

TOXICITY OF COLLOIDAL IODINE.*

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The importance of Iodine has long been recognized by the biologist and the physician. As a bio-element iodine is indispensable for the life of the vertebrates and is very largely used in almost all branches of medicine. Its use in therapeutics, although merely built upon empiricism is based upon its alterative, resorptive and probably chemo-therapeutic properties (1). It is highly esteemed as an efficient germicide and antiseptic in human and veterinary medicine. Lately it became valuable for X-ray examination as contrast medium.

For these various purposes iodine is being used in many forms and preparations. There is, however, considerable discrepancy of opinion as to the value of the individual preparation. In accordance with the present assumption the elementary atom of iodine is the ultimate effective agent. The objection made in literature to most of the iodine compounds is that the iodine is too firmly bound within the molecular structure to become effective. Therefore, the general tendency in its therapeutic use, with few exceptions, is to introduce the iodine into the body in forms in which it is easily liberated. These views prompted the physician to try preparations, *e. g.*, Mirion (2) and Pregl's solution (3). For the same reason many physicians prefer free iodine in the well-known forms of Tincture of Iodine and Lugol's solution. These latter preparations, however, although being generally used, have the disadvantage of containing alcohol and iodides, respectively.

It was, therefore, of considerable interest, that Chandler (4), in 1925 succeeded in producing a rather stable suspensoid of iodine which does not contain iodides and alcohol. This "colloidal Iodine" is prepared by the acidification at 0° C. of sodium iodohypoidite containing Acacia as protective colloid. It contains free iodine in an extremely finely divided form capable of remaining in suspension in water for a considerable length of time. It can be prepared in suspensions of any concentration and preserves its properties even when evaporated to a dry form. When either the emulsion or the powder is added to water the iodine goes into solution rapidly and forms a saturated solution of iodine in water. A saturated aqueous solution of iodine ordinarily requires several days for formation from crystalline iodine, owing to the slight solubility of iodine. (0.034% at 25.°) With the emulsoid, the production of a saturated solution is almost instantaneous. The excess of iodine beyond the saturation point remains in suspension in the original state of colloidal iodine, thus representing a depot from which iodine readily goes into solution whenever additional water is available or to replace iodine which has been removed from the aqueous phase through evaporation or chemical combination. The advantage of this feature may be demonstrated by applying colloidal iodine in high concentration or in powder form to the skin or wound. Only that portion of the iodine which goes into solution through the presence of moisture or added water will be active, while the rest remains inactive, forming a depot and thus being largely free of irritating action. As soon, however, as the dissolved iodine is resorbed, evaporated or has chemically combined, more colloidal iodine goes into solution from the colloidal depot, becoming active, and thus replacing the used or

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lost free iodine. From the chemical standpoint it is interesting that the iodine content of the suspension may always be titrated as readily as any aqueous or alcoholic iodine solution, so that the strength may be readily established.

The mentioned properties of the new colloidal iodine preparation render it promising for therapeutic purposes, provided that the toxicity is not excessive. As a basis for future therapeutic use we undertook a series of investigations as to the toxicity of colloidal iodine comparing it with Tincture of Iodine U. S. P. This comparison was carried out by means of intravenous injections as well as oral administration. In the following we present, briefly, the results of these investigations, and include the record of the experiments.

Rabbits weighing 1.5 to 2.5 Kg. received tincture of iodine and colloidal iodine in 1 and 2.5% solution intravenously, most of them in single doses, some at repeated administration in twenty-four hour intervals. Rabbits to which the preparations were administered by mouth by means of the stomach tube have been autopsied in order to determine the local corrosive action of the iodine on the stomach. The experiments show that with intravenous administration *ceteris paribus* tincture of iodine and colloidal iodine have the same fatal dose. With slow intravenous infusion continued until death occurs at a rate of about 10 mg. per minute about 90 mg. iodine per Kg. animal are fatal. When the intravenous injection is made rapidly, introducing the entire intended amount within a minute, about 40 mg. of iodine per Kg. kill the animal within approximately one-half an hour while 20 mg. may be administered similarly on several successive days until death occurs. Five mg. iodine per Kg. with the same rapid application is tolerated at repeated administration for at least five days. It is difficult to continue these latter experiments for a longer period of time on the same rabbit because of the local irritating action of iodine which manifests itself in form of an extended succulent edema of the rabbit's ear as well as thrombosis and obliteration of the veins. With the repeated administration of the higher doses the rabbits have loose bowel movements, stop eating and die in a cachectic way. Although there are considerable differences in the individual reaction of the animals as we generally observe in biology, we may say that iodine, applied intravenously, has the same toxicity whether used in the form of colloidal iodine or tincture of iodine.¹

The results of our experiments comparing colloidal iodine and tincture of iodine with *oral* administration are entirely different. Iodine in colloidal form is tolerated in 4-5 times higher doses than is the tincture. The tincture causes death within two hours after the oral introduction of 250 mg. iodine per Kg. rabbit in 2.5% solution. The corresponding effect is obtained after administration of 1250-1500 mg. colloidal iodine per Kg. in 5% solution. While 250 mg. iodine per Kg in form of the tincture makes an extended necrosis of the mucous membrane of the stomach the same amount of colloidal iodine applied under the same working conditions does not show any local corrosive or even irritating effect on the stomach. The two enclosed photographs illustrate these conditions. The stomach of the rabbit which received tincture of iodine has been obtained immediately after death

¹ The potassium iodide content of Tincture of Iodine U. S. P. does not seem to influence the outcome of these experiments. It may be calculated that even immediately after the injection, when the entire amount of tincture of iodine is still in the blood, the potassium level of the blood is maximally twice the normal.

of the animal, which occurred two hours after the administration of the drug (Experiment No. 30). The rabbit which received colloidal iodine behaved normally and was killed twenty hours after administration in order to obtain the stomach (Experiment No. 20). Only 1000 mg. of colloidal iodine per Kg. kill the animal 48 hours after administration and cause necrotic spots in the stomach.

According to the literature colloidal iodine, so far, has been very successfully and extensively used for the control of intestinal parasites, particularly in poultry (Chandler) (5). It seems that in very extended experiments, 0.6 Gm. of iodine in 2% suspension is for adult birds, very well tolerated and has no injurious effect. Chandler (6) also made a few experiments to treat dermatomycoses in human beings apparently with very encouraging results. In minor surgery this preparation is being introduced at present also.

Our toxicity experiments show that colloidal iodine, although similar in its systemic effect to tincture of iodine when administered intravenously, has a very

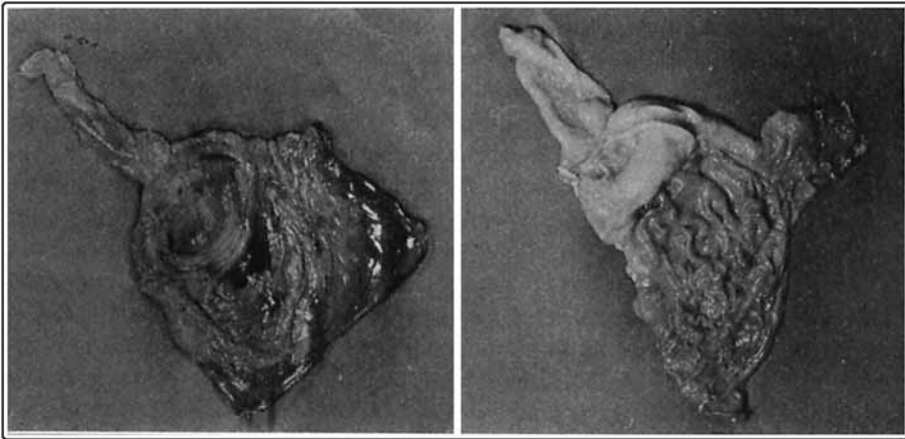


Fig. 1.—*Iodine Tincture*—150 mg. per Kg. rabbit by mouth. Fig. 2.—*Iodine Suspensoid*—250 mg. per Kg. rabbit by mouth.

much less corrosive action locally when introduced directly into the stomach. Its remarkable properties compared with other forms and preparations of iodine render it promising for the different branches of therapeutics.

RECORD OF EXPERIMENTS.

I. Intravenous injections (slow rate).

(a) Colloidal Iodine (Chandler).¹

- (1) 1.95 Kg. rabbit, Pernocton anæsthesia, used 8 cc. of 2.5% Iodine with uniform speed (ear vein) = 102 mg. I per Kg. Death in 9 minutes.
- (2) 2.00 Kg. rabbit, Pernocton anæsthesia, used 6.8 cc. of 2.5% Iodine (jugular vein) = 85 mg. I per Kg. Death in 13 minutes.
- (3) 1.40 Kg. rabbit, Pernocton anæsthesia, used 12.6 cc. of 1% Iodine (jugular vein) = 90 mg. I per Kg. Death in 20 minutes.

Average: 92 mg. Iodine per Kg. rabbit.

(b) Tincture of Iodine U. S. P.

- (4) 1.85 Kg. rabbit, Pernocton anæsthesia, used 7 cc. of 2.5% Iodine with uniform speed (ear vein) = 94 mg. I per Kg. Death in 7 minutes.

¹ We extend our thanks to Riedel-De Haen, Inc., New York, who kindly supplied us with the Pernocton ampuls.

- (5) 1.60 Kg. rabbit, Pernocton anæsthesia, used 5.3 cc. of 2.5% Iodine (jugular vein) = 83 mg. per Kg. Death in 8 minutes.
- (6) 1.65 Kg. rabbit, Pernocton anæsthesia, used 15.4 cc. of 1% Iodine (jugular vein) = 93 mg. I per Kg. Death in 24 minutes.

Average: 90 mg. Iodine per Kg. rabbit.

II. Intravenous injections (rapid rate, repeated). Injection fluid containing 2% Iodine, all injections in ear vein.

(a) Colloidal Iodine (Chandler).

- (7) 1.80 Kg. rabbit, used 5.4 cc. (corresponding 60 mg. Iodine per Kg. rabbit). Death 45 minutes later.
- (8) 1.40 Kg. rabbit, used 2.8 cc. (40 mg. Iodine per Kg.). Death 30 minutes later.
- (9) 2.05 Kg. rabbit, used 3.1 cc. (30 mg. Iodine per Kg.). Death 60 minutes later.
- (10) 1.60 Kg. rabbit, June 16th, 2.4 cc. (30 mg. Iodine per Kg.), June 17th, injection repeated. Death 30 minutes later.
- (11) 1.55 Kg. rabbit, June 14th, 1.55 cc. (20 mg. Iodine per Kg.). June 15th, repeated, June 16th, repeated. Death 60 minutes later.
- (12) 1.60 Kg. rabbit, June 18th, 0.8 cc. (10 mg. Iodine per Kg.), June 19th, repeated. Death three days later.
- (13) 2.00 Kg. rabbit, June 18th, 0.5 cc. (5 mg. Iodine per Kg.), June 19th, repeated, June 20th, repeated, June 21st, repeated, June 22nd, repeated. No more injections made because of the extended succulent œdema of the ears, thrombosis and obliteration of the veins.

(b) Tincture of Iodine U. S. P.

- (14) 1.85 Kg. rabbit, 5.55 cc. (60 mg. Iodine per Kg.). Death 10 minutes later.
- (15) 1.80 Kg. rabbit, 3.6 cc. (40 mg. Iodine per Kg.). Death 25 minutes.
- (16) 1.55 Kg. rabbit June 15th, 2.3 cc. (30 mg. Iodine per Kg.), June 16th repeated. Death 24 hours later.
- (17) 1.65 Kg. rabbit, June 14th, 1.65 cc. (20 mg. Iodine per Kg.), June 15th, repeated; June 16, repeated; June 17th, repeated. Death during the night following last injection.
- (18) 1.55 Kg. rabbit, June 18th, 0.78 cc. (10 mg. Iodine per Kg.), June 19th, repeated. Death during the following night.
- (19) 1.80 Kg. rabbit, June 18th, 0.45 cc. (5 mg. Iodine per Kg.), June 19th, repeated; June 20th repeated; June 21st repeated; June 22nd repeated. Injections stopped because of extended succulent œdema of ears, thrombosis and obliteration of veins. (Same effect as in Experiment No. 13.)

III. Oral administration (through stomach tube).

(a) Colloidal Iodine (Chandler).

- (20) 2.00 Kg. rabbit, 20 cc. of 2.5% Iodine (250 mg. Iodine per Kg.) remains healthy. Killed 20 hours later, mucous membrane of stomach normal (see photograph).
- (21) 1.60 Kg. rabbit, 16 cc. of 2.5% Iodine (250 mg. Iodine per Kg.) remains healthy.
- (22) 1.75 Kg. rabbit, 17.5 cc. of 2.5% Iodine (250 mg. Iodine per Kg.) remains healthy.
- (23) 1.65 Kg. rabbit, 16.5 cc. of 2.5% Iodine (250 mg. Iodine per Kg.) remains healthy. Twenty-four hours later dose repeated. Death twenty hours later. Autopsy: Almost no changes in mucous membrane of stomach.
- (24) 2.10 Kg. rabbit, 42 cc. of 2.5% Iodine (500 mg. Iodine per Kg.) remains healthy.
- (25) 1.75 Kg. rabbit, 35 cc. of 2.5% Iodine (500 mg. Iodine per Kg.) remains healthy. Twenty-four hours later dose repeated. Death eighteen hours later.
- (26) 2.30 Kg. rabbit, 69 cc. of 2.5% Iodine (750 mg. Iodine per Kg.) sick impression for twenty-four hours; no food intake during this time; then healthy.

- (27) 1.85 Kg. rabbit, 37 cc. of 5% Iodine (1000 mg. Iodine per Kg.) death forty-eight hours later. Autopsy: Brown and black spots of necrosis on cardinal half of stomach mucosa.
- (28) 1.70 Kg. rabbit, 42.5 cc. of 5% Iodine (1250 mg. Iodine per Kg.). Death twenty-six hours later. Autopsy: Black spots of necrosis of the stomach mucosa.
- (29) 1.80 Kg. rabbit, 54 cc. of 5% Iodine (1500 mg. Iodine per Kg.). Death twenty-five minutes later. Autopsy: Stomach mucosa necrotic, stomach brittle, tears when cut out.
- (b) Tincture of Iodine U. S. P.
- (30) 1.85 Kg. rabbit 18.5 cc. of 2.5% Iodine (250 mg. Iodine per Kg.). Death two hours later. Autopsy: Extended necrosis of stomach mucosa (see photograph).
- (31) 2.05 Kg. rabbit, 20.5 cc. of 2.5% Iodine (250 mg. Iodine per Kg.). Death two and one-half hours later. Autopsy: Large spots of necrosis of stomach mucosa.
- (32) 1.60 Kg. rabbit, 16.0 cc. of 2.5% Iodine (250 mg. Iodine per Kg.). Death one hour later. Autopsy: Extended necrosis of stomach mucosa.
- (33) 1.75 Kg. rabbit, 35 cc. of 2.5% Iodine (500 mg. Iodine per Kg.). Death fifteen minutes later. Autopsy: Brittle necrotic stomach; tears when cut out.

SUMMARY.

The paper deals with experimental investigations concerning the toxicity of colloidal iodine (Chandler) particularly in comparison to that of tincture of iodine, U. S. P. It is shown by experiments on rabbits that colloidal iodine and tincture of iodine have the same fatal dose with intravenous administration. This conclusion is based on slow, rapid and repeated injections.

Colloidal iodine has one-fourth to one-sixth of the local corrosive action on the mucous membrane of the stomach exhibited by Tincture of Iodine U. S. P. 250 mg. of iodine introduced by means of the stomach tube as tincture, causes an extensive necrosis of the stomach mucosa and is fatal to the animal within approximately 2 hours, while 1000–1500 mg. of iodine in colloidal suspension, similarly administered, has the same injurious effect.

Therefore, from the toxicological standpoint, colloidal iodine appears to be promising for therapeutic use.

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