CLINICAL NOTES

LATE MENINGEAL REACTION TO ETHYL IODOPHENYLUNDECYLATE USED IN MYELOGRAPHY

REPORT OF A CASE THAT TERMINATED FATALLY

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Ethyl iodophenylundecylate (Pantopaque) has been employed extensively as a contrast medium in myelography since it was first introduced about 10 years ago. Its widespread use is evidence that severe reactions are uncommon, and in our experience ethyl iodophenylundecylate has proved to be a most satisfactory agent. We had observed only transitory and minimal reactions until the case herein reported came to our attention. This case is noteworthy for several reasons. The serious complications were so long delayed (15 months) after the use of ethyl iodophenylundecylate in myelography that it might easily have been overlooked as an etiological factor.

The fatal termination was due to intracranial arachnoiditis, as a result of inadvertent introduction of the ethyl iodophenylundecylate into the basal cisternae during myelography. This emphasizes the importance of employing proper technique to avoid such an occurrence.

REPORT OF A CASE

A 33-year-old man was admitted to the hospital on Dec. 22, 1949, complaining of weakness of his legs, which he had first noticed in 1947 and which had gradually become worse until he had great difficulty in walking. He felt a tingling sensation in his legs and noted a decrease in the urinary stream. His past history was not relevant, except that he had had frequent "sinus trouble" and had had a goiter in childhood, which had been treated with iodine.

The results of the physical examination were essentially normal. Findings on neurological examination were absence of the lower abdominal and cremasteric reflexes, hyperactive patellar reflexes, and bilateral positive Babinski's reflexes. There was a slight diminution of vibration sense in the lower extremities and diminution to pinprick over the scrotum and penis. There was spastic paralysis of both lower extremities. The results of the urinalysis and routine blood studies were normal. The sedimentation rate was 4 mm., fasting blood sugar 85 mg. per 100 cc., and the nonprotein nitrogen 40 mg. per 100 cc. The blood Wassermann reaction was negative. X-ray films of the dorsolumbar spine revealed a moderate amount of marginal spurring on the anterior borders between the eighth and ninth thoracic vertebrae. There were only four vertebrae with true lumbar characteristics, and there was a spina bifida cleft at the arch of the first sacral segment. The spinal fluid pressure in the recumbent position was 210 mm. of water, and with compression of the jugular veins it rose to 430 mm. and fell promptly to 180 mm. The spinal fluid was clear and colorless, with no blood cells, a protein level of 24 mg. per 100 cc., and negative Wassermann and Lange reactions.

On Dec. 27, 1949, a myelogram was made, with the injection of 6 cc. of ethyl iodophenylundecylate in the lumbar subarachnoid space. The entire spinal canal was examined, and the appearances were considered within the limits of normal. There is no record on the chart that the ethyl iodophenylundecylate was removed. On the day after myelography the patient's temperature was elevated to a maximum of 102.2 F. He complained of some headache and a flushed face. On the second day after the myelography the highest temperature recorded was 99.2 F., and by the third day the temperature had returned to normal.

An exploratory laminectomy was done on Jan. 10, 1950. Numerous tortuous veins were found over the surface, extending from the ninth thoracic to the first lumbar segments, of the spinal cord. It was believed that the patient had an angioma. After coagulation of one of the large veins leading to the angioma occurred, the dura mater was closed with nonabsorbable surgical sutures. The wound healed by primary intention, convalescence was uneventful, and the patient said that he had more feeling in his legs, especially for heat or cold, than he had before the operation. He was discharged from the hospital on Jan. 28, 1950, with the diagnosis of hemangiomat of the spinal cord.

The patient was seen again as an outpatient on May 12, 1950, when he exhibited considerable improvement in his ability to walk but complained of occasional generalized headache. Almost a year later, April 4, 1951, he returned with a multitude of complaints referable not only to the lower extremities but to the head and upper extremities. In spite of these complaints, he had been working nine hours a day.

He was readmitted to the hospital on April 15, 1951. At that time his wife stated that his ability to walk had improved after the laminectomy. He was discharged in 15 months previously. The recurrent headaches previously noted had increased six months before and had become even severer during the last four weeks. He became lethargic, vomited, was incontinent, and was occasionally confused and irrational. No definite weakness of the extremities had been noted by the patient or the family.

Physical examination again did not reveal any abnormalities, but the neurological examination showed that he was disoriented as to time and had a slight nuchal rigidity but no papilledema. The blood pressure was 140/94 mm. Hg, pulse 82 per minute, and respirations 22 per minute. The laboratory results were as follows: urine normal, hemoglobin (photocolorimetric oxymoglobin determination) 16.65 gm. per 100 cc., red blood cells 5,520,000 per cubic millimeter, white blood cells 11,100 per cubic millimeter (89% neutrophils, 2% lymphocytes, 5% monocytes, and 1% eosinophils), blood sugar 140 mg. per 100 cc., and nonprotein nitrogen 30 mg. per 100 cc. A few days later, on April 17, 1951, more persistent vomiting and pronounced nuchal rigidity developed. X-ray films of the skull on April 17 showed considerable softened oil scattered in the posterior fossa and some in the cisterns about the sella and in the subarachnoid spaces, particularly in the region of the left island of Reil. No other abnormalities were noted.

Disorientation increased, and the Babinski phenomenon became bilaterally positive. There was flexion of the upper extremities and extension of the lower extremities with spasticity. The patient became semistuporous, and an emergent ventriculogram was made. This showed an internal hydrocephalus, with dilatation of the lateral ventricles, the third ventricle, and the aqueduct and upper portion of the fourth ventricle. The spinal fluid was slightly cloudy and contained 650 mg. per 100 cc. of protein, 650 mg. per 100 cc. of chlorides, and 259 white blood cells per cubic millimeter (65% polymorphonuclear leucocytes and 35% lymphocytes). The ventricular fluid contained 180,000 red blood cells and 318 white blood cells per cubic millimeter, in the same proportion as in the spinal fluid. The ventricular fluid sugar was 81 mg. per 100 cc. and the protein 300 mg. per 100 cc.

No organisms were seen on smear culture of either the spinal or ventricular fluid. Special bacteriological studies for tubercle bacilli and fungi were negative.

A suboccipital craniotomy was performed, at which time a complete block of the lower portion of the fourth ventricle was demonstrated. When this was released, there was a forceful gush of cerebrospinal fluid. Microscopic study of the tissue removed at suboccipital craniotomy showed countless neutrophils and lesser numbers of lymphocytes in the meninges.

From the departments of neurological surgery and pathology, University of Wisconsin Medical School, Dr. P. L. Kozelka of the University of Wisconsin supplied the chemical determinations.
and normal cerebellar tissue. There was temporary improvement after the suboccipital craniotomy, but death occurred suddenly two days later.

**Postmortem Examination.** No significant abnormalities were found, other than in the cranium and vertebral canal. Since a granulomatous lesion had been suspected, a very careful examination of all organs was performed; however, no evidence of tuberculosis or other granulomatous lesion was found. Examination of the brain revealed flattening of all gyri, narrowing of sulci, and severe hyperemia of all superficial vessels. The basal surface of thepons and medulla was covered with a greenish-gray exudate (fig. 14). When horizontal sections of the brain were made, the ventricles (fig. 18) were found to be enlarged. There was a small area of hemorrhage in the right occipital pole and another in the right hemisphere of the cerebellum, as well as some blood clots in the ventricles, no doubt the result of the surgical procedure. Examination of the spinal cord revealed tenuous, dilated blood vessels and a fibrinous exudate (fig. 2) over the lower thoracic portion of the cord. A section through the medulla (fig. 3A) showed it to be surrounded by cellular exudate and consisting of a fine fibrillar network containing many lymphocytes and a few plasma cells, the number of plasma cells varying in different areas. An occasional multinucleated giant cell was seen, as well as some fibroblasts. The cerebral vessels near the surface showed perivascular cuffing mainly with lymphocytes (fig. 3B). In addition to the cultures taken during life, the postmortem material was cultured especially for tubercle bacilli and fungi. All bacteriological studies were negative. Smears of the exudate as well as microscopic sections were stained by the following methods: Gram, Ziel-Nelsen, Kingley, Mallory’s phosphotungstic acid hematoxylin, and Kernohan’s stain for Torula, but no organisms were found. The diagnosis, according to the gross and microscopic picture, was that of arachnoiditis or chronic meningitis, which had produced a severe internal hydrocephalus. The history of the patient, the oil myelography, and the presence of opaque medium on the skull roentgenogram directed our attention to the possibility of a reaction to the iodine in the ethyl iodo phenylundecylate. A roentgenogram of the cerebellum and spinal cord taken after death showed areas of increased density in the region of the exudate (fig. 4). For this reason an x-ray photomicrograph (fig. 5) was made of a section through the medulla, which showed areas of greatly increased density corresponding to the meningeal exudate.

Finally, to obtain definite proof of the presence of iodine, material taken from the basal surface of the medulla was examined chemically for iodine. Nearly 20 mg. of iodine per 100 gms. of the material was reported. The total iodine content of the normal body is 20 to 50 mg., of which 50% is in muscle, 20% in the thyroid, 10% in skin, and 6% in skeletal tissue.1

**COMMENT**

The evidence that ethyl iodo phenylundecylate was responsible for the meningeal reaction or arachnoiditis in this patient is both negative and positive. Other etiological agents that might have caused meningitis were excluded by thorough bacteriological and microscopic studies during life as well as at autopsy. The autopsy did not reveal evidence of a possible source of primary infection. Having eliminated, as far as possible, other causal factors, we may consider the evidence that ethyl iodo phenylundecylate was responsible. For two days after myelography the patient had a fever, headache, and complained of a flushed face. This immediate reaction, not too unusual, was followed by an apparent quiescent period of nine months, during which the symptoms due to the original spinal cord lesion improved. There would appear to be two possible explanations of this asymptomatic period.

The meningeal reaction to the ethyl iodo phenylundecylate may have been minimal and only subsequently

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reactivated by some unknown factor. It would appear more probable that the meningeal reaction was low grade, was slowly progressive, and caused symptoms only when the exudate became extensive enough to produce obstruction to the free circulation of cerebrospinal fluid. The apparent latent period in this case might be of the brain and spinal cord. In addition, the special x-ray studies of microscopic sections demonstrated radiopacity in the subarachnoid exudate that could only result from ethyl iodophenylundecylate. As a final step in establishing the causal relationship, the chemical analysis of the affected meninges showed a tremendous increase of iodine content that can be explained only by the presence of ethyl iodophenylundecylate.

With further survey of our own cases we have not been able to prove any other instances of such severe reactions to ethyl iodophenylundecylate. We continue to employ it routinely, but with the usual safeguards of removing the medium at completion of the procedure and with special care to keep the neck extended so as to prevent its becoming lodged intracranially when the cervical region is examined. Judging by our own experience and that of others, the incidence of reaction is low. In the original experimental work Steinhausen and co-workers did note cyst formation in the subarachnoid space of dogs, and occurrence of slight meningeal reaction to ethyl iodophenylundecylate was noted by Peacher and Robertson. These authors stated, in referring to their case 28, that reaction might occur after an interval if ethyl iodophenylundecylate extends into the basal cisternae. Tarlov observed a pronounced inflammatory reaction, with thick soft stringy exudate of the arachnoid and nerve roots of the cauda equina, at laminectomy 60 hours after 3 cc. of ethyl iodophenylundecylate had been introduced intrathecally, and he termed this reaction "Pantopaque meningitis."

The reports of severe reactions to ethyl iodophenylundecylate have been rare when one considers how extensively it is used. The experimental observations of Steinhausen and co-workers indicated that it provoked less tissue reaction than iodized poppy seed oil. The immediate and late effects of the intrathecal injection of iodized oil were studied by Marcovich and co-workers, and there was a significant case report by Bucy and Speigel in 1943. An early paper on the subject was that of Wartenberg. Lindblom, in an article based

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2. Steinhausen, T. B., and others: Iodinated Organic Compounds as Contrast Media for Radiographic Diagnosis: Experimental and Clinical Myelography with Ethyl Iodophenylundecylate (Pantopaque), Radiology 40:1, 1940.
on the use of methiodal sodium (Abrodil) for myelography in 721 cases, reported complications in more than 54. Foster Kennedy and co-workers 8 reviewed the literature dealing with sequelae of spinal anesthesia and reported three cases of arachnoiditis in the spinal region. Other reports of meningeal reaction after spinal anesthesia and the introduction of other agents such as antibiotics intrathecally have appeared from time to
time.10

Sensitivity or tolerance of the subarachnoid space to these various substances is a matter of relativity. On this score ethyl iodophenylundecylate is no doubt safe, and its margin of safety can be increased by its removal on completion of myelography. The possibility that some reactions may be due to variation in the composition of the ethyl iodophenylundecylate that is supplied has been suggested. Other possible factors such as the introduction of impurities in the syringe or the presence of an idiosyncrasy to iodine must be considered. We have no observations that bear specifically on these problems, but in this case the evidence indicates that the ethyl iodophenylundecylate itself must have been the irritant.

The reaction observed in this case does emphasize the hazard of ethyl iodophenylundecylate being allowed inadvertently to enter the intracranial space. The disclosure of droplets of oil intracranially after myelography is not too uncommon. Often one cannot ascribe any signs or symptoms to their presence, but again the clinical picture may be clouded by the original condition for which the patient was subjected to this examination. The localization of the oil and its amount may be important factors, as was clearly true in this patient in whom an obstructive hydrocephalus was produced due to exudative arachnoiditis in critical areas. Sensitivity to ethyl iodophenylundecylate may be of importance, as may be any underlying disease that contributes to the intensity of the reaction.

That this complication of intracranial extension of the contrast medium can be prevented in the majority of instances by proper technique is well known. Judging by our experience, it still needs to be reemphasized. The indiscriminate use of any method of examination such as myelography by untrained personnel can lead to unnecessary complications. In discussing the injudicious use of myelography, Oldberg 11 made a plea for respect for the tissues of the central nervous system. We would add to this a plea for meticulous attention to details of technique in performing a valuable diagnostic technique such as myelography.

SUMMARY AND CONCLUSIONS

A patient died 15 months after myelography was done with ethyl iodophenylundecylate (Pantopaque), because of an exudative and adhesive arachnoiditis producing an obstruction of the fourth ventricle and basal cisternae.

That this meningeval reaction was due to ethyl iodophenylundecylate was indicated by x-ray studies both ante mortem and post mortem, by the chemical determination of iodine in the exudate, and by the microscopic examination. Although such a severe reaction to intracranially administered ethyl iodophenylundecylate is considered very unusual, it would appear that late reactions of milder degree may produce symptoms, the nature of which is overlooked. We would reemphasize the importance of careful attention to details of technique such as removal of the ethyl iodophenylundecylate after myelography and special measures to avoid its introduction into the intracranial subarachnoid space.

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MYXEDEMA HEART
ADVANCED FAILURE WITH RAPID RECOVERY

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Recent spectacular surgical therapy in certain cases of heart failure due to congenital anomalies and rheumatic valvular deformities seems to have overshadowed the fact that medical treatment also can produce dramatic improvement in cardiac decompensation from some types of heart disease. Among these, cardiac impairment resulting from thyroid deficiency can apparently be completely corrected. This is not true of the great majority of cases of heart disease, whether medical, surgical, or combined methods of treatment are used. The fact that myxedema in humans can cause diffuse cardiac enlargement, sluggish contractions, and electrocardiographic abnormalities that disappear only after the myxedema is controlled was recorded by Zondek in 1918. 8 Fahr's investigations in this country in 1925 9 confirmed Zondek's observations and showed that cardiac volume in cases of severe myxedema may be increased 100%. Lerman, Clark, and Means 1 in 1933 showed reduction in the transverse cardiac diameters in 37 out of 48 cases after thyroid therapy.

The following authors have presented cases with serial chest roentgenograms: Schnitzer and Gutmann, Master and Stricker, 9 Schoene and Pollock, 7 Kern and co-workers, 7 Allison, 8 and Ellis and co-workers. 7 None of the cardiac sinuses in these cases before treatment or before death appear to be as enlarged as that in the case herein reported, although in Schnitzer and Gutmann's case of myxedematous pericardial effusion the cardiac silhouette was nearly as huge in proportion to the chest size.

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