Intermittent oral administration of potassium iodide solution for the correction of iodine deficiency[1–3]

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ABSTRACT   Iodized salt and iodized oil are the main methods used to prevent iodine deficiency, but sometimes alternative approaches are needed. We tested the efficacy of various regimens for the intermittent administration of potassium iodide in Hwedza, Zimbabwe, an area of known severe iodine deficiency. We divided 304 schoolchildren aged 7–13 y into five equal groups that received iodine as a 10% solution of potassium iodide as follows: 8.7 mg every 2 wk (group A), 29.7 mg every month (group B), 148.2 mg every 3 mo (group C), 382 mg every 6 mo (group D), or 993 mg once (group E). The follow-up period was 13 mo. No adverse effects were encountered with any of these doses. After 6 mo, the median blood spot thyroglobulin concentration had decreased in all groups and had normalized in groups A and B to values found in iodine-sufficient populations. The number of children with elevated thyroid-stimulating hormone concentrations decreased in groups A–C, but the changes were not significant. Urine iodine concentration generally remained low in all groups but increased in group A. After 13 mo, mean thyroid volume measured by ultrasound had decreased in groups A and B to values comparable with those in iodine-sufficient areas, and was unchanged in the other groups. We conclude that oral potassium iodide is effective for the prophylaxis of iodine deficiency if given as a dose of 30 mg I monthly or 8 mg biweekly.   *Am J Clin Nutr* 1998;67:1279–83.

KEY WORDS   Iodine, potassium iodide, iodine deficiency, goiter, thyroid ultrasound, Zimbabwe, schoolchildren, thyroglobulin, thyroid-stimulating hormone, Lugol's solution

INTRODUCTION

Iodine deficiency poses a major threat to public health in many countries of the world, with more than one billion people at risk. The documented harmful effects include stillbirth, low birth weight, increased neonatal mortality, cretinism, goiter, impaired mental function, and retarded development. The term *iodine deficiency disorders* (IDDs) was coined to emphasize this wide range of effects (1). The immediate cause of IDDs is subnormal concentrations of circulating thyroid hormones, which result from insufficient iodine intake.

Iodized salt and intermittent administration of iodized oil are the chief prophylactic measures adopted for the correction of iodine deficiency. Sometimes additional approaches are needed when implementation of salt or oil programs is delayed, not feasible, or inadequate. Direct administration of iodine as potassium iodide is an attractive alternative. Such solutions (unlike iodized oil) are easily prepared, readily available, simple, and cheap.

Direct oral administration of iodine has proven effective in correcting iodine deficiency. Indeed, in the first trial of mass prophylaxis (in the United States in 1917) 2 g NaI was administered in 0.2-g doses over a period of 2 wk twice a year. This program was accompanied by a 60% reduction in goiter prevalence over 1 y, compared with a 14% reduction in the control group (2). In early trials in Switzerland, 10–15 mg iodide given weekly were shown to be similarly effective (3). However, a more recent trial in Zaire showed little apparent effect of a single large dose of potassium iodide when compared with iodized oil, as assessed by changes in serum thyroxine concentrations after 8 mo (4).

The major drawback of the administration of iodine solutions is that they must be given individually and repetitively. Iodized oil shares the disadvantage of requiring individual administration, oral or intramuscular, in doses of 200–400 mg I every 18 mo to 2 y. Iodine is stored in muscle depots, if given intramuscularly, and also in fat. Iodide is stored only in the thyroid, but the thyroid's conservation mechanisms for it are extensive, as attested by the prolonged effect with twice yearly administration cited above (2).

The wealth of experience with iodized oil has shown that giving intermittent large doses of iodine, although quite effective in preventing IDDs, has no major adverse metabolic effects (5). The only serious problem encountered has been iodine-induced hyperthyroidism (6). This occurs principally in older subjects with long-standing nodular goiter after iodine supplementation in any form, including iodized salt, to a previously deficient community and is not recognized to be a problem in younger subjects.

Lugol's solution is widely available as an antiseptic. It contains free iodine (50 g/L), which in large doses can be toxic to the

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gastrointestinal tract. Potassium iodide has no such harmful effects and doses ≤2.0 g are safe (4, 6); the only occasional side effect is mild iodism (eg, salivation and lacrimation).

Our study therefore addressed the question of how often, and in what dose, potassium iodide solution should be given to achieve effective prophylaxis of iodine deficiency. The answer can provide a means of assessing whether a supplementation program based on periodic potassium iodide solution will be practical in a given area of endemic deficiency. It will also be a guide to the optimum dosage regimen for the use of potasium iodide, and by extension, of Lugol's solution, in the management of goitrous subjects in a clinical setting.

SUBJECTS AND METHODS

Study area

The study took place in part of Hwedza District in east-central Zimbabwe, a tribal area 150 km southeast of Harare, at an altitude of ≈1000 m. This location was selected because it was shown previously to have severe IDDs (7), but was not scheduled for iodized oil distribution during the first phase of Zimbabwe's IDD control program. At the time of the study iodized salt was not available in local stores.

Study population

We recruited 304 children (goitrous and nongoitrous) aged 7–13 y, of both sexes, who were attending one of the two primary schools in the study area, whose parents consented, and who were expected to remain at the same school for 1 y. The children were divided randomly among five equal groups (A–E) matched for age distribution and sex. Four groups had 61 children each, the fifth had 60. The mean ages of the groups ranged from 10.05 to 10.18 y, and the proportion of males ranged from 51% to 53%.

Ethical approval

Ethical approval for the study was granted by the Medical Research Council of Zimbabwe and the Human Investigation Committee, University of Virginia. Approval for the research was obtained from the provincial and district medical officers and from local education officers and the head teachers of the selected schools. All parents of children eligible to enter the study were sent a letter written in Shona explaining the research and requesting consent for inclusion of their child.

Treatment protocol

Subjects in each of the five groups were given a 10% KI solution (contains 76.4 g I/L or 4.24 mg I/drop) according to the regimens outlined in **Table 1**. Because the benefits of iodine in severe iodine deficiency are now unequivocal, it was considered unethical to have an untreated control group. The dosage calculation was based on experience with oral iodized oil capsules, with which iodine concentrations in urine decay exponentially from the time of administration (8).

Smaller doses were given by using a dropper bottle and larger doses by using a graduated syringe. All initial doses and the larger doses of iodide (groups C, D, and E) were administered by members of the study team. Those receiving larger doses were given a cup of water to drink immediately afterward. Children in groups A and B received some doses of iodide from teachers in the schools according to prepared schedules. When possible, dates of adminis-

TABLE 1
Dose of potassium iodide administered to five groups of school children

Group	Dose	Interval between doses	Total dose in 1 y	Annualized average daily dose
	mg I		*mg I*	*mg I*
A, biweekly	8.7	2 wk	235	0.62
B, monthly	29.7	4 wk	386	0.99
C, every 3 mo	148.2	3 mo	593	1.63
D, every 6 mo	382	6 mo	764	2.09
E, yearly	993	Dose given once	993	2.72

tration were timed to coincide with weekdays during school terms. Administration during the school holidays proved difficult and most children did not receive iodide then. The majority of children in group A received 21 of a possible 27 doses (total dose: 183 mg), and the majority of children in group B received 11 of a possible 13 doses (total dose: 327 mg). Children in the other groups received all the prescribed doses.

Measurements

The following indexes were measured at the times specified (time 0 was just before administration of the first dose): *1*) side effects after the initial dose; *2*) thyroid size by ultrasonography at 0 and 13 mo; *3*) height at 0 and 13 mo; *4*) urinary iodine at 0, 1, and 6 mo (just before the next dose when appropriate); *5*) thyroid-stimulating hormone (TSH) in a blood spot at 0 and 6 mo; and *6*) thyroglobulin in a blood spot at 0 and 6 mo.

Observers were masked to the status of children with regard to group. Because of various logistical problems, it was not possible to carry out TSH, thyroglobulin, and urinary iodine analyses at 13 mo.

Height was measured by one observer using a portable stadiometer. Ultrasonographic assessment of thyroid size was carried out by using a portable ultrasound machine with a 5-MHz linear transducer (SDR 1200; Philips, Amelo, Netherlands). The volume of each lobe was calculated as the product of maximal depth, width, and length, multiplied by a correction factor of 0.479 (9). A measure of standardized thyroid volume for each child was derived according to the formula log(thyroid volume)/(height), to allow for the effects of growth. This approach was derived from the work of Ueda (10), who found that of the physical variables measured, log(thyroid volume) was most closely correlated with height.

Spot urine samples were collected in plastic jars with screw tops. Later that day, after remixing, 2.4-mL aliquots of urine were transferred to small storage tubes with tightly fitting screw caps. Strenuous efforts were made to avoid contamination of urine by potassium iodide; in particular, iodide administration took place only after all urine samples had been collected and sealed. Urine samples were stored at −20 °C until analyzed. Urinary iodine estimations were carried out in the Department of Biochemistry of the University of Zimbabwe by using a standard method involving digestion of urine with chloric acid under mild conditions and detection of iodine manually in a colorimeter by ceric ammonium sulfate reduction (11).

Finger-prick blood samples were collected from each subject onto filter paper, allowed to dry, placed into individual envelopes, and stored at room temperature until delivered to the laboratory. TSH and thyroglobulin assays were carried out on the filter paper samples in the Medzinische Universität zu Lübeck, Lübeck, Germany, according to methods described elsewhere (12). A change in reporting method by the laboratory for the 6-mo data resulted in many values being recorded as <1 U/L.

Statistical analysis

Results were entered into an EXCEL spreadsheet (Microsoft Corp, Seattle) on a personal computer for univariate analysis. Further analysis was carried out by using the SAS (SAS Institute, Cary, NC) and STATA (State Corporation, College Station, TX) programs. The distribution of the values of thyroid volume, thyroglobulin, and urine iodine were found to be positively skewed and they were logarithmically transformed. Results for these variables are presented as geometric means with geometric 95% confidence limits and medians. The Shapiro-Wilk W test was used to test for normal data. For normally distributed data [log(thyroid volume) and standardized thyroid volume] the paired t test was used to compare differences within groups between baseline and follow-up and one-way analysis of variance (ANOVA) was used to establish whether differences between baseline and follow-up results varied significantly among the five groups under study. Multiple-range analysis was then used to determine which groups were significantly different from the others. In addition, analysis of covariance was used to determine whether outcome results were significantly different among the five groups while taking into account the baseline values. The distribution of log(thyroglobulin) and log(urine iodine) did not satisfy the criteria for normality, and nonparametric tests were used as follows with the original values: the Wilcoxon signed-rank test to compare differences within groups between baseline and follow-up, and the Kruskal-Wallis test for significant differences between baseline and follow-up results among the five groups. Serum TSH data were categorized as either below or equal to or above the upper limit of normal (4.4 mU/L), and TSH was subsequently treated as a categorical variable.

RESULTS

Three hundred four children (146 females and 158 males) aged 7–13 y were recruited; 246 (81%) of these were present at the final follow-up after 13 mo.

Side effects of potassium iodide

No immediate adverse effects were noted. Some children complained about a sour taste. One month later, at the first fol- low-up visit, the children were asked if they experienced any side effects after taking the medicine. Sore throat, headache, and abdominal pain were reported by a few children in all groups. One child in group E complained of sore cheeks. There was no evidence that any child developed hyperthyroidism during the course of the study.

Height

Mean heights for the five treatment groups at 0 and 13 mo are shown in **Table 2**. The mean change in height did not differ significantly among the various groups.

Thyroid volume

Geometric mean and median thyroid volume and mean and median standardized thyroid volumes for the five treatment groups at 0 and 13 mo are shown in Table 2. Although the results of ANOVA are given in the table, analysis of covariance gave similar results. Thyroid volume decreased significantly in groups A and B, increased in group C, and was unchanged in groups D and E. Standardized thyroid volume decreased in groups A and B, but was unchanged in groups C–E.

Thyroglobulin

Geometric mean and median thyroglobulin concentrations for the five groups at 0 and 6 mo are shown in **Table 3**. Thyroglobulin declined in all, but the changes did not differ significantly among the five groups. Median thyroglobulin values in groups A and B at 6 mo were below values reported in healthy European children (12).

Thyroid-stimulating hormone

The number with values above normal in each group at baseline and follow-up were, respectively: group A, eight compared with three ($n = 52$); group B, three compared with two ($n = 52$); group C, two compared with one ($n = 55$); group D, four compared with five ($n = 47$); and group E, four compared with six ($n = 50$). The proportion with values above normal at baseline and follow-up was not significantly different in any group (by exact binomial probabilities).

TABLE 2
Changes in height and thyroid volume from baseline to 13 mo for paired data only[1]

	Group A (n = 42/43)	Group B (n = 54/55)	Group C (n = 50/50)	Group D (n = 52/52)	Group E (n = 47/48)
Height (m)					
Baseline	1.322 ± 0.031[2]	1.307 ± 0.027	1.347 ± 0.027	1.345 ± 0.025	1.328 ± 0.029
13 mo	1.377 ± 0.031	1.356 ± 0.028	1.396 ± 0.028	1.394 ± 0.026	1.377 ± 0.030
Thyroid volume (ml)					
Baseline	7.6 (6.3, 9.2) [9.0][3]	8.5 (7.0, 10.5) [7.9]	9.4 (7.7, 11.6) [10.5]	9.3 (7.9, 10.9) [8.7]	9.2 (7.6, 11.0) [8.2]
13 mo	5.8[4] (4.8, 7.1) [6.2]	7.2[5] (5.9, 8.9) [6.9]	10.8[6,7] (9.3, 12.5) [10.1]	9.9 (8.5, 11.6) [9.2]	10.1 (8.5, 11.7) [9.4]
Standardized thyroid volume[8] (log mL/m)					
Baseline	0.66 ± 0.06	0.70 ± 0.07	0.72 ± 0.06	0.72 ± 0.05	0.72 ± 0.05
13 mo	0.55 ± 0.06[4]	0.63 ± 0.06[4]	0.74 ± 0.04	0.72 ± 0.05	0.73 ± 0.05

[1] Group A, biweekly potassium iodide administration; group B, monthly; group C, every 3 mo; group D, every 6 mo; group E, yearly. n = number with two height measurements/number with two thyroid volume measurements. Groups A and B significantly different from the others for change in mean log (thyroid volume) and standardized thyroid volume, $P = 0.0001$ (ANOVA and Duncan's multiple-range test).

[2] Arithmetic mean ± 95% CI.

[3] Geometric mean; 95% confidence limits for the geometric mean in parentheses and median in brackets.

[4,6] Significant change between baseline and 13 mo paired t test: [4] $P < 0.001$, [5] $P < 0.01$, [6] $P < 0.05$.

[7] Increase in thyroid volume.

[8] Log10 (thyroid volume)/height.

TABLE 3
Change in thyroglobulin concentration from baseline to 6 mo for paired data only[1]

	Group A (n = 53)	Group B (n = 55)	Group C (n = 57)	Group D (n = 52)	Group E (n = 53)
			μg/L		
Baseline	17.5 (10.0, 30.5) [28]	19.5 (12.3, 31.0) [29]	20.0 (12.3, 32.5) [26.9]	27.8 (17.4, 44.4) [32.5]	26.2 (17.5, 39.2) [36]
6 mo	5.7[2] (4.5, 7.3) [6]	9.5[2] (7.4, 12.3) [11]	13.5[2] (10.1, 18.0) [14]	20.6[3] (15.7, 27.1) [22.5]	16.5[2] (12.6, 21.8) [18]

[1] Group A, biweekly potassium administration; group B, monthly; group C, every 3 mo; group D, every 6 mo; group E, yearly. Geometric mean; 95% confidence limits in parentheses and medians in brackets. When results were reported as <2 μg/L, analysis was done with the value of 1.0; the upper limit of normal was 20 μg/L. There were no significant differences among groups for change in thyroglobulin (Kruskal-Wallis test).

[2,3] Significant change between baseline and 6 mo (Wilcoxon signed-rank test): [2] $P < 0.001$, [3] $P < 0.01$.

Urine iodine

Geometric mean and median urine iodine concentrations for subjects in each of the five groups at 0, 1, and 6 mo are shown in **Table 4**. Differences between 0 and 6 mo were not significant in any group. There was also no significant difference in overall change in urinary iodine across the five groups.

DISCUSSION

This study confirmed that large doses of iodide are safe. Some children received nearly 1 g iodide without any adverse effects except possibly one case of sialadenitis. Furthermore, no adverse effects of large doses on thyroid function were documented.

Four main indicators were used in this study to judge the adequacy of iodine supplementation: thyroid volume, TSH, thyroglobulin, and urine iodine. Without treatment, thyroid volumes would be expected to increase by ≈10% over 1 y from normal growth. Thyroid volume was therefore related to height to adjust for the effect of growth (10). The other variables measured would not be expected to change significantly without treatment. Although some of the follow-up measures at 1 y are not available, the overall results are broadly consistent with each other. However, note that at 6 mo children in both groups D and E had only received one dose of potassium iodide; the total dose given by this time was therefore smaller in group D.

Mean standardized thyroid volumes declined significantly in those children receiving iodide either every 2 wk (group A) or every month (group B). Although the end thyroid volume was smaller in group A, it was also smaller at baseline, and overall change in thyroid volume did not differ significantly between groups A and B. In the remaining groups thyroid volumes increased, but when adjusted for height they showed no significant change.

Thyroglobulin concentration in blood spots decreased in all the treatment groups. Although the decline was greatest in groups A and B, it was not significantly different from that in the other groups. TSH declined in groups A–C, but it is debatable whether this has clinical importance. Median TSH concentrations were entirely within the normal range throughout the study.

Urine iodine concentrations showed huge variability and were very high in some subjects. Although urine iodine increased considerably within all groups between 0 and 1 mo, this effect was not sustained and all groups saw a decline in mean concentration to near baseline by 6 mo. It seems possible that some children might have been exposed to an extraneous source of iodine at 1 mo, possibly by environmental contamination after the administration of huge doses at the beginning of the study. We do not have an explanation for the differences between 1 and 6 mo in group A. Possibly some children were given doses of iodine on the wrong date. Generally, it appears that most of the administered dose was lost within a short period of time.

Outcome indicators for assessing adequate iodine supplementation were studied extensively before (8). Urine iodine is normally expected to be the most helpful indicator in an iodine supplementation program, but in our study its value was more limited. Other indicators, notably thyroid volume and thyroglobulin, were more useful and indicated a significant dose-related response. We found that standardizing thyroid volume for height was useful in accommodating the effect of growth and we recommend that this measure be considered further in other investigations. In agreement with previous reports (8), TSH was not a sensitive indicator in this age group.

We conclude that intermittent iodine administration is effective and practical for the prophylaxis of iodine deficiency in schoolchildren if given at least once a month. The interval between doses appears to be the most important factor—the dose itself need not be very large. Giving large doses at 3-mo or longer intervals does have some effect, but it does not compare with that of giving iodized oil, whose action may be sustained for 1 y or longer (8).

TABLE 4
Changes in urine iodine at baseline, 1, and 6 months for subjects with values for all three times[1]

Time	Group A (n = 42)	Group B (n = 51)	Group C (n = 53)	Group D (n = 48)	Group E (n = 47)
Baseline	0.11 (0.08, 0.14) [0.11]	0.11 (0.08, 0.15) [0.12]	0.06 (0.04, 0.09) [0.07]	0.08 (0.06, 0.12) [0.09]	0.12 (0.09, 0.16) [0.14]
1 mo	0.44 (0.23, 0.81) [0.23]	0.20 (0.13, 0.29) [0.19]	0.18 (0.13, 0.25) [0.17]	0.23 (0.16, 0.33) [0.21]	0.16 (0.12, 0.23) [0.17]
6 mo	0.15 (0.08, 0.29) [0.12]	0.07 (0.05, 0.11) [0.10]	0.04 (0.03, 0.05) [0.05]	0.07 (0.05, 0.11) [0.07]	0.10 (0.06, 0.17) [0.10]

[1] Group A, biweekly potassium iodide administration; group B, monthly; group C, every 3 mo; group D, every 6 mo; group E, yearly. Geometric mean; 95% confidence limits in parentheses and medians in brackets. Where results were reported as >1000 mg/L (>7.87 μmol/L), analysis was done with the value 1000; when reported as <1 μg/L, analysis was done with the value 1 (0.008 μmol/L). There were no significant differences among groups for change in urine iodine (Kruskal-Wallis test), and there were no significant differences in any group between baseline and 6 mo (Wilcoxon signed-rank test). To convert values to μg/L multiply by 127.

Although it is no substitute for the universal iodization of salt, regular potassium iodide administration is a practical method of iodine supplementation in selected areas. Iodide doses of ≈ 30 mg every month or 8 mg every 2 wk are probably appropriate and can be delivered conveniently as a simple solution by using a dropper bottle. Further work may show that smaller doses are adequate once the initial iodine deficiency is corrected. Iodized salt has reached Hwedza District since this study was carried out, but intermittent potassium iodide administration may be useful in parts of Africa and elsewhere with small-scale salt production that is not easily amenable to iodization. ☘

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