THE EFFECT OF IODIZED OIL ON THE MENINGES OF THE SPINAL CORD AND BRAIN

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The use of contrast media is a well established and necessary adjunct to the roentgen examination of many parts of the body. It is desirable that such media should be safe, reliable, simple in application, and readily available. For general purposes, substances of high contrast are preferable, especially in the examination of thick or dense parts of the body. Substances of high atomic weight such as thorium, iodine, bromine, and their derivatives or compounds are commonly used. Substances of low contrast, such as dilute preparations of the above named elements and, various gases are often unsatisfactory because slight variations in their thickness (indicating the presence of organic lesions) may easily be overlooked. In the investigation of diseases of the spinal cord and spinal canal, one of the safest and most satisfactory opaque media yet developed is iodized poppy seed oil (lipiodol), containing 54 per cent iodine in combination. By the use of this medium, Camp (4), Robinson (19), and many others (9, 10) have shown that diseases of the spinal cord and associated tissues can frequently be discovered when all other diagnostic methods, including pneumomycelography, have failed. Such an opaque medium is, therefore, of great value and, if safe, its use should be approved, at least until a superior one has been developed.

Since iodized poppy seed oil remains in the cerebrospinal system once it has been injected into the subarachnoid space, its mere presence has been held to blame for innumerable symptoms which patients with organic disease of the spinal column or spinal cord have developed subsequent to its injection (6, 15, 16). Well known physicians have stated that, "the use of lipiodol in outlining the lumbocaudal sac and in locating the level of a complete block is unjustified" (25). "Due to the likelihood of bad effects, we have attempted to substitute air for lipiodol" (26). "Of all the complications (of spinal canal lesions) the worst is the presence of iodized oil as shown by the x-ray films" (25). In view of these astounding, and in our opinion erroneous, statements, it is believed that the clinical and pathologic reactions attributed to lipiodol should be reviewed and the status of its alleged harmful effects brought up to date.

EXPERIMENTAL OBSERVATIONS

Experimental work on animals was reported by Ayer and Mixter (1) in 1924 using large doses of iodized sesame oil (in amounts approximately five times as great as conventional amounts used in humans) they found high spinal fluid cell counts following cisternal injection.

Davis, Haven, and Stone (6), in 1930, reported the results of intracisternal injection of lipiodol in 10 dogs. In eight of them they found a severe leptomeningeal reaction and concluded that the injection of iodized oil into the subarachnoid space was a dangerous procedure. They did not report the findings in control dogs. All of their animals had artificially produced subarachnoid blocks.

In 1931, Lindblom (12) performed a critical investigation on the effects of various iodized oils on the meninges. He found that the degree of irritation caused by the oil varied with the amount of free fatty acid: sesame oil with an acidity of

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0.6 produced no irritation; refined poppy seed oil with an acidity of 2.4 produced moderate irritation; while ordinary poppy seed oil with an acidity of 6.5 produced marked irritation. He has found that the oil was found to have collected in large lakes outside the cerebral hemispheres while in the other, it was distributed in numerous small droplets, especially in the basal cisternæ. When the brain was re-

Fig. 1. Roentgenogram of the skull of N. S., a laborer, who had 10 c.c. of lipiodol injected into the cisternal subarachnoid space 14 years previously! This patient, then aged 58, had symptoms of a spinal cord tumor. The large amount of lipiodol was used in error (from 3 to 5 c.c. being the usual amount). No roentgen evidence of tumor was found and the patient was not operated upon. He improved gradually and now hobbles around with the aid of two walking sticks. He has large amounts of lipiodol scattered throughout the skull, chiefly in the basal cisternæ and about the cerebellum, and a large lake of about 5 c.c. in the spinal cul-de-sac, still movable! He has no symptoms or neurologic findings attributable to the oil.

the iodized product of the oil caused greater irritation than the oil itself, the free fatty acid being transformed into iodic fatty acid. He regarded lipiodol as an impure iodized oil but found that its impurities were absorbed comparatively easily, while the iodized oil itself was absorbed slowly. He noted in rabbits that after the injection of oils that were absorbed slowly, a sort of “pseudotumor” or fatty granuloma was sometimes found in the subarachnoid cavity. These granulomas did not always develop and when they did develop they took at least six months. Two rabbits were given injections of 1 c.c. each of lipiodol and were killed after six months. Before the brains were extracted moved from the former, two large lakes of oil were found on it, surrounded and infiltrated with new-grown connective tissue. At another place there was a pachymeningitic reaction, which on incision also showed droplets of oil. Histologic examination showed that these formations consisted of fatty phagocytes of various sizes, surrounded or infiltrated with new-grown connective tissue (fatty granulomas). In the other specimen, in which the oil was separated into small droplets, there were no granulomas; numerous small droplets were found in the arachnoid membrane itself, but without reaction. Lindblom observed, “The literature contains a few cases of dissection on humans after lipiodol
scriptions it seems likely that fatty granulomas were present in some of them. These granulomas appear to develop when the oil gathers in large lakes. Further investigation is required to confirm this point.

CLINICAL AND PATHOLOGIC OBSERVATIONS

Immediately after the subarachnoid injection of fresh lipiodol in amounts of from 2 to 5 c.c., there is an increase in the white cell count of the spinal fluid which lasts.

Fig. 2. Roentgenograms of the spine of F. B., an elevator operator, who had 5 c.c. of lipiodol injected into the cisternal subarachnoid space 14 years previously! This patient, then aged 27, had symptoms of spinal cord tumor. Roentgen examination disclosed marked erosion of the dorsal aspects of the lower lumbar bodies, and complete block of the opaque oil at the level of the third lumbar disc. Laminectomy disclosed an "inoperable neurofibroma," only a small portion of which could be removed. The patient gradually improved and is still working. He has no detectable symptoms resulting from the lipiodol. Large droplets of oil remain in the spinal canal; there are a few droplets in the basal cisternae and cerebral ventricles. Most of these are fixed. The roentgenograms on the left were made in 1926, those on the right in 1939.

and also to determine whether or not these granulomas have any clinical significance."

Bruskin and Propper (3) reported the results of experimental myelo-encephalography in dogs in 1931. They injected iodiopin subdurally and found no disturbances of sensation or motor function. Pathologic examination after from one to three months revealed granulation-tissue formations over the spinal cord; in some areas there was destruction of the gray substance of the cord itself; however, it should be noted that the oil was injected for about four days. There is sometimes mild hyperemia about the site of injection. In some patients there are symptoms of mild headache, cramps in the lower limbs, and mild accentuation of the backache of which the patient has so often been complaining. There is sometimes a transitory rise in temperature of about 2 degrees Fahrenheit. This reaction lasts for one or two days and usually subsides without leaving any residual symptoms. Sicard and Forestier (22, 23), who introduced lipiodol for diagnosis as well as therapy,
diseased area sometimes caused a transient but quite endurable pain.” They noted that in paralytics there was sometimes an increase of spasticity and slight inhibition of the sphincters. In tabetics there were short crises of shooting pains, tingling of signs of spinal cord compression and irritation developed. Subarachnoid injection of lipiodol revealed a block at the level of the seventh thoracic vertebra. Laminectomy was performed at the level of the fourth thoracic vertebra; nothing abnor-

the lower limbs, and transitory disturbances of the sphincters. In all of their cases reactions of this kind disappeared completely within four days. They believed that a simple lumbar puncture was capable of producing similar effects in certain cases. They noted that the opaque oil disappeared very slowly from the cerebrospinal system.

Maclaire (14), in 1925, and Sharpe and Calvert also found the animal was found and the incision was closed. The patient grew worse and five months later laminectomy was performed at the level of the tenth thoracic vertebra; some lipiodol was found encysted in adhesions and there was considerable local arachnoiditis. Maclaire and Sharpe believed that the lipiodol alone brought on the meningeal inflammation. Sicard, discussing this case, believes that the adhesions and arachnoiditis antedated the
transient aseptic meningitis following intracisternal injection of iodized oil in 13 cases. Wolsohn and Morrissey, in 1927, reported inflammatory changes around tumors in two cases following lipiodol injection.

In 1929, Globus and Strauss (9) reported the results of subarachnoid injection of lipiodol in 64 cases. They concluded that in only one out of this group was there any clinical evidence of meningeal irritation; in this patient there was transient vasomotor disturbance and pain in segments approximating the level of the oil and tumor. They noted that 25 patients who had had iodized oil in their spinal canals for more than two years were normal neurologically, both as regards clinically

documented arachnoid space and showed no evidence of any adhesive process.” In one instance a necropsy was performed three and one-half months after injection; they found no evidence of any inflammatory process of the meninges at the site at which the

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Fig. 4. Photomicrographs from two of several small nodules (pseudogranulomas) found at autopsy on the cerebellum of a laborer who had 3 c.c. of lipiodol injected into the lumbar subarachnoid space one year previously. This patient, aged 40, died of multiple sclerosis and chronic glomerulonephritis. The lipiodol had been injected to confirm or exclude the presence of a spinal cord tumor at the level of the seventh thoracic segment. No tumor was found. He had multiple, peculiar clinical symptoms and neurologic findings both prior and subsequent to the injection of the oil. When, at autopsy, numerous small yellow granules were found scattered over the meninges of the brain and cord it was at first thought that he had severe leptomeningeal and possibly neurologic changes from the lipiodol. However, histologic studies revealed no lesions in the neural tissues proper, in the vicinity of the lipiodol; merely small areas of fibrous proliferation, round-cell infiltration, and a few foreign body giant cells (containing minute fat deposits) in the arachnoid itself. The lipiodol droplets lay chiefly on the meninges over the lower 5 cm. of the spinal cord and the cauda equina, and over the base of the brain.
cisternal injection of lipiodol, but gave no histologic details. Hampton and Robinson, in 1936, reported the absence of any serious or permanent reaction following the use of 2 c.c. of lipiodol in over 100 examinations, and 5 c.c. in 75 examinations. They observed that the oil often produced a definite reaction, lasting for several days, characterized by elevation of the spinal fluid cell count, changes in the color and composition of the fluid, headaches, increase in the pain of which the patient complained, and slight fever. They comment that those who use the oil most frequently find the fewest reactions. They state that the oil did not become encysted even after two years. However, they do not recommend the indiscriminate use of the oil “and examine the upper thoracic spine only when symptoms referable to that portion of the canal are present ... which may account for the infrequency of some of the untoward reactions which others attribute to the use of lipiodol.” At the time of their report they did not seem to realize that the oil travelled up to the upper spinal regions and even the skull in a majority of cases, when the patient returned to bed or resumed his occupation.

The use of iodized oil in the study of the subarachnoid spaces of the skull and the cerebral ventricles was first attempted in 1926. In 1932, Sicard and Foretier advised that its use for this purpose be discontinued owing to early reactions in the form of severe headache and pyrexia. However, they reported that no untoward late effects were noted in their cases. These authors also reported on the use of “ascending lipiodol,” a special light oil containing only 11 per cent iodine, in the examination of the ventricles; they tried it both plain and emulsified with spinal fluid. They reported that the latter mixture was extremely irritating and advised against its use in ventriculography.

In 1933, Brandt (2) reported the case of a patient with tuberculous spondylitis in whom 2 c.c. of iodipin had been injected into the lumbar subarachnoid space five and one-half months prior to autopsy. At autopsy numerous bright yellow nodules, varying from 1 to 4 mm. in diameter and resembling grapes in shape, were seen about the base of the brain, being especially numerous in the region of the basal cisternae. These appeared to lie between the pia mater and the brain. They were easily movable and burst on slight pressure. Chemical examination showed that these nodules contained iodine. Microscopic examination showed only a structureless membrane. No pathologic changes attributable to the iodine could be found in the neighboring brain.

Ouchi (18), in 1935, reported 25 cases in which he had used opaque oil for myelography. In several of these cases he noted mild early reactions, such as nausea, irritability, pyrexia, and so forth, all of which disappeared within a week. In one instance he erroneously injected the oil in a case of tuberculous meningitis; shortly thereafter the patient died. Ouchi attributed the patient’s death to the meningitis and not to the lipiodol. However, he believed that it may well have aggravated the patient’s disease. In seven cases he believed the oil exercised a therapeutically beneficial influence. In no cases did he meet with late harmful effects nor did he think the oil showed any tendency to become encapsulated or form granulomas, “as described in the literature.”

Schüller (20), in 1936, investigated patients with possible tumors at the base of the brain by suboccipital or intraspinal injection of 40 per cent iodipin. He recommended this contrast filling of the basal cisternae because: (1) the material was stable and there were no immediate or late unfavorable reactions; (2) the material was easily visible under the fluoroscopic screen, and (3) following investigation of the basal cisternae the opaque oil could be displaced into the spinal subarachnoid space and thereby retained for further, later investigations of the cisternae. His article contains nine illustrations showing oil in the skull, mostly in the form of lakes.

Lysholm (13), in 1938, discussed his experience with ventriculography, using
both air and opaque oils, based on a total material of 3,408 cases during 10 years. Of these cases, 123 were lipiodol examinations. Concerning the latter he comments that undesirable reactions sometimes occurred and that air is preferable and much less harmful.

Garland and Morrissey (8), in 1940, reported on a group of 25 cases, 23 of whom had had lumbar and two cisternal injections of lipiodol several months or years prior to examination. In most cases 5 c.c. had been used, but in one case, in error, 10 c.c. had been injected. This particular case was a patient with a fibroma of the lumbar portion of the spinal canal; he has been followed now for 14 years and has no symptoms attributable to the opaque oil, all of which is still in the cerebrospinal system. Of the entire 25 cases, approximately two-thirds showed collections of opaque oil intracranially, and all showed varying amounts in the spinal portion of the cerebrospinal system. All of the patients were examined neurologically and their symptoms and findings compared with those on their records prior to the time of injection of the opaque oil. In none of these cases were there any symptoms or neurologic findings which were not present prior to the injection or which could be ascribed to the presence of the oil.

SUMMARY OF CLINICAL AND PATHOLOGIC REACTIONS

Following the injection of small amounts (from 2 to 5 c.c.) of fresh lipiodol into the lumbar subarachnoid area there is often slight pain about the sacrum and coccyx, and sometimes mild headache and fever. These symptoms usually subside spontaneously within five days. In a small percentage of cases, coccygeal pain is relatively severe, and this may persist for as long as three months, finally subsiding spontaneously.

The immediate pathologic changes consist of increased spinal fluid cell count and slight hyperemia about the site of injection of the oil. The late pathologic changes consist of small, round-cell and fibroblastic proliferation about the oil, especially about the smaller droplets which become scattered along the spinal canal. These small droplets often become encapsulated, resulting in miliary nodules on the surface of the cord (pseudogranulomas). In about two-thirds of cases, some oil is present in and about the basal cisterns of the skull, usually in droplets which gradually become encapsulated.

The major quantity of the oil tends to persist in one or two fairly large "lakes," which remain movable for an indefinite period, and may be used for exploring the spinal canal months or years after the original injection.

We have previously (8) reviewed the autopsy findings reported in the literature, including the detailed findings in one case in which the opaque oil had lain in the cerebrospinal system for approximately one year. It has been emphasized before and should be repeated here that many of the tiny droplets plus their surrounding fibrous proliferations resemble miliary tubercles or granulomas of any type, and at first glance have led pathologists to conclude that some serious lesion of the brain or cord was present. Histologic examination will reveal that the changes are confined to the meninges and that the underlying neural tissues are normal (at least as far as any secondary effect from the lipiodol is concerned).

SUMMARY

Fresh iodized poppy seed oil (lipiodol) may be injected with safety into the subarachnoid areas of the spinal canal. The main drawback to its use is that it remains visible indefinitely in roentgenograms of the patient's cerebrospinal system. Such roentgenograms frequently cause apprehension on the part of the patient and his physician, to say nothing of such compensation boards and juries as happen to see them. However, opaque
materials such as mercury and bismuth have remained in patients' tissues for years and are visible in roentgenograms of their pelves and other areas. They have remained in these tissues without causing any harm; indeed, like lipiodol, they have been used both diagnostically and therapeutically with benefit. Until a superior opaque contrast medium has been discovered, we believe that the use of lipiodol is thoroughly justified in cases in which it is indicated. Its indiscriminate use, or its use without complete preliminary clinical, laboratory, and roentgenologic study remains unjustified—as does the use of any other contrast medium, gaseous or liquid.

BIBLIOGRAPHY


DISCUSSION

JOHN D. CAMP, M.D. (Rochester, Minn.): I was very much pleased with the way Dr. Bell presented his material. I think that he emphasized what is quite an important part of this whole problem. We all understand the various fundamental defects associated with the roentgenologic recognition of protruded intervertebral discs, but he emphasized that we must be sure, as the result of our examination, to rule out the presence of associated pathology which may be lurking in the background and masquerading as a protruded disc.

Our experience certainly has borne that out. We have a group of cases, as I have
said on previous occasions, of low thoracic tumors which have imitated discs neurologically and of course it would be a tragedy to take out a disc and leave a tumor in such a patient.

Statistics indicate that many patients with tumors in the spinal canal may have low back or sciatic pain. I do not mean that the tumor always produces the pain, but in our series 50 per cent of the patients with tumors in the thoracic area of the spinal cord have complained of low back or sciatic pain and 30 per cent of our patients with tumors in the cervical canal have complained of low back and sciatic pain. This emphasizes, I think, the necessity of a thorough neurologic examination before any contrast agent is introduced into the spinal subarachnoid space.

I think the amount of iodized oil one cares to use is probably not so extremely important, if we confine our observations to the lumbar region of the spinal canal. Dr. Bell elects to use 2 c.c. I prefer to use 5 c.c. I agree with Dr. Bell that 2 c.c. will probably show the majority of protruded intervertebral discs in the lumbar area. However, I think that whenever we put iodized oil into the spinal canal, the examination is not complete unless we rule out pathology above the conus, and from my experience I feel that I am unable to rule out efficiently small, non-obstructing tumors without 5 c.c. of oil. Smaller amounts of oil will pass by a small tumor without revealing its presence.

As to the differentiation between the deformity which results from the presence of a hypertrophied ligamentum flavum and that of a protruded intervertebral disc, I think it is an academic distinction. We know that practically all protruded discs have an associated hypertrophy of the ligamentum flavum, so the roentgenologic distinction is not important; it is just a little nicety in diagnosis which is sometimes gratifying to make. I feel that many times one can make a diagnosis of hypertrophy of the ligamentum flavum with or without the presence of a disc.

I have had no experience whatever with thorotrast. I would like to compliment Dr. Nichols on this beautiful piece of research. From his roentgenograms and exhibit, there is no doubt that thorotrast has some advantages over iodized oil so far as radiographic possibilities are concerned. Thorotrast shows the nerve roots beautifully and would be an ideal means to point out some of these small tumors. Unfortunately, for the present at least, the use of thorotrast seems confined to visualization of the lumbar canal. My only hesitancy in wanting to use thorotrast or recommending it would be that it is an intense irritant when it is in the soft tissues and I know that it is impossible to do lumbar punctures at least many of them, without getting some of the medium in the epidural space occasionally.

I have seen only one patient in which a study of the lumbar subarachnoid space by means of thorotrast was attempted. Fortunately, the injection was not done at our institution. Following the injection, the patient promptly developed paralysis of the bladder. Roentgenograms at the time of his admission to the Clinic showed a large amount of thorotrast in the lumbar canal and all the nerve roots were well outlined.

Dr. Garland mentioned one point which I would like to emphasize; that is, the necessity of using fresh lipiodol. Fresh lipiodol is transparent and has a very, very faint yellow color. When lipiodol begins to deteriorate with the liberation of free iodine, it is an intense irritant. I think many of the so-called reactions from lipiodol are due to the use of deteriorated oil. You should be very careful in selecting an ampoule of lipiodol to be sure that it does not have a brown tinge to it. If it has, it should be discarded.

I do not know whether or not it is permissible for a discussant to discuss remarks of a previous discussant but I was a little intrigued by Dr. Fincher's remark that air was preferable to oil. I like air

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1 Dr. Fincher's discussion not returned for publication.
very much. I happen to like lipiodol a little better, and my reason for liking lipiodol is based on the fact that in my experience lipiodol has been more accurate than air for this work.

I think there is a very definite place for air, or oxygen myelography. We have made about five hundred examinations with it and will continue to use it. However, I think that when one uses air, he should use it advisedly, and with a full appreciation of its diagnostic limitations and accuracy.

In our experience, a positive air study is worth about 83 per cent. However, in the cases in which we made a negative diagnosis from the air films, we were wrong in 77 per cent of the patients who were operated upon. Maybe there has been something wrong in the way I have examined these films. I certainly have looked at them hard enough! Nevertheless, so far as we are concerned, a negative air study is not worth very much. It helps us to rule out a space-occupying lesion in the lumbar canal fairly well but as far as determining the presence or absence of a protruded disc, I do not believe a negative spinogram is worth much at present.

You might summarize the situation by saying that if you get a positive finding with air, you are that much ahead. If the findings are negative, then you must take stock of the situation and decide whether you are going to use iodized oil or thorotrast or whether you want to be guided by the patient’s symptoms and explore him directly.