L (0.5 ml/kg or 100 mg/kg) prior to death. All these deaths were attributed to the effect of the contrast medium on the meninges. Meningitis was observed grossly and histologically. Cultures of the cerebrospinal fluid revealed no pathogens though microabscesses of the cord in the cat receiving
Pantopaque suggested a possible concomitant bacterial infection in this case (Fig. 3). Except for the presence of residual contrast material, no gross abnormalities of the spinal cord and meninges were noted in any of the other animals which were sacrificed.

On the basis of a histological examination of the spinal cord and meninges, the animals could be classified into the following well defined groups: (a) no recognizable reaction (Fig. 4); (b) small clusters of inflammatory cells along the pia-arachnoidal lining (Fig. 5); (c) marked infiltration of the subarachnoid space with inflammatory cells (Fig. 6); (d) alteration of the spinal cord itself (Table II). In 3 cats receiving SH 617L, degeneration of anterior horn cells was observed (Fig. 7). The spinal cord of one injected with Pantopaque revealed extensive myelomalacia. Pantopaque also produced some mild inflammatory response in the meninges of every animal receiving this compound. The spinal meninges and the cord of those animals injected with Ethiodol emulsion and Conray did not differ significantly from the controls. A normal spinal cord and meninges were also found in 2 cats surviving SH 617L administration.

III. Absorption: Conray, a water-soluble preparation, was completely absorbed from the subarachnoid space within two hours. SH 617L was much more slowly absorbed but was not visible radiographically after three months. Only traces of Ethiodol emulsion and small amounts of Pantopaque were evident after three months (Figs. 8 and 9).

DISCUSSION

In evaluating the results of this preliminary study, it is recognized that conclusions based on experimental animal data do not always necessarily apply to man. It is also noted that, in an attempt to emphasize any toxic properties which these compounds might possess, the dosages employed were larger (5—10X) than those recommended for man. Nevertheless, an experimental activity of this nature provides indicative information.
The severe meningeal reactions observed in 4 of 6 animals following SH 617L myelography would indicate that this compound has considerable toxic potential for man. This has, indeed, been confirmed by European clinical investigators in recent reports of mild-to-severe meningeal reactions to SH 617L (1, 7, 21). The relatively normal meningeal appearance of 2 surviving cats when examined at one and three months following SH 617L injection would suggest that the meningeal response produced by SH 617L is transitory and diminishes as the compound is absorbed. As this suspension of virtually insoluble radiopaque material would be expected to settle in the most dependent portions of the subarachnoid space, it is also possible that further histologic investigation of these areas might reveal

Fig. 7. Anterior horn cell degeneration (SH 617L).

<table>
<thead>
<tr>
<th>Material Injected</th>
<th>Length of Experiment</th>
<th>Gross Findings</th>
<th>Microscopic Findings</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Saline</td>
<td>1 week</td>
<td>normal</td>
<td>o</td>
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<tr>
<td></td>
<td>1 month</td>
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<td>3 months</td>
<td>normal</td>
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<tr>
<td>Pantopaque</td>
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<td>normal</td>
<td>#/#</td>
<td>Died 4 days after injection</td>
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<td></td>
<td>1 month</td>
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<td>3 months</td>
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<tr>
<td>SH 617L</td>
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<td>1 month</td>
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<td>3 months</td>
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<td>Died 2 days after injection</td>
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<td>Ethiodol Emulsion</td>
<td>1 week</td>
<td>normal</td>
<td>o</td>
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<td>1 month</td>
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<td>3 months</td>
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<td>Conray</td>
<td>1 week</td>
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<td></td>
<td>3 months</td>
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Legend
- o - No evidence of abnormality
- # - Small focus of meningeal inflammation
- ## - Marked meningeal inflammation
- ### - Marked meningeal inflammation and spinal cord changes
pathologic changes. For a fair comparison of the different media, however, the same spinal levels were studied in all animals. Pantopaque has previously been shown to produce significant meningeal irritation and even hydrocephalus in dogs (11, 12, 19, 20, 23). In this study, only one cat showed clinical evidence of Pantopaque toxicity, but every animal demonstrated some degree of meningeal inflammation histologically. This was usually characterized by isolated clumps of leukocytes along the pia-arachnoid lining, though one of the “chronic” animals showed a well defined inflammatory arachnoid cyst.

There is some experimental evidence to indicate that Pantopaque is more irritating to the meninges in emulsified form, implying that reduction of particle size increases the total area of exposure and thus promotes a greater meningeal response (13). The emulsion of Ethiodol (prepared with lecithin) used in this study, however, was extremely well tolerated by the animals. The spinal cords and meninges of these cats showed no significant abnormalities.

The behavioral reactions of cats during the injections of Conray and the hypertonicity of this compound, characteristic of all water-soluble media, would suggest that it might be extremely irritating and painful for unanesthetized human patients, but Conray myelography has been performed in at least 13 unanesthetized patients. With one exception, they tolerated the material quite well (4, 5). Some complained of transient headache and pruritus or “drawing sensations” in the lower extremities. Diluted Conray and lower total dosages might explain in part the mild reactions in these patients as compared to the cats in this study. In the present investigation, no pathologic changes of the meninges were observed following Conray injection. In this regard, it is of note that in one patient reported by Campbell et al. (5), hyperpyrexia, hypotension, and tachycardia developed, and death occurred twenty-four hours following Conray myelography. No gross or histologic changes attributable to Conray were found in this patient.

The anatomic differences of the cat and human spinal canal make it difficult to arrive at any firm conclusions regarding the comparative radiographic efficacy of the different media evaluated in this study. In particular, the cat subarachnoid space is quite small in comparison to that of man. Therefore, a compound with radiographic density of excellent diagnostic quality in man (i.e., methiodal) provides insufficient contrast for good spinal cord definition in the cat. It might be inferred that the recently developed media, being less dense, would be superior to Pantopaque in revealing anatomic detail on human myelograms. Recent clinical reports, however, show a growing dissatisfaction with the contrast provided by SH 617L (7). A new low density (13 per cent iodine) Pantopaque solution may prove to offer advantages over the usual solution containing 30.5 per cent iodine (10).

This study would indicate essentially complete absorption of the newly developed contrast media from the subarachnoid space within three months. Of interest, however, is that most of the Pantopaque also disappeared radiographically during that period of time—a rate of disappearance considerably higher than that previously observed in man (2, 18, 26). This would suggest either a very efficient absorption capability of the cat perineural lymphatics or possible dispersal of the medium into the intracranial subarachnoid space, which was not routinely studied. In any case, the observed rapid absorption of the non-water-soluble compounds, SH 617L and Ethiodol emulsion, must be viewed with scepticism. Further human studies are necessary to determine accurately the clinical absorption of these compounds.

**SUMMARY AND CONCLUSIONS**

Pantopaque, SH 617L, Ethiodol emulsion, and Conray were evaluated in cats
Figs. 8 and 9. Spine radiographs obtained three months after the subarachnoid injection of Pantopaque (A), SH 617L (B), Ethiodol emulsion (C), and Conray (D).

Fig. 8 (upper). Lateral views.
Fig. 9 (lower). Postero-anterior views.

with respect to toxicity, radiographic characteristics, and absorption.

Following Pantopaque myelography, the cats showed uniform evidence histologically of acute and chronic meningeal irritation. By virtue of its greater density, Pantopaque was superior to the other agents in the definition of the cat subarachnoid space. It was also the most poorly absorbed of the media tested.

SH 617L produced a faint contrast and caused severe meningitis in the animals, indicating a significant toxic hazard in its clinical use.

Ethiodol emulsion was characterized by satisfactory contrast, no demonstrable toxicity, and essentially complete absorption after myelography. This agent would
appear to show promise and warrants further investigation.

Conray was rapidly absorbed, produced adequate contrast, and caused no histologic evidence of toxicity in the cat. The animal behavior during injection and early clinical reports, however, suggest that further evaluation is necessary before this agent is used further in human myelography.

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REFERENCES

SUMMARIO IN INTERLINGUA

Evaluation Experimental de Pantopaque e de Altere Recentemente Disveloppate Substantias de Contrast Myelographic

Pantopaque, SH 617L, emulsion de Ethiodol, e Conray esseva evaluate in cattos relative a lor toxicitate, lor characteristicas radiographic, e lor absorption. Post myelographia a Pantopaque, le cattos monstrava uniformemente signos histologic de acute e chronic irritation meninge. Gratias a su plus grande densitate, Pantopaque esseva superior al altere agentes in le definition del spatio subarachnoide in cattos. Illo esseva etiam le minus fortemente absorbite del substantias testate. SH 617L produceva un debile contrasto e causava sever meningitis in le animales, suggere un significative risco de toxicitate in uso clinic. Emulsion de Ethiodol esseva characterisate per un contrasto satisfactori, nulle demonstrabile toxicitate, e un essentialmente complete absorption post le myelographia. Iste ultime agente pare esser sufficientemente promittente pro justificar investigationes additional. Conray esseva absorbite rapidemente, produceva adequate grados de contrasto, e causava nulle signo histologic de toxicitate in le cattos. Tamen le comportamento del animales durante le injection suggere—como le prime currentemente disponibile reportos clinic lo face—que un evaluation addition es necessari ante que iste agente pote esser usate plus extentemente in le myelographia hunam.