

Oral Iodized Oil for Correcting Iodine Deficiency: Optimal Dosing and Outcome Indicator Selection*

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ABSTRACT

Oral iodized oil is the major alternative to iodized salt for correcting endemic iodine deficiency. This study responds to a need for better guidelines in its use. Schoolchildren, aged 6–11 yr, from a severely iodine-deficient area of Algeria received iodized poppy seed oil (Lipiodol) in a single oral dose containing 120, 240, 480, or 960 mg iodine (groups A–D) or in an im injection of 480 mg iodine (group E). Thyroid volume by ultrasonography had not changed 395 days after treatment in groups A, B, and C, had decreased in groups D and E. Urinary iodine concentration rose rapidly from an initial median of 0.21 $\mu\text{mol/L}$, but fell below 0.79 $\mu\text{mol/L}$ (the currently accepted level for indicating iodine deficiency) by 150 days for groups A and B, and by 395 days for

groups C and D. Median serum TSH and T_4 levels were normal before and after treatment, whereas high initial serum thyroglobulin values decreased in all groups after iodized oil treatment.

For correcting iodine deficiency in children, we recommend single oral doses of Lipiodol containing 240 mg iodine for 6-month coverage or 480 mg for 12 months. These doses may not completely sustain iodine sufficiency, but will prevent the worst of the iodine deficiency disorders. Additionally, we conclude that the urinary iodine concentration is the most useful epidemiological indicator for assessing current iodine status, and thyroid volume and serum thyroglobulin levels are the best markers for assessing chronic effects. (*J Clin Endocrinol Metab* 79: 20–24, 1994)

OVER one billion people live in areas of iodine deficiency and risk its consequences (1–3). The worst of these so-called iodine deficiency disorders (IDD) is permanent damage to the developing brain. Cretinism is the most obvious manifestation of brain damage and may affect up to 10% of the population in the most severely afflicted areas. Many other persons in these areas have more subtle mental and neurological deficits. The World Health Assembly, the World Summit for Children, and more than 140 individual countries have recognized the importance of iodine deficiency as a problem of public health, particularly in developing countries, and have pledged its elimination by the year 2000 (4).

Iodized salt is the best means for supplying iodine to deficient populations, but usually requires several years to effectively reach the most afflicted areas. Iodine-deficient regions needing more immediate supplementation usually rely on iodinated vegetable oil as the major temporary measure while implementing salt iodization programs (5–9). Iodized oil administered by im injection is highly effective, but requires specialized supplies and personnel and carries the risk of transmitting hepatitis, human immunodeficiency virus, and other infectious agents through needle contamination. These drawbacks have led to the increasing use of iodized oil orally despite a lack of definitive information

about its optimal dose or duration of effect. To develop better guidelines, we have used five indicators to study Algerian schoolchildren given one of several doses of iodized oil.

Subjects and Methods

The study was conducted in a mountainous area of Algeria, 200 km east of Algiers, 1300 meters above sea level, with a goiter prevalence of 51%, a cretinism prevalence of 1.1%, and a mean urinary iodine concentration of 0.127 $\mu\text{mol/L}$. Children aged 6–11 yr, of both sexes, attending two local schools were assigned randomly to 1 of 5 treatment groups of approximately 40 students each. The goiter prevalence by palpation was 65%. Each student received a single administration of iodized poppy seed oil (Lipiodol Ultrafluide, Guerbet, Paris, France; containing 480 mg iodine/mL) as follows: group A, 0.25 mL (120 mg I) orally; group B, 0.5 mL (240 mg I) orally; group C, 1.0 mL (480 mg I) orally; group D, 2.0 mL (960 mg I) orally; and group E, 1.0 mL (480 mg I) im. Subjects were assessed initially by height, weight, thyroid sonography, urinary iodine, and serum levels of TSH, T_4 , thyroglobulin, and antibodies to thyroid peroxidase. All measurements except serum thyroglobulin were repeated 395 days after the administration of iodized oil. Additional samples of urine were collected after 7, 30, 70, and 150 days, and samples of serum for TSH, thyroglobulin, and free T_4 determinations were obtained at 150 days. Informed consent was obtained from the subjects, their parents, and local authorities under procedures approved by the Algerian National Institute of Public Health and the Human Investigations Committee of the University of Virginia.

Ultrasonography was performed by one examiner (R.G.) using an Aloka Echo Camera SSD-210DX11 with a 5-mHz linear transducer. Thyroid volume was calculated as the sum of the products of maximal thickness, width, length, and a correction factor of 0.479 for each lobe (10).

Urinary iodine was measured, after digestion, on a Technicon Autoanalyzer (Technicon Corp., Tarrytown, NY) (11). For comparison with other studies, we also measured the creatinine concentration of urine samples collected at 395 days for all five groups and at 270 days for

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groups A and B, and found that the I/creatinine ratio, expressed as micrograms of I per g creatinine, was an average of 111 times the value for iodine concentration, in micromoles per L.

Serum TSH was measured using a RIA kit (Behring Werke, Marburg, Germany). The manufacturer's stated normal range for 1966 euthyroid subjects was 0.25–4.0 $\mu\text{U/mL}$; validation on 30 euthyroid subjects in our laboratory gave 4.56 $\mu\text{U/mL}$ as the upper limit of normal.

Serum free T_4 was also measured by a RIA kit (Behring), with the normal range given as 0.70–1.90 ng/dL (12–24 pmol/L); validation on 30 euthyroid subjects in our laboratory gave an identical normal range.

Serum thyroglobulin was measured by an immunoluminometric assay (12). The upper limit of normal in iodine-sufficient children in this assay is 20 ng/mL (13).

Antithyroid thyroid peroxidase antibodies were measured using a commercial kit (Henning, Berlin, Germany).

Statistical analyses

The Kruskal-Wallis test with multiple *post-hoc* tests (Nemenyi) was used for the comparison of the five groups. Comparisons between times within each group were calculated by the Wilcoxon matched pairs, signed ranks test (for parameters with data at two time points) and the Friedman test with multiple *post-hoc* tests (for parameters with data at three or more time points) (14).

Results

Height and weight

At 395 days of follow-up, the mean weight was 26.8 \pm 5.3 kg (\pm SD; median, 25.0), a mean gain of 6.6%, and the mean height was 128 \pm 10 cm (median, 127), a mean gain of 6.8%. The five treatment groups, A–E, did not differ from each other in height or weight before or after iodine treatment.

Thyroid size

Table 1 shows mean and median values for the thyroid volume before and 365 days after iodized oil treatment. Values in groups A, B, and C did not change, and those in groups D and E decreased. The degree of change among groups A, B, and C was not significant; all three differed from groups D ($P < 0.01$) and E ($P < 0.05$). Group D did not differ from group E.

Urinary iodine (Table 2)

The initial combined median for all groups was 0.21 $\mu\text{mol/L}$ iodine, and each group had a rapid rise 7 days after iodine administration. Intervals between iodine administration and return of the median urinary iodine levels for each group to

values below 0.79 $\mu\text{mol/L}$ (10 $\mu\text{g/dL}$) were: A, 30 days; B, 150 days; and C and D, 395 days. Group A fell below 0.40 $\mu\text{mol/L}$ by 150 days, and group B fell below this value by 270 days. At 395 days, the medians for groups C, D, and E were 0.40 $\mu\text{mol/L}$ or above. The proportions of individual samples with urinary iodine concentrations below 0.40 $\mu\text{mol/L}$ at 395 days for each of the five groups were: A, 84%; B, 62%; C, 53%; D, 23%; and E, 0%. The mean urinary iodine concentration after treatment differed ($P < 0.005$) from pre-treatment means for groups B, C, D, and E, but not for group A. The five groups did not differ from each other in urinary iodine concentration before treatment, but each group differed from the other four at each follow-up time after treatment ($P < 0.001$).

Serum TSH (Table 3)

Initial mean and median levels did not differ among the five groups and were within the normal range, but 13% of individuals had values above 5 $\mu\text{U/mL}$. At the 395 day follow-up, groups A, D, and E had no level greater than 5 $\mu\text{U/mL}$, whereas group B had 3% and group C had 2% of the levels above this value. Mean TSH levels in all groups were significantly lower ($P < 0.001$) 150 and 395 days after iodine administration, although they were still within the normal range. At 395 days, the difference in TSH level between groups A and E was barely significant ($P < 0.05$).

Serum free T_4 (Table 4)

Initial mean and median values were in the normal range, but 6% of individual values were low. All groups increased their serum T_4 after iodized oil ($P < 0.001$), and only one child (in group D) had a value below the normal range on follow-up. At 395 days after treatment, free T_4 values in group A were lower and those in group E higher than values in each of the other four groups ($P < 0.01$).

Serum thyroglobulin (Table 5)

Initial values were elevated several-fold over normal in all groups, with considerable scatter. All were markedly lower at the 150 day follow-up, but the median values for groups A, B, and C were still above the upper normal limit of 20 ng/mL (11). The fractions of total individual values above this limit for each group were: A, 68%; B, 47%; C, 56%; D, 24%; and E, 6%.

TABLE 1. Changes in thyroid volume 395 days after iodized oil treatment

	Group				
	A	B	C	D	E
No. of subjects	39	32	40	35	36
Vol (mL) at 0 days	5.1 \pm 2.1 (5.0)	4.9 \pm 1.8 (4.8)	4.8 \pm 2.8 (4.0)	5.7 \pm 2.5 (5.4)	5.6 \pm 2.2 (5.3)
Vol (mL) at 395 days	5.5 \pm 2.8 (4.6)	4.5 \pm 1.7 (4.0)	4.3 \pm 1.8 (3.7)	3.7 \pm 1.6 (3.3)	3.8 \pm 1.5 (3.8)
Change (%), 0–395 days ^a	+11.2 \pm 48 (0.0)	–1.5 \pm 41.7 (–4.3)	+1.1 \pm 44.5 (–4.7)	–29.2 \pm 35.0 (–38.2)	–22.9 \pm 41.5 (–30.7)

Each child in groups A–D received an oral dose of Lipiodol containing iodine as follows: A, 120 mg iodine; B, 240 mg; C, 480 mg; and D, 960 mg. Each child in group E received 480 mg iodine, as Lipiodol, im. Values are the mean \pm SD; medians are in parentheses.

^a Calculated for each child before deriving means and medians, to reduce the effects of variability among individuals; thus, this table line is not simply the difference between the two preceding lines.

TABLE 2. Changes in urinary iodine concentrations after iodized oil treatment

Days after iodine	Group				
	A (n = 36)	B (n = 36)	C (n = 33)	D (n = 28)	E (n = 36)
0	0.28 ± 0.13 (0.21)	0.23 ± 0.13 (0.20)	0.21 ± 0.12 (0.20)	0.23 ± 0.13 (0.20)	0.25 ± 0.13 (0.21)
7	17.0 ± 8.26 (16.1)	20.0 ± 11.7 (18.3)	24.2 ± 12.4 (20.6)	26.4 ± 15.0 (25.6)	33.7 ± 11.4 (33.6)
30	0.80 ± 0.37 (0.76)	3.31 ± 2.88 (1.75)	2.50 ± 1.03 (1.98)	4.66 ± 2.98 (4.09)	18.4 ± 3.87 (19.5)
70	0.51 ± 0.27 (0.41)	1.31 ± 0.81 (1.20)	1.65 ± 0.080 (1.66)	2.24 ± 1.43 (1.87)	12.1 ± 3.03 (12.0)
150	0.30 ± 0.16 (0.32)	0.85 ± 0.43 (0.78)	1.07 ± 0.40 (0.86)	1.26 ± 0.63 (1.04)	9.65 ± 2.03 (9.36)
270	0.26 ± 0.12 (0.21)	0.44 ± 0.41 (0.38)			
395	0.25 ± 0.16 (0.20)	0.34 ± 0.18 (0.31)	0.48 ± 0.32 (0.40)	0.79 ± 0.59 (0.55)	2.90 ± 1.92 (2.37)

The dosage schedule for each group is given in Table 1. Values are the mean ± SD, expressed as micromoles per L; medians are in *parentheses*.

TABLE 3. Changes in serum TSH levels after iodized oil treatment

Days after iodine	Group				
	A (n = 38)	B (n = 37)	C (n = 41)	D (n = 36)	E (n = 34)
0	3.2 ± 2.0 (2.6)	2.8 ± 1.6 (2.5)	3.7 ± 2.7 (2.7)	3.8 ± 2.4 (3.2)	3.1 ± 1.6 (2.7)
150	2.0 ± 1.1 (1.7)	1.7 ± 0.9 (1.7)	2.0 ± 0.9 (1.9)	2.4 ± 1.4 (2.0)	2.2 ± 1.0 (2.1)
395	2.0 ± 1.0 (2.0)	1.8 ± 1.1 (1.8)	2.0 ± 0.9 (1.7)	2.0 ± 0.7 (2.0)	1.7 ± 0.8 (1.5)

The dosage schedule for each group is given in Table 1. Values are the mean ± SD, expressed as microunits per mL; medians are in *parentheses*. Reference range for iodine-sufficient normal subjects, 0.1–4.0 mU/L.

TABLE 4. Changes in serum free T₄ levels after iodized oil treatment

Days after iodine	Group				
	A (n = 38)	B (n = 36)	C (n = 41)	D (n = 36)	E (n = 34)
0	12 ± 2 (12)	12 ± 2 (12)	12 ± 2 (12)	12 ± 2 (12)	12 ± 2 (12)
150	14 ± 2 (14)	14 ± 3 (14)	14 ± 2 (14)	14 ± 2 (14)	14 ± 2 (15)
395	13 ± 2 (14)	14 ± 2 (14)	14 ± 2 (14)	15 ± 2 (15)	16 ± 3 (15)

The dosage schedule for each group is given in Table 1. Values are the mean ± SD, expressed as picomoles per L; medians are in *parentheses*. Reference range for iodine-sufficient normal subjects, 9–24 pmol/L.

TABLE 5. Changes in serum thyroglobulin levels 150 days after iodized oil treatment

Days after iodine	Group				
	A (n = 19)	B (n = 19)	C (n = 16)	D (n = 17)	E (n = 17)
0	143.6 ± 124.8 (98.5)	83.5 ± 41.0 (98.5)	213.9 ± 147.4 (175.0)	122.1 ± 157.0 (77.0)	128.1 ± 141.4 (62.0)
150	70.6 ± 115.5 (31.0)	18.0 ± 8.2 (22.0)	24.4 ± 13.1 (24.0)	16.9 ± 18.2 (14.0)	11.3 ± 5.0 (12.0)

The dosage schedule for each group is given in Table 1. Values are the mean ± SD, expressed as nanograms per mL; medians are in *parentheses*.

Antithyroid peroxidase antibodies

Titers were negative in all groups before and after iodized oil treatment.

Discussion

In this study the different indicators of iodine status had varying degrees of usefulness. Urinary iodine, thyroid volume, and serum thyroglobulin were all valuable. Although complementary, they measure different components of iodine nutrition. Urinary iodine reflects recent iodine ingestion and can change in days with variations in dietary iodine. In contrast, iodine availability affects thyroid volume and serum thyroglobulin more chronically over a period of months or even years. Thyroid size has traditionally been assessed by neck palpation. The technique is simple, inexpensive, and readily available, but may be somewhat unreliable when

applied to small thyroids, particularly in children. Ultrasonography, by contrast, is precise, reproducible, and free from observer bias. Simple portable instruments can be carried to the field, as in this study, and assessment requires only a few minutes for each subject. Where feasible, we prefer ultrasonography over neck palpation alone. Urinary iodine is also a practical field indicator; samples are easy to obtain and analyze, particularly using simplified methods (15). Serum thyroglobulin proved a sensitive indicator in this study, as in others. It can be measured in dried blood spots and should be practical in surveys where such samples are available. In contrast, the serum TSH and T₄ measurements were not useful in the present study, and we do not recommend them for routine epidemiological surveillance in school-aged children.

All children receiving iodized oil in the present study showed some response, but the degree of response varied

among the five groups. Thyroid volume was unchanged 395 days after iodized oil administration in groups A, B, and C, and had decreased markedly in groups D and E. Normative ultrasound data for the 50th percentile of thyroid volume in iodine-sufficient populations range from 1.4 mL in 6-yr-olds to 3.8 mL in 12-yr-olds (Gutekunst, R., unpublished data). Thus, the initial median thyroid volume in our study greatly exceeded these values for iodine-sufficient children, and by 395 days, no group had returned to the 50th percentile value.

A recent International Expert Committee on Indicators ["Indicators for Assessing Iodine Deficiency Disorders and Their Control Programmes," report of a joint WHO/UNICEF/International Council for the Control of Iodine Deficiency Disorders (ICCIDD) consultation November 3–5, 1992, draft report September 1993] defined a median urinary iodine concentration of 10 $\mu\text{g}/\text{dL}$ (0.79 $\mu\text{mol}/\text{L}$) or greater as indicating no iodine deficiency in a population, 5.0–9.9 $\mu\text{g}/\text{dL}$ (0.40–0.78 $\mu\text{mol}/\text{L}$) as mild deficiency, 2.0–4.9 $\mu\text{g}/\text{dL}$ (0.16–0.39 $\mu\text{mol}/\text{L}$) as moderate deficiency, and less than 2.0 $\mu\text{g}/\text{dL}$ (<0.16 $\mu\text{mol}/\text{L}$) as severe deficiency. By this classification, all groups in the present study began with moderate iodine deficiency. After iodine treatment, group A had returned to mild deficiency by 30 days and to moderate deficiency by 150 days, group B to mild deficiency by 150 days and to moderate deficiency by 395 days, groups C and D to mild deficiency between 150–395 days, and group E was still iodine sufficient at 395 days.

Median TSH levels were in the normal range before iodine treatment, but 28% were higher than the assay's upper normal limit. Median values decreased significantly after iodized oil treatment; however, the magnitude of the response did not correlate closely with the size of the iodine dose. The median serum free T_4 level before iodine treatment was normal and increased after iodine administration; it did not differ significantly among the treatment groups. Serum thyroglobulin, on the other hand, was markedly elevated before treatment and fell sharply after iodine administration in all groups, more so in those given the larger oral doses or im administration.

Taken together, these indicators show that an oral dose of 120 mg iodine as iodized oil provided fully adequate iodine for only about 1 month, 240 or 480 mg for about 6 months, and 960 mg for about 6–13 months. Intramuscular iodized oil (480 mg) gave fully adequate coverage for at least 13 months. Despite a suboptimal iodine concentration in urine, with lengthening follow-up after the lower doses of oral iodized oil, serum thyroglobulin and TSH levels showed considerable improvement 5 and 13 months after iodine administration, and the median thyroid size did not increase in any group despite a year's increase in age and body size.

In a 1987 review, all of 10 cited studies using various iodinated vegetable oils containing from 240–960 mg iodine showed a response to oral iodized oil, and its duration of effect was roughly related to the severity of the initial iodine deficiency (5). Different conditions among these reports included geographic location, severity of iodine deficiency, age of study subjects, follow-up intervals, and indicators employed (usually only urinary iodine and goiter prevalence by

palpation). In the study of Eltom *et al.* (6), schoolchildren in the highly deficient area of Darfur, Sudan, received 400 mg iodine as Lipiodol orally. One year later, the following changes were noted; goiter prevalence decreased from 67% to 36%, urinary iodine increased from 57.1 to 196.4 μg iodine/g creatinine, serum T_4 increased from 73.7 to 92.4 nmol/L, and TSH decreased from 7.2 to 3.6 mU/L. These results were similar to those in another group given the same dose im, whereas an untreated control group showed little change.

More recently, Lazarus *et al.* (9) gave oil containing 480 mg iodine orally to adults in a severely deficient area of Senegal (median urinary iodine, 0.08 $\mu\text{mol}/\text{L}$; 62% goiter prevalence), and 12 months later found that the median urinary iodine had risen to 0.19 $\mu\text{mol}/\text{L}$, and median serum TSH had decreased from 1.5 to 0.58 $\mu\text{U}/\text{mL}$. In a severely iodine-deficient area of Zaire, Phillips and Osmond (7) reported that the goiter prevalence in the entire population 2 yr after the oral administration of 960 mg iodized oil had decreased from 64% to 54%, and the mean urinary iodine was 0.27 $\mu\text{mol}/\text{L}$ compared with 0.14 $\mu\text{mol}/\text{L}$ in an untreated control group and 0.69 $\mu\text{mol}/\text{L}$ in a group given 960 mg iodized oil im. In another study from Zaire, Tonglet *et al.* (8) gave two groups of young adults oral doses of oil containing 47 and 118 mg iodine, respectively. One year later, the median urinary iodine concentrations were 0.20 and 0.24 $\mu\text{mol}/\text{L}$, respectively; goiter prevalence, as assessed by palpation, had decreased by 44% and 52% respectively; and median serum TSH levels had decreased in both groups, although they had been in the normal range before treatment.

The present study has several advantages over most previous studies using oral iodized oil, as follows: 1) the use of ultrasound assessed thyroid size more accurately than does palpation and allowed comparison with international standards; 2) the five indicators characterized iodine effects more completely than in previous publications; 3) the study design permitted a detailed description of dose effectiveness while avoiding the ethically complex issue of untreated controls; and 4) we focussed on children, who are more vulnerable to the effects of iodine deficiency and whose thyroids are more responsive to its correction, perhaps explaining why the low doses recommended by Tonglet *et al.* (8) for adults were much less effective for children in our study.

Millions of doses of oral iodized oil are given each year. Iodized oil represents a substantial expenditure for the countries and international agencies providing it, and considerations of cost effectiveness demand clear dosage guidelines. In planning treatment programs for iodine-deficient children, our data suggest that it is reasonable to recommend 240 mg iodine in the form of oral Lipiodol for up to 6 months of coverage and 480 mg for up to 1 yr. These doses may not completely correct iodine deficiency, but will keep it in the mild range and prevent hypothyroidism and cretinism while awaiting the effective introduction of iodized salt or another more permanent measure.

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