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Iodine Supplementation: Comparison of Oral or Intramuscular Iodized Oil with Oral Potassium Iodide. A Controlled Trial in Zaire

DAVID I W PHILLIPS*, TIM D LUSTY**, CLIVE OSMOND* AND DAVID CHURCH†

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A community-based controlled trial of iodine supplementation comparing oral or intramuscular iodized oil with oral potassium iodide has been carried out in 23 severely iodine-deficient villages in Eastern Zaire. The overall goitre prevalence in the population (n = 5999) was 61% and mean urinary iodine excretion in sample of 57 women 10.9 (SD 6.8) μg/g creatinine.

All adults in three groups of four villages were given single doses of potassium iodide of 0.5 g, 1.0 g, and 2.0 g respectively. A fourth group was given oral iodized oil (2 ml) and a fifth placebo-treated. A further three villages were given intramuscular iodized oil (2 ml). The effectiveness of supplementation was assessed by measurements of bloodspot thyroxine (T_4) concentration in women of reproductive age in the villages. The effects of iodide were small and inconsistent. Eight months after supplementation with oral iodized oil the distribution of T_4 concentrations was similar to that seen with intramuscular oil. We conclude that oral iodized oil is an effective alternative to injected oil and would be feasible for iodine supplementation in remote areas with untrained people.

Dietary iodine deficiency continues to impair the economic development, quality of life and educability of millions of children and adults.[1] A resolution passed by the 39th World Health Assembly (1986) has called for the eradication of iodine deficiency within the next five to ten years. In many developing countries prevention of iodine deficiency by the addition of iodine to salt or other foodstuffs has proved ineffective due to administrative difficulties in manufacturing the salt, in ensuring that iodized salt replaces locally produced salt, and in distributing it to the remote areas where iodine deficiency is often most severe.[2,3] Single, intramuscular, injections of a slow-release preparation of iodine-containing oil provide supplementation for between three and five years,[4] but have obvious disadvantages as a public health measure, including expense, the need for trained personnel and the risk of spreading hepatitis B or AIDS.

Studies in schoolchildren[5,6] and selected groups of goitre patients[7,8] show that a single oral dose of iodized oil can reduce goitre size and increase urinary iodine excretion for one to two years. Experience with this method of administration is limited and in particular there is no information as to its effectiveness in women of reproductive age, the most important target group for supplementation. Periodic administration of oral potassium iodide has also successfully reduced goitre prevalence,[9] but it is not known whether large single doses could successfully correct iodine deficiency for a prolonged period.

There is an urgent need for simple methods of oral iodine prophylaxis. We report the results of a community-based controlled trial of supplementation comparing single doses of oral or intramuscular iodized oil with oral potassium iodide in women of reproductive age in a severely iodine deficient area of Zaire.

METHODS

The trial was conducted in a group of villages west of Jomba (Figure 1) located in the north Kivu area of Eastern Zaire. Following a pilot study, 23 adjacent villages were selected in the most severely affected area lying at altitudes of between 1400 and 2300 metres and comprising a total population of 7174. Between October 1985 and January 1986 village censuses were obtained and the villages visited by a survey team.

* MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO9 4XY, UK.
** Health Unit, Oxfam, 274 Banbury Road, Oxford OX2 7DZ, UK.
† Regional Biochemical Genetic Screening Service, Peterborough District Hospital, Peterborough PE3 6DA, UK.

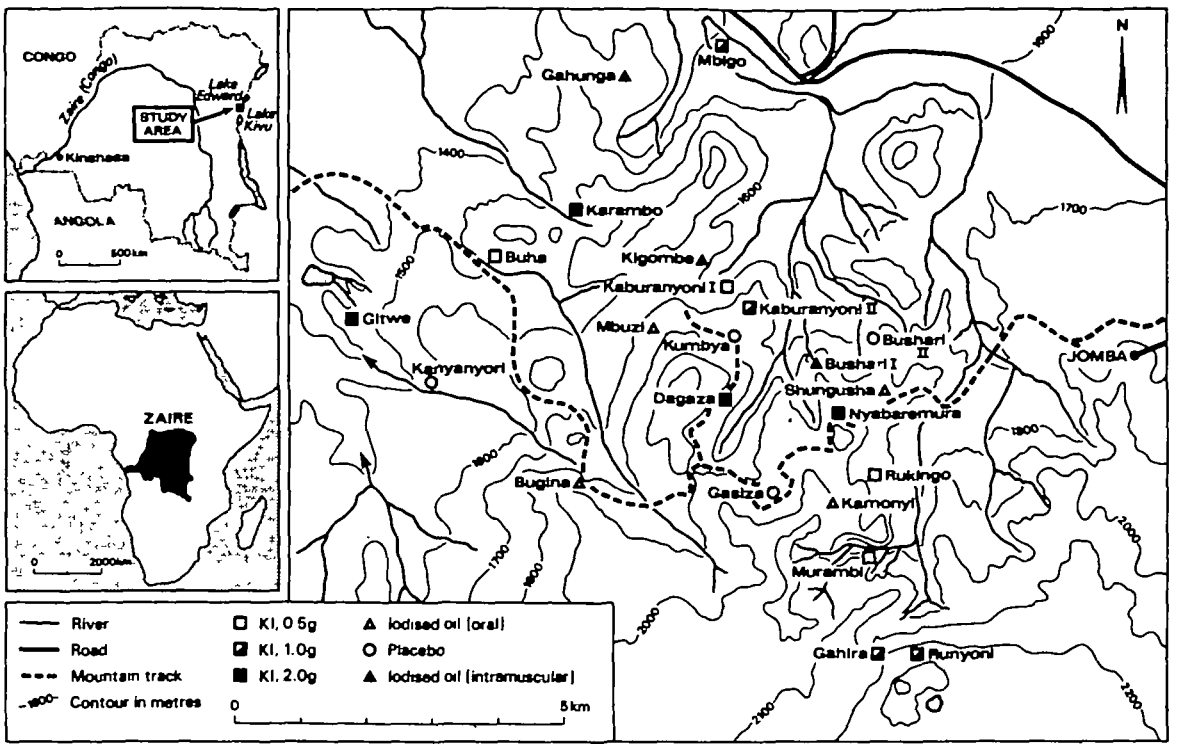

FIGURE 1 *Location of study area.*

Demographic data were recorded and the thyroid glands of everyone examined.

Goitres were graded using a modified WHO classification[10] into two categories—'palpable' (thyroid enlarged but not visible with the head held in the normal position), and 'visible' (goitre visible with the head in normal position). Goitre rates were indirectly age–sex standardized using the overall rates in the 23 villages as the standard rates. The purpose of standardization was to correct for differences in age and sex distribution within the villages.

Filter paper bloodspot samples for thyroxine (T_4) analysis were obtained by finger prick from approximately 35 women of reproductive age (15–44 years) in each village. The women were a systematic sample of all women of reproductive age in the village. Details of pregnancy and recent reproductive history were also obtained. Radio-immunological T_4 determination with 4.25 mm blood discs was carried out by a method in use for routine neonatal screening. The assay incorporates a T_4-I^{125} label of high specific activity (Amersham International) and rabbit anti-T_4 antibody. Radioactivity in the antigen-antibody complex was measured following precipitation with polyethylene glycol. The interassay coefficients of variation were 12.9% for 15.5 nmol/l T_4 (n = 7) and 6.7% for 61.1 nmol/l T_4 (n = 7). Stored bloodspots showed a decline in recoverable T_4 activity of 6% per month.

Urinary iodine excretion before supplementation was measured using a standard method[11] in a sample of 57 women (aged 15–44) from three of the villages.

Twenty of the 23 villages were allocated in rotation to five treatment groups, each group comprising four villages. In three of the groups everyone over the age of ten was given a single dose of potassium iodide, KI (10% solution in syrup) of 0.5 g (group one), 1.0 g (group two) and 2.0 g (group three). The fourth group was given a single 2 ml oral dose of iodized oil (Lipiodol, May and Baker, Dagenham) and the fifth, placebo (syrup) treated.

The remaining three randomly selected villages were given 2 ml intramuscular iodized oil. In each of the treated villages children aged two to ten years were given half of the adult dose of potassium iodide or iodized oil, and under two years left untreated.

Within each of the treatment groups two of the four villages were revisited at four and the other two at eight months following supplementation. The three villages given intramuscular iodized oil were followed up at eight months. Effectiveness of treatment was assessed by reduction in the size of goitres and by measurements of bloodspot thyroxine concentrations.

TABLE 1 *Prevalence of goitre by age and sex in the combined population of the 23 villages*

Age group	Women and girls: No. of subjects	No. with palpable or visible goitre (%)	No. with visible goitre (%)
0–4	632	130 (21)	6 (1)
5–14	824	638 (77)	200 (24)
15–24	583	531 (91)	287 (49)
25–34	408	371 (91)	180 (44)
35+	699	504 (72)	208 (30)
Age group	**Men and boys: No. of subjects**	**No. with palpable or visible goitre (%)**	**No. with visible goitre (%)**
0–4	621	141 (23)	12 (2)
5–14	847	596 (70)	96 (11)
15–24	470	347 (74)	115 (24)
25–34	336	204 (61)	49 (15)
35+	526	158 (30)	28 (5)

(Age uncertain in 53 subjects.)

RESULTS

Prevalence of Goitre and Cretinism

Of the 7174 people reported as living in the 23 villages 5999 (83.6%) were examined during the initial visit. Total goitre prevalence (palpable and visible) was 60.9% (males 51.6%, females 68.5%). Visible goitre was present in 19.9% (males 10.8%, females 28.0%).

All age groups were affected (Table 1). In both sexes the total goitre prevalence increased sharply after infancy to reach a peak of 91% in women, and 74% in men at age 15–24. Visible goitre prevalence was also highest in this age group (women 49%, men 24%). Thereafter goitre rates declined in both sexes, a decline that was most marked in men.

Six children (three male and three female) showed features of neurological cretinism, a prevalence of 0.1%. They were between three and ten years old, mentally retarded and deaf-mute, and in four cases showed signs of spastic diplegia.

Among the 889 women of reproductive age for whom initial bloodspot thyroxine (T_4) measurements were obtained, the median T_4 concentration was 34 nmol/l (range 4–145). Median T_4 levels in the 23 villages ranged from 22.0 to 53.5 nmol/l. There was an inverse correlation between the median village T_4 values and both the total goitre rate and village altitude (rank correlation coefficient, $r = 0.56$, $p<0.01$, and -0.60, $p<0.01$, respectively). Mean urinary iodine excretion in the sample of 57 women, was found to be 10.9 (SD 6.8) μg per g creatinine. Fifty-one (89%) of the women had urinary excretion less than 20 μg/g.

Effect of Supplementation

The follow-up was 82.9% (range between villages 74.6% to 91.3%) and 94% in the subset of women of reproductive age for whom bloodspot thyroxine measurements were obtained. Table 2 shows the changes in age–sex standardized prevalence of total and visible goitre in the treatment groups. Goitre prevalences are shown separately for the pairs of villages followed up at four and eight months after supplementation. In this analysis prevalences are based on the rates in individuals attending both the initial and follow-up visits. There were no statistically significant reductions (test for comparison of proportions) in

TABLE 2 *Changes in the age–sex standardized total and visible goitre prevalence in the pairs of villages within each treatment group followed up four and eight months after supplementation*

	Total goitre prevalence (%)			Visible goitre prevalence (%)		
		Months after supplementation			Months after supplementation	
	Before	4	8	Before	4	8
0.5 g KI	58	57		18	18	
	70		65	30		27
1.0 g KI	59	56		20	20	
	57		61	19		19
2.0 g KI	59	56		21	19	
	62		60	21		18
Oral iodized oil	65	61		20	18	
	62		58	19		14
Placebo	56	61		17	19	
	63		59	21		21
Intramuscular iodized oil	59		57	20		17

TABLE 3 *Changes in median bloodspot thyroxine levels among women of reproductive age in the pairs of villages followed up four and eight months after supplementation*

	No. of samples	Median bloodspot thyroxine (nmol/l)		
		Before	Months after supplementation 4	8
0.5 g KI	82	39	42	
	67	30		38
1.0 g KI	70	28.5	42	
	78	42		44
2.0 g KI	76	39	38	
	79	27		37
Oral iodized oil	81	23	40	
	59	36.5		66.5
Placebo	76	33	24	
	76	33		33
Intramuscular iodized oil	98	41		65.5

goitre prevalence in any of the groups though almost all the groups showed a slight improvement.

Table 3 shows the corresponding median thyroxine (T_4) concentrations in bloodspot samples among women of reproductive age in the treatment groups. Amongst the groups given potassium iodide the increases in median T_4 are small in comparison with the large statistically significant increases seen in the oral iodized oil treated group particularly at eight months after supplementation and also in the villages given IM iodized oil. The mean, within individual, increase eight months after supplementation in the group given oral iodized oil was 30.5 nmol/l (95% CI 24.2 to 36.8) and in the group given IM iodized oil was 34.8 nmol/l (95% CI 26.6 to 43.0). T_4 concentration in the placebo treated villages declined or remained unchanged. At eight months after supplementation the median T_4 levels in the groups given intramuscular and oral iodine were similar (65.5 and 66.5 nmol/l respectively). The distributions of T_4 values in the two groups are shown in Figure 2.

Table 3 shows that the post-supplementation levels in the three groups treated with KI were similar at around 40 nmol/l. Pre-supplementation levels, however, varied between 27 and 42 nmol/l suggesting that the increase in median thyroxine values was determined largely by the initial levels. An analysis of the results taking into account the variation in initial T_4 levels was carried out. It also allowed for the alterations in T_4 levels resulting from pregnancy in women during the initial or follow-up visit and the decline occurring with storage of samples. A regression equation was formulated to assess treatment and covariate effects (Appendix). The model was fitted by least squares. Parameter estimates are given in the Appendix. The results coincided with the conclusions from Table 3. It is important to consider treatment parameters α and β together in interpreting the model. For example, they predict that an individual whose initial T_4 value was 30 nmol/l would have T_4 levels at eight months of 44 nmol/l with 0.5 g KI, 36 nmol/l with 1.0 g KI, 41 nmol/l with 2.0 g KI and 60 nmol/l with oral iodized oil. In the placebo treated group the corresponding predicted value would be 33 nmol/l and in the group given intramuscular iodized oil, 74 nmol/l. Though pregnancy and the decline in T_4 values associated with sample storage showed strongly significant independent effects, the treatment effects were not greatly altered by inclusion of these variables in the model, because they were well balanced between groups.

Seven women treated with intramuscular iodized oil (Figure 2) had post-supplementation T_4 values in excess of 130 nmol/l (range 133–200 nmol/l). All had visibly enlarged goitres and in the two with the highest T_4 values (175 and 200 nmol/l) the goitre was very large and nodular. The seven women had very low pre-supplementation T_4 values ranging from 10 to 28 nmol/l. This accounts for the large treatment effect predicted by the regression model for low initial T_4 values ($\alpha = 144$ in the group treated with IM iodized oil (Table A1).

DISCUSSION

This study is a large community-based controlled trial of oral iodine supplementation in an African population with severe iodine deficiency. The age-specific goitre prevalences (Table 1) are typical for an iodine deficient population. High prevalences were observed in children after infancy, young adults and among women of reproductive age reflecting the increased iodine requirements at these times. Despite the high frequency of goitre and severe iodine deficiency, overt cretinism was found to be relatively uncommon. This may have been in part due to underascertainment of cases. All the cases of cretinism in the present survey were of the neurological form, a finding that contrasts with the predominance of myxoedematous cretinism—characterized by hypothyroidism and growth retardation—in other iodine deficient areas of Zaire.[12] The low frequency of cretinism may, therefore, also be due to the absence of myxoedematous cretinism in the community.

In this study the method of T_4 determination in dried bloodspots was used to assess the effectiveness of supplementation. The method is advantageous as it does

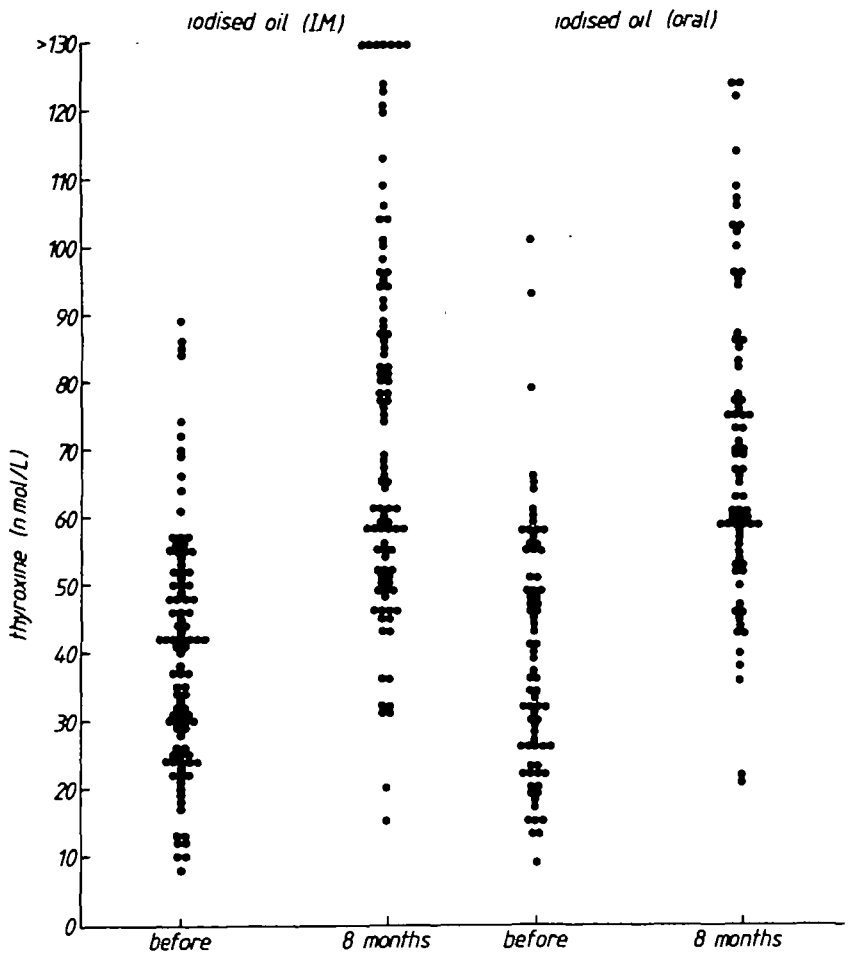

FIGURE 2 *Distribution of bloodspot T_4 values before and eight months after supplementation in the groups of villages treated with oral or intramuscular iodized oil.*

not require venepuncture and the transportation of specimens is greatly facilitated. However, there is a decline in T_4 levels with prolonged storage.

The T_4 measurements have been restricted to women of reproductive age who are the most important target group for supplementation as correction of iodine deficiency prior to conception is necessary in mothers in order to prevent neurological damage to the fetus.[13]

Oral iodized oil produced large statistically significant rises in T_4 levels at both four and eight months after supplementation. Changes in T_4 levels after single doses of potassium iodide were small and inconsistent. The increase in T_4 eight months after oral oil treatment was as large as that seen after intramuscular iodized oil. The absence of a reduction in goitre prevalence in the groups of villages treated with either oil or intramuscular iodized oil may be the result of many of the enlarged glands being hard or nodular, suggesting underlying fibrous changes. Goitres affected in this way would be unlikely to respond to correction of iodine deficiency. Treatment with oral iodized oil was not associated with significant side effects. Transient sialadenitis (pain or swelling of the salivary glands) was observed in 24% of adults or children given the 2 ml dose. Seven of the women treated with intramuscular iodized oil had, on follow-up, high T_4 levels—an effect which was not seen with the oral oil treated group. Though a definite diagnosis of iodine induced thyrotoxicosis cannot be made without data on plasma protein binding, it is likely to have occurred in at least two of the women treated with intramuscular iodized oil. Oral oil treatment may, therefore, be associated with a lower risk of iodine induced hyperthyroidism.

The results of this study suggest that yearly administration of oral iodized oil would be effective in cor-

recting iodine deficiency in communities. Large-scale supplementation with oral iodized oil would be feasible in remote areas with untrained people. Long-term follow-up is planned to determine the duration of effectiveness of oral oil at and beyond two years after supplementation.

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APPENDIX

The form of the equation was:

$$y_i = x_i + \alpha_{t(i)} \exp(-\beta_{t(i)} x_i) + \gamma u_i + \delta v_i + \epsilon d_i + e_i$$

where for individual i,

x_i = initial thyroxine level

y_i = final thyroxine level

u_i = 1 if pregnant at the initial measurement, 0 otherwise

v_i = 1 if pregnant at the final measurement, 0 otherwise

$d_i = N'_i - N_i$

where

N_i = no. of days between initial sample collection and analysis

N'_i = no. of days between final sample collection and analysis

t(i) = treatment received

$\alpha_{t(i)}$, $\beta_{t(i)}$ assess the effect of treatment, and are to be estimated

γ, δ, ϵ are further repressions coefficients, and e_i represents error.

α represents the treatment benefit from an initial thyroxine level of zero.

β determines how this benefit is modified by the initial thyroxine level.

TABLE A1 *Parameter estimates for the model*

	Months after supplementation			
	4		8	
	α	β	α	β
0.5 g KI	49.1	0.0364	24.4	0.0185
1.0 g KI	37.6	0.0230	26.6	0.0481
2.0 g KI	43.4	0.0558	45.9	0.0463
Oral iodized oil	36.6	0.0127	58.6	0.0229
Placebo	20.1	0.1050	13.4	0.0531
Intramuscular iodized oil	—	—	144	0.0398

Storage (ϵ) = 0.196.
Pregnancy at initial visit (γ) = −18.6.
Pregnancy at final assessment (δ) = 12.4.
(Standard errors available upon request.)