Iodinated Organic Compounds
As Contrast Media for Radiographic Diagnoses

VI. Experimental Studies on Emulsions of Ethyl Iodophenylundecylate (Pantopaque)\(^1\)

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In the course of the experimental work leading to the development of pantopaque (ethyl iodophenylundecylate), it was observed that stable aqueous emulsions could be obtained easily with the medium (1, 2). Study of these emulsions has shown that they have the property of coating and adhering to mucosa and that they seem well adapted to the visualization of certain body cavities. In experimental examinations in dogs and other laboratory animals the most promising results have been obtained in bronchography, although satisfactory delineation may be produced in a number of other types of examination.\(^2\)

Stable emulsions of ethyl iodophenylundecylate are formed when a 50 per cent mixture by volume with water containing up to 1 per cent of a surface active agent is passed numerous times through a colloid mill or other type of homogenizer. The surface active agents studied included bile salts, various neutral soaps, and a number of synthetics. Of these, oleyl methyl taurine (Igepon T gel) was found to be the most satisfactory when dissolved in the water phase at a concentration of 0.6 per cent. On standing, the emulsion prepared with Igepon T as a surface active agent separates into a lower milky phase, containing about 70 per cent of ethyl iodophenylundecylate, and a clear upper aqueous phase. The two phases are readily redispersed on shaking, and the resulting emulsion does not settle out for some hours. The two phases are easily separated by aspiration, or the emulsion may be diluted with isotonic saline. The size of the oil droplets in the emulsion varies somewhat with the mode of preparation, but usually they are of the order of 1.5–3.5 microns. Both the 50 and the 70 per cent emulsions may be readily injected through needles and catheters of small bore.

As reported previously (2), ethyl iodophenylundecylate has a measurable toxicity in rats and mice which is consistent with the absorbability of the medium. The process of emulsification leads to an enormous increase in surface, and this in turn affects the values of the toxicity constants. The increase in surface does not

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\(^2\) A 50 per cent emulsion is available for investigational use from Dr. H. Sidney Newcomer, E. R. Squibb & Sons, 745 Fifth Ave., New York 22, N. Y.
Fig. 1. Bronchography in dogs with 70 per cent ethyl iodophenylundecylate emulsion. A. Overfilling obtained with intratracheal injection of 10 c.c. of the emulsion in a 12-kg. dog supine. B. C, and D. Bronchial mucography obtained with 3 c.c. of the emulsion in an 8 kg. dog in a prone position. The roentgenograms were made over a period of fifteen minutes, the first view being taken ten minutes after introduction of the medium. Note that the upper lobe is uniformly filled.
alter significantly the LD 50 in mice as obtained by intraperitoneal injection, but does influence markedly the value found in rats. The intraperitoneal LD 50 of ethyl iodophenylundecylate has been reported to be 19 grams/kg. for 24-hour kill, while that of the emulsion has been found to be of the order of 2 grams/kg. It appears, on the basis of comparative work with other species, that the rat is particularly sensitive to ethyl iodophenylundecylate. Both ethyl iodophenylundecylate and its emulsion produce the same kind of pathological changes in the liver and kidneys of rats and mice when administered at or near the lethal level.

**Experimental Studies**

**Bronchography:** The spreading and coating properties of the emulsion were studied by making bronchograms in dogs. Other laboratory animals were briefly examined as experimental subjects but were found to be unsatisfactory.

By the procedure that was finally adopted, a dog, anesthetized with nembutal, was placed in a prone position on an animal table and rotated onto its left side. The table supporting the animal was then elevated 30° at the head, and 2 to 15 c.c. of the 70 per cent emulsion were injected under direct vision down the trachea through a small rubber tube. After two or three minutes the table was returned to a horizontal position and a series of roentgenograms was taken at intervals of five to ten minutes. Usually there was little change in the bronchogram after the first exposure. The emulsion often is seen in the smaller radicles of the bronchial system on the day following the original bronchographic study. Seven to ten days later, however, the lung fields are roentgenographically clear.

Typical bronchograms obtained by this procedure, as well as one made with the dog supine, are shown in Figure 1.

Attempts to obtain good bronchograms in anesthetized dogs with lipiodol or pantopaque proved uniformly unsatisfactory. The distribution of the media was poor. Nebulization of pantopaque was even more unsatisfactory, perhaps because of the shallow respiration that accompanies nembutal anesthesia.

Among the 16 dogs used in the bronchographic study there was one death, due to pneumonic processes initiated by a contaminant which was identified as a type of *Vibrio*. There was no evidence in the other animals of any toxic effects. Lung sections taken from four of the dogs that were autopsied showed little, if any, change that could be attributed to the effects of the medium. This was particularly well demonstrated in a 40-lb. old collie that was subjected to bronchography on four occasions at intervals of two weeks each. During the period of experimentation the dog was in excellent clinical condition. When it was killed, two weeks after the last bronchogram had been obtained, the lungs appeared darker than normal, but the gross appearance and texture were not inconsistent with the age of the animal. Microscopic sections revealed no changes that could be attributed to the use of the medium.

**Retrograde Pyelography and Cystography:** In two experiments with dogs the peritoneum was opened, the right and left ureters were isolated, and about 2 c.c. of the 50 per cent emulsion were injected into each kidney under slight pressure. Roentgenograms (Fig. 2) taken from these experiments show that some of the medium adheres to the wall of each kidney pelvis so that there is good to fair delineation of the calices for some time after the bulk of the medium has run out of the pelvis. Follow-up roentgenograms showed that some of the medium remains in the pelvis for several days.

Similar experiments in cystography (Fig. 3) in dogs gave excellent delineation of the urethra and the bladder, with some adherence to the walls of the bladder for twenty-four hours after the examination had been completed. This was particularly noticeable with the male animals.

The findings on autopsy of the dogs used for retrograde pyelography and cystog-
raphy were unremarkable both grossly and microscopically.

**Hysterosalpingography:** The uteri of two dogs and three rabbits were exposed by laparotomies. The proximal ends of the uteri were clamped off, and an attempt was made to force the 50 per cent emulsion through the fallopian tubes. In every instance this was unsuccessful. After roentgenograms were made, the clamps were removed and the animals closed up. Subsequent roentgenograms showed that the medium remained in the uterine passages for several hours. There were no obvious disturbances in the behavior of the animals subsequently. One of the dogs was killed after eighteen days, and the other bred. The uterine passages were found to be normal in the case of the sacrificed animal, and were assumed to be functioning properly when the second dog was delivered in due course of a litter of 5 pups.

**Cholangiography:** Roentgenograms made following injection of the hepatic tree operatively exposed in dogs, rabbits, and rats, showed that the opacity of the 50 per cent medium was adequate for the delineation of small ducts. Two dogs were carried along after operation, and sections were made of the liver. There was no evidence of damage.

**Intravenous Injections:** The early preparations of the 50 per cent emulsion could not be injected intravenously with any safety, but as the technic of preparing the emulsion was improved it was found that amounts up to 1 c.c. kg. could be injected into the saphenous veins of dogs without immediate or subsequent effects. No attempt was made to determine the lethal dose, however. In rabbits, injections of 0.5 c.c. kg. in a marginal ear vein produced no early or late EKG changes.

**DISCUSSION**

The experimental work shows that the 50 per cent emulsion of ethyl iodophenylundecylate prepared with the aid of oleyl methyl taurine is non-toxic in the regions and at the concentrations studied. The animal experiments are not relevant as to the production of transient irritating ef-
fects in clinical practice. There appears to be no really satisfactory method of studying this problem in animals.

One logical application of the emulsion to clinical diagnoses appears to be in relation to problems of thoracic surgery. With the current procedures, many bronchograms made with the aid of iodized oils fail to give adequate information concerning the extent and degree of disease. In recognition of this, some work is in progress to improve the results obtained with the existing media. Thus, Fariñas (3) has developed a technic for spraying iodized oils into the bronchi in order to get surface coating. To distinguish this procedure and its results from conventional bronchography, Fariñas has introduced the term “mucosography.” As is evident from the illustrative bronchograms obtained with dogs through the use of the 70 per cent emulsion, the coating is of a type that reveals the details of the mucosa.

It seems evident that there would be little difficulty in adapting the experimental procedure to clinical practice.

The other applications that are suggested from the animal work are not so striking, and adaptation to clinical practice may not be profitable in all fields. Nevertheless, in examinations such as cystography, urethrography, hysterosalpingography, retrograde pyelography, and cholangiography, the formation of a coating that will remain for some time may reveal additional information.

In addition to the emulsion proposed in this paper, there are a number of emulsions of iodized oils that have received study both experimentally and clinically. Emulsions prepared from water-acacia mixtures with campiodol (4) or iodochlorol have been available for retrograde pyelography for some years but have not attained
wide use. This is due in part to the fact that their viscosity is relatively high, and usually it has been necessary to inject them from a syringe rather than by a gravity method.

In 1938 a very interesting 50 per cent emulsion of ethyl trifiodostearate, prepared and stabilized with the aid of lecithin and gelatin, was introduced in Germany under the name Jodsol for hepatosplenography (5, 6, 7). Since then Jodsol has been studied for angiography (8) and phlebography (9) but it is still partially in the experimental stage. Apparently the medium must be stored under refrigeration to prevent the oil particles from coalescing, and this is obviously a great disadvantage. In clinical use, up to 80 c.c. are injected intravenously, and adequate shadows of the blood vessels are obtained if the iodine concentration is 20 per cent or more.

It is uncertain whether the presently described emulsion of ethyl iodphenylundecylate is suitable for intravenous work. More experimental studies will have to be done before it can be considered for this type of application. Nevertheless, the particle size of the droplets is of the correct magnitude and the emulsion does not break down when stored for long periods of time at room temperature.

SUMMARY

Experimental studies in dogs and other laboratory animals show that emulsions of ethyl iodphenylundecylate (pantopaque) and water, prepared with the aid of 0.6 per cent of the surface active compound oleyl methyl taurine, have the property of coating and adhering to mucosal surfaces. The application of a 70 per cent medium to bronchography, and of a 50 per cent medium to a variety of other diagnostic problems, is illustrated by experimental work in dogs.

REFERENCES


SUMARIO

Las Emulsiones de Yodofenilundecilato de Étilo como Medios de Contraste

Los estudios experimentales en perros y otros animales de laboratorio muestran que las emulsiones de yodofenilundecilato de etilo (Pantopaco) y agua, preparadas con la ayuda de 0.6 por ciento del compuesto activo superficial, oleilo-metilo-taurina, poseen la propiedad de recubrir las superficies de las mucosas, adhiriéndose a las mismas. La aplicación de un medio de 70 por ciento a la broncografía y de un medio de 50 por ciento a otros varios problemas de diagnóstico queda demostrada por la experimentación en perros.