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Iodine Supplementation with Oral or Intramuscular Iodized Oil. A Two-Year Follow-up of a Comparative Trial

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A controlled trial of iodine supplementation comparing oral with intramuscular iodized oil has been carried out in an iodine deficient area of Zaire. Two years after the administration of 2 ml of oral iodized oil to the population of four villages the overall goitre prevalence had fallen from 64 to 54%. In a further two villages given 2 ml of intramuscular oil the prevalence fell from 65 to 50%. The effectiveness of supplementation was also assessed by measuring changes in thyroid function in women of reproductive age. Among women in the villages given oral iodized oil, the geometric mean thyroxine concentration, measured in dried bloodspots, rose from 27.2 to 52.6 nmol/L at the two-year follow-up. This was similar to the response of the intramuscularly treated villages in which thyroxine levels rose from 32.1 to 65.4 nmol/L. There was no change in goitre prevalence or thyroid function in two control villages. Oral iodized oil is a cheaper and simpler alternative to the injected form providing effective iodine prophylaxis for up to two years after a single dose.

The control of iodine deficiency continues to be a problem in areas of the world where the iodization of foodstuffs is impractical. Though single, intramuscular, injections of iodized oil have been used to provide a long lasting supply of iodine, as a public health measure they have the disadvantage of expense, the need for trained personnel and the risk of transmitting parenterally spread disease. Pilot studies based on selected populations of schoolchildren or goitre patients have indicated that iodized oil can be used orally, but there are no data on its duration of action in unselected populations. A controlled trial in an iodine deficient area of Zaire[1] has demonstrated that among women of reproductive age, who are the most important at-risk group, oral iodized oil was as effective as the intramuscular form for up to eight months after a single dose. The increase in thyroxine concentration in dried blood spots, which was used to monitor the effectiveness of iodine supplementation, was much greater than that observed with an equivalent dose of oral potassium iodide. We now report the results of a two-year follow-up of this trial comparing oral with intramuscular iodized oil.

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METHODS

The trial was carried out in the North Kivu area of Zaire as previously described.[1] Briefly, 20 villages were allocated to five treatment groups, each group comprising four villages. Three of the groups were given graded doses of potassium iodide, the fourth received oral iodized oil (2 ml Lipiodol, May and Baker, Dagenham) and the fifth was placebo treated. A further three villages were given 2 ml of intramuscular iodized oil. In each of the villages, children aged two to ten years were given half the adult dose, and those under two years were left untreated.

As endemic cretinism and mental retardation are the most serious consequences of iodine deficiency and can be prevented by ensuring that women of childbearing age have an adequate iodine supply, the effectiveness of supplementation was determined in women of this age by measurement of bloodspot thyroxine concentration. Fingerprick blood samples were obtained from a systematic sample of approximately 35 women of

reproductive age (15–44 years) in each village. Goitre rates in the villages were measured using a WHO classification[2] into two categories—'palpable' (thyroid enlarged but not visible with the head in the normal position), and 'visible' (goitre visible with the head in the normal position). The goitre rates were indirectly age-sex standardized, using as the standard population villagers who attended both the initial and follow-up examination.

Two years after supplementation, the populations of the villages treated with oral or intramuscular iodized oil and the placebo treated villages were re-examined, goitre rates assessed, and blood samples obtained from the same women as previously. Blood spots were also obtained from infants and neonates born in the two-year interval following supplementation. They were identified through a simple birth register kept by a village health worker. Thyroxine and thyrotrophin (TSH) levels in the blood spots were measured with standard methods in use for neonatal screening, and urinary iodine concentrations in casual urine samples by the method of Benotti and Benotti.[3]

RESULTS

Goitre Rates

Follow-up was carried out in all of the four villages treated with oral iodized oil, two of the three villages given intramuscular iodized oil, and three of the four control villages. In these nine villages 71% of the initially treated population (n=2 371) was re-examined (range between villages 55% to 78%).

Two years after supplementation the age-sex standardized total goitre prevalence in the villages given oral iodized oil fell significantly from 64% to 54%, a similar change to that observed in the villages given intramuscular iodized oil where the prevalence fell from 65% to 50% (Table 1). There was little change in the control villages. Likewise the visible goitre prevalence fell from 19% to 8% in the orally treated villages, and from 24% to 8% in the intramuscularly treated villages.

Thyroid Function

At the two-year follow-up examination bloodspots were obtained from 89% of the women of reproductive age from whom samples were collected initially. Table 2 shows the changes in thyroxine concentrations among women in the treatment groups. As the data are markedly skewed they are expressed as geometric means, and are based on women attending both the initial and the follow-up visits. Before supplementation the mean thyroxine concentration in the three groups ranged from 27.2 to 33.7 nmol/L. The level in the orally treated group was significantly lower than in the other two groups. After six months the thyroxine concentration in the groups who had received oral or intramuscular oil had almost doubled reaching 52.7 and 69.9 nmol/L respectively. At the two-year follow-up the thyroxine levels in these groups were virtually unchanged. In contrast the mean thyroxine level in the control group declined at six months but two years after supplementation was similar to the presupplementation level.

Urinary Iodine Excretion

During the follow-up study casual urine specimens were obtained from systematic samples of women of reproductive age in the treatment groups. As the urinary creatinine excretion in this population was found to be very low, the mean excretion in each group was calculated instead of the urinary iodine/creatinine ratio. Table 3 shows that the geometric mean urinary iodine excretion in the group given oral iodized oil (33.6 μg/L) was almost double that observed in the untreated control village (17.6 μg/L). Urinary excretion in the intramuscularly treated group (86.6 μg/L) was, however, nearly five times the control value.

Thyroid Function in Infants

Table 4 shows the results of an analysis of thyroxine levels in bloodspots obtained from infants and neonates during the two-year follow-up visit and who were born either during the first or the second year after supplementation of the respective groups. Within each group infants born during the first year, and who were therefore older, had lower levels than those born

TABLE 1 *Changes in the age–sex standardized total goitre and visible goitre prevalence two years after supplementation with oral or intramuscular iodized oil*

	Total goitre prevalence (%)		Visible goitre prevalence (%)	
	Before	Two years after supplementation	Before	Two years after supplementation
Intramuscular iodized oil (n = 378)	65 (2.5)	50 (2.6)	24 (2.2)	8 (1.4)
Oral iodized oil (n = 758)	64 (1.7)	54 (1.8)	19 (1.4)	8 (1.0)
Control (n = 554)	63 (2.0)	66 (2.0)	21 (1.7)	20 (1.7)

Standard errors included in brackets.

TABLE 2 *Changes in bloodspot thyroxine concentration among women of reproductive age after supplementation with oral or intramuscular iodized oil. (Geometric means are shown together with 95% confidence intervals based on log transformation)*

	Blood thyroxine (nmol/L		
		After supplementation	
	Before	6 months	2 years
Intramuscular iodized oil (n = 72)	32.1 (28.7–35.9)	69.9 (62.6–78.1)	65.4 (58.4–73.1)
Oral iodized oil (n = 130)	27.2 (24.4–30.3)	52.7 (48.3–57.4)	52.6 (48 0–57.6)
Conrol (n = 96)	33.7 (30.2–37.8)	23.5 (20.8–26.7)	34.0 (29 3–39.4)

during the second year, though in the control group the difference was small. Infants whose mothers had received intramuscular iodized oil had higher thyroxine levels than those whose mothers had received oral iodized oil, but these in turn had higher levels than in the control group. Blood spot TSH levels measured on the same samples were found to be above the laboratory reference range in four out of 59 infants (range 7.7-35.1 mU/L) in the control group, compared with only one of 87 infants whose mothers had received oral iodized oil and none of the 47 whose mothers had received injected iodized oil.

DISCUSSION

This study is a community-based controlled trial comparing single doses of oral with intramuscular iodized oil in an unselected, iodine deficient population in Central Africa. Both forms of the oil appeared to be equally effective in reducing goitre prevalence (Table 1) though the effect of observer bias cannot be excluded.

Among women of reproductive age bloodspot thyroxine levels showed large, statistically significant, increases with both the oral and intramuscular forms of iodized oil throughout the two-year period. Although the thyroxine levels achieved were higher in the intramuscularly treated women, this group also had higher presupplementation levels. In our previous analysis we showed that if allowance is made for this difference in initial levels, the effects of the oral and intramuscular treatments were shown to be comparable up to eight months after supplementation. If this adjustment is made for the data in Table 2, the results indicate that oral and intramuscular iodized oil had similar effects throughout the two-year follow-up period. Although the thyroxine concentrations could also have been affected by pregnancy as a result of the rise in thyroid binding globulin, the present conclusions were not altered by this as the proportions of pregnant women were well balanced between the treatment groups.

These results may be compared with the measurements of urinary iodine excretion observed two years after supplementation in the three groups (Table 3). The use of the mean urine iodine content in this anlaysis as an indicator of iodine nutrition is a validated alternative to the more usually quoted iodine/creatinine ratio especially in populations with low protein intakes and therefore low urinary creatinine excretion.[4] Two years after supplementation, iodine excretion in the group given oral oil was less than half that in the group who had received intramuscular oil. Yet despite this decline in iodine excretion, the orally treated group were able to maintain high thyroxine levels presumably as a result of the ability of the thyroid to store iodine.

Neonates and young infants in iodine deficient communities are also susceptible to hypothyroidism in

TABLE 3 *Mean urinary iodine excretion among women of reproductive age two years after supplementation with oral or intramuscular iodized oil (geometric means are shown together with 95% confidence intervals based on log transformation)*

	Geometric mean urinary excretion (μg/L)	95% confidence interval
Intramuscular iodized oil (n=18)	86.6	55.8–134.2
Oral iodized oil (n=19)	33.6	23.9– 47.3
Control (n=19)	17.6	13.1– 23.6

TABLE 4 *Bloodspot thyroxine concentrations in infants born in the first year or second year after iodine supplementation of their mothers*

	Mean bloodspot T_4 (nmol/L)	
	1st year	2nd year
Intramuscular iodized oil (n=47)	94.8 (10.6)	108.4 (6.8)
Oral iodized oil (n=87)	85 7 (4.1)	98.8 (5.8)
Control (n=59)	78.2 (7.6)	80.2 (7.8)

Standard errors included in brackets.

early life and its consequent effects on mental and physical development. Infants born in the interval following supplementation of their mothers will necessarily depend on iodine contained in the breast milk, which in turn depends on the maternal iodine balance. In this area of Zaire where breastfeeding is usual for the first two years of life, we have assessed iodine nutrition in young infants by measuring thyroxine and thyrotrophin in dried bloodspots. The results (Table 4) show that thyroxine levels in the infants born to mothers treated with injected or oral iodized oil were higher than those observed in the control group, though the highest levels were achieved in the infants of the intramuscularly treated women. Raised thyrotrophin levels indicating hypothyroidism were not found in any of the infants in the group who had received intramuscular oil but were observed in one of the 87 infants in the orally supplemented group and four of the 59 controls.

Compared with injected iodized oil there have been few studies evaluating oral iodized oil. Reports from Argentina,[5] The Sudan,[6] Bolivia[7] and China[8] are based on selected populations or the population studied is unspecified. Most show adequate levels of iodine supplementation two years after a single dose of oral iodized oil as judged by a urinary iodine excretion of more than 50 μg/g creatinine. However, only a limited comparison is possible with the present study because of the lack of data on thyroid hormone levels.

In conclusion the oral and injected forms of the iodized oil were equally effective in reducing goitre prevalence and in normalizing thyroid function in women of reproductive age. The rise in urinary iodine excretion in adults and the changes in thyroid function in young infants following oral oil were lower than that observed with the injected form. This could be explained, at least in part, by the initially more severe iodine deficiency in the orally treated villages suggested by the lower thyroxine values among women in this group (Table 2). The simplicity and lower cost of oral iodized oil, however, make its use preferable in isolated communities where there is an urgent need for iodine prophylaxis.

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