Iodinated Organic Compounds as Contrast Media for Radiographic Diagnoses

III. Experimental and Clinical Myelography with Ethyl Iodophenylundecylate (Pantopaque)¹

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Ethyl iodophenylundecylate is one of a number of iodinated organic liquids that has been studied as a contrast medium for myelography. This new medium is a mixture of isomeric esters of which the principal constituent is probably that shown in the accompanying formula. It contains 30.5 per cent iodine and has a density of 1.208 at 20°C. The name Pantopaque¹ was coined for this mixture to provide radiologists and clinicians with a convenient designation. The chemistry of this and of related diagnostic aids is discussed elsewhere (1, 2).

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\begin{align*}
\text{CH}_3 \\
\text{I} \quad \text{CH} \quad \textöl (\text{CH}_2)\textöl \text{COOC}_2\text{H}_5
\end{align*}
\]

Ethyl iodophenylundecylate (provisional).

Prior to its clinical use, ethyl iodophenylundecylate was tested intrathecally in dogs in a series of comparative experiments against iodized poppy-seed oil. In these tests the new medium proved to be much easier to handle, produced discomfort of shorter duration, and in most of the animals was almost completely absorbed within a year. The clinical results have paralleled those obtained in animal experimentation.

As is shown in Table I, iodized poppy-seed oil is twenty-two times as viscous as ethyl iodophenylundecylate at 25°C., and seventeen times as viscous at 37.5°C.

Because the new medium is so fluid, it is easily injected or removed with an 18- or 20-gauge needle and flows freely in the spinal canal immediately after injection. In dogs, however, where lumbar punctures are nearly impossible, and where the space relations of the canal are such that both media flow very slowly, practically none of the injected material can be removed.

Following intrathecal injection of 3 to 5 c.c. of ethyl iodophenylundecylate in dogs, there is a period of slight fever, lasting one or two days, as is shown in Chart I. During this time the dogs are clinically well, but a fair proportion may exhibit mild distress when the head is bent. After two or three days, however, this symptom dis-

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Table I: Coefficients of Viscosity of Myelographic Media

<table>
<thead>
<tr>
<th>Medium</th>
<th>25°C</th>
<th>37.5°C</th>
</tr>
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<tbody>
<tr>
<td>Ethyl iodophenylundecylate</td>
<td>0.372</td>
<td>0.217</td>
</tr>
<tr>
<td>Iodized poppy-seed oil</td>
<td>8.06</td>
<td>3.76</td>
</tr>
<tr>
<td>Ratio</td>
<td>1:22</td>
<td>1:17</td>
</tr>
</tbody>
</table>

Chart 1. Typical transient fever following intrathecal injection of ethyl iodophenylundecylate in dogs.

¹ These studies were aided by a grant from the Research Laboratories of the Eastman Kodak Company. They were presented before the Radiological Society of North America, at its Twenty-eighth Annual Meeting, Chicago, Ill., Nov. 30–Dec. 4, 1942, and submitted for publication in June 1944.

² Pantopaque is a registered trade-mark.
appears. With iodized poppy-seed oil, on the other hand, there is no fever, but the period of distress when the head is bent may persist for ten to fourteen days. Sections taken from the spinal cords of dogs sacrificed at varying intervals show that both media are encysted after a lapse of about six weeks. The encystment is particularly noticeable in the cauda equina area and is not found generally throughout the cord. Typical sections showing the type of encystment that occurs are reproduced in Figure 1. As is evident from these photomicrographs, the size of the cysts with ethyl iodophenylundeceylate is considerably less than that of those produced by iodized poppy-seed oil; this is probably referable to the greater viscosity of the poppy-seed oil. Cord sections taken at intervals from dogs injected intrathecally with ethyl iodophenylundeceylate show that the physiological response about the cysts is essentially a foreign body reaction.

Acute toxicities for ethyl iodophenylundeceylate were determined by intraperitoneal and intravenous injections. The LD 50 for intraperitoneal injections was found to be 4.6 gm./kilogram for mice and 19 gm./kilogram for rats. Control experiments with iodized poppy-seed oil showed no toxic effects with rats even when the medium was injected intraperitoneally at a level of 25 gm./kilogram. The injected ethyl iodophenylundeceylate was completely absorbed in six weeks, however, while the iodized poppy-seed oil was not absorbed during the life of the experimental animal. The more rapid rate of absorption of the new medium may well be the sole cause of its relatively greater toxicity. Intravenous injections in dogs showed that ethyl iodophenylundeceylate was without effect at a level of 0.5 gm./kilogram but was lethal at a level of 1.0 gm./kilogram. Emulsification with water containing small amounts of Igepon T (sodium oleyl-methyltaurine) or of methyl cellulose reduced the toxicity considerably, and doses of 1.0 gm./kilogram were given intravenously to dogs with safety.

With the assurance from these experimental studies that the new medium was safe, it was first tested clinically on Nov. 23, 1940, by Drs. Paul Garvey and Nathaniel Jones in Case I, reported below. The absence of untoward developments led to its use in 4 additional patients. The satisfactory outcome in these first few cases was followed by a wider use, until now the new medium has been tested in numerous clinics. The most extensive series of cases has been compiled by Dr. William P. Van Wagenen (Rochester, N. Y.), Dr. R. Glen Spurling (Louisville, Ky.), and Dr. William V. Cone (Montreal, Canada). From their experience it is evident that the best results are obtained if 3 to 5 c.c. of ethyl iodophenylundeceylate are injected and

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Fig. 1. Cyst formation in the spinal cord of dogs following intrathecal injection of (A) ethyl iodophenylundeceylate and (B) of iodized poppy-seed oil. The sections represent extremes in pathology.

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As of November 1942.
later removed by the general procedure of Kubik and Hampton (3). In this way up to 90 per cent of the injected medium is easily removed and the small amount of residuum is completely absorbed within a few weeks.

CASE HISTORIES

Case I (Unit No. 171887): A 53-year-old male with complete paralysis from the waist down as the result of pressure on the dorsal cord from a dissecting aortic aneurysm was injected on Nov. 23, 1940, with 5 c.c. of ethyl iodophenylundecylate at L4 after removal of 8 c.c. of crystal-clear spinal fluid. Fluoroscopy showed a persistent constriction at L3 and L4, and also between L4 and L5. The patient experienced no reaction from the injection. Death occurred from a rupture of the aneurysm seventeen days later. A postmortem examination showed that the contrast medium was still mobile. Sections (Fig. 3) of the spinal cord showed a few polymorphonuclear cells around the nerve roots. There was no evidence of encystment in any portion of the cord.

Case II (Unit No. 173025): A 28-year-old white male with embryoma of the left testicle with bone and pulmonary metastases was injected with 8 c.c. of ethyl iodophenylundecylate on Jan. 7, 1941. Films (Fig. 2) taken at intervals up to May 29, 1941, show a gradual absorption of over half of the injected contrast medium. Immediately after injection the Pantopaque became immobile as a result of filling the nerve sheaths, particularly the sheaths of the sciatic nerves. During the week immediately
Fig. 3. Case I: Section from the spinal cord seventeen days after injection of ethyl iodophenylundecylate. A few polymorphonuclear cells are seen.

Fig. 4. Case III: Reaction about probable site of extradural injection of ethyl iodophenylundecylate.

Following the injection, the patient had a slight paresthesia in the lower leg. Otherwise there were no clinical symptoms. Death occurred at home and an autopsy was not obtained.

Case III (Unit No. 183121): A 29-year-old female with clinical symptoms of a ruptured nucleus pulposus was injected on Sept. 5, 1942, with 3 c.c. of ethyl iodophenylundecylate. A diagnosis of extramedullary compression between L4 and L5 was somewhat equivocal. The contrast medium was removed and the patient was placed on fracture boards. On Sept. 21, 1942, 3 c.c. of Pantopaque was again injected, but fluoroscopy showed that some of it was extradural. For several days the patient experienced increased leg pain, especially after manipulation. Finally, on Sept. 28, 1942, a third examination was made with 3 c.c. of ethyl iodophenylundecylate and a positive diagnosis of a
lesion at the disk space of L4 on the left side was obtained. A laminectomy was performed on Sept. 30. A section taken at the probable site of the extradural injection showed striated muscle and fibrous tissue. In the section reproduced in Figure 4 dense fibrous connective tissue is seen having a structure consistent with that of ligamentum flavum. In this tissue there is no evidence of any inflammatory reaction. Other portions of the section show striated muscle and areas of fairly loose connective tissue. Some of the striated muscle bundles appear to contain more than their normal number of nuclei, while others show considerable degenerative change. Instead of normal striated myofibrils the muscle sheaths contain a granular débris. This degeneration could be due to some local irritant, but similar changes are often seen without any known foreign matter in the vicinity. Several areas of the less dense connective tissue show infiltration by polymorphonuclear leukocytes in addition to many small round cells and a few larger monocytes. No definite droplets of contrast medium are seen, and there is no localized focal necrosis or abscess formation.

SUMMARY

Ethyl iodophenylundecylate (Pantopaque), a new contrast medium for myelography, is more fluid and is therefore more easily injected and removed than previously described oil-type contrast media. In addition to these physical advantages, the medium is absorbed from the subarachnoid space with relative rapidity.

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REFERENCES


DISCUSSION

Capt. Frank H. Mayfield, M.C. (Percy Jones General Hospital, Battle Creek, Mich.): Doctor Strain and his co-workers have developed a material which, to my mind, is the most satisfactory for myelography that is yet available. That little is said in their paper of the clinical value of this material reflects the extreme conservatism of the men who have worked with Pantopaque, and this attitude is further evidenced by the rigid control which they have maintained over the product during its experimental stage.

I first became familiar with Pantopaque in January 1942. Prior to that time, Major Spurling and Major Bell of Louisville had used it a great deal and, on their recommendation, some was forwarded to me for experimental clinical use as a check on their results. I was not aware at the time of the work being done at other clinics except at the University of Rochester.

We had been using lipiodol for myelography and for the most part had found it a fairly satisfactory contrast medium. There were, however, two outstanding objections to its use. First, it is a very viscid oil with high surface tension and at times, on fluoroscopy, we saw filling defects which we thought were due either to herniated disk or tumor, which at operation proved to be small normal anatomical variations. Second, we found it difficult to remove lipiodol completely, because of a tendency to break up into droplets and its viscosity.

Our experience with pneumomyelography had never been satisfactory, though I am thoroughly aware of the excellent results obtained by Doctor Chamberlain in Philadelphia and Doctor Camp and his associates at the Mayo Clinic, and, indeed, by many other groups.

Pantopaque has solved many problems. It is a much less viscid oil than lipiodol, it moves within the spinal canal more rapidly, and because of its lessened surface tension it fills the root sleeves better and does not show false filling defects. Furthermore, it is easily removed. In most instances one can recover by simple aspiration nearly all of the material, the usual experience being to leave one or two minute droplets.

The technic for removing the oil is that described by Hampton and Kubik. Lumbar puncture is done with the patient lying on his face, the needle being inserted at either the fourth or fifth interspace and carried through until it touches the anterior wall. The oil is then collected about the end of the needle under fluoroscopic observation, after which it is removed by simple aspiration.

Prior to entering the Army, I had used Pantopaque in approximately 30 cases. In most of them the oil was removed, but in 2 cases it was not removed. The cases in which the oil was removed showed no meningeal reaction. Those in which some of the oil was left showed a mild cellular response, and in one of the two in which none of the oil was removed, a mild meningismus occurred, lasting about three days. No residual symptoms were observed.

The highest cellular reaction was one thousand cells at the end of forty-eight hours. The count after administration of Pantopaque was from 50 cells. This is almost identical with our experience with lipiodol. I think, therefore, that the toxic potentialities of the two drugs are the same.

Pantopaque, however, has two outstanding advantages. First, it is a more satisfactory medium for diagnostic purposes. Second, it can be removed more completely and more easily than lipiodol, thereby overcoming the one outstanding objection to the use of contrast media, namely, the moral and legal objection to leaving in the spinal canal.
Myelography with Pantopaque

A foreign body which is visible on the x-ray plate. Dr. Strain has mentioned the comparative absorbability of Pantopaque and lipiodol, and from my experience I find that Pantopaque is absorbed, or rather loses its radiopacity, much more rapidly than lipiodol. In those cases where only a few droplets of Pantopaque were left, it was no longer demonstrable after two to four months. In the two instances where about 3 to 4 c.c. of oil was left, it could not be shown on x-ray plates six months later. Lipiodol is visible usually for two to four years, and occasionally never disappears. While, as recommended by the author, Pantopaque should be removed, in the event that one is not successful in removing it, I am convinced that no harm will result.

There is one situation in which lipiodol is slightly more satisfactory than Pantopaque. Lesions of the cervical area are sometimes difficult to visualize with Pantopaque because the oil moves so rapidly that the defect is missed. With the more viscous lipiodol, small cervical deformities will be seen that might be missed with Pantopaque.