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EFFECT OF POTASSIUM IODATE ON ENDEMIC GOITRE AND PROTEIN-BOUND IODINE LEVELS IN SCHOOL-CHILDREN

NEVIN S. SCRIMSHAW
Ph.D. Harvard, M.D. Rochester
REGIONAL ADVISOR IN NUTRITION, PAN-AMERICAN SANITARY BUREAU (W.H.O.); DIRECTOR, INSTITUTE OF NUTRITION OF CENTRAL AMERICA AND PANAMA (INCAP)

ADELA CABEZAS
M.D. El Salvador
CHIEF, NUTRITION SECTION, DEPARTMENT OF HEALTH, EL SALVADOR

FABIO CASTILLO
M.D. El Salvador
ASSISTANT DIRECTOR, INCAP

JOSÉ MÉNDEZ
M.S. Illinois
CHIEF, PROTEIN STUDY SECTION, INCAP

From the Institute of Nutrition of Central America and Panama, Guatemala

ALTHOUGH potassium iodide has long been used as a source of iodine in the treatment and prophylaxis of endemic goitre, the possibility of using potassium iodate seems to have been overlooked except for a reference by Murray and Pochin (1951). This compound, because of its greater stability in the presence of impurities and moisture, seems to offer many advantages for the iodisation of salt, especially for areas in which purifying and drying the salt is economically or culturally impracticable.

Leblond and Süe (1941) studied the thyroidal uptake of radio-iodine in rats after the intravenous administration of $^{128}IO_3$ and found that the iodine of iodate can be concentrated by the thyroid. They suggested that the thyroid can extract "ionised iodine" only after its transformation to iodide has taken place, and that the iodate was converted to iodide before its accumulation by the thyroid. The study by Murray and Pochin (1951), in which sodium iodate labelled with tracer amounts of radio-iodine (^{131}I) was given orally to 6 normal people, indicated that the iodine from iodate can also be accumulated by the human thyroid. However, no clinical reports of the effectiveness of potassium iodate in reducing the incidence of endemic goitre have been published.

The present studies were designed to test the effectiveness of potassium iodate in comparison with potassium iodide in reducing the incidence of endemic goitre in school-children in an area in which this type of goitre was highly endemic. The protein-bound iodine in the serum was also determined in a representative group as a possible means of further comparing the effects of potassium iodide and of potassium iodate.

Material and Methods

Children 5 to 14 years of age were studied in two rural schools in El Salvador and one school in Guatemala. The initial incidence of endemic goitre in the children in the public schools in these localities varied from 34 to 57%. After the first examination the goitrous and non-goitrous children were listed separately by sex and age, and assigned alternately to one of three groups. All the children received, once a week, tablets of similar appearance; but the tablets of the first group contained dextrose, those of the second group 6·5 mg. of potassium iodide, and those of the third group 8·5 mg. of potassium iodate. The iodide and iodate tablets were intended to supply 5 mg. of iodine weekly, an amount ordinarily ingested by persons using salt iodised at the level of 1 part in 10,000.

Most of the children missed one or more weeks' treatment during the trials. Children were dropped from the study if they received less than half the weekly tablets given in each trial, and if they were absent from the final examination. Owing to the resulting slight change in the size of the groups, the percentage of endemic goitre on the first examination was not exactly the same among the children remaining in a group as it was in the original random selection.

Endemic goitre was not diagnosed unless careful palpation suggested that the thyroid was more than four to five times the normal size (Cabezas et al. 1953). A thyroid larger than this was usually visible with the head thrown back and was classified in size 1. If the thyroid was clearly visible on inspection with the child's head in the normal position, it was classified as size 2. Most of the thyroid enlargement reported here belonged to the first category. The presence of nodules was also recorded.

Except for the first examinations in El Salvador, each child was assessed independently by two of us. The children were examined by school grades so that the examiners did not know at any time to which treatment group a child belonged. In El Salvador the results of examiner A. C. are used in the tabulations presented, and in Guatemala those of N. S. Borderline cases might be called negative by one observer and positive by the other, but this inevitable disagreement had no significant effect on the results. Divergent ratings between two examiners were given in about 15% of the re-examinations owing to the difficulty of discriminating when the size of the gland appeared reduced " almost to normal."

The first examinations were made in July, 1951, and the last in October, 1952. The duration of treatment ranged from fifteen to twenty-five weeks. Owing to special circumstances, the final examinations in Guatemala were made four weeks after the end of the twenty-five weeks' treatment. At this time samples of blood were obtained at random within each treatment group. Serum-protein levels were determined by the method of Lowry and Hunter (1945) and protein-bound iodine by the method of Barker et al. (1951).

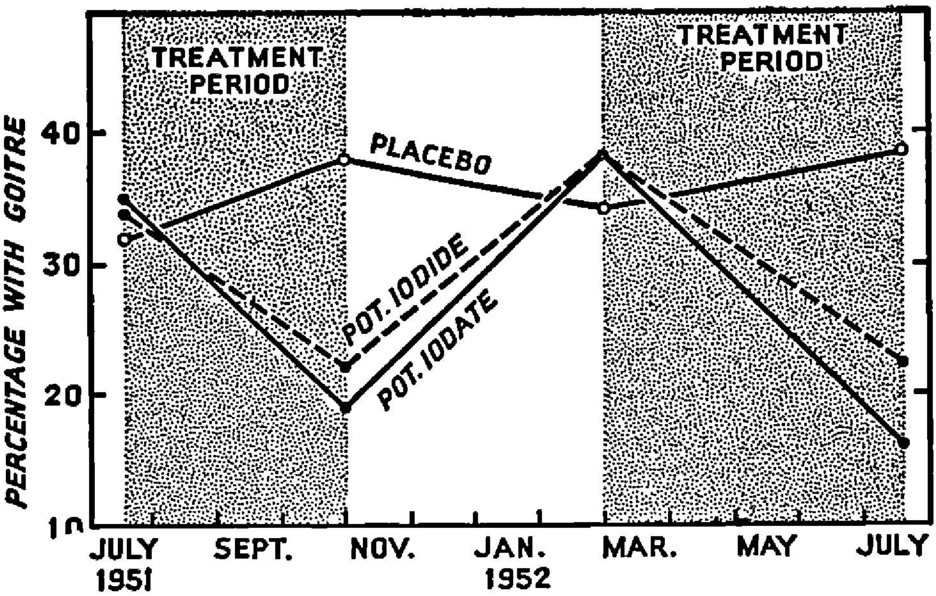
Results

The results of the two trials in El Salvador are given in table I. Data from the two localities in El Salvador have been combined because the results showed only minor differences. It will be seen that during the first fifteen weeks the number of goitres increased by 6% among the children receiving placebo, but was reduced by 40% in those treated with iodide, and by 44% in those treated with iodate. The second trial lasted twenty weeks and showed a decrease of 6% with placebo, 33% with iodide, and 44% with iodate.

The accompanying figure indicates that, despite the drop in incidence after both the iodide and iodate treatments, the incidence of endemic goitre in El Salvador returned essentially to its original value at the end of sixteen weeks without treatment. Renewed administration of either iodide or iodate brought the incidence

TABLE I—EFFECTS OF PLACEBO, POTASSIUM IODIDE, AND POTASSIUM IODATE ON ENDEMIC GOITRE IN EL SALVADOR

—	Treatment	No. of children	No. with goitre: July 19, 1951	No. with goitre: Oct. 30, 1951	% change
Trial I	Placebo	188	67	71	+6
	Potassium iodide	180	67	40	−40
	Potassium iodate	193	66	37	−44
			March 1, 1952	July 20, 1952	
Trial II	Placebo	90	31	29	−6
	Potassium iodide	86	30	20	−33
	Potassium iodate	88	39	22	−44



to the levels previously observed after treatment. The elimination of children not present for all four examinations would have greatly reduced the number of children who could be included in this figure. Accordingly all the children present at each examination are included, if not disqualified for poor attendance. The decrease in incidence in the treated groups was approximately the same at the end of both treatment periods.

In one of the schools in El Salvador it was possible to continue the treatment of the original groups of trial 1 until Sept. 30, 1952, an additional nine weeks. The percentage of children with endemic goitre observed at that time was 27 in the placebo group, 11 in the iodide group, and 10 in the iodate group. These groups contained 89, 85, and 71 children respectively at this time.

The third trial was made in Guatemala, with results (table II) very similar to those found in El Salvador. The examinations showed no change in incidence in the control group, but a drop of 62% in the iodide group and 69% in the iodate group.

At the end of the trial in Guatemala the three treatment groups were subdivided into the children who had been found to have endemic goitre upon initial examination and those classified as normal at the time. The serum-protein and protein-bound iodine levels for the 12–15 samples of blood drawn at random from each of the resulting six groups about four weeks after the last treatment are shown in table III. The much lower values observed in the controls are highly significant statistically. They are also lower than the "normal" values reported, for example, by Davison and Letton (1951) for the United States and by de Mowbray and

Tickner (1952) for England. No significant differences were observed between the children receiving potassium iodide and those receiving potassium iodate. No sex differences in the blood levels were apparent.

Discussion

These results seem to show conclusively that potassium iodate, given by mouth, can furnish the iodine necessary for the treatment or prophylaxis of endemic goitre. They confirm previous indications that such therapy must be continuous if the incidence of goitre is to be kept low in an endemic area. Probably the incidence of goitre after treatment in Guatemala would have been lower if nodular goitres had not been so common. Despite obvious reduction in the size and prominence of the gland, it was often necessary to classify a thyroid as goitrous after treatment, because moderately large nodules persisted.

TABLE II—EFFECTS OF PLACEBO, POTASSIUM IODIDE, AND POTASSIUM IODATE ON ENDEMIC GOITRE IN GUATEMALA

Treatment	No. of children	No. with goitre		% decrease
		Before treatment April, 1952	4 weeks after 25 weeks' treatment	
Placebo	51	28	28	0
Potassium iodide	57	34	13	62
Potassium iodate	51	26	8	69

The determinations of the protein-bound iodine leave little doubt that iodine originating from both potassium iodate and potassium iodide was bound to protein in the blood-serum. They do not tell us, however, whether this iodine was present in thyroxine molecules. de Mowbray and Tickner (1952) assembled reports of cases in which administration of large amounts of inorganic iodide led to formation of iodine compounds which were apparently adsorbed by the serum-proteins without changing the circulating thyroxine level. Danowski et al. (1950) reached a similar conclusion. On the other hand, Gross and Leblond (1951), using radioactive iodide (^{131}I) and paper chromatography, showed that labelled thyroxine appeared in the blood-stream of rats on a low-iodine diet three hours after the administration of the iodide, and was still present in considerable quantities at twenty-four hours. Further, the clinical response which we have reported suggests that the level of circulating thyroid hormone was probably raised by the treatment. Apart from the specific interpretation of the values of protein-bound iodine, it is of interest that iodate and iodide were equally effective in raising the level of the protein-bound iodine.

Potassium iodate possesses desirable chemical and physical properties for the iodisation of crude and moist salt. It is evident, therefore, that these favourable results with potassium iodate in the treatment of endemic goitre have practical significance for those areas of the world in which tropical climate, moisture, economic factors, or local customs make the iodisation of salt with potassium iodide economically impracticable or otherwise unacceptable.

The clinical and biochemical results of this study were made available in preliminary form to the W.H.O. study group on endemic goitre which met in London last December. The group also had reference to unpublished studies by Dr. W. L. M. Perry, of the National Institute for Medical Research, indicating a wide margin of safety for potassium iodate in animal toxicity trials. They concluded that, where iodisation of salt is indicated, but it is not practicable to prepare or to market a salt which is dry and free from impurities, potassium iodate should be used.

We agree with the practical value of this recommendation by the W.H.O. study group. However, since it implies the administration of potassium iodate to whole populations for an indefinite period, we think that further long-term studies to rule out any possible chronic or cumulative toxicity of this compound would be worthwhile.

TABLE III—EFFECTS OF PLACEBO, POTASSIUM IODIDE, AND POTASSIUM IODATE ON SERUM-PROTEIN AND PROTEIN-BOUND IODINE LEVELS

—	No. of children	Total protein (g. per 100 ml.)		Protein-bound iodine (µg. per 100 ml.)	
		Mean	Standard deviation	Mean	Standard deviation
Placebo :					
No goitre ..	12	6·68	0·37	2·56	1·21
Goitre	12	6·60	0·20	2·80	1·23
Potassium iodide :					
No goitre ..	12	6·59	0·41	4·80	0·95
Goitre	14	6·55	0·49	5·46	1·40
Potassium iodate :					
No goitre ..	12	6·44	0·40	5·03	1·14
Goitre	15	6·65	0·25	4·93	0·98

Summary

811 school-children in El Salvador and 197 in Guatemala, with an initial incidence of endemic goitre of 34% and 57% respectively, were treated weekly with placebo, with 6·5 mg. of potassium iodide, or with 8·5 mg. of potassium iodate.

During treatment periods of fifteen and twenty weeks in El Salvador and twenty-five weeks in Guatemala the prevalence of goitre did not change significantly in the children receiving placebo ; but in those receiving potassium iodide it was reduced by 40%, 33%, and 62% in the three trials, and in those receiving potassium iodate it was reduced by 44%, 44%, and 69%.

The first group studied in El Salvador was re-examined after sixteen weeks' suspension of treatment, and the prevalence of endemic goitre was found to have returned to the original values.

Twenty additional weeks' treatment had the same effect as observed previously. Part of this group received the tablets for an additional nine weeks and showed a significant further decrease in the incidence of goitre.

Four weeks after the end of the twenty-five weeks' treatment in Guatemala no significant differences were observed in protein-bound iodine between children receiving potassium iodide and those receiving potassium iodate. The average level of protein-bound iodine in 24 children receiving placebo was 2·68 μg. per 100 ml. (s 1·20), in 26 receiving iodate it was 5·1 μg. (s 1·19) and in 27 receiving iodide it was 4·97 μg. (s 1·04). No differences in the levels of protein-bound iodine were attributable to the presence or absence of goitre on initial examination.

It is concluded that potassium iodate and potassium iodide in doses containing equal amounts of iodine are about equally effective in the treatment of endemic goitre. Since potassium iodate appears to possess several important advantages for the iodisation of salt in tropical and humid regions, its use for this purpose should be explored.

The tablets were furnished by the Chilean Iodine Educational Bureau, of London, through the courtesy of Dr. Francis C. Kelly. We wish to express our thanks to Dr. Frederick W. Clements, former chief of the nutrition section of the World Health Organisation, for suggesting this project, and to the teachers of the schools of Opico and Tonacatepeque in El Salvador and in Santa María de Jesús in Guatemala whose coöperation made it possible. Dr. J. Antonio Muñoz and the members of the nutrition field unit of the Department of Public Health of Guatemala, rendered invaluable assistance, and Dr. Juan Allwood Paredes, director of the Department of Health of El Salvador, was most helpful. The studies of protein-bound iodine were initiated with the help of Dr. Beverly T. Towery and carried out with the technical assistance of Ofelia Paz y Paz. We are indebted to Dr. Towery for criticism of this report.

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