Bull. Org. mond. Santé
Bull. World Hlth Org. } 1953, **9**, 211-216

THE EFFECTS OF ADMINISTRATION OF SODIUM IODATE TO MAN AND ANIMALS*

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Manuscript received in April 1953

SYNOPSIS

Acute and chronic toxicity tests with sodium iodate were carried out on mice and rabbits to determine the feasibility of using sodium iodate in the place of iodide for the iodization of salt. It was found that mice tolerated single oral doses of 250 mg of sodium iodate per kg of body-weight, while rabbits tolerated twice-weekly oral doses of 10 mg per kg of body-weight for six weeks. Long-term oral administration of sodium iodate to rabbits and their offspring at a level of 1 mg per kg of body-weight twice weekly, for periods of up to one year, produced no signs of ill-health. Histological examination showed that the livers, kidneys, and retinae of these rabbits were normal. The equivalent weekly amount for a man weighing 70 kg would be 140 mg. It is therefore concluded that it would be safe to recommend the iodization of salt with sodium iodate to a level of 1 part of $NaIO_3$ in 20,000 parts of salt. On the basis of a weekly intake of 70 g of salt, this would provide 3.5 mg of $NaIO_3$, which is equivalent to 2.2 mg of iodine. Finally, the author considers that sodium iodate should be used for the iodization of salt only when the type of salt available or the environmental conditions cause excessive loss of iodine from iodide.

The object of carrying out toxicity tests on sodium iodate was to establish the feasibility of using it in place of iodide for the iodization of salt where crude salt only is available, or, possibly, where the environmental conditions lead to excessive loss of iodine from the salt during storage.

Little definite information is available in standard textbooks about the therapeutic use, pharmacological action, and toxicity of alkali iodates. They are said to be like chlorates in acting as strong oxidizing agents, the iodates being more toxic. Iodates have been used therapeutically to a limited extent; for example, iodic acid was used orally in doses of up to 50 mg daily by Comas y Martinez [3] over long periods for the treatment of tuberculosis and leprosy. Iodates have a local disinfecting action, and Belnap [1] used sodium iodate together with *p*-nitrophenol successfully in the local treatment of pruritus ani, when this was due to fungous infection.

* This article will also be published, in Spanish, in the *Boletín de la Oficina Sanitaria Panamericana.*

In 1941 Sorsby [8] drew attention to the action of a German preparation " Septojod ", which was in use for several purposes, but in particular for puerperal sepsis. Several publications had appeared in Germany between 1920 and 1940 reporting blindness in man followed by diffuse pigmentary changes all over the fundus oculi resembling those of retinitis pigmentosa. " Septojod " contains several iodine compounds, but Sorsby, and later Cima,[2] showed by tests on rabbits that the effects could be reproduced by injections of sodium iodate.

When a dose of 50 mg of sodium iodate per kg of body-weight was injected into rabbits, it was not fatal, but after an interval of about seven days produced the characteristic pigmentary changes in the retina. Such animals showed no other pathological signs. Larger doses, however, were fatal, and the liver then showed diffuse cloudy swelling.

Sorsby maintained that the iodate had a selective toxicity for the retina.

Macciotta [5] made quite a careful study of the behaviour of iodates and their toxic effects. She found that rabbits tolerated well 0.05-0.2 g of potassium iodate (KIO_3) per kg of body-weight, when given by mouth. There were no harmful effects, and the urine contained iodide but no iodate. However, much smaller doses—60-70 mg per kg—given subcutaneously produced toxic symptoms. She obtained similar results on dogs. The symptoms were haemolysis, diarrhoea, vomiting, and intense neuromuscular depression. Macciotta argued that it was the iodate itself that was toxic, as any liberated iodine would probably be taken up by the iodination of protein. Thiosulfate injections counteracted the toxicity of iodate.

Maxwell [6] in 1930 found that injections of 75 mg of potassium iodate per kg of body-weight in rabbits were toxic, and that 100 mg per kg were lethal. The toxicity of iodate was increased by simultaneous injection of iodide. He recorded no signs of the toxicity, stating only that " iodism " occurred.

The possibility of using sodium iodate to replace potassium iodide in the iodization of salt under certain conditions necessitated the carrying out of toxicity tests. Acute toxicity tests were made on mice and rabbits by Dr. W. L. M. Perry at the National Institute for Medical Research, London. The results of these tests and of repeated oral dosing are given in table I.

Tissues from the rabbits which died in these tests, and from the rest which were killed, were taken for histological examination, but no pathological changes were detected in the retinae, livers, or kidneys.

It must be borne in mind that the retinal degeneration observed by Sorsby and others occurred only if the animals survived for seven days after a suitably strong, but non-lethal, dose.

Dr. Perry's tests led him to conclude that, since rabbits tolerated 20 mg per kg of body-weight weekly, man would probably tolerate 1-1.4 g weekly; it would therefore be safe on this basis to iodize salt with iodate at a level

TABLE I. RESULTS OF ACUTE TOXICITY TESTS WITH SODIUM IODATE ON MICE AND RABBITS

MICE
Sodium iodate **intravenously**
100 mg per kg of body-weight tolerated by 10/10 (no symptoms)
250 mg per kg of body-weight killed 10/10 in 12 hours
Sodium iodate **orally**
250 mg per kg of body-weight tolerated by 10/10 (no symptoms)
750 mg per kg of body-weight killed 7/10 within 3 weeks
2,500 mg per kg of body-weight killed 10/10 in 12 hours
RABBITS
Sodium iodate **intravenously**
10 mg per kg of body-weight tolerated by 3/3 (no symptoms)
50 mg per kg of body-weight killed 1/2 within 3 days
100 mg per kg of body-weight killed 3/3 within 2 days
Sodium iodate **orally** (biweekly dosing for 6 weeks)
1 mg per kg of body-weight tolerated (no symptoms)
10 mg per kg of body-weight tolerated (no symptoms)
100 mg per kg of body-weight killed 2/3 after 2 doses

of 1 part of $NaIO_3$ in 1,000 parts of NaCl, since 50 g of such NaCl would contain 50 mg of $NaIO_3$.

These quantities correspond, of course, to amounts of iodine quite outside the range required for the prevention of endemic goitre. Considering that the generally accepted level for the daily requirement of iodine is 100-150 μg, this would be adequately covered by an intake of 2 mg of sodium iodate per week.

Therefore, if a salt were iodized at a level of 1 part of $NaIO_3$ (65% iodine) in 20,000 parts of NaCl, then the weekly intake, on the basis of 10 g of salt per day, would be 70 g of salt containing 3.5 mg of $NaIO_3$ and equivalent to 2.2 mg of iodine.

A limited number of tests were carried out on persons in my own laboratory, using orally administered solutions of sodium iodate (see table II). The solution was tasteless, and no effects were noted.

As these tests indicated that the amounts of iodate needed to give a suitable intake of iodine were quite outside the toxic range, long-term dosing of rabbits was started.

Rabbits were chosen because of their greater sensitivity to retinal degeneration. Two groups were used.

Group 1. Three males and 4 females at 6 weeks of age were given 1 mg of sodium iodate per kg of body-weight biweekly by mouth; this is equi-

TABLE II. DAILY ORAL DOSAGE OF FOUR PERSONS WITH SODIUM-IODATE SOLUTION

Subject	μg of $NaIO_3$ orally			
	1st day	2nd day	3rd day	4th day
F	500	500	—	—
M	500	500	1,000	1,000
E	500	500	—	—
B	500	500	—	—

valent to 140 mg weekly for a 70-kg man. Two rabbits were killed after four months, and five after eight months. All the animals maintained good health, ate well, and gained in weight.

Group 2. These were offspring of Group 1, produced and suckled during the iodate administration. They were given orally 1 mg of sodium iodate per kg of body-weight biweekly from the age of two months. Three rabbits were killed after 5½ months' dosing with iodate and two after 7 months; two rabbits were still alive and thriving after 14 months. All these animals also maintained good health and ate well throughout.

Some of each group of rabbits were examined ophthalmoscopically, while still alive, by Dr. Sorsby, an expert on this subject. He found no signs of retinal degeneration in these animals. It is not possible to observe any defect of vision in rabbits from their general behaviour. When each rabbit was killed, a general postmortem examination was made, and the eyes were fixed in Zenker's fluid for histological examination. Pieces of the thyroid, liver, and kidneys were taken for general histological examination and for the demonstration of alkaline phosphatase, which in my opinion gives a good indication of kidney function.

To sum up the results of the histological examinations, I judged the livers, kidneys, and thyroids to be normal in appearance in every animal dosed.

The eye sections, which I was not competent to judge, were examined by Dr. Sorsby and Dr. Katherine Tansley. Both these experts maintained that there was no evidence of retinal degeneration.

This continued dosing of rabbits seems to provide more conclusive evidence of the safety of using iodate for salt iodization than do the acute toxicity tests.

Iodization with iodate, then, at a level of 1 part of $NaIO_3$ in 20,000 parts of NaCl, means, as previously stated, a weekly intake in man of 3.5 mg of $NaIO_3$ for 70 g of salt. It should be noted that, for a 70-kg person, the amount of iodate comparable with rabbit long-term dosing would be 140 mg weekly.

We have information (personal communication) from Dr. H. H. Green of the Ministry of Agriculture and Fisheries, London, that long-term administration of sodium iodate in a salt lick for sheep and lambs, given at a level of 7 mg of iodate weekly over a period of five months to several thousand animals, was not accompanied by any noticeable ill-effects. It is a practice in the Ministry's work to use iodate when it is deemed that iodide would be unstable. The iodine of the iodate was obviously available to the thyroid in these trials.

Wyngaarden, Wright & Ways [9] showed that the administration of 0.1 millimol of iodate (in common with certain other monovalent anions) inhibited the collection and retention of the iodide ion by the thyroid gland of rats chronically treated with propylthiouracil. This effect is obviously not specific to the iodate ion and probably has little bearing on the present investigation.

The availability of the iodine of sodium iodate has been tested by two sets of observers, using iodate labelled with radioactive iodine, ^{131}I. Leblond & Süe [4] injected labelled sodium iodate into rats and found that the iodine was available to the thyroid gland. They maintained that it has first to be freed from the iodate.

Dr. Pochin [7] has tested the availability in human subjects. Six persons with normal thyroids were given orally labelled sodium iodate —70 μg of carrier iodate with 25 microcuries of radioactive iodine. After three days the thyroids contained on an average 38% of the ingested radioactive iodine. In further tests, three patients with normal thyroid and kidney function were given successive doses of labelled iodate. The radioactive iodine uptake from iodate was only 10% less than from iodide. More iodine was excreted.

It is obvious that the iodine given as iodate is available to the thyroid gland, but possibly less readily so than the iodine of iodide.

It is not suggested that iodate should be employed universally, but only when the type of salt available or the environmental conditions cause excessive loss of iodine from iodide.

RÉSUMÉ

L'emploi d'iodate alcalin au lieu d'iodure a été préconisé lorsqu'il s'agit d'iodiser du sel brut ou de conserver le sel iodé dans des conditions peu favorables à la stabilité de l'iode. On possède peu de renseignements sur l'action pharmacologique et la toxicité éventuelle des iodates alcalins pour l'homme. Des essais systématiques récents sur les souris et les lapins ont montré que ces derniers toléraient 20 mg d'iodate, administrés par voie buccale, par kg de poids du corps et par semaine. On peut en déduire que l'homme supportera des doses qui sont de beaucoup supérieures à celles que requiert la prophylaxie du goitre. Du sel iodaté (1 partie d'iodate de sodium pour 20.000 parties de sel) consommé à raison de 10 g par jour assure à l'organisme 2,2 mg d'iode par semaine.

Aucun symptôme morbide n'a été observé chez des moutons, léchant du sel iodaté, à raison de 7 mg par semaine durant 5 mois.

Des lapins ont été soumis au régime iodaté et suivis durant quatre ou huit mois. Ils recevaient des doses correspondant à 140 mg par semaine pour un homme de 70 kg. Leur descendance a été suivie aussi. Aucun des lapins de l'une ou l'autre génération n'a présenté de symptôme morbide. Les coupes histologiques du foie, des reins et de la thyroïde étaient normales. La dégénérescence de la rétine, observée antérieurement par certains auteurs chez des lapins ayant reçu des injections d'iodate, n'a été constatée chez aucun des animaux soumis aux expériences décrites dans cette étude.

L'iode de l'iodate de sodium est utilisé par la thyroïde, peut-être un peu moins rapidement que l'iode de l'iodure de potassium.

L'emploi des iodates se justifie dans les cas où les conditions de conservation peuvent provoquer de fortes pertes d'iode dans le sel ioduré.

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