New model for describing urinary iodine excretion: its use for comparing different oral preparations of iodized oil[1–3]

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ABSTRACT Iodine excretion in urine after oral dosing with iodized oil is influenced by various factors involved in the retention and elimination of iodine by the body. In a study comparing different treatments of severely iodine-deficient schoolchildren from Malawi, a hyperbolic function was found to describe changes in urinary iodine concentration over time more adequately than a simple exponential function. Compared with oil A, comprising ethyl esters of iodized fatty acids, the retention and elimination of iodine from oil B, comprising triacylglycerol esters of iodized fatty acids, were significantly greater. The mean duration of effectiveness of oral iodized oil, based on urinary iodine concentrations >0.40 μmol/L, was estimated to be 13.7, 9.9, and 52.5 wk for a single dose of iodized oil A (490 mg I), a split dose of iodized oil A (2 × 245 mg I), and a single dose of iodized oil B (675 mg I), respectively. Dividing the dose of oil A into two equal amounts given on consecutive days did not improve its efficacy. *Am J Clin Nutr* 1995;61:1257–62.

KEY WORDS Iodine deficiency, iodized oil, urinary iodine concentration, retention, elimination, duration of effectiveness

INTRODUCTION

Iodine deficiency has been a major world health problem for centuries (1). Although salt iodization is usually the control method of choice, dosing with iodized oil is often used before salt iodization can get under way. Because of the extra costs and health risks associated with dosing parenterally, oral dosing with iodized oil is increasingly being used in iodine-deficiency control programs (2). There are many iodized oil preparations based on poppy seed oil for both injection and oral use. One type of oil (oil A), initially developed for intramuscular administration, is a mixture of ethyl esters of iodized fatty acids (each molecule comprising one iodized fatty acid moiety esterified to ethanol) whereas in another type of oil (oil B), the iodized fatty acids are present as triacylglycerol esters (each molecule comprising three fatty acid moieties esterified to glycerol). The latter, which is cheaper to produce, is more viscous but quite suitable for oral use in both capsules and from a dispenser. Because the chemical nature of iodized oil preparations can influence their effectiveness in combatting iodine deficiency (3), we compared iodine excretion in urine after oral dosing with either oil A or oil B. It is expected that oil B is absorbed from the small intestine as neutral fat, which consists of triacylglycerol esters. The mechanism by which ethyl esters are absorbed remains unclear. In addition, the effect of giving half of the total dose of oil A on each of 2 consecutive days (split dose) on urinary iodine excretion was also examined.

To compare the different treatments, we examined the empirical performance of two mathematical models to describe the pattern over time of urinary iodine excretion after oral dosing with iodized oil. The first is a single-compartment model in which the proportion of iodine eliminated remains constant over time and is described by a simple exponential function. If this proportion changes over time, it may be expected that more than one compartment or mechanism is involved in the process. Such a process can be described by a multiple exponential function or more simply by a hyperbolic function, which has fewer degrees of freedom. An encompassing equation nesting both the simple exponential and the hyperbolic models was used to test which of the two models more adequately describes the observed urinary iodine excretion after oral iodized oil administration. The preferred model was used to compare the different treatments in the study.

SUBJECTS AND METHODS

Subjects

The study was approved by the Ethics Committee of the National Council for Medical Research of Malawi in 1989. Informed consent for each child was obtained from the parents or guardians before the study commenced. The children were examined by a medical assistant from Ntcheu District Hospital.

Apparently healthy 8-, 9-, and 10-y-old schoolchildren, treated for mixed intestinal parasitic infestations, from four

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schools in Ntcheu District, Malawi, were selected to participate in the study (n = 326). From these children, groups were randomly selected by age and sex to receive a single dose of 1 mL oil A (Lipiodol UF, 490 g I/L; Laboratoire Guerbet, Aulnay-sous-Bois, France, n = 215), a single dose of 1.25 mL oil B (Oriodol, 540 g I/L; Laboratoire Guerbet, n = 37), two doses each of 0.5 mL on 2 consecutive days of oil A (n = 39), or a single dose of 1 mL neutral poppy seed oil (no iodine; Laboratoire Guerbet, n = 35). The neutral poppy seed oil or placebo group was used to signal possible interference from uncontrolled sources of iodine and received an oral dose of iodized oil after 44 wk. The doses of iodized oil were administered orally by using dispensers (Englass Dispensing Devices; The English Glass Co, Ltd, Leicester, UK) delivering 0.5 mL oil A (split dose), 1.0 mL oil A (single dose or neutral poppy seed oil), or 1.25 mL oil B.

Thyroid size was graded by two independent observers using the palpation technique as recommended by the World Health Organization (4). For all subjects the goiter grading was done by the same persons before and 40 wk after oral iodized oil administration. In case of doubt, the lower goiter grade was recorded. Reproducibility within and between the observers was ≈90% and 80%, respectively.

Assessment of urinary iodine excretion was based on the concentration of iodine in casual urine. Urine samples were collected during the morning under the supervision of two field assistants. At baseline, casual urine samples were collected on 2 consecutive days before iodized oil administration. During the 4th, 8th, 20th, 40th, and 44th wk after oral iodized oil administration (5), urine samples were collected on 3 consecutive days.

Urinalysis

All urine samples, preserved with thymol, were sent to the Department of Human and Animal Physiology of Wageningen Agricultural University, where they were stored at −20 °C before laboratory analysis. Iodine was assayed after alkaline digestion by using the Sandell-Kolthoff reaction (6–8) adapted for use with a microtiter plate reader (Thermomax; Molecular Devices Corporation, Palo Alto, CA) coupled to a personal computer equipped with special software (SOFTMAX, Molecular Devices Corporation, Palo Alto, CA). All samples were assayed in duplicate and when measurements differed by >10% from their mean, the analysis was repeated in duplicate.

Modeling iodine excretion over time

If, after oral dosing with iodized oil, the proportion of iodine excreted by the body remains constant, the change in iodine concentration in urine with time can be described by a simple exponential function:

$$I_T = \alpha_1 \exp(-\gamma_1 T), \quad \alpha_1 \geq 0, \quad \gamma_1 \geq 0 \qquad (\textit{model 1})$$

where I_T is urinary iodine concentration at time T, T is time (wk) after dosing, α_1 is urinary iodine concentration at T = 0, and γ_1 is a constant relating urinary iodine excretion to the amount of iodine in the body.

If there are two compartments, a second exponential term can be introduced as follows:

$$I_T = \alpha_x \exp(-\gamma_x T) + \alpha_y \exp(-\gamma_y T)$$

The description of iodine excretion may require the introduction of even further exponential terms, which increases the number of degrees of freedom. This would mean that observations at more time points are required to estimate the parameters in the equations. Thus we propose the use of a hyperbolic function that is independent of the number of compartments involved. The concentration of iodine in urine is described as follows when this function is used:

$$I_T = \alpha_2 T^{-\beta_2}, \quad \alpha_2 \geq 0, \quad \beta_2 \geq 0 \qquad (\textit{model 2})$$

where α_2 is iodine retention capacity (urinary iodine concentration at T = 0), and β_2 is the iodine elimination rate.
Given estimates for α_2 and β_2 and the value I* (urinary iodine concentration associated with iodine deficiency), a model-based duration of effectiveness T* can be calculated. In this study I* was chosen as 0.40 μmol/L, which is associated with moderate iodine deficiency (9).

Finally, to test which of models 1 and 2 more adequately describes the pattern of iodine excretion in urine over time, the following encompassing equation can be used that nests both models:

$$I_T = \alpha_{1,2} T^{-\beta_2} \exp(-\gamma_1 T), \quad \alpha_{1,2} \geq 0,$$

$$\beta_2 \geq 0; \ \gamma_1 \geq 0 \qquad (\textit{model 3})$$

If γ_1 = 0, model 3 equals model 2, whereas if β_2 = 0, model 3 equals model 1.

Statistical analysis

The urinary iodine data of subjects with at least one observation at each of the five time points of measurement were included in the analysis (n = 208). When more than one observation was available at a measurement point, the average iodine concentration was calculated. At baseline, the four groups were compared by using descriptive statistics for nutritional indicators ($\bar{x}$, SD), total goiter prevalence, and iodine status (median urinary iodine concentration and 25th and 75th percentiles).

A k-sample median test (10) was used to compare at each measurement point the urinary iodine concentrations of the single-dose oil A group (the reference group) with those of the split-dose oil A and the oil B groups. Briefly, the 95% CI around the median for the treatment groups was calculated by using ±2 SD and when a median value of the reference group did not fall within the respective 95% CI of a treatment group, the difference for that time point is reported as statistically significant ($P < 0.05$).

The mathematical functions, transformed into log-linear equivalents, were fitted to the five values for urinary iodine concentration in the three treatment groups. The parameters α_1, α_2, β_2, and γ_1 were estimated by using the maximum likelihood estimation technique (11) in which each individual's average urinary iodine concentration is considered. Measurement errors were assumed to be log-normally distributed (*see* footnote in **Table 1**). Student's t statistics were used to test for differences between the estimated coefficients β_2 and γ_1 of model 3 for the two treatment groups compared with the reference group to determine which of the two nonnested models describes the data better. Multiple-regression methods

TABLE 1
Comparison of urinary iodine patterns after treatment with oil A (single dose or split dose) or oil B (single dose) based on three models[1]

	Single-dose oil A	Single-dose oil B	Split-dose oil A
Retention rate (α, μmol/L)			
Model 1	0.613 (16.11)[2]	3.082 (7.30)[2]	1.258 (3.35)[2]
Model 2	1.372 (8.99)[2]	11.765 (4.20)[2]	0.566 (6.08)[2]
Model 3	3.873 (4.57)[2]	20.374 (2.13)[2]	1.638 (1.68)
Elimination rate (β, μmol · L^{-1} · wk^{-1})			
Model 1	—	—	—
Model 2	0.480 (12.73)[2]	0.860 (10.53)[2]	0.512 (4.99)[2]
Model 3	1.207 (8.76)[2]	1.249 (4.19)[2]	0.697 (1.85)
γ			
Model 1	0.023 (10.55)[2]	0.046 (9.31)[2]	0.027 (4.60)[2]
Model 2	—	—	—
Model 3	−0.043 (−5.48)[2]	−0.023 (−1.36)	−0.011 (−0.51)
δ[3]			
Model 1	1.091	0.990	1.055
Model 2	1.066	0.944	1.041
Model 3	1.051	0.942	1.044

[1] Model 1: $\ln I_T = \ln \alpha_1 - \gamma_1 T + \epsilon_1$, $\epsilon_1 \approx N(0,(\delta_1)^2)$; Model 2: $\ln I_T = \ln \alpha_2 - \beta_2 \ln T + \epsilon_2$, $\epsilon_2 \approx N(0, (\delta_2)^2)$; Model 3: $\ln I_T = \ln \alpha_{1,2} - \beta_2 \ln T - \gamma_1 T + \epsilon_3$, $\epsilon_3 \approx N(0_1(\delta_3)^2)$; where $\epsilon_{1,2,3}$ are log-normally distributed residuals and $\delta_{1,2,3}$ are the SDs of the regressions. Student's t values are given in parentheses. Oil A is Lipiodol UF and oil B is Oriodol, both from Laboratoire Guerbet, Aulnay-sous-Bois, Cedex, France.

[2] Significant at $P < 0.05$.

[3] Denotes the SE of the regression.

were used to compare the efficacy of oil B and the split dose of oil A with that of a single dose of oil A.

RESULTS

As shown in **Table 2,** the four groups were comparable with regard to weight, height, midupper-arm circumference, and total goiter. **Table 3** shows the median urinary iodine concentrations throughout the study. There were no significant differences in urinary iodine concentrations among the four groups at baseline. Because 50% of the entire group under study had urinary iodine concentrations <0.16 μmol/L, the population could be regarded as being severely iodine-deficient (9). For those who had received oil B, the urinary iodine concentration 4 wk after dosing was significantly higher than in those who received oil A and this difference persisted throughout the period of observation up to 44 wk ($P < 0.001$). For the groups in which the subjects had received oil A either as a single or as a split dose, a large decrease in urinary iodine concentration was observed from 4 to 8 wk. The urinary iodine concentrations in the single-dose oil A and placebo groups were slightly but not significantly increased at 40 wk compared with 20 wk. In the placebo group, urinary iodine concentrations remained low throughout the study, indicating that there was no iodine contamination.

In Table 1, the parameters obtained for the three models are presented. For both models 1 and 2, the estimates of γ and β, respectively, are significant for all three treatment groups. The SEs of the regression coefficient for model 2 are smaller than for model 1 ($\delta_2 < \delta_1$) for all three treatment groups. This finding indicates that model 2 fits the data better than does model 1. For model 3 (encompassing model), the estimates of β are positive and significant whereas the estimates of γ are all negative, violating the requirements of the model, and insignificant for oil B and the split dose of oil A, further supporting the inference that model 2 is superior to model 1. Thus, for comparison of the three treatment groups, only parameters derived from model 2 were used for subsequent statistical analysis.

A graphical representation of the data using model 2 is presented in **Figure 1.** Iodine concentration in urine remained above the cutoff concentration for moderate iodine deficiency ($I^* < 0.40$ μmol/L; 9) much longer in the oil B group ($T^* =$

TABLE 2
General characteristics at baseline of children in each of the groups[1]

	Single-dose oil A		Single-dose oil B		Split-dose oil A		Placebo[2]	
	Boys (n = 58)	Girls (n = 64)	Boys (n = 14)	Girls (n = 19)	Boys (n = 13)	Girls (n = 11)	Boys (n = 13)	Girls (n = 16)
Height (cm)	125.7 ± 5.9[3]	127.1 ± 7.9	125.2 ± 6.1	126.1 ± 6.3	126.3 ± 7.2	125.9 ± 6.3	126.1 ± 6.1	126.8 ± 6.9
Weight (kg)	24.8 ± 4.3	27.0 ± 3.9	24.7 ± 4.7	26.3 ± 5.1	23.9 ± 5.3	26.7 ± 4.9	24.5 ± 4.2	25.9 ± 5.1
MUAC (cm)[4]	17.6 ± 1.1	18.4 ± 1.3	17.2 ± 1.4	18.2 ± 1.3	17.4 ± 1.4	17.9 ± 1.6	17.7 ± 1.3	18.1 ± 1.7
Number of subjects with goiter	30	42	7	11	7	8	6	10

[1] Oil A is Lipiodol UF and oil B is Oriodol, both from Laboratoire Guerbet, Aulnay-sous-Bois, France.

[2] Poppy seed oil.

[3] $\bar{x}$ ± SD.

[4] Midupper-arm circumference.

TABLE 3
Median urinary iodine concentration in each of the groups throughout the study[1]

Time (wk)	Single-dose oil A (n = 122)	Single-dose oil B (n = 33)	Split-dose oil A (n = 24)	Placebo (n = 29)
		μmol/L		
0	0.15 (0.11, 0.23)	0.17 (0.12, 0.26)	0.16 (0.12, 0.26)	0.19 (0.10, 0.40)
4	1.07 (0.43, 2.60)	4.11[2] (2.53, 7.00)	0.54[2] (0.25, 2.23)	0.12[2] (0.08, 0.29)
8	0.37 (0.17, 0.88)	1.50[2] (0.94, 3.62)	0.24 (0.17, 0.55)	0.08[2] (0.05, 0.15)
20	0.27 (0.13, 0.54)	1.04[2] (0.41, 1.65)	0.27 (0.15, 0.50)	0.05[2] (0.04, 0.12)
40	0.32 (0.16, 0.54)	0.80[2] (0.48, 1.21)	0.30 (0.14, 0.57)	0.16 (0.07, 0.30)
44	0.23 (0.09, 0.40)	0.41[2] (0.23, 0.79)	0.14 (0.05, 0.35)	0.09 (0.03, 0.23)

[1] 25th and 75th percentiles are given in parentheses. Oil A is Lipiodol UF (490 mg I) and oil B is Oriodol (675 mg I), both from Laboratoire Guerbet, Aulnay-sous-Bois, France.
[2] Significantly different from single-dose oil A, $P < 0.05$.

55 wk) than in the two groups that received oil A. The efficacy of oral iodized oil administration did not improve when the dose of oil A was divided over 2 d.

Table 4 gives values for iodine retention (α) and elimination (β) estimated by using model 2. Both parameters were significantly higher in the oil B group than in each of the oil A groups. No differences in retention and elimination were found between the single-dose and split-dose oil A groups. Before oral iodized oil administration, the total goiter prevalence was 55.2% and 68.3% for all boys and girls, respectively. Forty weeks later, total goiter among the subjects who had received iodized oil was reduced by >80% to 12.4% and 16.7% for boys and girls, respectively. There were no differences in total goiter at 40 wk among the three treatment groups. In the placebo group total goiter increased by 7.4%.

DISCUSSION

The pattern of excretion of iodine in urine after administration of iodized oil was described by exponential functions, as is usually done in pharmacokinetics and toxicokinetics (12). The underlying theoretical assumption for using an exponential model with one compartment, as in model 1, or more compartments is that the proportion of iodine in the body that is excreted in the urine is constant over time. We have considered an alternative model (model 2) in which this is not necessarily the case and in which the time-related rate of iodine excretion after oral administration of iodized oil is described as a hyperbolic function. This enables the retention capacity and duration of effectiveness to be estimated, even though the proportion of iodine excreted may change over time. Model 2 does not allow the number of compartments or physiological processes involved in iodine elimination to be determined, but for such purposes studies under laboratory conditions possibly using radioisotopes are more appropriate than field studies of this type. However, because the number of parameters is less for the hyperbolic function than for a multiple exponential function, the number of time points required to describe urinary iodine excretion adequately is less with the hyperbolic function. In addition, model 2 allows variables to be introduced for subject-specific characteristics. These variables can be either binary, such as for sex and the presence or absence of infection, or continuous, such as for age and anthropometric indexes. For this purpose the model can be extended as follows:

$$I(T,x) = (\alpha_0 + \alpha_1 x)\, T^{-(\beta_0 + \beta_1 x)}$$

where I is urinary iodine concentration, x is subject specific characteristics, $\alpha_{0,1}$ is retention capacity, and $\beta_{0,1}$ is iodine elimination rate.

The values in Table 2 show a rapid decrease in urinary iodine from 40 to 44 wk in the oil B group and a slight but insignificant increase in both oil A groups between 20 and 40 wk. As shown by the lower residual errors, model 2 is less sensitive than model 1 to such fluctuations, which may have been due to seasonal or other causes. As shown above, model 2 allows the inclusion of variables that could describe the effect of other factors on the pattern of iodine excretion.

Until now, only limited information has been available on the efficacy of orally administered iodized oil for control of iodine deficiency. Three studies describe little or no difference between injected and orally administered iodized oil during 2 y of follow-up (13–15). Eltom et al (16) also demonstrated that a single oral dose of iodized oil type A (400 mg I as ethyl esters of iodized fatty acids) was effective for ≥2 y in schoolchildren whereas Tonglet et al (17) reported that urinary iodine concentrations in adults remained normal for 6–9 mo after oral dosing with 47 mg I and 118 mg I present in the same type of iodized oil. However, when Bautista et al (18) dosed children orally with 400 mg I as type A iodized oil, they found that urinary iodine concentrations returned to baseline concentrations after

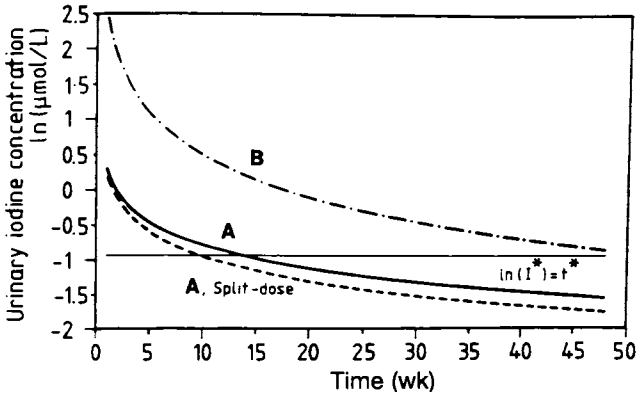

FIGURE 1. Urinary iodine excretion (in natural logarithms) after oral iodized oil administration as described by model 2. I* is the cutoff concentration of urinary iodine indicating moderate iodine deficiency (0.40 μmol/L). Oil A is Lipiodol UF and oil B is Oriodol, both from Laboratoire Guerbet, Aulnay-sous-Bois, France.

TABLE 4
Iodine retention, elimination, and duration of effectiveness based on model 2 in schoolchildren given oral iodized oil as a single dose of oil A, a single dose of oil B, or a split dose of oil A[1]

	Single-dose oil A (n = 122)	Single-dose oil B (n = 33)	Split-dose oil A (n = 24)
Retention rate (α, μmol/L)	1.372 (8.99)[2]	11.765 (4.20)[2]	1.258 (3.35)[2]
Elimination rate (β, μmol · L^{-1} · wk^{-1})	0.480 (12.73)[2]	0.860 (10.53)[2]	0.512 (4.99)[2]
Duration of effectiveness (T*, wk)	13.731 (13.66)[2]	52.510 (6.99)[2]	9.854 (4.84)[2]
Comparison with single-dose oil A			
α	—	10.939 (9.02)[2]	−0.114 (−0.29)
β	—	0.380 (4.65)[2]	0.032 (0.31)
T	—	38.779 (5.61)[2]	−3.876 (−1.90)

[1] Asymptotic Student's t values in parentheses. Oil A is Lipiodol UF and oil B is Oriodol, both from Laboratoire Guerbet, Aulnay-sous-Bois, France.
[2] Significant at $P < 0.05$.

6 mo. In the present study oil A containing 490 mg I was found to be effective for 13.7 wk, which is in line with the findings of Bautista et al (18). However, oral dosing with oil B containing 675 mg I was found to be effective for ≈55 wk, as indicated by the length of time for which the urinary iodine concentration remained above a concentration associated with moderate iodine deficiency (0.40 μmol/L). Although the subjects in the oil B group received 37% more iodine than those in the oil A group, a fourfold increase in duration of effectiveness is striking. It was our intention to provide equal amounts of iodine to both groups but although this was not achieved, it is clear that oil B was more effective than oil A. From our results it appears that the triacylglycerol preparation is to be preferred to the ethyl ester preparation. Fortunately, it is also cheaper to produce. More work comparing equal doses of iodine in different types of oil will be needed to establish without doubt which kind of iodized oil would be best for use in iodine-deficiency control programs.

Administration of the iodized oil (oil A) in two equal doses on 2 consecutive days did not improve the efficacy of the treatment. Thus, there is no advantage of splitting the dose, although repeating the dosing after a break of >2 d may prove to be more effective. It is somewhat surprising to note that Tonglet et al (17) found that single doses of small amounts of oil A (47 and 118 mg) were effective in maintaining adequate urinary iodine concentrations for 6–9 mo. On the basis of our work with children, such low doses cannot be recommended, at least not in children. In fact, most studies carried out so far have reported adequate iodine excretion in urine over a longer period of time than we found in children (13–15, 16–19). In this paper, the shortest period of protection against iodine deficiency ever reported is presented. It may be that the dosage of iodine required by children is higher because of their lower retention, more rapid excretion, or even higher requirements.

The reduction of total goiter rates in this study, after oral administration of iodized oil, to about one-fourth of those previously is in line with results reported by Watanabe et al (13) but more pronounced than those described by other authors (14, 15, 17, 18). No differences in total goiter reduction were found between the treatment groups but this may be due to the relatively small number of subjects in the different groups. Furthermore, this study did not last long enough to permit the study of goiter recurrence, which may be related to the amount of iodine stored in the thyroid after oral dosing.

The wide variation in efficacy of oral iodized oil remains. Possible explanations for some of the differences observed may be the severity of the initial iodine deficiency, goiter, and the age and sex of the subjects (20). In addition, the presence of intestinal parasites, the nutritional status, and the energy balance at the time the oral dose was given may interfere with absorption and metabolism of the iodized oil and the storage and subsequent release of iodine in the body. Further research needs to be carried out to study the impact of these factors.

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