Iodinated Organic Compounds
As Contrast Media for Radiographic Diagnoses

VIII. Studies on Tetraiodophthalimidoethanol as a Medium for Gastro-Intestinal Visualization

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Apparently no serious attempt has been made to utilize iodinated organic compounds for the visualization of the gastro-intestinal tract. Iodized oils are used to a limited extent for specialized examinations, and there are occasional reports of experimental attempts to employ other iodinated compounds.

To evaluate the possibilities of particulate iodinated organic compounds for gastro-intestinal work, tetraiodophthalimide (I), tetraiodophthalimidomethane (II), and tetraiodophthalimidoethanol (III) were synthesized and studied experimentally in dogs and to a limited extent clinically. It was soon apparent that the parent compound, tetraiodophthalimide, produced increased motility of the stomach. Although this effect may be useful for certain specialized problems, it does not appear to be a desirable quality for general use. Attention was then turned to tetraiodophthalimidoethanol. After some study it was found that this medium, when ground in water to a particle size of 1 to 2 microns, formed a suspension that had a number of desirable qualities. In comparison with barium sulfate suspensions, tetraiodophthalimidoethanol suspensions do not settle out as readily, are not so gritty, delineate more completely experimentally produced gastric lesions, adhere better to the bowel wall, and apparently do not inspissate so readily.

Tetraiodophthalimidoethanol is a light yellow solid with a slightly greenish cast. The medium contains 73 per cent iodine and is considerably more opaque to x-rays than barium sulfate. The preparation of suitable aqueous suspensions on an experimental scale is a time-consuming process, since the product of chemical synthesis must be micronized in the dry state and then ground in a ball mill with water for several weeks. A properly prepared suspension is essentially non-settling at concentrations above 15 per cent by weight and becomes very thick at concentrations above 30 per cent.

Studies on toxicity are still somewhat incomplete, but it appears that tetraiodophthalimidoethanol is of about the same order of toxicity as barium sulfate. Oral administration to fasting rats in doses up to 15 grams/kg. produced no toxic symptoms. Intraperitoneal injections in mice

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were productive of toxic manifestations at the range of 7.5 to 10 grams/kg. In comparison, barium sulfate suspensions when injected intraperitoneally in mice produced similar but less severe reactions at the same level of 7.5 to 10 grams/kg. Growth curves of rats raised on diets containing 4 per cent of added tetraiodophthalimidoethanol were more nearly normal than those obtained with 4 per cent added barium sulfate, but this may be due entirely to the effect of particle size, since the tetraiodophthalimidoethanol averaged about 10 microns, and the barium sulfate 1 to 2 microns.

**Experimental Studies**

**Preparation of Suspensions:** Tetraiodophthalimidoethanol as obtained by synthesis consisted of needles varying in particle size from 3 to 25 microns. Suitable suspensions with a particle size of 1 to 2 microns were prepared from the stock material either by wet ball-milling with water for ten to twelve weeks or by wet ball-milling of a micronized product for two to three weeks. The ball-milling was done in a 1-gallon apparatus using charges of about 2 kg., of which usually 25 per cent was the iodinated medium. Periods of ball-milling shorter than those specified were inadequate to reduce the particle size uniformly to 1.5 to 2 microns.

Commercial barium sulfate was found to have a particle size of 1.5 to 3 microns, and to be fairly uniform in composition. By micronizing or by wet ball-milling, the size of the particles could be reduced to 1 to 2 microns, and the uniformity could be improved slightly. Suspensions were prepared either by wet grinding or by following the clinical practice of stirring barium sulfate with water mechanically. For some of the work, gelatin (1) or starch was added to give better suspensions.

**Gastro-Intestinal Series in Dogs:** Initially the iodinated medium was compared with barium sulfate suspensions by studying the delineation of the rugal pattern in normal dogs. Although the iodinated medium uniformly gave more satisfactory visualization of the rugae, it was felt that the experimental test was not critical enough. A much more satisfactory test object was found in dogs in which marginal stomach ulcers had been produced by the general technic developed by Code and Varco (2). In such dogs an ulcer is produced by intramuscular injections of histamine-beeswax following various types of gastrojejunostomy. The anatomical relationships that are produced are illustrated by the photograph (Fig. 1) of a stomach of one of the dogs used in the work. Comparative studies were made with barium sulfate suspensions and with tetraiodophthalimidoethanol suspensions in 4 such dogs. In 3 dogs an ulcer or stomach lesion was demonstrated with the iodinated medium, but in only one of these was the stomach lesion delineated when barium sulfate was used. In the fourth dog no lesion could be demonstrated either with the iodinated medium or with barium sulfate and none was found on autopsy. The comparison of the two media in one dog is shown in Fig. 2, in which a filling defect at the line of anasto-
mosis is visualized in the examination conducted with tetraiodophthalimidoethanol, but not in the one with barium sulfate.

The technic of the examination was varied somewhat with each animal. First each dog was anesthetized with nembutal
Fig. 3. Double contrast studies of the bowel of the same dog, comparing the adherence of tetraiodophthalimidoethanol and barium sulfate. A and B, made with tetraiodophthalimidoethanol, show uniform coating both in the lateral and anteroposterior views. Studies with barium sulfate are shown in C, where the coating is very poor, and D, where the medium has settled to the dependent portion of the bowel to give a fair coating.
and placed in a supine position. By means of a stomach tube, a dose of 50–70 c.c. of the suspension of the contrast medium under study was then given. A series of roentgenograms was then made at intervals during the first thirty minutes with the animal in various positions. As a variant, the dog was placed in an upright position with the hindquarters supported by a sling.\(^2\) No one position was uniformly satisfactory, but with each dog there was usually an ideal position.

Because of the extensive alterations in the arrangement of the intestines as a result of the operative intervention, roentgenograms taken more than thirty minutes after the administration of the medium were difficult to interpret.

To study the inspissating characteristics of tetraiodophthalimidoethanol, the feces of dogs fed with the medium were compared with those given barium sulfate. Almost uniformly the consistency of the feces was much softer when the iodinated medium was used. An extended experiment was carried out with a 10-kg. dog that was to be sacrificed in connection with another problem. This animal received two doses daily of 19 grams of tetraiodophthalimidoethanol for a period of eight days. At autopsy the entire digestive tract was found to be filled with varying amounts of the yellow tetraiodophthalimidoethanol, and the consistency was found to become progressively harder as the rectum was approached. Both grossly and microscopically the tissue of the digestive tract was unremarkable.

**Opaque Enemas in Dogs:** The procedure for the visualization of the large bowel of the dog was varied from time to time, but the following technic is typical of the method giving the most uniform results:

The dog was anesthetized with nembutal, placed in a supine position, and given a tepid enema of isotonic saline. Usually from 3 to 5 liters of saline were necessary to clear the large intestine of all feces. About an hour after the saline enema was completed, the dog was given an enema of the radiopaque medium under consideration. Nembutal markedly relaxes the anal sphincter, and it was impossible for the dog to retain the enema without the use of a Foley catheter. Even with this device, retention was often difficult because the catheter would slip out over the smooth mucosal surface. After a waiting period of fifteen minutes, corresponding to the time involved clinically in fluoroscopy, the medium was expressed by gentle palpation of the abdomen, and the large intestine was insufflated through the Foley tube with 70 to 100 c.c. of air. Routine anteroposterior and lateral films were taken after each step in the procedure. Following the examination, the dog was rested for four to seven days before the procedure was repeated with the same or another radiopaque medium.

To appraise the adherence of each medium to the mucosal surfaces, it was necessary to take both anteroposterior and lateral films after the air insufflation. Thus the coating on all surfaces of the bowel wall could be studied (Fig. 3). The roentgenograms were then graded to evaluate the comparative excellence of the delineation of the bowel wall with the various suspensions.

For an examination to be considered "excellent," 75 per cent or more of the bowel wall in both views had to be covered with a uniform thin coating of the medium. Roughly half of the bowel had to be coated if the examination was to be rated as "good." An examination was considered "fair" if less than 50 per cent of the bowel wall was delineated. Variable results were obtained in the "poor" examinations. In most of them little if any of the mucosal surface was covered with medium, while in some series the medium had settled out of suspension onto the dependent bowel wall. Table I summarizes the 33 examinations which were done, using 6 dogs. The data on barium sulfate include the results obtained with U.S.P. barium sulfate, I-X barium sulfate, barium sulfate and starch, and barium sulfate and gelatin.

\(^2\) The authors are indebted to Dr. Ross Golden for the suggestion that this position be employed.
according to the formula published by Abel (1). In passing, it may be noted that most of the modified barium sulfate formulas were less satisfactory than barium sulfate per se.

CLINICAL STUDIES

In all, 36 oral examinations and 4 opaque enema studies were carried out clinically with the suspensions of tetraiodophthalimidoethanol. Many of the early examinations were made with suspensions in which the particle size was of the order of 3.5 to 8 microns, and the findings were not remarkable. It became apparent from these preliminary trials that the suspensions of tetraiodophthalimidoethanol were easier to take than barium sulfate suspensions. The patients found the taste of the suspension of the iodinated medium comparable to that of milk of magnesia.

The increased palatability of suspensions of tetraiodophthalimidoethanol over barium sulfate suspensions was brought out particularly well in a student experiment that was conducted on the relative rates of passage of white and "peeled wheat" breads through the stomach. In the course of this work, measured amounts of the two kinds of bread were soaked in the suspension of either barium sulfate or of tetraiodophthalimidoethanol and ingested on an empty stomach. After a number of experiments of this type, the student group was unanimously in favor of the use of the iodinated medium. None of the students noted any effects that might be attributed to the series of weekly doses of 20 to 25 grams of tetraiodophthalimidoethanol.

Eighteen hospital cases were examined with the suspension of the iodinated organic medium. Several of these were studied, also, with the aid of barium sulfate meals. In only one instance did the examination with tetraiodophthalimidoethanol disclose a lesion that was not revealed by barium sulfate. In this case there was an area in the small intestine that was delineated by tetraiodophthalimidoethanol but not by barium sulfate; there was no opportunity to confirm this observation.

Several of the patients examined with tetraiodophthalimidoethanol were in terminal stages of disease, and in two cases it was possible to study autopsy material. In these patients there was no evidence of the medium in the intestine, nor were there any findings that could be attributed to the use of the medium.

At no time did any of the patients or student investigators find that tetraiodophthalimidoethanol was productive of undue constipation. The consistency of the feces was firmer, as would be expected as a result of adding an undigested solid organic compound, but laxatives were not required for adequate elimination. This comparison with barium sulfate is inadequate, because the retention of normal mobility is due in part to the fact that the greater opacity of the iodinated compound permitted the use of small amounts.

DISCUSSION

The first consideration for any preparation proposed for use as a contrast medium is a proper appraisal of its toxicity. Tox-

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<th>Medium</th>
<th>Tetraiodophthalimidoethanol</th>
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<td></td>
<td>Excellent</td>
<td>Good</td>
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city studies on a medium advocated for use in gastro-intestinal work should include a consideration of the response of animal tissues to the preparation in the digestive tract, in the peritoneal cavity, and in the lower respiratory tract. The studies on tetraiodophthalimidoethanol have been quite complete with respect to the digestive tract, moderately complete with regard to the peritoneal cavity, and inadequate in relation to the respiratory system. The information available from the animal studies is adequate for clinical appraisal in selected cases, however, but should be supplemented by further observations if the medium proves promising in clinical applications. Many problems are difficult to solve satisfactorily. In illustration, there may be cited the question of whether it is safe to use barium sulfate in infants, where there is the possibility that some of the medium may on occasion be aspirated into the respiratory tract. The relatively rare occurrence of barium sulfate entering the peritoneal cavity through perforation of an ulcer has raised similar questions. From a practical point of view, the damage to the system resulting from such peritoneal escape appears to be tolerable (3).

At the outset of the work, it was felt that the property of remaining in suspension was the most important aspect of a radiopaque medium designed for use in gastro-intestinal work. The many admixtures that are made with barium sulfate to accomplish this purpose naturally influenced this point of view. As the work progressed, it became apparent that adherence to the gastric mucosa was of equal, if not greater, importance, if progress were to be made in increasing the accuracy of the gastro-intestinal series or of the opaque enema study. It is quite apparent from the results of the oral administration of barium sulfate and of tetraiodophthalimidoethanol to dogs with stomach lesions that the accuracy of the delineation was much greater with the iodinated medium than with the standard barium sulfate.

With the opaque enemas the double contrast studies were uniformly better with tetraiodophthalimidoethanol than with barium sulfate. Surprisingly, the incorporation of additives with barium sulfate appeared to decrease the adherence of the medium to the bowel wall. This was not always apparent when anteroposterior views alone were taken, but became evident only when both lateral and anteroposterior exposures were made.

Although experimentally the iodinated medium is superior to barium sulfate in that it does not settle out as readily, adheres better to the bowel wall, and apparently does not inspissate as readily, it remains to be shown that these advantages make for more accurate interpretations in normal clinical practice. From the limited clinical experience that is now available, it can be said only that suspensions of tetraiodophthalimidoethanol are more palatable than barium sulfate and appear to be free of toxic reactions. Before a large scale clinical trial can be considered, it must be shown that an iodinated organic compound, one that will be relatively expensive, will give enough information to justify the cost. Work is under way to make a critical comparison clinically of such new media in selected cases.

**Summary**

Comparative studies in dogs of barium sulfate suspensions and of tetraiodophthalimidoethanol suspensions show that the iodinated medium gives more complete and more accurate delineation of experimentally produced stomach lesions. Double contrast enema studies in dogs were similarly much more satisfactory with the iodinated organic medium than with barium sulfate. A limited clinical experience with tetraiodophthalimidoethanol has shown that the new medium is more palatable than barium sulfate, and apparently as safe to use. Further use of the new medium is dependent on the outcome of critical comparisons with barium sulfate in selected clinical cases.
REFERENCES


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DISCUSSION

Ray Carter, M.D. (Los Angeles, Calif.): One can only discuss this paper optimistically, and perhaps wishfully, because of the well known deficiencies of our ordinary barium medium. Attempts to improve the qualities of barium have met with only moderate success, and now, when mucosal pattern studies are crucial, any potential improvement is of great interest. As a matter of fact, improvement doesn’t have to be outstanding, as this appears to be at first sight. Even if it gives a reasonable improvement of our roentgenologic images, it will be well worth while.

The cost, of course, always has to be considered, but there are fallacies here. The cost of the opaque material is a minor part of the cost of an examination. Any reasonable added expense would actually be an economy if it increased the information obtained.

Thorium dioxide sol has served well in the alkaline medium of the colon, but we do not yet have a contrast substance that shows so clearly the mucosal pattern in the stomach. It will be interesting to see what mucosal pattern will be revealed in the small intestine by this new medium. Here again minute details are crucial.

Again, one can only hope this medium will prove to be safe, reasonable, economical, and thoroughly useful.

Robert R. Newell, M.D. (San Francisco, Calif.): Of course, I have no experience with this material. I have been discouraged about the shortcomings of barium, and many years ago I made some experiments with alginic acid to keep barium from settling out. They were very successful but I never had the energy to complete them. Maybe I will some day.

Various things ought to be investigated, of course, if barium seems sufficiently unsatisfactory that one could really afford to spend ten dollars a patient in order to get some other material which might be slightly better.

We have tried umbrathor, the less expensive thorium dioxide suspension, for contrast enemas; we were told that it had the advantage that it precipitated out on the mucosa. It does, but that is a disadvantage rather than an advantage, so we have returned to barium for contrast studies. I was interested to see the very high smears obtained around the inside of the colon in dogs. If this material proves to smear itself over the inside of the large intestine better than barium does, I should say that it would be very well worth using for contrast enemas, because I think that the search for polyps in the colon now leaves us with too many oversights. We could afford to spend almost any amount of time and effort to better our percentage of success in that region.

Maurice Feldman, M.D. (Baltimore, Md.): I would like to ask Dr. Strain what effect this medium has on other structures of the body, whether he has made any blood studies, and whether there is any iodine absorption, and how the drug is eliminated.

Hans Armin Jarre, M.D. (Detroit, Mich.): There is no need of repeating again the disadvantages which we have encountered with barium, but it is a pleasure to hear that some efforts are being made to obtain a better contrast medium. In that respect it might be worth while to reopen a chapter which has been given very little attention during the past.

There is one chemical at least available which is excreted by the gastric mucosa: neutral red. Some years ago I persuaded the University of Wisconsin and Dr. Pohle to experiment with neutral red, combining iodine in various forms with derivatives of this chemical, and while the results were not successful in the sense that they were practical in radiologic application, it was nevertheless possible to obtain a faint accumulation of such chemicals in the gastric mucosa and probably in the gastric glands themselves.

It is quite possible that research, as we have heard today, may be conducted along similar lines and that the possibilities of excretion of contrast material by the gastric wall may be re-investigated, so that functioning areas may be more readily differentiated from non-functioning areas—that normal areas may be differentiated from pathological areas.

William H. Strain, Ph.D. (closing): We don’t know all the answers on the pharmacology of tetradodiphthalimidoethanol, but we do know, that it is not absorbed to any extent. We have had a number of blood iodine determinations made and expect to have some further analyses carried out; to date all have been in the “physiological range.” The particle size will influence somewhat the amount of absorption, and until we have decided on just the particle size we shall want to use there is no particular point in further studies.

As brought out in the paper, we have incorporated the medium in diets of rats—a sort of standard procedure with many new drug preparations—to see how it influenced the rate of growth. To our surprise, tetradodiphthalimidoethanol retarded the
growth less than barium sulfate. We think the explanation is entirely a physical one, since the barium sulfate particles were slightly smaller.

We have made some intravenous injections in experimental animals. This is a very interesting experiment because the particle size determines where the particular medium will go, and in EKG measurements there is a convenient tool for determining whether the capillaries of the lungs become plugged. We are going to do some additional work of this sort. We now have a stock of a variety of particle sizes, and we should be able to do a rather polished job on the distribution in the organs of experimental animals.

**SUMARIO**

El Tetracyodofthalimidoetanol como Medio Gastrointestinal

Estudios comparados de las suspensiones de sulfato de bario y de tetracyodofthalimidoetanol realizados en los perros revelan que el medio yodado facilita una delineación más completa y exacta de las lesiones producidas experimentalmente en el estómago. Los estudios con enemas de doble contraste fueron igualmente más satisfactorios con el medio orgánico yodado que con el sulfato de bario. Una limitada prueba clínica con el tetracyodofthalimidoetanol demuestra que el nuevo medio posee sabor más agradable que el sulfato de bario, y es aparentemente igualmente inocuo. El empleo ulterior del tetracyodofthalimidoetanol depende del resultado de las comparaciones analíticas con el sulfato de bario en casos clínicos.