THE ORAL ADMINISTRATION OF SODIUM TETRAIODOPHENOLPHTHALEIN FOR CHOLECYSTOGRAPHY[1]

By LESTER R. WHITAKER, M.D., Boston, Massachusetts, GIBBS MILLIKEN, M.D., Galveston, Texas, and EDWARD C. VOGT, M.D., Boston, Massachusetts

THE work of Graham, Cole, and Copher (1, 2, 3), upon the intravenous injection of sodium tetrabromphenolphthalein for the purpose of cholecystography has aroused widespread interest in medical circles, and has opened up a field of great possibilities. Because of the somewhat complicated technique of administration and the tendency to reaction following it, however, clinicians and roentgenologists have been slow to adopt the method, and have been hoping for a simpler and less troublesome means whereby shadows of the gall bladder might be obtained. For these reasons we attempted the oral administration of the drug, sodium tetraiodophenolphthalein. Graham and his collaborators have been trying new methods of giving sodium tetrabromphenolphthalein by mouth and by rectum, but their results have not been published (4). In our hands sodium tetraiodophenolphthalein by intravenous injection gives shadows superior to those produced by the bromine compound (5). This, with its comparatively slight toxicity in the amounts necessary to obtain shadows, gave reason to suppose that the drug would also be superior for oral administration.

Experimental work on giving the drug by mouth was stimulated by an interesting observation made by M. C. Sosman, roentgenologist at this hospital. In doing a routine gastro-intestinal series following cholecystography by intravenous injection, Sosman noticed that the gall-bladder shadow, which was absent at 24 hours, had reappeared at the end of 72 hours. This indicated that after the salt had been excreted by the biliary system some of it was absorbed from the alimentary canal and again excreted in the bile, thus allowing a second cholecystogram 72 hours after the first. In dogs, 0.4 grams of the salt per kilogram of body weight, given by stomach tube in 1 per cent solution, produced good gall-bladder shadows in from 12 to 24 hours.

Preliminary trials. Since the dogs suffered no ill effects except vomiting in some cases, we decided to perform the test upon a human subject. Consequently a dose of 0.1 gram per kilogram, about twice the dose for intravenous injection, was taken with the stomach empty in a 5 per cent solution followed by a pint of water. There was a slight iodoform taste with an astringent quality which persisted until acid fruit juice was taken. Aside from a temporary sense of nausea experienced shortly afterward and a loose bowel movement 4 hours later, the taking of the drug caused no inconvenience. The fæces gave a strong test for sodium tetraiodophenolphthalein. The gall-bladder shadow began to appear after 6 hours and was very distinct in 12 hours (Fig. 1).

Seven house officers at this hospital then kindly volunteered to submit to the test. The drug was given in doses of 0.1 gram per kilogram of body weight in 5 per cent solution with malted milk. The taste and astringency were not disguised by this method; one of the subjects vomited after 10 minutes; another after an hour and a half. In the other 5 there was a temporary nausea. One had a moderate diarrhœa. Six out of the 7 showed definite gall-bladder shadows, even though in 1 case the salt was retained only 10 minutes.

The ease with which shadows were produced by the oral administration of sodium tetraiodophenolphthalein and the temporary character of the nausea in most cases made us believe that if a method could be found whereby the substance would pass through the stomach without coming in contact with the mucous membrane, nausea would be avoided, and the test would become practical. Several methods were tried, until finally pills of the salt, double coated with salol in syrup of Tolu, answered the requirement. One subject took a dose in this form of about 0.045 gram per kilogram of body weight, the average intra-

[1] From the Surgical Clinic and Department of Roentgenology at the Peter Bent Brigham Hospital, Boston, Massachusetts. Read before the Harvard Medical Society, January 27, 1925.

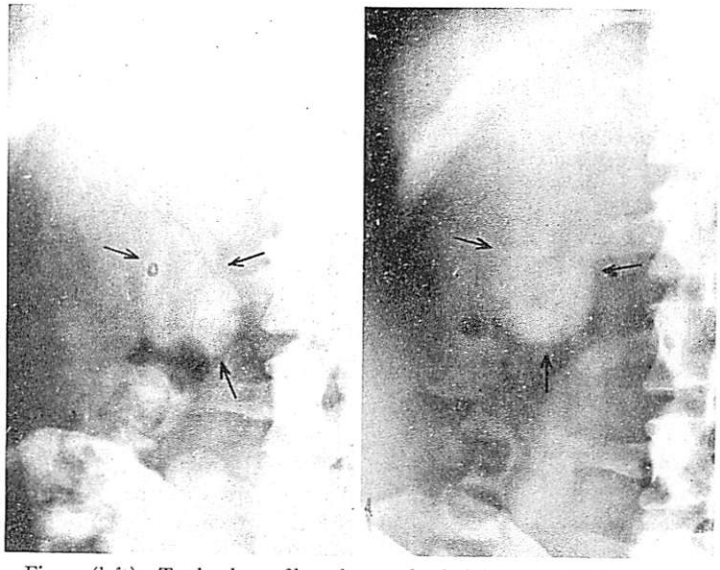

Fig. 1 (left). Twelve-hour film after oral administration of 0.1 gram per kilogram of sodium tetraiodophenolphthalein in 5 per cent solution. Same subject as in Figures 2, 3, and 4.

Fig. 2. Twelve-hour film after intravenous injection of 0.08 gram per kilogram of sodium tetrabromphenolphthalein. Compare with Figures 1, 3, and 4.

venous dose, and about one-half the calculated dose for oral administration. He experienced no symptoms whatever. X-ray 4 hours afterward showed that all the pills had left the stomach and three of the 6 taken were still intact. A cholecystogram after 6 hours showed a well outlined shadow of the gall bladder. At the 12 hour interval this shadow was more distinct. Three of the pills were still undissolved, and the shadow had thus been obtained by one-half the intravenous dose.

Again four house officers volunteered to act as subjects to test this new method. One-half gram pills with a double coat of salol were used. A light supper was taken and then 0.1 gram per kilogram of body weight was given in doses divided over an hour or more. None of the subjects showed any definite symptoms except that one had a free bowel movement a few hours after taking the drug. Guiac tests and microscopic examination of the stools were negative. Twelve-hour roentgenograms showed distinct gall-bladder shadows in all the subjects.

Further tests. Following this preliminary trial the test was repeated on 12 other supposedly normal subjects; and then was utilized for diagnostic purposes in 50 patients. By fluoroscopy it was found that with the double salol-coated pills a large proportion of them went through the alimentary tract without being dissolved. Even with single-coated pills some of them passed through. Probably the reason for this was that the pills were made by hand and a uniform salol coat could not be applied.[1] In spite of this fact, however, definite gall-bladder shadows were produced in 93 per cent of the normal subjects and 65 per cent of the patients. In a small number of cases the films were poor because the patient could not hold the breath. A number of the others who did not show shadows gave clinical evidence of gall-bladder disease. One of these proved to have a pathological gall bladder at operation. The absence of a shadow by the intravenous method has meant a pathological condition of the gall bladder in 100 per cent of our proved cases (6). On the whole the shadows produced by the oral method were less dense than those by the intravenous method with the iodine salt,

[1] A satisfactory product has been evolved by Davies, Rose and Company, Manufacturers of Pharmaceutical Preparations, 24 Thayer St., Boston, Massachusetts, to whom we are indebted for valuable assistance in the development of a method for oral administration of the drug.

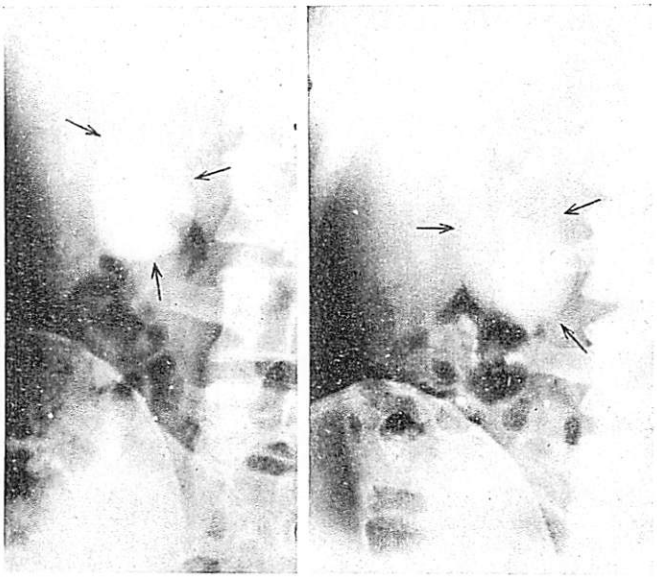

Fig. 3 (left). Nine-hour film after intravenous injection of 0.05 gram per kilogram of sodium tetraiodophenolphthalein. Compare with Figures 2 and 4.

Fig. 4. Twelve-hour film after oral administration of 0.1 gram per kilogram of sodium tetraiodophenolphthalein in salol-coated pills. Same subject as in Figures 1, 2, and 3.

though there were numerous exceptions to this rule (Figs. 5 and 6).

Because of the fact that the shadows by oral administration of the drug are somewhat faint, the roentgenographic technique must be exceptionally good and particular pains taken to eliminate respiratory movements which tend to erase the shadows. The patient should not be told to take a deep breath, but a moderate breath—one cannot hold the diaphragm perfectly still after filling his lungs to the limit. Furthermore, reliance should not be placed on a single exposure but several should be made at each interval. All this is important since the absence of a shadow, granted perfect technique, almost certainly indicates cholecystic disease.

We do not wish, however, to overemphasize the lessened density of the cholecystograms by the oral method for many of them compare favorably with those obtained by the intravenous method of giving both sodium tetrabromphenolphthalein and sodium tetraiodophenolphthalein. This is illustrated by comparing Figures 2, 3 and 4, which show roentgenograms of the same normal individual in whom all three methods were employed.

It is of interest to note here the difference in the subject's symptoms with the three methods. After the bromine salt injection (Fig. 2) he vomited and was quite ill; after the iodine salt injection (Fig. 3) he felt sleepy and somewhat weak; but after the iodine salt by mouth in pills (Fig. 4) he felt no symptoms whatever.

MANAGEMENT OF THE PATIENT

The patient does not have to be hospitalized in order to carry out the test, in fact he can proceed with his usual activities. Five-grain salol-coated pills are issued, enough to amount to a dose of 0.08 gram per kilogram of body weight (from 3.5 to 6.5 grams). Not more than 20 pills are given. Since the salt seems to be harmless in this form, a large dose is given in order to insure shadows. A light supper of bread and tea, coffee, cocoa or milk is allowed, and starting at 8 or 9 o'clock p.m., four pills are taken every 15 minutes with half a glass of water, until the whole number is

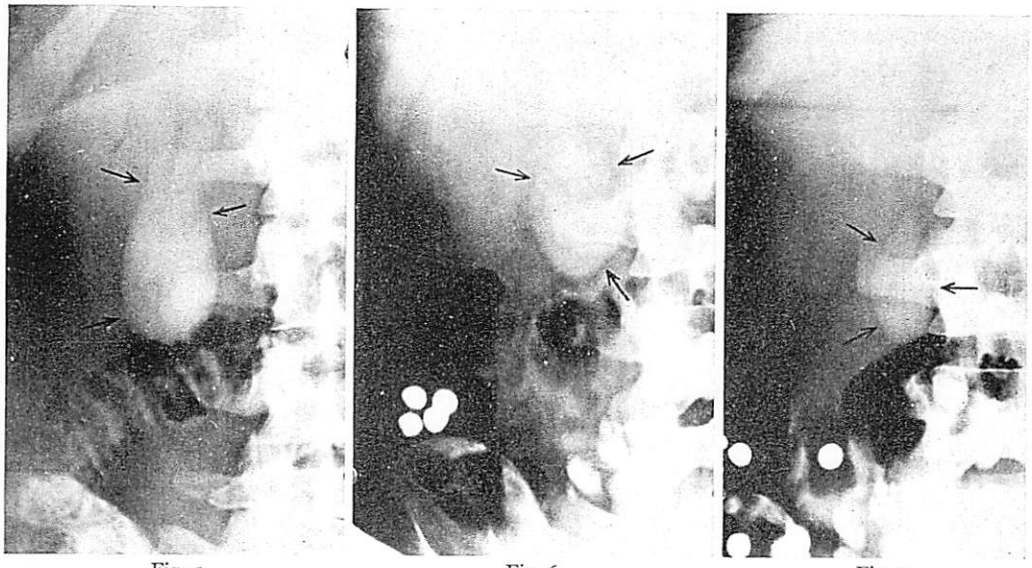

Fig. 5. Fig. 6. Fig. 7.

Fig. 5. Twelve-hour film after oral administration of 0.1 gram per kilogram of sodium tetraiodophenolphthalein in salol-coated pills. This shadow is as clear-cut as we have obtained by any method.

Fig. 6. Twelve-hour film after oral administration of 0.1 gram per kilogram of sodium tetraiodophenolphthalein in salol-coated pills. Note the presence of 4 undissolved pills in the cæcum.

Fig. 7. Fourteen-hour film on same patient as in Figure 6, taken 45 minutes after a meal. Note the marked diminution in size of the shadow of the gall bladder during digestion of the meal.

exhausted. The patient lies in bed on his right side during the period of taking the pills and for an hour or more thereafter. The next morning the patient comes to the X-ray department and roentgenograms are made 12 and 15 hours after taking the pills, no food being eaten meanwhile. After the 15 hour film the patient eats a meal, and an hour afterward, more roentgenograms are made. The purpose of these films after the meal is to see if the gall bladder shrinks down during digestion which indicates that the gall-bladder wall maintains its normal contractility (Figs. 6 and 7).

SYMPTOMS AFTER THE SALT IS TAKEN

Of 44 persons thus tested whose symptoms were recorded, 27 had no symptoms whatever; 5 vomited one to three times; 5 had a mild diarrhœa; 7 had slight nausea. These reactions were not so severe in their effects upon the patient as those which sometimes come after intravenous injection of the salt. The vomiting with the oral method is probably due to gastric irritation by the drug on account of imperfections in the salol coat of the pills, or possibly to the salol itself; while the vomiting with the intravenous method is probably toxic.

In general the effect on the patient is much less noticeable with oral than with intravenous administration. After the former the patient, in most cases, feels perfectly well, while after the latter he often feels somewhat enervated.

There is one caution which should be observed in the oral administration of sodium tetraiodophenolphthalein in salol coated pills. Salol is decomposed in the intestine into salicylic acid and phenol, and with the large dose of salol given in the coating of the pills there is some danger of phenol poisoning. This is apparently slight, however, since the maximum amount of salol ingested would be about 20 grains and none of the 66 individuals in our series showed symptoms of phenol poisoning even though no measures were taken to counteract its effects. We would advise, however, that a dose of magnesium sulphate be given after the last roentgenograms to neu-

tralize any phenol present and to remove the undecomposed salol from the intestine.[1]

More experience will be needed before final conclusions can be reached in regard to the comparative value of the oral and the intravenous methods of giving sodium tetraiodophenolphthalein for cholecystography. Both methods may be capable of improvement, but at present the oral method has several important advantages. Some of these are: that it is convenient, both for the patient and the physician; that it can be used by any roentgenologist in his office; and that in general it gives fewer troublesome symptoms. The advantages of the intravenous method, on the other hand, are that it gives somewhat better shadows, that it is better controlled, and perhaps more dependable.

With our present knowledge of the oral method for cholecystography, we would suggest that patients suspected of having gall-bladder disease first be given the drug by mouth. If a normal, clearly outlined shadow which diminishes rapidly in size during digestion is obtained (Figs. 6 and 7), the probability of gall-bladder disease is slight. If, on the other hand, the shadow is imperfect or absent (provided the technique has been good) then an intravenous injection of the drug should be made in order to confirm the findings. The results to date by the intravenous method have yielded correct diagnoses in 95 per cent of our proved cases (6).

[1]The manufacturers are now making the pills with a coating of stearic acid which makes this unnecessary.

SUMMARY

The oral administration of sodium tetraiodophenolphthalein is being used in this clinic for cholecystography in the form of pills coated with salol in syrup of Tolu.[1]

Cholecystograms have been produced in 93 per cent of normal subjects by this method. We advise the use of the oral method first in cases suspected of gall-bladder disease, to be followed by the intravenous method in the few instances in which the result with the former is not conclusive.

The advantages of the oral method are that it relieves many patients of the hospitalization necessary for the intravenous method, and that it causes them very little inconvenience and few unpleasant symptoms.

BIBLIOGRAPHY

1. Graham, E. A., and Cole, W. H. Roentgenologic examination of the gall bladder. Preliminary report of a new method utilizing the intravenous injection of tetrabromphenolphthalein. J. Am. M. Ass., 1924, lxxxii, 613.
2. Graham, E. A., Cole, W. H., and Copher, G. H. Visualization of the gall bladder by the sodium salt of tetrabromphenolphthalein. J. Am. M. Ass., 1924, lxxxii, 1777.
3. Idem. Roentgenological visualization of the gall bladder by the intravenous injection of tetrabromphenolphthalein. Ann. Surg., 1924, lxxx, 473.
4. Idem. Cholecystography: an experimental and clinical study. J. Am. M. Ass., 1925, lxxxiv, 14.
5. Whitaker, L. R., and Milliken, G. A comparison of sodium tetrabromphenolphthalein with sodium tetraiodophenolphthalein in gall-bladder radiography. Surg., Gynec. & Obst., 1925, xl, 17.
6. Milliken, G., and Whitaker, L. R. The clinical use of sodium tetraiodophenolphthalein for cholecystography. Surg., Gynec. & Obst. 1925, xl, 646.