Prevention and control of iodine deficiency: studies on the efficacy of oral iodized oil

Carina A. Furnée

Promotor: Dr. J.G.A.J Hautvast
Hoogleraar in de leer van de voeding en de voedselbereiding

Co-promotoren: Dr. Ir. F. van der Haar
Gastdocent humane voeding
Operations Manager
Program Against Micronutrient Malnutrition
Emory University School of Public Health Atlanta (USA)

C.E. West, Ph.D., D.Sc.
Universitair hoofddocent humane voeding
Visiting Professor
Emory University School of Public Health Atlanta (USA)

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Proefschrift

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in de landbouw- en milieuwetenschappen
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Stellingen

1. Voor de mens geldt dat de jodium / creatinine verhouding in urine-mosters niet geschikt is als maat voor jodium-status.
dit proefschrift

2. Gejodeerde vetzuren in oraal toe te dienen gejodeerde olie dienen aanwezig te zijn als triacylglycerolesters in plaats van als ethylesters.
dit proefschrift

3. De effectiviteit van oraal toegediende gejodeerde olie wordt nadelig beïnvloed door de aanwezigheid van darmparasieten.
dit proefschrift

4. Jodiumdeficiëntie verhindert sociaal-economische vooruitgang.

5. Nederlanders die minder dan vier boterhammen per dag eten lopen het risico struma te ontwikkelen.

6. Recent onderzoek heeft aangetoond dat de consumptie van flavonoïden het risico op coronaire hartaandoeningen verlaagt*. Een schaduwkant is echter dat dit type polyfenolen de jodiumhuishouding nadelig kan beïnvloeden.

Hertog MGL, Feskens EJM, Hollman PCH, Katan MB, Kromhout D. Flavonols, Flavones, and risk of coronary heart disease. The Lancet 1993;342:-1007-11.

7. Het verdient aanbeveling dat dag- en weekbladen die resultaten van wetenschappelijk onderzoek rapporteren niet alleen puntschattingen maar ook de daarbij behorende standaardfouten vermelden.

8. Westerse bezorgdheid over de bevolkingsdemografie in Derde Wereldlanden wordt in hoofdzaak gevoed door eigenbelang.

9. In veel gevallen is het gezegde "Wat de boer niet kent, dat eet hij niet" ook van toepassing op referees die worden gevraagd te oordelen over het al dan niet publiceerbaar zijn van artikelen in wetenschappelijke tijdschriften.

10. Het feit dat in Nederland "grootouders" in het dagelijks taalgebruik hebben plaatsgemaakt voor "opa en oma" typeert het verloren gegane respect voor ouderen.

Stellingen behorend bij het proefschrift van Carina A. Furnée, 'Prevention and control of iodine deficiency: studies on the efficacy of oral iodized oil'.

Wageningen, 14 juni 1994.

Aan mijn moeder

Abstract

Iodized oil, either injected or given orally, is the major alternative to iodized salt for controlling iodine deficiency. Oral administration has considerable advantages despite its shorter duration of effect. Little information is available on factors which influence the effect of orally administered iodized oil. In this dissertation the efficacy of oral iodized oil is studied with regard to the type of oil used, the dosage technique, intestinal parasites, nutritional status, sex and the consumption of raw cassava. The studies were carried out among Malawian school children. All results are based on iodine concentrations in casual urine samples collected at regular intervals after oral dosing with iodized oil. A model has been developed to describe the urinary iodine excretion pattern over time based on the retention and rate of elimination of iodine for subjects with different characteristics. The estimated durations of effectiveness were 13.7, 9.9 and 55.2 weeks for a single dose of iodized oil A (ethyl esters of iodized fatty acids; 490 mg iodine in 1 mL), a split-dose of oil A (2 x 245 mg iodine in 0.5 mL), and a single dose of iodized oil B (triacylglycerols; 675 mg iodine in 1.25 mL), respectively. In general, the duration of effectiveness of iodized oil A was significantly increased in subjects treated for parasitic infestations. For *Entamoeba histolytica* it appears that the absorption of oral iodized oil A is greatly disturbed as the assessed duration of effectiveness was found to be only 2 weeks for the untreated subjects. Children with a relatively large subcutaneous fat mass retained more iodine than subjects with little subcutaneous fat. For goitrous subjects both the retention and elimination of iodine were increased. A reduction in midupper-arm circumference during the study increased the duration of effect. Based on the cumulative frequency distributions, of individually assessed durations of effectiveness, oral dosing with iodized oil was less effective in girls than in boys, and in those who consumed raw cassava than those who did not.

Contents

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All of the data reported in this thesis were collected in Ntcheu District and I am

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1 Introduction

Endemic goiter and cretinism have been recognized as major world health problems for centuries. The primary etiologic factor, iodine deficiency, was identified in the 1890s although goiter was recognized in earliest history and treated by giving seaweed or burnt sponge to eat (1). Current estimates place 1,000 million people at risk of iodine deficiency of whom approximately one quarter are affected by goiter, the most noticeable feature of the disease (2). When severe, iodine deficiency can result in endemic cretinism. Less severe deficiency of iodine results in varying degrees of impairment of mental, psychomotor and physical development and increased risk of abortion and stillbirth in pregnant women. In order to cover this range of symptoms, Hetzel (3) introduced the term iodine deficiency disorders (IDD). Although the problem of IDD is worldwide, its major devastation is in developing countries even though available technology for its prevention makes it the micronutrient deficiency most amenable to quick and effective control and prevention (3-5).

The following text provides a concise outline on iodine nutrition and methods of controlling IDD. Some background information is also given on iodine deficiency in Malawi and on the studies carried out in the framework of this research project on factors effecting retention, absorption and duration of effectiveness of oral iodized oil.

Iodine nutrition

Iodine is an essential constituent of the thyroid hormones T_4 (thyroxine or 3,5,3'5'-tetraiodothyronine) and T_3 (3,5,3'-triiodothyronine). The major role of iodine arises from the importance of thyroid hormones in growth and development of human beings and animals.

The 1989 Recommended Daily Allowance (RDA) for iodine in the United States is in the range of 40-120 μg for children up to the age of 10 years and 150 μg for older persons. An additional 25 and 50 μg are recommended during pregnancy and lactation, respectively (6).

Iodine is mainly derived from food. In general, foods of animal origin, especially

marine fish, contain more iodine than those from plants. When produced on iodine-rich soils foods, both of animal and plant origin, contain more iodine than the same food from iodine-poor soils, thus a great variation is observed in the iodine content of foods. Furthermore, some of the iodine in food is lost with cooking and from what is left not all is absorbed (7). Iodine deficiency is likely to occur in populations living in areas where the soil has been depleted of its iodine content and where the people live only on locally grown food.

Goitrogens

Although lack of iodine is the most important factor in the development of goiter it has also been attributed to naturally occurring agents producing goitrogenetic and/or antithyroid effects. Antithyroid compounds can be divided into three categories according to the way in which they act on iodine metabolism (8). The first group comprises thiocyanates or thiocyanate-like compounds such as cyanogenic glycosides, and isothiocyanates. They are present in a variety of staple foods such as cassava, maize, bamboo shoots, sweet potatoes, and lima beans or they contain cyanogenic glycosides which release cyanide which is readily converted to thiocyanate in the body. Because of its chemical similarity to iodine, thiocyanate either ingested or released in the body inhibits the active process of iodine concentration in the thyroid gland, stimulates the active release of iodine from the thyroid, and may inhibit its binding in the gland. A second group of goitrogens comprises thiourea, thionamide-like goitrogens, thioglycoside, bioflavonoids, and aliphatic disulfides. These substance reduce thyroid hormone production in a complex manner by interfering with crucial steps in thyroid hormone synthesis within the thyroid gland. Isothiocyanates, mentioned in the first group of goitrogens, can react spontaneously with amino groups to form thiourea and thionamide-like substances. Bioflavonoids are important constituents of a wide variety of plants. High concentrations have been found in various staple foods in tropical countries such as millet, sorghum, beans, and ground nuts. Aliphatic disulfides are present in onions and garlic. A third group of goitrogenetic substances, including excess iodine, calcium, fluoride and lithium, has been shown to interfere with thyroid function. Bacterial contamination, pollution, malnutrition and poor socioeconomic conditions appear to enhance the action of goitrogenetic factors in iodine-deficient areas (8).

Methods of controlling iodine deficiency

There are three main approaches to increasing iodine intake: salt iodization; periodic administration of iodized oil; and fortifying water, food or condiments other than salt, with iodine. Salt iodization has proven to be an inexpensive, highly effective means of preventing iodine deficiency. Because of its cost effectiveness, salt iodization is the method of choice in most countries (9). However, it may not be a suitable means of iodine prophylaxis in areas where people consume salt only in small amounts or not at all, where salt production is a cottage industry, or where iodized salt production or importation is impractical or impossible for other reasons. In these situations, administration of iodized oil is an alternate means of iodine prophylaxis. In addition, this method is extremely useful as an interim measure during the preparatory phase prior to the introduction of general salt iodization. Both intramuscular and oral administration of iodized oil are safe, proven methods for the prevention and control of iodine deficiency. There is wide experience with using injections of iodized oil which provide effective prophylaxis for several years with some people claiming a duration of effectiveness up to 5 years. However, programs using iodized oil injections require the expense of providing materials (needles, syringes and means to ensure that they are maintained sterile) and health workers qualified to give the injections. Such programs carry the risk of improper handling of needles with the consequent possibility of spreading viral diseases such as hepatitis B and the human immunodeficiency virus (HIV). Oral administration of iodized oil, on the other hand, has been used increasingly since 1974 despite the high variability in results and its shorter duration of effectiveness (10-15). Iodized oil, either in a capsule or from a dispenser, can be given by any responsible person without any medical or paramedical training.

Iodine deficiency in Malawi

In 1983 preliminary surveys were undertaken by Thilly and Swennen to assess the public health dimension of endemic goiter and the severity of iodine deficiency disorders in each of the three administrative regions in Malawi (16). It was estimated that approximately one million people were severely iodine deficient and that two million people lived in moderate endemic iodine-deficient areas.

Since salt is not produced or processed in Malawi, non-iodized salt is imported

from South Africa. Thus, any decision to iodize salt in Malawi would require the building of new plants and warehouses. In contrast to the situation in many other countries, the distribution of iodized salt throughout the country would not be difficult. The main problem is that the total quantity of salt imported from neighbouring countries is insufficient to serve as the basis for a nationwide IDD control program. The best approach for Malawi would be to increase and to coordinate the importation of high quality salt and to take all the necessary steps to manufacture and distribute iodized salt.

In 1985 those with goiter received an iodized oil injection and a registration card. The iodized oil injection campaign was planned to be repeated every four years. However, due to the high additional costs of the injection campaign, the Ministry of Health in Malawi decided in 1989 to switch to oral administration of iodized oil capsules (each providing 200 mg iodine per person) through the primary health care system. Presently iodized oil, either for oral used or for an injection, is available at the health centres in those districts where iodine deficiency is prevalent and upon request will be given to anyone who needs iodine supplementation.

Until enough salt can be imported and iodized in Malawi, iodized oil will be needed in areas where moderate or severe iodine deficiency is prevalent.

Study objectives

The general aim of the studies described in this dissertation was to improve the effectiveness of oral administration of iodized oil in controlling iodine deficiency. The specific aims were firstly to compare the duration of effectiveness of a single oral dose of two preparations of iodized oil each containing the same dose of iodine. One preparation, initially developed for intramuscular injection, consists of ethyl esters of iodized fatty acids obtained from poppy-seed oil. It has been used in many national programs using oral iodized oil to combat iodine deficiency. The second preparation consists of triacylglycerol esters of iodized fatty acids from poppy-seed oil. It is more viscous than the ethyl ester preparation but quite suitable for oral use either in capsules or from a dispenser. The second specific aim was to study the effect of splitting the single dose of iodized oil, containing ethyl esters of iodized fatty acids, into two equal portions and giving them on two consecutive days. The fourth was to study the impact of intestinal parasites on the efficacy of orally administered iodized oil. The fifth specific aim was to

determine whether nutritional status, sex, energy balance and the consumption of raw cassava play a role in the iodine retention, the iodine elimination rate and the duration of effectiveness of orally administered iodized oil.

In addition, we considered the appropriateness of using the ratio of iodine to creatinine in urine as an indicator for iodine status as all our results are based on the concentration of iodine in urine after dosing with iodized oil.

Study design

Subjects were selected from 8, 9, and 10-y-old children attending four primary schools in Ntcheu District, Malawi, where goiter is highly prevalent (16). The schools were selected on the basis of the number of pupils attending and on their accessibility from the main highway through Ntcheu District. 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 a parent or guardian before the start of the study. As only apparently healthy subjects were considered suitable for enrolment in the study, all children were examined by a medical assistant from Ntcheu District Hospital. Children with a significantly enlarged liver or spleen, indicative of disease which may interfere with fat or protein metabolism, or with a mid upper arm circumference < 15.5 cm, indicative of protein-energy malnutrition, were excluded from the study ($n = 16$).

From the total group of apparently healthy subjects ($n = 486$) stool samples were examined microscopically for the presence of intestinal parasites. Those subjects with single intestinal parasites only ($n = 120$) were randomly allocated to receive or not to receive anti-parasitic therapy before oral administration of a single dose of iodized oil type A (ethyl esters of iodized fatty acids). All children with mixed infections ($n = 334$) received appropriate medication to treat their intestinal parasites. A group of 32 subjects had no intestinal parasites. The subjects who were either treated for their intestinal parasitic infestation or did not have intestinal parasites ($n = 366$) were randomly assigned to receive either a split dose of oil A ($n = 39$), a single dose of oil B (triacylglycerol esters of iodized fatty acids, $n = 37$), a carbohydrate rich drink 15-30 minutes prior to receiving a single dose of oil A ($n = 38$), neutral poppy-seed oil ($n = 35$) or a single dose of oil A ($n = 217$).

Initial iodine status was calculated, per subject, as the average of two iodine

concentrations measured in two casual urine samples each of which were taken on two consecutive days, collected before iodized oil administration. Further, weight, height, four skinfolds (biceps, triceps, subscapular and supra-iliaca), midupper-arm circumference measures, goiter grades and demographic information were collected, at base-line, for each subject.

For follow-up, urine samples were collected during the 4th, 8th, 20th, 40th, and 44th week after iodized oil administration. In those weeks of measurement, three casual urine samples were collected; each one of three consecutive days. The average urinary iodine concentration per subject was calculated per week of measurement and was considered to reflect the iodine status during that particular week. The anthropometric data were collected at two/three monthly intervals. Goiters were graded 10 months after oral iodized oil administration.

Outline of this dissertation

The urinary iodine-creatinine ratio for evaluating iodine status is critically appraised in Chapter 2. In Chapter 3 a new model for describing urinary iodine excretion over time is introduced and subsequently used to compare retention, elimination and duration of effectiveness of different preparations of oral iodized oil. The impact of intestinal parasites on absorption, elimination and duration of effectiveness of oral iodized oil administration is studied in Chapter 4, while in Chapter 5 the effect of nutritional status, energy balance and goiter on oral iodized oil administration are considered. In Chapter 6 methods are proposed for assessing the prevalence rate of iodine deficiency, based on urinary iodine concentrations below 0.40 μmol/L, after oral dosing with iodized oil. These methods are used to compare the prevalence rates of iodine deficiency for the two types of iodized oil, for boys and girls and for the subjects who did and did not consume raw cassava. A general discussion is provided in Chapter 7.

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2 A critical appraisal of goiter assessment and the ratio of urinary iodine to creatinine for evaluating iodine status*

Carina A. Furnée, Frits van der Haar, Clive E. West and J.G.A.J. Hautvast

Abstract

Iodine status can be evaluated by goiter assessment and measurement of urinary iodine concentration in either 24-h urine collections or in casual samples. It is often impossible to make 24-h collections. Therefore, iodine concentration in casual samples is often expressed in terms of urinary creatinine, assuming creatinine excretion to be constant between and within individuals. In this study large inter and intraindividual variations were observed in the creatinine content of casual samples ranging from 0.6 - 9.87 mmol/L. Further, the urinary iodine-creatinine ratio correlated significantly with the creatinine concentration; Spearman's rank-order correlation coefficient, $r_s = 0.39$ ($P < 0.001$). If creatinine is a suitable parameter to correct for variations in iodine excretion, no correlation would be expected. We conclude that the iodine-creatinine ratio in casual urine samples is an unsuitable indicator for evaluating iodine status in areas where large inter and intra individual variations in urinary creatinine excretion exist.

Introduction

Assessment of goiter prevalence and measurement of urinary iodine in school-aged children are the methods most commonly used to determine whether and to what extent communities are affected by lack of iodine. Results from goiter assessment in a population often provide the stimulus for further research into the severity of the iodine deficiency problem. For urinary iodine excretion, measurement in 24-h samples is considered to provide a precise quantitative measure (1) but accurate collection of 24-h urine samples in the field is often not possible (2). Thus, in the assessment of the iodine status of populations, the concentration of iodine in casual urine samples is often related excretion of creatinine is constant not only between individuals but also within individuals

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throughout the day and from day to day.

In this study, the prevalence of goiter is assessed among 8, 9, and 10-y-old school children in Ntcheu, Malawi. Further, the appropriateness of relating iodine excretion in casual urine samples to that of creatinine for determining iodine status is evaluated. The data in this study were collected in Malawi as part of a research project on factors influencing the effectiveness of oral administration of iodized oil in combatting iodine deficiency.

Subjects and methods

Study design

Subjects were selected from 8, 9, and 10-y-old school children (n = 502) attending four primary schools in Ntcheu District, Malawi, where goiter is prevalent (6). The schools were selected on the basis of having a sufficient number of pupils attending and on their accessibility as they were close to the main highway in Malawi which connects the Northern, Central and Southern Regions of the country. Informed consent for each child was obtained before the start of the study from parents or guardians. As only apparently healthy subjects were considered suitable for entry into the study, all children were examined by a medical assistant from Ntcheu District Hospital. Children with significantly enlarged liver or spleen, indicative of disease which may interfere with fat or protein metabolism, or with a midupper-arm circumference < 15.5 cm, indicative of protein-energy malnutrition, were excluded from the study (n = 16). Thyroid gland size was graded by two independent observers, using the palpation technique as recommended by the World Health Organization (WHO) (1). To maximize the accuracy of grading the thyroid size, the width of the thumb tip of the subject served as reference for normal thyroid size. As palpation provides rough measures only, the reproducibility was emphasized; in the case of an anomaly the lowest goiter grade was considered valid. Reproducibility within and between the observers was approximately 90 % and 80 %. From each subject, one casual urine sample per day was collected on each of two consecutive days (between 0730 and 1100) under the supervision of field assistants. Within 4 h of collection, approximately 1 g/L thymol was added to each sample.

The study was approved by the Ethics Committee of the National Council for Medical Research of Malawi in 1989.

Urinary analysis

Duplicate aliquots of urine were sent to the Department of Human and Animal Physiology of Wageningen Agricultural University where they were stored at -20°C prior to laboratory analysis. Iodine concentration in urine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (7-9) adapted for use with a microtitre plate reader (Thermomax, Molecular Devices Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with special software (*Softmax*, Molecular Devices Corporation). The limit of detection or sensitivity, was 0.04 μmol/L. Recoveries of iodate and iodide were 95 - 105 % and 92 - 100 %, respectively. All samples were assayed in duplicate and when measurements differed by > 10 % from their mean, the analysis was repeated in duplicate. The average of the duplicate measurements was used in the data analysis. Possible interference of the iodine assay by thiocyanate was examined by adding various amounts of potassium thiocyanate to a series of urine samples but the method was found to be insensitive to the presence of thiocyanate.

The creatinine concentration in the urine samples was determined by the Jaffé method (10) using the microtitre plate reader referred to above. The limit of detection was 0.1 mmol/L while precision was 0.2 mmol/L and 0.1 mmol/L for creatinine concentrations < 2 mmol/L and > 2 mmol/L respectively. Recovery was 100 %. All samples were assayed in triplicate and when measurements differed by > 5 % from the mean, the analysis was repeated in triplicate. The average of the three measurements was used in the data analysis.

Statistical analysis

The *Statistical Package for Social Sciences (SPSS)* was used for statistical analysis (11). Differences between days in urinary iodine excretion and creatinine were examined with Wilcoxon's signed-rank test. The non-parametric Mann-Whitney *U* test was used to examine associations between the prevalence of goiter and the concentration of iodine in urine in absolute terms and relative to urinary creatinine. The association between urinary iodine concentration, urinary creatinine concentration and the ratio of iodine to creatinine (iodine/creatinine) was examined using Spearman's rank-order correlation coefficient (r_s).

Results

Sixteen children with a mid upper arm circumference < 15.5 cm were excluded from the study and two children died of unknown causes before the study was completed. No children were found with enlargement of liver or spleen. The prevalence of total goiter in the study population was 56 % and 69 % for boys and girls respectively. From 396 children, two casual urine samples were collected on two consecutive days and data have been presented for these children.

Table 1 shows the variation in iodine concentration, creatinine concentration and iodine/creatinine in the casual urine samples collected from the school children (n = 396). Large inter-individual variation was observed both in urinary iodine and creatinine excretion, ranging from 0 - 0.19 μmol/L and 0.60 - 9.77 mmol/L respectively. The median intra-individual CVs for urinary iodine, urinary creatinine, and urinary iodine/creatinine were 39.2 %, 48.2 %, and 50.7 %, respectively.

No statistically significant correlation was found between urinary iodine and urinary creatinine for the populations as a whole but for iodine concentrations < 0.40 μmol/L, the correlation was statistically significant (r_s = 0.49, P < 0.001). Furthermore, iodine concentration relative to that of creatinine in the whole population was significantly related to urinary creatinine concentration (r_s = 0.39, p < 0.001). Estimates of the severity of iodine deficiency based on the concentration of iodine in urine and on iodine-creatinine do not coincide (**Table 2**). No correlation was found between the size of the thyroid, as determined by either urinary iodine concentration or

Table 1 Iodine concentration, creatinine concentration and the ratio of iodine to creatinine in casual urine samples from schoolchildren in Ntcheu District, Malawi[1]

	Iodine	Creatinine	Iodine/creatinine
	μmol/L*	mmol/L*	
Day 1	0.20 (0.05 - 1.86)	3.70 (0.92 - 9.77)	52.1 (17.6 - 315.4)
Day 2	0.09 (0.02 - 0.44)[2]	2.50 (0.60 - 7.00)[3]	37.5 (11.1 - 162.5)[4]
Average of both days	0.15 (0.06 - 0.75)	3.15 (1.35 - 7.19)	44.8 (17.8 - 211.2)

[1] Values are medians; 5th and 95th percentile in parenthesis. n = 396.

[2,3,4] Significantly different from day 1 value (Wilcoxon's signed-rank test for matched pairs) [2]P < 0.001 (Z = -10.7), [3]P < 0.001 (Z = -6.79), [4]P < 0.001 (Z = -8.13).

Table 2 Classification of the severity of iodine deficiency among school children by urinary iodine concentration and the ratio of iodine to creatinine in Ntcheu District, Malawi[1]

Categories of iodine deficiency	Iodine/creatinine[2]		Iodine concentration[3]	
None	> 89.1	(16.9)	> 0.79	(4.3)
Mild	44.6 - 89.1	(49.9)	0.40 - 0.79	(6.0)
Moderate	22.3 - 44.6	(36.1)	0.16 - 0.40	(38.4)
Severe	< 22.3	(7.0)	< 0.16	(51.3)

[1] n = 396. Percent of subjects in parentheses.
[2] Based on the WHO indicators (1).
[3] Based on the WHO/UNICEF/ICCIDD (International Council for Control of Iodine Deficiency) indicators (unpublished observations, 1993).

Table 3 Prevalence of goiter by stage, and average urinary iodine concentration among school children by sex and age, in Ntcheu District, Malawi

	Boys			Girls			
	0	1A	1B	0	1A	1B	2
Number of goitrous subjects							
8 y	5	8	0	4	15	1	0
9 y	40	35	12	26	46	9	0
10 y	42	40	15	32	44	22	1
Total	87	83	27	62	105	32	1
Average iodine concentration (μmol/L)[1]							
8 y	0.14	0.15	--	0.21	0.11	0.41	--
9 y	0.23	0.14	0.12	0.15	0.16	0.11	0.10
10 y	0.15	0.20	0.20	0.17	0.17	0.20	0.19
Total	0.16	0.17	0.14	0.16	0.16	0.16	0.17

[1] Based on mean iodine concentration of day 1 and 2 per subject.

iodine concentration expressed in terms of creatinine using the non-parametric Mann-Whitney *U* test. The number of goitrous subjects was higher among girls than in boys as can be seen in **Table 3**. However, there was no difference between the sexes in urinary iodine concentration expressed in absolute terms.

Discussion

In this study we assessed a prevalence of total goiter among 8, 9, and 10-y-old children and found percentages of approximately 56 and 69 % for boys and girls, respectively. The median iodine concentration, average of two consecutive days, confirms the presumption, based on the goiter assessment, of a significant health problem in Ntcheu District as a result of iodine deficiency. We believe that a goiter survey is a good measure for assessing iodine deficiency in a population. School children can be regarded as a healthy sub-sample of a population and they are conveniently accessible. A goiter prevalence of 5 %, or more among school aged children indicates that iodine deficiency is a public health problem which requires attention. The cut-off of 5 % allows some margin for the inaccuracy of goiter assessment and causes for goiter other than iodine deficiency (13).

No apparent differences were found for absolute urinary iodine concentration between the sexes in the three age groups. However, the prevalence of goiter was highest among the girls which indicate that girls are at a higher risk for developing goiter than boys.

Daily urinary excretion of iodine closely reflects iodine intake, and has been used as a measure of iodine status in many large-scale nutrition surveys (11). Because it is often impossible to collect 24-h samples of urine, urinary iodine concentration is often expressed in terms of urinary creatinine in order to correct for variations in urinary output. However, iodine/creatinine correlated highly with urinary creatinine. If relating iodine concentration to that of creatinine excretion is appropriate, its correlation coefficient should approach zero. Thus our results demonstrate that expressing urinary iodine concentration in terms of urinary creatinine concentration is not appropriate. These findings are consistent with those of Greenblatt et al (5) and Bourdoux et al (2,12).

Despite variations in urine output, urinary iodine concentration remains a valuable and useful parameter for assessing current iodine status in a population, especially when

possibilities for the assessment of blood parameters are absent. As it is often not possible to follow large groups of subjects for a long time when measurements are complicated, time consuming or expensive we suggest that fewer subjects can be used provided that corrections are made for the day-to-day variation in urinary output. This can be achieved by repeated sampling per subject thus retaining a high level of precision and power. Therefore we suggest that iodine concentration should be measured in two or more casual urine samples from the same individuals taken on consecutive days. Two urine samples from a approximately 40 randomly selected school children would provide a adequate quantitative measure of the current status of iodine intake with a power of 0.8 and 95 % confidence. When three urine samples are taken, the population size required to reach the same power and confidence can be reduced to 21 subjects. WHO/UNICEF/ICCIDD has recently suggested modified cut-off points to assess the severity of iodine deficiency by measuring the iodine concentration in casual urine samples (13). Using their criteria, 95.7 % of the children in this study would be regarded as deficient (urinary iodine concentration < 0.79 μmol/L) of whom 51.3 % were classified as severely deficient (urinary iodine concentration < 0.16 μmol/L).

As the mean and median urinary iodine concentrations do not coincide, indicating that the distribution is not symmetric, it is appropriate to evaluate iodine deficiency at the population level in terms of the median or the log of the mean iodine concentration in urine. It is not appropriate to use the mean without it being log transformed as the extreme values dominate its value. The median urinary iodine excretion level was 0.16 μmol/L which, in terms of the criteria laid down by WHO/UNICEF/ICCIDD (13) indicates that Ntcheu District is severely iodine deficient.

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3 New model for describing urinary iodine excretion: its use for comparing different oral preparations of iodized oil*

Carina A. Furnée, Gerard A. Pfann, Clive E. West, Frits van der Haar, Daan van der Heide and Joseph G.A.J. Hautvast

Abstract

Urinary iodine concentration, after oral dosing with iodized oil, reflects the mutual effects of the physiological mechanisms involved in the retention and elimination of iodine. A model has been used to describe the urinary iodine excretion over time. As efficacy is determined by retention and elimination a model-based duration of effectiveness can be assessed. They were estimated to be 13.7, 9.9 and 55.2 weeks for a single dose of iodized oil A (ethyl esters of iodized fatty acids; 490 mg iodine), a split-dose of oil A (2 x 245 mg iodine), and a single dose of iodized oil B (triacylglycerol esters of fatty acids; 675 mg iodine), respectively. Compared to oil A, the iodine retention and elimination of oil B were significantly increased. Dividing the dose of oil A into two equal amounts given on consecutive days did not improve efficacy.

Introduction

Iodine deficiency has been a major world health problem for centuries (1). Although salt iodisation is the usual control method of choice, dosing with iodized oil is often used before salt iodisation 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 a number of iodized oil preparations based on poppy-seed oil for both injections and oral use. One type of oil (oil A), initially developed for intra-muscular administration, is a mixture of ethyl esters of iodized fatty acids (separated fatty acids which have been iodized) while in an other type of oil (oil B), the iodized fatty acids are present as triacylglycerol esters (three iodized

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fatty acids esterified with glycerol). The latter, which is cheaper to produce, is more viscous but quite suitable for oral use both as capsules and from a dispenser. Since 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 two consecutive days (split dose) on oral iodine excretion was also examined.

In order to compare the different treatments, we have first examined the empirical performance of two statistical models to describe the urinary iodine excretion pattern through time after oral dosing with iodized oil. The first model is a single exponential equation which can be easily translated into a 1 compartment model, in which the iodine elimination rate remains constant over time. If the rate of iodine elimination after oral dosing with iodized oil changes over time, it may be expected that more than one mechanism is involved in the process of iodine decay. In this case, the iodine concentration in the urine always reflects the grand total of the mutual effects of the mechanisms involved in iodine elimination. Such an elimination process can be described using a hyperbolic function of urinary iodine excretion over time. An encompassing equation nesting both the single exponential and the hyperbolic model was used to test which of the two models most accurately described the urinary iodine excretion pattern after oral iodized oil administration. That model is used for the subsequent analysis to compare the different treatment groups used in this study.

Subjects and methods

Subjects

Apparently healthy 8, 9, and 10-y-old school children, treated for mixed intestinal parasitic infestations, from four schools in Ntcheu District, Malawi, were selected to participate in the study (n = 326). 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.

From the total group of subjects three small groups of 37, 39 and 35 subjects were

randomly selected, by age and sex, to received either a single dose of 1.25 mL oil B (Oriodol, 540 mg iodine in 1 mL, Laboratoire Guerbet, Aulnay-sous-Bois CEDEX, France), 0.5 mL oil A (Lipiodol UF, 490 mg iodine in 1 mL, Laboratoire Guerbet) on each of two consecutive days (2 x 245 mg iodine), or 1 mL of neutral poppy seed oil (no iodine, Laboratoire Guerbet). All other subjects (n = 217) served as controls and received a single dose of 1 mL oil A (490 mg iodine). The placebo group (neutral poppy seed oil) was use to signal possible interference of uncontrolled sources of iodine and received iodized oil after 44 weeks. The doses of iodized oil were administered orally using dispensers (Englass Dispensing Devices, The English Glass Co. Ltd., Leicester, England) 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 (4,5). For all subjects the goiter grading was done by the same persons, before and 10 months after oral iodized oil administration. In case of doubt the lowest goiter grade was recorded. Reproducibility within and between the observers was approximately 90 % and 80 %.

Measurement of urinary iodine excretion was based on the concentration of iodine in casual urine samples. The samples were collected during the morning under the supervision of two field assistants. At baseline, iodine status, per subject, was determined from the average iodine concentration in two casual urine samples each collected on two consecutive days before iodized oil administration. Subsequent values were based on the average of the iodine concentration in three urine samples each collected on consecutive days during the 4th, 8th, 20th, 40th and 44th week after oral iodized oil administration (5).

Urinary analysis

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 prior to laboratory analysis. Iodine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (6-8) adapted for use with a micro titre plate reader (Thermomax, Molecular Devices Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with special software (*Softmax*, Molecular Devices Corporation). All

samples were assayed in duplicate and when measurements differed by < 10% from their mean, the analysis was repeated in duplicate.

Modelling iodine excretion over time

If iodine, after oral dosing with iodized oil, is excreted from the body in the urine at a constant rate its relationship with time can be described in an exponential one-compartment model (9):

$$I_T = \alpha_1 \exp(-\gamma_1 T),\ \alpha_1 \geq 0,\ \gamma_1 \geq 0; \qquad \text{(Model 1)}$$

where I_T = urinary iodine concentration at time T;

T = time (w) after dosing;

α_1 = urinary iodine concentration at T = 0;

γ_1 = constant parameter relating urinary iodine excretion to the amount of iodine in the body.

An exponential two-compartment model, which can be used when two distinct linear phases determine iodine decay, yields the following expression:

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

In general, however, the number of phases of iodine elimination is unknown a priori, while the aggregate effects of multiple mechanisms are observed as the concentration of iodine in the urine through time. We propose a multi-phase iodine elimination model to describe the relationship between iodine excretion and time without fixing the number of excretion mechanisms involved in advance. This multi-phase model of the process of iodine decay is as follows:

$$I_T = \alpha_2 T^{-\beta 2},\ \alpha_2 \geq 0,\ \beta_2 \geq 0; \qquad \text{(Model 2)}$$

where I_T = urinary iodine concentration at time t;

T = time (w) after dosing;

α_2 = retention capacity;

β_2 = iodine elimination rate.

Given estimates for α_2 and β_2 and the value of I^* (urinary iodine concentration values associated with iodine deficiency (unpublished observations; UNICEF/WHO/ICCIDD 1993), the model-based duration of effect, T^*, can be calculated. In this study I^* was

chosen to be 0.40 μmol/L which is associated with moderate iodine deficiency.

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

$$I_T = \alpha_{1,2}\, T^{-\beta_2} \exp(-\gamma_1 T),\ \alpha_{1,2} \geq 0,\ \beta_2 \geq 0;\ \gamma \geq 0; \qquad \text{(Model 3)}$$

If $\gamma_1 = 0$, Model 3 equals Model 2; whereas if $\beta_2 = 0$, Model 3 equals Model 1.

Statistical analysis

The urinary iodine concentrations of those subjects with at least one observation at each of the five points of measurements were considered for statistical analysis (n = 208). For each subject with more than one observation per week of measurement, the average iodine concentration was calculated.

At base-line the control group, the two treatment groups and the placebo group were compared using descriptive statistics with regard to nutritional indicators (mean, SD), total goiter and iodine status (median urinary iodine concentration and 25th and 75th percentile).

The median urinary iodine concentration per measurement point in the two treatment groups (split-dose oil A and oil B) was compared to that in the control group (oil A) using the k-sample median test (10). In short, a 95 % CI was estimated around the median, per treatment group, using its $\pm$ 2 SD. If the median value of the control group did not fall within the interval of the treatment group the difference is reported statistically significant ($P < 0.05$).

The models, transformed into log-linear equivalents, were fitting to the five measuring points of urinary iodine concentration in the control group and the two treatment groups. The parameter α_1, α_2, β_2, and γ_1 were estimated using the maximum likelihood estimation technique (11) in which each individual average urinary iodine concentration is considered. Measurement errors were assumed to be log-normally distributed (see footnote of Table 2). Student's t-statistics were used to test for differences between the estimated coefficients β_2 and γ_1 of Model 3 for the oil B and oil A split-dose group versus the controls (oil A single dose) to infer which of the two non-nested models

Table 1 General characteristics, at base-line, of the 8, 9 and 10-y-old boys and girls in the control group, the two treatment groups and the placebo group, Ntcheu, Malawi[1,2]

	Single dose oil A		Single dose oil B		Split-dose oil A		Neutral poppy-seed oil	
	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)	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[3], cm	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)
Total goiter, n	30	42	7	11	7	8	6	10

[1] Mean (SD).
[2] Oil A is Lipiodol UF; oil B is Oriodol.
[3] Midupper-arm circumference (cm).

describes the data better. Multiple regression methods were used to test for difference in the efficacy of iodized oil in the control group and the two treatment groups.

Results

A description of the 8, 9, and 10-y-old boys and girls in the control group, the two treatment groups and the placebo group, with regard to weight, height, mid upper arm circumference and total goiter, is given in Table 1. The 4 groups were comparable.

In Table 2, the descriptive statistics on urinary iodine at base-line (w = 0) and after dosing (w = 4, 8, 20, 40, and 44) are presented. There was no difference in urinary iodine concentration between the 4 groups at baseline. For those who had received 1.25 mL oil B (675 mg iodine), the urinary iodine concentration 4 w after dosing was significantly higher than in the other groups receiving iodized oil and this difference persisted throughout the period of observation up to 44 w ($P < 0.001$). For both groups in which the subjects had received 1 mL oil A either as a single dose (490 mg iodine) or

Table 2 Descriptive statistics on urinary iodine concentrations (μmol/L) for the control group, the two treatment groups and the placebo group[1-3]

Time w	Oil A 1 x 1.0 mL $n = 122$	Oil B 1 x 1.25 mL $n = 33$	Oil A 2 x 0.5 mL $n = 24$	Poppy-seed oil 1 x 1.0 mL $n = 29$
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] 25 percentile and 75 percentile are given in parentheses.
[2] $P < 0.05$ comparing other columns to the first at each measuring point.
[3] Oil A is Lipiodol UF, oil B is Oriodol.

a split dose (2 x 245 mg iodine) a large decrease in urinary iodine concentration was observed from week 4 to 8.

The urinary iodine concentration in the control and placebo group increase slightly during week 40 (not significant) as compared to week 20. In the placebo group urinary iodine remained low throughout the study indicating that there was no iodine contamination.

In **Table 3**, the parameters values obtained from the three models are presented. For both Model 1 and Model 2, the estimates of β_2 and γ_1 are significant. For all three treatment groups the standard errors of the regression coefficient for Model 2 are smaller than for Model 1 ($\delta_2 < \delta_1$). This implies that Model 2 fits the data better than Model 1. For Model 3 (encompassing model), the estimates of β_2 are positive and significant whereas the estimates of γ_1 are all negative violating the requirements of the model, and insignificant for oil B and the split-dose of oil A, further supporting the conclusion that Model 2 is superior to Model 1. Thus, for comparison of iodine retention and elimination and the duration of effectiveness between the three treatment groups only the urinary iodine excretion pattern as described by Model 2 is 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 level regarded as moderately iodine deficient, $I^* < 0.40$ μmol/L (9), much longer in the oil B group ($T^* = 55$ w) than in the oil A groups (see also **Table 4**). Dividing the dose of oil A over two days did not improve the efficacy of oral iodized oil administration.

In **Table 4**, the values for iodine retention (α_2) and elimination (β_2) assessed using Model 2 are presented. Both parameters are significantly higher in the oil B group than in the oil A group. No differences in retention and elimination were found between the single 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. Ten months 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 between the control group and the 2 treatment groups. In the placebo group total goiter increased with 7.4 %.

Table 3 Comparison of urinary iodine patterns after treatment with oil A (single dose or split-dose) or oil B (single dose) based on three models[1-3]

		α	β	γ	δ[4]
1X oil A					
	Model 1	0.613 (16.11)	--	0.023 (10.55)	1.091
	Model 2	1.372 (8.99)	0.480 (12.73)	--	1.066
	Model 3	3.873 (4.57)	1.207 (8.76)	-0.043 (-5.48)	1.051
1 X oil B					
	Model 1	3.082 (7.30)	--	0.046 (9.31)	0.990
	Model 2	11.765 (4.20)	0.860 (10.53)	--	0.944
	Model 3	20.374 (2.13)	1.249 (4.19)	-0.023 (-1.36)	0.942
2 X oil A					
	Model 1	1.258 (3.35)	--	0.027 (4.60)	1.055
	Model 2	0.566 (6.08)	0.512 (4.99)	--	1.041
	Model 3	1.638 (1.68)	0.697 (1.85)	-0.011 (-0.51)	1.044

[1] Model 1: $\ln I_T = \ln \alpha_1 - \gamma_1 T + \epsilon_1$, $\epsilon_1 \sim N(0,(\delta_1)^2)$;
Model 2: $\ln I_T = \ln \alpha_2 - \beta_2 \ln T + \epsilon_2$, $\epsilon_2 \sim N(0, (\delta_2)^2)$;
Model 3: $\ln I_T = \ln \alpha_{1,2} - \beta_2 \ln T - \gamma_1 T + \epsilon_3$, $\epsilon_3 \sim N(0,(\delta_3)^2)$; where $\epsilon_{1,2,3}$ are log-normally distributed residuals and $\delta_{1,2,3}$ are the standard deviations of the regressions.

[2] Students t-values are given in parentheses.

[3] Oil A is Lipiodol UF; oil B is Oriodol.

[4] δ denotes the standard error of the regression.

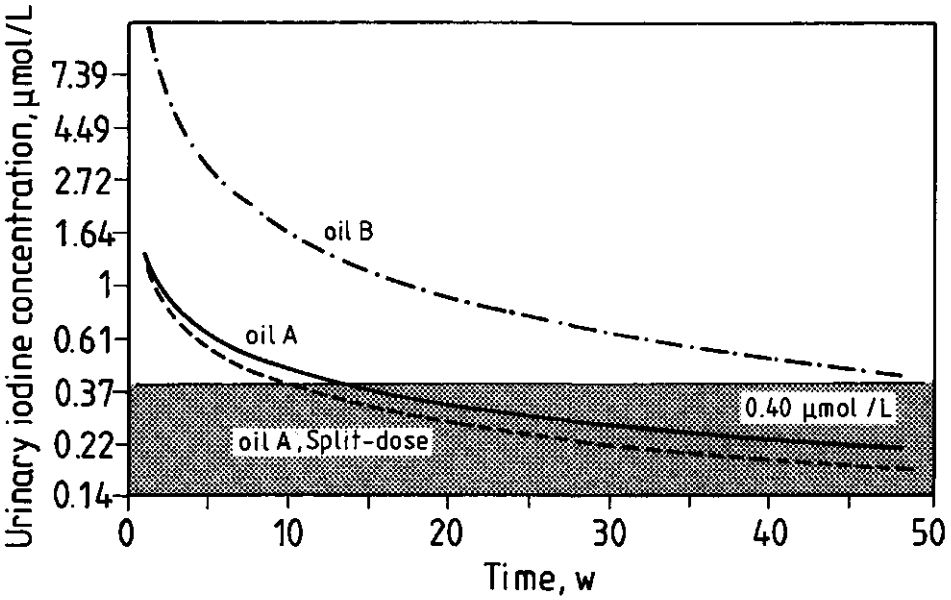
Table 4 Iodine retention, elimination and the model-based duration of effectiveness after oral administration of iodized oil for school children given either a single dose of oil A, a single dose of oil B or a split dose of oil A[1,2]

	1 X 1 mL oil A (n = 122)	1 X 1 mL oil B (n = 33)	2 X 0.5 mL oil A (n = 24)
Retention (α_2)	1.372 (9.00)	11.765 (4.20)	1.258 (3.35)
Elimination (β_2)	0.480 (12.73)	0.860 (10.53)	0.512 (4.99)
Duration of effectiveness (T^*)	13.731 (13.66)	52.510 (6.99)	9.854 (4.84)
Test: $\alpha_{treatment} = \alpha_{control}$		10.939 (9.02)	-0.114 (-0.29)
Test: $\beta_{treatment} = \beta_{control}$		0.380 (4.65)	0.032 (0.31)
Test: $T^*_{treatment} = T^*_{control}$		38.779 (5.61)	-3.876 (-1.90)

[1] Asymptotic Student's t-values are given in parentheses.

[2] Oil A is Lipiodol UF; oil B is Oriodol.

Figure 1 Urinary iodine excretion (in natural logarithms) after oral iodized oil administration as described by Model 2[1,2]



[1] For description of Model 2, see text. I^* is the level of urinary iodine concentration indicating moderate iodine deficiency (0.40 µmol/L).

[2] Oil A is Lipiodol UF; oil B is Oriodol.

Discussion and conclusions

The basic principles for approaching the data in this study with exponential compartment models have been derived from pharmacokinetics and toxicokinetics (12). The underlying theoretical assumption for using the theoretical exponential one-compartment model (Model 1) is that the proportion of iodine in the body which is excreted in the urine is constant over time. Alternatively, we considered a model (Model 2) in which the iodine excretion rate varies through time, without making a prior assumption about the number of processes involved in the elimination of iodine. This model can be described as a hyperbolic relation between the rate of iodine excretion and time passed after oral administration of iodized oil. It enables us to determine the retention capacity and the duration of effectiveness, even though the excretion rate may

change through time. Given the number of observations in this study, Model 2 does not allow the unravelling of the number physiological processes involved in iodine elimination. Studies for such purposes would best be done under laboratory conditions possibly using radioisotopes. However, an additional advantage of Model 2 is that we can draw conclusions from its parameters by introducing variables for subject-specific characteristics including binary variables, such as sex and presence/absence of infection and continuous variables, such as age and anthropometric parameters. 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 = urinary iodine concentration;

T = time (w) after dosing;

x = subject specific characteristics

$\alpha_{0,1}$ = retention capacity;

$\beta_{0,1}$ = iodine elimination rate.

The values in Table 2 show a rapid decrease from week 40 to 44 in oil B and a slight increase in oil A from week 20 to 40. Model 2, as used in this study, does not account for the ups and downs in iodine excretion which may be induced by seasonal characteristics. As shown above, the model is suitable for inclusion of explanatory variables which will facilitate further research into factors which influence the efficacy of oral iodized oil.

So far no information is available on the effectiveness of orally administered iodized oil for control of iodine deficiency. Four studies describe little or no difference between injected and orally administered iodized oil during a period of 2 years follow up (13-15). However, when Bautista et al dosed children orally with iodized oil type A (containing 400 mg iodine), they found that urinary iodine levels returned to base-line levels after 6 months (16). Eltom et al demonstrated a single oral dose of 2 capsules containing iodized type A oil (400 mg iodine, ethyl esters of iodized fatty acids) to be effective for at least two years in school children (17) while Tonglet et al (18) reported that urinary iodine concentrations in adults remained normal for 6-9 months after oral dosing with 0.1 (47 mg iodine) and 0.25 mL (118 mg iodine) of the same type of iodized oil. In this study, 1 mL oil A (490 mg iodine) was found to be effective for 13.7 w which

is in line with the findings of Bautista et al (16). However, oral dosing with the same dose of 675 mg iodine in 1.25 mL oil B was found to be effective for approximately 55 weeks. Although the subjects in the oil B group had received 27 % more iodine than in the oil A group a four-fold increase in duration of effectiveness is striking. It was intended to provide equal doses of iodine in all groups. Although this was not achieved, it is clear that oil B is more effective than oil A. Thus the triacylglycerol ester preparation is to be preferred to the ethyl ester preparation. Fortunately it is also cheaper.

In studies in China, both iodized soybean and walnut oil (triacylglycerol esters) have been used orally (14,15). Although no data are available for urinary iodide excretion in the first six months, data from six months to three or four years after oral dosing suggest that the iodized soybean oil provides protection for a longer period of time than iodized walnut oil. Assuming that the preparations are comparable in properties such as iodine content (bound and free), the difference could perhaps be attributed to the number of iodine atoms in each triacylglycerol molecule or fatty acid moiety. Since soybean oil contains less polyunsaturated fatty acids (ca 60 % linoleic and linolenic acid) than walnut oil (ca 75 % linoleic and linolenic acid), it would contain less iodine per triacylglycerol molecule than walnut oil. This may lead to a greater retention of iodine from the iodized soy bean oil compared with the walnut oil which is in line with the results of the work of Van der Heide et al (3) in both humans and rats. They found that iodized olive oil (ca 10 % linoleic acid) was more effective than iodized ethyl esters of fatty acids from poppy seed oil (oil A, ca 60 % linoleic acid). However, in these experiments they compared preparations differing not only in fatty acid composition but also differing in contains of ethyl esters and glyceryl esters. In the present study using poppy seed oil-based preparations, the triacylglycerol preparation (oil B) was more effective than the mixture of ethyl esters of iodized fatty acids (oil A).

Administration of the iodized oil (oil A) in two equal doses on two 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 more than 2 days may prove to be effective. It is somewhat surprising to note that Tonglet et al (18) found that single doses of small amounts of oil A (47 mg and 118 mg) were effective in maintaining adequate urinary iodine levels for 6 to 9 months. Based on our work with children, such low doses cannot be recommended at least in children. In fact, most studies carried out so far (13-

15, 16-19) have reported adequate levels of iodine excretion in urine over a longer period of time than we found in children. In this paper, the shortest period of protection against iodine deficiency ever reported is presented. It may be that the dosage required by children is higher because of 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 quarter of those previously is in line with results reported by Watanabe et al (13) but more pronounced than that described by other authors (14-17). No differences in total goiter reduction was 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 explained by the severity of the initial iodine deficiency, goiter and by 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 of giving the oral dose 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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4 The impact of intestinal parasites on the efficacy of oral iodized oil in controlling iodine deficiency

Carina A. Furnée, Clive E. West, Frits van der Haar, and Joseph G.A.J Hautvast

Abstract

Subjects with a single parasitic infestation, *Entamoeba histolytica, Ascaris lumbricoides*, or hookworm were randomly allocated, per parasite type, to receive (treated) or not receive (untreated) anti-parasitic therapy prior to an oral dose of iodized oil (ethyl esters of iodized fatty acids). Urinary iodine concentrations were measured at regular intervals after the intervention to evaluate the duration of effectiveness. For the untreated subjects in general the duration of effectiveness was 9.2 weeks shorter ($P < 0.001$) than for their treated counterparts (16.8 weeks). Treatment of subjects infested with *Entamoeba histolytica* increased the duration of effectiveness from 2 to 21 weeks.

Introduction

Iodine deficiency exists in areas where the soil has been depleted of iodine and the diet of the population predominantly consists of locally grown foods (1). Salt iodization is an inexpensive, highly effective means for preventing iodine deficiency (2). However, difficulties and delays in achieving effective salt iodization in areas where iodine deficiency requires immediate attention, demand other measures. The major alternative to salt iodization is iodized oil given either by injections or orally (3). There is wide experience with injecting iodized oil which provides effective prophylaxis for periods possibly up to five years (4). Administration of iodized oil orally has practical advantages over injections and has been used increasingly since 1974. However, the results are highly variable and its duration of effectiveness is shorter ranging from 6 months to two years (5-10). Factors which may influence the absorption and retention of oral iodized oil have so far received little attention. This study compares the efficacy of oral dosing with iodized oil in subjects who have or have not received anti-parasitic medication to treat either *Entamoeba histolytica, Ascaris lumbricoides* or hookworm prior to receiving

iodized oil orally.

Subjects and methods

Subjects

Subjects were selected from 8, 9, and 10-y-old school children (n = 502) attending four primary schools in Ntcheu District, Malawi, where goiter is highly prevalent. The schools were selected on the basis of having a sufficient number of pupils attending and on their accessibility as they were close to the main highway in Malawi which connects the Northern, Central and Southern Regions of the country. The study was approved by the Ethics Committee of the National Council for Medical Research of Malawi in 1989. Informed consent was obtained from parents or guardians of each child before the onset of the study. As only apparently healthy subjects were considered suitable for entry into the study, all children were examined by a medical assistant from Ntcheu District Hospital. Children with significantly enlarged liver or spleen, indicative of disease which may interfere with fat or protein metabolism, or with a midupper-arm circumference below 15.5 cm, indicative of protein-energy malnutrition, were excluded from the study (n = 16).

Intestinal parasites

From the total group of apparently healthy subjects two fecal specimens each taken on two consecutive days were collected and microscopically examined immediately, in duplicate by the Kato thick smear technique using approximately 50 mg of stool to detect parasite ova (11,12). Eosine dye (2% eosin in saline) and potassium iodo-iodide colouring (3 g potassium iodide and 2 g iodine in 100 mL water) was used for detection and determination of flagellates and amoebae (12). Egg counts were recorded for *Ascaris lumbricoides* and hookworm and a qualitative record was kept for all other parasites and different species of amoeba and specifically for *Entamoeba histolytica* (10 X objective; cysts 10-15 μm in diameter, round, 2-4 nuclei). A subject was classified as a cyst passer if *Entamoeba histolytica* cysts were detected on two direct smear slides. All stool samples were examined by an experienced microscopist of the Bilharzia Research Institute, Lilongwe, Malawi. One in every ten stool samples was evaluated by a parasitologist of the Department of Intestinal Parasitology of Kamuzu Central Hospital, Lilongwe, Malawi,

to ensure correct diagnosis. The laboratory tests were carried out in a field laboratory with limited equipment.

Study design

This study is one of a number of studies on factors which may affect retention, elimination and effectiveness of oral iodized oil administration for control and prevention of iodine deficiency. The effect of treating intestinal parasites on the effectiveness of oral iodized oil in general was studied in a randomized double blind intervention study. In addition, the effect of treating *Ascaris lumbricoides*, hookworm and *Entamoeba histolytica* infestations was studied specifically because of their prevalence within the study population.

Following examination of the stool samples in the total group of children (n = 502), those classified as *Entamoeba histolytica* cyst passers (n = 34) or infested with *Ascaris lumbricoides* (n = 33) or hookworm (n = 53) only, were randomly allocated, per parasite group, either to receive (treated) or not to receive (untreated) either the broad spectrum anti-helminth albendazole (Alzental, Shin Poong Pharm. Co. Ltd., Seoul, South Korea) or the broad spectrum antimicrobial agent metronidazole (Metronidazol, Sterling Products International Ltd., Blantyre, Malawi) before oral iodized oil administration. The choice of using albendazole and metronidazole for treating the respective parasitic infections was made in consultation with Ntcheu District Hospital who supplied the medication. Subjects without intestinal parasites (n = 30) or with mixed infestations (n = 336) were not considered in this study.

Ascaris lumbricoides was treated with a single dose of 400 mg albendazole. Hookworm cases were given a single dose of 400 mg albendazole daily for 3 consecutive days. *Entamoeba histolytica* cyst passers received 200 mg metronidazole 3 times a day for 5 consecutive days. Per day, the first dose was taken under the supervision of a field assistant, the second dose was taken before leaving school under the supervision of the class teacher. For the third dose the subjects were given instructions to take the dose before going to bed.

Two weeks after the onset of anti-parasitic therapy the subjects received 1 mL, 490 mg iodine, Lipiodol Ultra Fluide (Laboratoire Guerbet, Aulnay-sous-Bois Cedex, France) orally using a dispenser (Englass Dispensing Devices, The English Glass Co.

Ltd., Leicester, England). The type of iodized oil used in this study comprised of a mixture of iodized ethyl esters. Subjects infested by less common parasites and those infested by two or more intestinal parasites received appropriate anti-parasitic treatment, as suggested by Ntcheu Hospital, but were not enroled in this study. One week after oral iodized oil administration two stool samples per treated subject were collected and examined in duplicate, as described above, to establish the cure rates of metronidazole and albendazole.

Measurement of urinary iodine excretion was based on the concentration of iodine in casual urine samples as it was not possible to collect 24-h samples. Samples were collected between 0730 and 1100 at school under the supervision of field assistants. The iodine status of the subjects at baseline was determined from the average iodine concentration in urine samples collected on two consecutive days before iodized oil administration. Subsequent values were based on the average iodine concentration in casual urine samples collected on three consecutive days, per subject, during the 4th, 8th, 20th, 40th and 44th week after oral iodized oil administration (13).

Urinary analysis

The urine samples, preserved with approximately 1 g thymol, were sent to the Department of Human and Animal Physiology of Wageningen Agricultural University where they were stored at -20° C prior to laboratory analysis. Iodine concentration in urine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (14-16) adapted for use with a microtitre plate reader (Thermomax, Molecular Devices Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with special software (*Softmax*, Molecular Devices Corporation). The limit of detection or sensitivity was 0.04 μmol/L. Recoveries of iodate and iodide were 100 % and 97 % respectively. All samples were assayed in duplicate and when measurements differed by $<$ 10 % from their mean, the analysis was repeated in duplicate. The average of the duplicate measurements was used in the data analysis. Possible interference of the iodine assay by thiocyanate was examined by adding various amounts of potassium thiocyanate to a series of urine samples but the method was found to be insensitive to the presence of thiocyanate.

Statistical analysis

The data of those subjects of whom at least one urinary iodine concentration was assessed during at least three weeks of urine collection were eligible for further statistical analysis. Average urinary iodine concentrations, per week of measurement, were calculated for the total group of treated subjects (n = 58) and untreated (n = 52) subjects. In addition, median urinary iodine concentrations were calculated per parasite group for treated and untreated subjects.

The changes in iodine status over time after oral dosing with iodized oil can be described by a model (17):

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

Where
- I_T = Urinary iodine concentration at time t;
- T = Time (w) after dosing with iodized oil;
- x = (0,1) Variable containing information about untreated (0) and treated (1) intestinal parasitic infestation;
- α_0 = Iodine retention for untreated subjects;
- α_1 = Iodine retention for treated subjects;
- β_0 = Rate of iodine elimination for untreated subjects;
- β_1 = Rate of iodine elimination for treated subjects.

The model was used to calculate iodine retention and elimination for untreated (α_0 and β_0) and treated (α_1 and β_1) subjects general and per intestinal parasites (*Entamoeba histolytica*, *Ascaris lumbricoides* and hookworm).

Given that I^* is 0.40 μmol I/L urine which represents the level below which subjects are regarded as suffering from moderate iodine deficiency (18), the model-based duration of effectiveness in the different groups (T^*) was calculated.

Non-linear regression analysis was carried out to study the impact of intestinal parasites and anti-parasitic treatment on iodine retention, iodine elimination and the duration of effectiveness of orally administered iodized oil, using the model as described above, which describes the urinary iodine excretion patterns in each group. Asymptotic Student's t-values were computed to test for significance differences between the iodine retention for untreated (α_0) and treated subjects ($\alpha_0 + \alpha_1$), and between iodine elimination for untreated (β_0) and treated subjects ($\beta_0 + \beta_1$). The goodness of fit of the model

(adjusted R^2) was computed to determine the correlation of the urinary iodine excretion within each of the study groups.

Results

In **Table 1**, the prevalence of intestinal parasites in apparently healthy school children in Ntcheu District, and the iodine status per group is presented. *Entamoeba histolytica*, *Ascaris lumbricoides*, and hookworm were highly prevalent in the study population. The worm burden of *Ascaris lumbricoides* was low as all egg counts/g were less than 7000. For hookworm the egg count/g were distributed between 3000 and 8000 indicating moderate worm burdens. No differences in age, sex and median urinary iodine concentration were found between the different study groups. The cure rates of albendazole and metronidazole were 96 and 89 % respectively.

The median urinary iodine concentrations after oral dosing with iodized oil (during the 4th, 8th, 20th, 40th and 44th week) for the different treatment groups are given in **Table 2**. During the 4th week, all untreated subjects had significantly lower urinary iodine concentrations than the treated subjects ($P < 0.001$). The same was true for the untreated subjects in general and for those infested with *Entamoeba histolytica* and hookworm specifically compared to the treated subjects during the 8th week of follow up ($P < 0.05$). During week 20, 40 and 44 the median urinary iodine concentrations were comparable in all study groups although they remained slightly higher for those who had received anti-parasitic treatment.

Table 1 Prevalence of intestinal parasites and median urinary iodine concentration of apparently healthy school children, Ntcheu District, Malawi (n = 484)

	No parasites	*Entamoeba histolytica*	*Ascaris lumbricoides*	*Necator americanus*
Mean age, y [SD]	9.5 [0.8]	9.4 [0.9]	9.5 [0.8]	9.4 [0.9]
Prevalence of parasites, %	6.0	67.6	26.0	63.2
Median urinary iodine concentration, μmol/L[1]	0.17 (0.12, 0.26)	0.18 (0.12, 0.26)	0.17 (0.11, 0.26)	0.17 (0.08, 0.26)

[1] 25th and 75th percentile in parentheses.

Table 2 Median urinary iodine concentration (μmol/L) after oral iodized oil administration of subjects who did or did not receive medication against intestinal parasites[1]

	Total group		*Entamoeba histolytica*		*Ascaris lumbricoides*		Hookworm	
	Treated (n = 58)	Untreated (n = 52)	Treated (n = 16)	Untreated (n = 8)	Treated (n = 26)	Untreated (n = 18)	Treated (n = 16)	Untreated (n = 26)
Time, w								
4	1.20 (0.46, 3.80)	0.59 (0.14, 1.29)	1.52 (0.54, 2.83)	0.27 (0.17, 0.63)	1.10 (0.42, 3.41)	0.57 (0.16, 1.11)	1.88 (0.63, 3.41)	0.85 (0.39, 1.79)
8	0.72 (0.17, 1.03)	0.34 (0.13, 0.89)	0.42 (0.21, 1.02)	0.17 (0.12, 0.76)	0.55 (0.31, 0.87)	0.45 (0.27, 0.72)	0.89 (0.40, 1.36)	0.28 (0.21, 0.91)
20	0.32 (0.18, 0.72)	0.27 (0.13, 0.59)	0.33 (0.17, 0.63)	0.18 (0.13, 0.49)	0.34 (0.27, 0.61)	0.30 (0.19, 0.54)	0.29 (0.23, 0.89)	0.22 (0.15, 0.69)
40	0.28 (0.13, 0.58)	0.24 (0.13, 0.47)	0.35 (0.16, 0.61)	0.18 (0.13, 0.46)	0.34 (0.11, 0.58)	0.32 (0,11, 0.57)	0.29 (0.14, 0.53)	0.32 (0.11, 0.58)
44	0.23 (0.08, 0.43)	0.19 (0.13, 0.38)	0.25 (0.13, 0.43)	0.17 (0.12, 0.48)	0.27 (0.13, 0.82)	0.17 (0.09, 0.39)	0.25 (0.13, 0.47)	0.18 (0.09, 0.39)

[1] 25th and 75th percentile given in parenthesis.

Table 3 The iodine retention capacity, the iodine elimination rate and the duration of effectiveness of orally administered iodized oil of Malawian school children who were or were not treated for intestinal parasitic infestations[1-3]

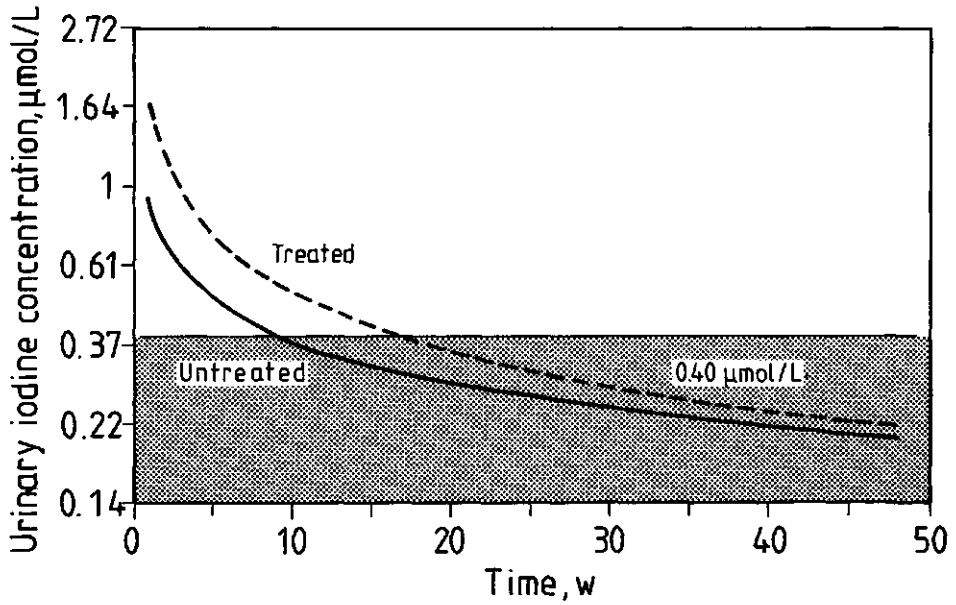
		Total group	*Entamoeba histolytica*	*Ascaris lumbricoides*	Hookworm
Iodine retention capacity for untreated	α_0	0.91 (3.30)	0.48 (2.49)	1.11 (3.30)	0.98 (3.62)
Iodine retention capacity for treated	$\alpha_0 + \alpha_1$	1.81 (2.55)	3.37 (1.18)	2.43 (1.48)	1.24 (2.66)
Iodine elimination rate for untreated	$ß_0$	0.38 (5.98)	0.31 (1.38)	0.42 (4.07)	0.38 (4.04)
Iodine elimination rate for treated	$ß_0 + ß_1$	0.52 (1.72)	0.71 (2.62)	0.63 (2.74)	0.49 (3.83)
Duration of effectiveness for untreated	T^*_0	9.2 (5.56)	2.0 (0.98)	12.1 (4.28)	11.4 (4.14)
Duration of effectiveness for treated	T^*_1	16.8 (10.94)	21.0 (2.49)	18.4 (6.17)	10.8 (3.79)
Difference in duration of effectiveness	T^*_1-T^*_0	7.6 (3.45) [0.001]	19.0 (2.19) [0.032]	6.3 (0.93) [0.353]	0.6 (0.17) [0.865]

[1] For the number of subjects per group, see Table 2.
[2] Asymptotic Student's t-values in round parentheses.
[3] *P*-values in square parentheses.

In **Table 3**, the parameters for retention and elimination of iodine after oral iodized oil administration, which describe the urinary iodine excretion pattern, using the hyperbolic function, are given for the different study groups. The asymptotic Student's t values, given in **Table 3**, indicate a statistically significant improved retention of iodine for treating intestinal parasites in general. The model-based duration of effectiveness for untreated (T_0^*) and treated subjects (T_1^*) in general is 9.2 and 16.8 weeks respectively, the difference of 7.6 weeks being statistically significant ($P < 0.001$). Graphical representations of the urinary iodine excretion patterns for untreated and treated intestinal parasitic infestations in general, as described by the hyperbolic function, are presented in **Figure 1**.

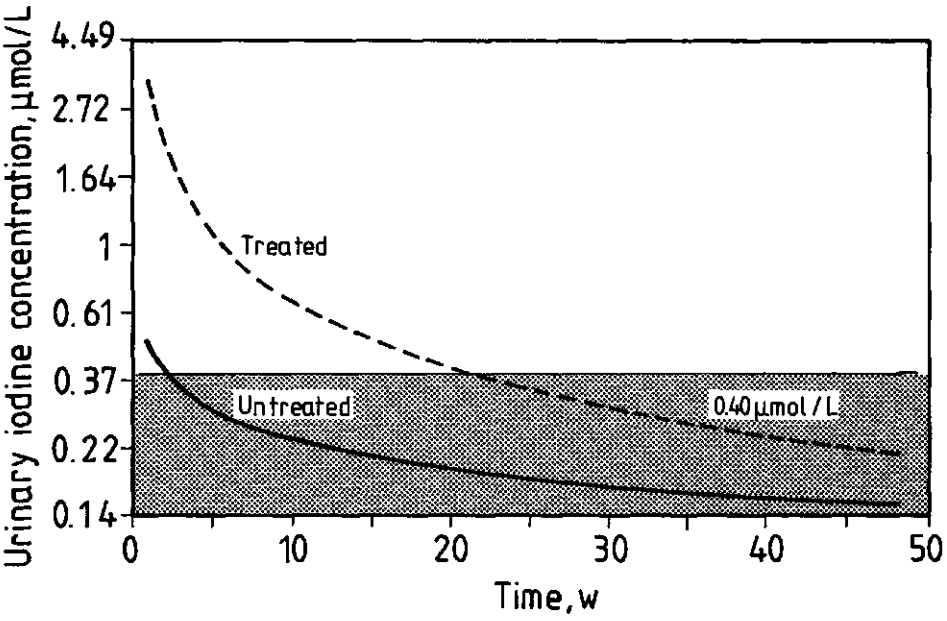
No difference in iodine retention and elimination was found between treated and

Figure 1 Urinary iodine excretion (in natural logarithms), after oral iodized oil administration in apparently healthy school children treated and untreated for intestinal parasites before oral dosing with iodized oil, Ntcheu District, Malawi[1]



[1] For description of model, see text. I^* is 0.40 μmol/L, the level of urinary iodine concentration below which there is moderate iodine deficiency.

Figure 2 Urinary iodine excretion (in natural logarithms), after oral iodized oil administration in apparently healthy school children treated and untreated for *Entamoeba histolytica* before oral dosing with iodized oil, Ntcheu District, Malawi[1]



[1] For description of model, see text. I* is 0.40 µmol/L, the level of urinary iodine concentration below which there is moderate iodine deficiency.

untreated *Entamoeba histolytica* cyst passers. Despite this result, which may be due to the limited number of observations, an adjusted R^2 value of 0.24 was found for *Entamoeba histolytica* cyst passers meaning that the goodness of fit of the hyperbolic function for the urinary iodine excretion pattern within this group was high. This indicates that *Entamoeba histolytica* has a large effect on the efficacy of orally administered iodized oil. This notion is confirmed when looking at the model-based duration of effectiveness; for untreated and treated subjects, the duration of effectiveness is 2 w and 21 w respectively ($P < 0.05$) as can be seen in **Table 3**. Graphical representations of the urinary iodine excretion patterns for the untreated and treated *Entamoeba histolytica* cyst passers, as described by the model, are presented in **Figure 2**.

No significant differences were found in the retention and elimination of iodine between treated and untreated *Ascaris lumbricoides* and hookworm. However, both retention and elimination rate are slightly increased for treated subjects. Adjusted R^2 values were 0.15 and 0.09 for *Ascaris lumbricoides* and hookworm respectively indicating that a large variance in urinary iodine concentration confuses the urinary iodine excretion pattern as described by the model.

Discussion and conclusions

Intestinal parasitic infestations are an important cause of chronic diarrhoea in which fat absorption can be reduced by 50 % of normal (19). It may be expected that some intestinal parasites reduce the absorption of orally administered iodized oil. Their possible role in the malabsorption of iodized oil is biologically plausible as *Ascaris lumbricoides* has also been associated with the malabsorption of vitamin A (20-22). However, so far no studies have been described on the effect of intestinal parasites on the effectiveness of oral iodized oil administration for control and prevention of iodine deficiency.

The prevalence of intestinal parasites found in the study population is in accordance with that reported in Malawi. As we did not recover worms after treatment of hookworm it was not possible to diagnose specific infections with *Necator americanus*. However, this species is the predominant hookworm found in Ntcheu District, Malawi, as reported by the District Hospital.

All subjects who had received anti-parasitic treatment showed significantly higher urinary iodine concentrations during the 4th week after oral administration of iodized oil compared to those who were not treated. This indicates an improvement of iodized oil absorption after treating intestinal parasites in general.

Entamoeba histolytica has a cosmopolitan distribution which occurs characteristically in endemic form. An infestation by this pathogenetic amoeba is characterized by acute and chronic phases (23). The infestation rate is low in young children, but in the school age group the incidence reaches that of the general population. In this study the subjects infested by this amoeba species were so-called chronic cyst passers without significant symptoms. We are aware of the growing view that what is currently called *Entamoeba histolytica* is in fact two species, one of which is invasive and

the other non-invasive (24). Unfortunately the cysts of the two species are indistinguishable by microscope. As we did not detect trophozoites containing blood corpuscles, to distinguish between the two species of *Entamoeba histolytica*, we cannot be certain which one we observed. Nevertheless, the vast impact of *Entamoeba histolytica* on the estimated duration of effectiveness of oral iodized oil administration is alarming; only two weeks for the untreated subjects. The fact that in this study no significant distinction was found in iodine retention between untreated and treated cyst passers may be due to the limited number of observations for the untreated *Entamoeba histolytica* cyst passers ($n = 8$) as urinary iodine concentration remains an index with a highly day to day variation. As *Entamoeba histolytica* is a parasite of the large bowl, and oils and fats (triacylglycerol esters) are absorbed from the small bowl, it remains unclear by what mechanism this parasite might be expected to impair the absorption of the ethyl esters of iodized fatty acids. A possible explanation may be that iodized ethyl esters are not, like triacylglycerols, absorbed from the small intestine, but for the large bowl. A general effect of this parasite may be that it stimulates bowl movement. In this case the increased passage time of the ethyl esters through the large bowl may not leave sufficient time for the absorption of the iodized ethyl esters thus affecting the availability of dose of iodine. It may be expected that the effectiveness of a type of iodized oil in which the iodized fatty acids are present as triacylglycerol esters will not be influenced by intestinal parasites of the large bowl.

Ascaris lumbricoides and hookworm are common parasites of the small intestine of man and have a world-wide distribution. For subjects who had received anti-parasitic treatment the median urinary iodine concentrations, 4 weeks after oral iodized oil administration, were higher compared to those subjects who had not received anti-parasitic therapy. This indicates that the absorption of iodized oil was improved for subjects who were treated for *Ascaris lumbricoides* and hookworm. Although the iodine retention was increased for treated subjects the iodine elimination rate was also increased which resulted in comparable durations of effectiveness between treated and untreated infestations. This result by itself disputes the need of a dose of 480 mg iodine for children. The dose of iodine can probably be reduced without affecting the duration of effectiveness. However, further research is needed to establish the optimal dose of iodine for oral iodized oil administration.

It may be possible that the effect of *Ascaris lumbricoides* on the absorption of iodized oil is underestimated in this study as the worm burdens were light (< 7000 egg count/g) (21). In addition, the type of iodized oil which was used in this study, ethyl esters of iodized fatty acids, may not be affected by intestinal parasites of the small intestine. Further research is needed to study the effect of intestinal parasites of the small intestine on the efficacy of an oral dose of iodized oil which consists of triacylglycerol esters of fatty acids.

Entamoeba histolytica cyst passers treated with metronidazole remained above iodine deficiency level (0.40 μmol/L) for 21 weeks which exceeds the average duration of effectiveness of the type of oral iodized oil by far. This suggests an effect of metronidazole on the absorption of the iodized ethyl esters. It does not treat *Entamoeba histolytica* specifically as it is a very broad spectrum antimicrobial agent which acts against a wide range of anaerobic bacteria as well as intestinal protozoa. Bacterial overgrowth of the small intestine is common in children in developing countries which leads to deconjugation of bile salts and poor fat absorption in general (25). The observed increase in the efficacy of orally administered after metronidazole treatment may also be the result of treating bacterial overgrowth.

Since no cases of *Giardia duodenalis* were found in the study population, it was not possible to study the impact of giardiasis on retention and the duration of effect of oral iodized oil administration. *Giardia duodenalis*, a flagellate with a world wide distribution, is one of the most important causes of chronic diarrhoea with impaired fat absorption in developing countries (26-28). It can be expected that *Giardia duodenalis*, like *Entamoeba histolytica*, greatly reduces the efficacy of oral iodized oil. Other studies will need to investigate the effect of giardiasis on the efficacy of oral iodized oil.

From the results in this study it can be concluded that the duration of effectiveness of orally administered iodized oil is significantly reduced by intestinal parasitic infestations in general. In case of infestations by *Entamoeba histolytica* it would appear that anti-parasitic therapy is imperative when an oral iodized oil preparation consists of iodized ethyl esters since we found no effect of oral iodized oil on the urinary excretion of iodine in untreated subjects. Given the teratogenicity associated with metronidazole, its side effects, its cost and the practicability of treating everyone before administering iodized oil orally, it is unlikely to be acceptable. However, the impact of *Entamoeba*

histolytica may be overcome by using an iodized oil which contains triacylglycerol esters of iodized fatty acids. In this case more research is needed on the role of intestinal parasites of the small intestine on the effectiveness of this type of oral iodized oil.

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5 Nutritional status and the efficacy of orally administered iodized oil for controlling iodine deficiency

Carina A. Furnée, Clive E. West, Frits van der Haar and Joseph G.A.J. Hautvast[1]

Abstract

The relation between nutritional status and the efficacy of oral iodized oil for controlling iodine deficiency was studied in a randomized intervention study. No relationship was found between the efficacy of orally administered iodized oil and the initial height-for-age, weight-for-height and midupper-arm circumference. Children with a relatively large subcutaneous fat mass retained more iodine than subjects with little subcutaneous fat ($P < 0.02$) which resulted in a prolongation of the duration of effectiveness of 7.6 weeks. For goitrous subjects both retention and elimination of iodine were increased. The duration of effectiveness was approximately 15 weeks longer ($P < 0.05$) for the goitrous subjects. Changes in height, weight, weight-for-height or subcutaneous fat mass were not related to the efficacy of oral iodized oil. A reduction in midupper-arm circumference prolonged the duration of effectiveness by 6 weeks ($P < 0.05$).

Introduction

Studies on orally administered iodized oil for control of iodine deficiency have so far revealed large variations in its duration of effect (1-6). These large variations confuse the results of measurements for effective control of iodine deficiency using oral iodized oil. The study described here aims at contributing towards an understanding of the impact of the initial nutritional status, energy balance, iodine status and the initial size of the thyroid gland on the retention, elimination and the duration of effectiveness of orally administered iodized oil. Further, the effect of changes in nutritional status are considered. An understanding of the factors affecting absorption, retention and elimination of iodine after oral dosing with iodized oil may contribute to a more effective control of

iodine deficiency when oral iodized oil is the prophylactic measure of choice.

Subjects and methods

Subjects

Subjects were selected from 8, 9, and 10-y-old school children (n = 502) attending four primary schools in Ntcheu District, Malawi, where goiter is highly prevalent. The schools were selected on the basis of having a sufficient number of pupils attending and on their accessibility as they were close to the main highway in Malawi which connects the Northern, Central and Southern Regions of the country. 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 before the start of the study from parents or guardians. As only apparently healthy subjects were considered suitable for entry into the study, all children were examined by a medical assistant from Ntcheu District Hospital. Children with significantly enlarged liver or spleen, indicative of disease which may interfere with fat or protein metabolism, or with a midupper-arm circumference < 15.5 cm, indicative of protein-energy malnutrition, were excluded from the study (n = 16). Stool samples were microscopically examined for intestinal parasite infestations and those subjects with intestinal parasites received appropriate anti-parasitic medication two weeks prior to receiving oral iodized oil.

Anthropometry

Weight, height, midupper-arm circumference and biceps, triceps, subscapular, and supra-iliaca skinfolds measurements were assessed as described by Jelliffe and Jelliffe, 1989 (7) at two/three monthly intervals. In short, weighing was done on a electronic weighing scale, precise to the nearest 0.1 kg with a digital display which was frequently rechecked for accuracy using calibration weights. The subjects wore minimum clothing and no shoes. Height measurements were taken using a Microtoise, precise to the nearest 0.1 cm, using a portable measuring board to ensure a vertical position. Midupper-arm circumference was taken on the upper left arm half way between the acromial process of the scapula and the olecranon process of the ulna using a flexible measuring tape which was checked for accuracy at regular intervals using a ruler. Four skinfolds measurements (biceps, triceps, subscapular and supra-iliaca) were taken twice on the left side of the

body using a Halpenden calliper (Holtain Ltd. Crymmych, UK) which was set at zero before each measuring session. Throughout the study all measurements were taken by the same person. Weight, height and midupper-arm circumference measurements were taken in duplicate, skinfolds were measured in triplicate at three monthly intervals. The average of the two measurements was used in the statistical analysis. During each measuring round a standardization test for all measurements was carried out with ten randomly selected subjects. Both precision and accuracy of all measurements were satisfactory at each measuring round.

Study design

This study is one of a number of studies on factors which may affect retention, elimination and effectiveness of oral iodized oil administration for control and prevention of iodine deficiency.

A group of randomly selected subjects (n = 202) received 1 mL, 480 mg iodine, Lipiodol Ultra Fluide (Laboratoire Guerbet, Aulnay-sous-Bois Cedex, France) orally using a dispenser (Englass Dispensing Devices, The English Glass Co. Ltd., Leicester, England). Within this group, 37 randomly selected subjects received a carbohydrate-rich drink (Fantomalt, 100g in 100 mL of water; 1610 kJ, Nutricia, the Netherlands) over a period of 15 to 30 min prior to receiving Lipiodol UF. A placebo group (n = 35) received 1 mL neutral poppy-seed oil (Laboratoire Guerbet). The data of the remaining group of subjects are not considered in this study as they had received an alternative type of iodized oil, had only one type of intestinal parasites or had received a split dose of iodized oil.

Measurement of urinary iodine excretion was based on the concentration of iodine in casual urine samples as it was not possible to collect 24-h samples. Samples were collected during morning hours at school under supervision of field assistants. The iodine status of the subjects at baseline was determined from the median values of the iodine concentration in urine samples collected on two consecutive days before iodized oil administration. Subsequent values were based on the median values of the iodine concentration in casual urine samples collected on three consecutive days during the 4th, 8th, 20th, 40th and 44th week after oral iodized oil administration (8).

The thyroid gland was graded by palpation as recommended by the World Health

Organization (9). For all subjects the goiter grading was done by the same person, before and 40 weeks after oral iodized administration. This person was not aware of the difference in the treatment schedules. Double checking was done by one of the authors who had no direct access to the treatment schedules and previous measurements. In case of doubt the lowest goiter grade was recorded.

Urinary analysis

The urine samples, preserved with approximately 1 g thymol, were sent to the Department of Human and Animal Physiology of Wageningen Agricultural University where they were stored at -20° C prior to laboratory analysis. Iodine concentration in urine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (10-12) adapted for use with a microtitre plate reader (Thermomax, Molecular Devices Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with special software (*Softmax*, Molecular Devices Corporation). The limit of detection, sensitivity, was 0.04 μmol/L. Recoveries of iodate and iodide were 100 % and 97 % respectively. All samples were assayed in duplicate and when measurements differed by > 10 % from their mean, the analysis was repeated in duplicate. The average of the duplicate measurements was used in the data analysis. Possible interference of the iodine assay by thiocyanate was examined by adding various amounts of potassium thiocyanate to a series of urine samples but the method was found to be insensitive to the presence of thiocyanate.

Statistical analysis

For analysis only the data of those subjects with at least one urinary iodine concentration at 4 points of measurement were considered. Per group the median urinary iodine concentration was calculated per week of measurement using each individuals average urinary iodine concentration, calculated from the casual urine samples collected during that particular week.

To distinguish between subjects with different height-for-age and weight-for-height characteristics, z-scores were calculated using the NCHS (National Center for Health Statistics) reference population (13). The standard deviation (SD) was used as cut-off point for the identification of the subjects. For weight, midupper-arm circumference and

the sum of skinfolds the actual group mean was calculated and the SD was used as cut-off point for identification.

To study the effect of an increase or decrease in weight, weight-for-height, midupper-arm circumference and the sum of skinfolds the second measurement, taken two months after oral iodized oil administration was subtracted from the base-line measurement taken before oral dosing with iodized oil. The mean change was calculated per indicator and the SD was used as cut-off point for identification.

The changes in urinary iodine concentrations over time after oral dosing with iodized oil can be described by the following equation (14):

$$I(T,x) = (\alpha_0 + \alpha_{1,2})\, T^{-(\beta 0 + \beta 1,2)}$$

where,

- I = urinary iodine concentration (μmol/L);
- T = time (w) after oral dosing with iodized oil;
- x = nutritional indicator or second minus first measurement;
- α_0 = iodine retention capacity of subjects with z-scores or measurements between -1 SD and +1 SD;
- α_1 = iodine retention capacity of subjects with z-scores or measurements smaller than -1 SD, a decrease in x (second minus first measurement $\leq$ 0), goiter stage 0 or a negative energy balance;
- α_2 = iodine retention capacity of subjects with z-scores or measurements greater than + 1 SD, an increase in x (second minus first measurement $>$ 0), goiter stage $>$ 0 or a positive energy balance;
- β_0 = iodine elimination rate of subjects with z-scores or measures between -1 SD and +1 SD in x;
- β_1 = iodine elimination of subjects with z-scores or measurements smaller than -1 SD in x, a decrease in x (second minus first measurement $\leq$ 0), goiter stage 0 or a negative energy balance;
- β_2 = iodine elimination rate of subjects with z-scores or measurements greater than + 1 SD, an increase in x (second minus first measurement $>$ 0), goiter stage $>$ 0 or a positive energy balance.

The parameters α_0, α_1, α_2, β_0, β_1 and β_2 were estimated using urinary iodine

concentrations for subjects with different nutritional characteristics; the parameters for the measures of the nutritional indicators, expressed in terms of z-scores of height-for-age and weight-for-height or weight, midupper-arm circumference and the sum of skinfolds distributed between -1 and +1 SD have been given subscript 0. Subscripts 1 and 2 characterize the parameters for subjects in relation to the measures of the nutritional indicators less than -1 SD and greater than +1 SD respectively.

Given estimates for α_0, α_1, α_2, β_0, β_1 and β_2 and values for I^*, being the cut-off points indicating urinary iodine concentration values associated with the degree of the severity of iodine deficiency as suggested by WHO/UNICEF/ICCIDD (15), a model-based duration of effectiveness can be calculated. In this study the model-based duration of effectiveness (T^*) was assessed for $I^* = 0.40$ μmol/L, moderate iodine deficiency (15).

Non-linear regression analysis was carried out to study the impact of the initial nutritional status, initial urinary iodine concentration, goiter, energy balance, and alterations in nutritional indicator values, based on the model as described above, to compare the urinary iodine excretion patterns in the groups with different nutritional characteristics. Asymptotic Student's t-values were computed to test the significance of differences between the parameters α_0, $\alpha_0 + \alpha_1$ and $\alpha_0 + \alpha_2$, and between β_0, $\beta_0 + \beta_1$ and $\beta_0 + \beta_2$. The goodness of fit of the model (adjusted R^2) was computed to determine the correlation of the urinary iodine excretion within each of the study groups.

Results

In **Table 1** the mean weight, height, weight-for-height, midupper-arm circumference and sums of skinfolds are given as well as the median urinary iodine concentration and the total goiter percentages before and 40 weeks after oral dosing with either iodized oil or neutral poppy-seed oil. With regard to all variables considered, the study group and the placebo group were comparable before the onset of the study. After 40 weeks the nutritional indicators in the study group and the placebo group were still comparable indicating no effect of iodine supplementation on these indicators. In the iodine supplemented groups the median urinary iodine concentration remained above 0.16 μmol/L, indicative of severe iodine deficiency, up to week 40. In the placebo group the urinary iodine concentration remained low throughout the study. Total goiter, was reduced from 62.9 % to 20.8 % in the iodized oil treated group and had increased from

Table 1 Nutritional status of the subjects at base-line and 40 weeks after receiving either oral iodized oil or neutral poppy-seed oil, Ntcheu, Malawi[1]

	Iodized oil		Poppy-seed oil	
	Base-line	40 w	Base-line	40 w
n	197	197	33	33
Energy balance, n	35	35		
Weight, kg	25.3 (3.6)	26.7 (4.0)	25.2 (3.9)	26.1 (3.3)
Height, cm	126.2 (7.1)	129.6 (7.2)	127.2 (6.4)	130.1 (6.5)
Weight / Height, kg/cm	0.20 (0.02)	0.21 (0.02)	0.20 (0.03)	0.20 (0.02)
MUAC[2], cm	18.2 (1.4)	18.1 (2.8)	18.1 (1.0)	18.1 (1.1)
Sum of skinfolds, mm	20.8 (7.5)	18.6 (4.4)	19.8 (3.5)	18.3 (3.2)
Urinary iodine concentration (μmol/L)[2]	0.15 [0.11, 0.23]	0.32 [0.16, 0.54]	0.19 [0.10, 0.54]	0.16 [0.07, 0.30]
Total goiter, %	62.9	20.8	60.0	65.7

[1] Mean (SD).
[2] Midupper-arm circumference.
[3] Median [25th percentile, 75th percentile].

60.0 % to 65.7 % in the placebo group. After 40 weeks the median urinary iodine concentration in the iodize oil treated group had returned to base-line value and was again comparable to that in the placebo group.

In **Table 2** the relationship between nutritional indicators and parameters of iodine retention capacity and excretion is shown. An effect on both iodine retention (α) and elimination (ß) was observed for weight-for-height. The duration of effectiveness (T^*) for children of low (< -1 SD) and high (> 1 SD) weight-for-height was 14.6 and 21.3 weeks, respectively, but the difference was statistically only marginally significant ($P = 0.08$). Subjects with a high sum of skinfolds (> 1 SD) retained more iodine ($P < 0.02$) than those with a low sum of skinfolds (> -1 SD) ($\alpha_2 < \alpha_1$) but there were no differences between their respective iodine elimination rates ($ß_1 = ß_2$).

The initial urinary iodine concentration had no effect on retention (α), elimination (ß) and the duration of effectiveness (**Table 3**). Both iodine retention (α_2) and elimination ($ß_2$) and hence duration of effectiveness were significantly increased in goitrous subjects

Table 2 The statistical relationship between the initial nutritional status and the retention, elimination and duration of effectiveness of oral iodized oil, Ntcheu, Malawi[1]

	Height-for-age	Weight-for-height	Midupper-arm	Sum of skinfolds
$\bar{x}$, SD			18.14, 1.49	20.42, 9.04
$\bar{Z}$, SD	-1.41, 1.07	-0.24, 0.65		
α_0	1.27 (4.33)[2]	0.93 (3.87)[2]	7.22 (4.83)[2]	2.71 (4.40)[2]
α_1	-0.23 (1.11)	-0.94 (2.02)[3]	-0.32 (3.73)[2]	-0.78 (2.19)[3]
α_2	-0.04 (0.15)	2.43 (2.48)[3]	-0.30 (4.74)[2]	-0.02 (2.87)[2]
β_0	-0.03 (0.65)	0.35 (5.09)[2]	2.25 (5.97)[2]	0.58 (4.39)[2]
β_1	-0.11 (1.28)	-0.28 (2.79)[2]	-0.10 (4.41)[2]	-0.01 (0.59)
β_2	0.01 (0.06)	0.42 (3.05)[2]	-0.09 (4.33)[2]	-0.00 (0.32)
R^2	0.15	0.17	0.17	0.18
T_1	17.4 (8.19)[2]	14.6 (7.71)[2]	15.2 (10.05)[2]	13.0 (10.06)[2]
T_2	13.3 (6.58)[2]	21.3 (6.05)[2]	16.9 (6.93)[2]	20.6 (6.87)[2]
T_2-T_1	-4.1 (1.38) [0.162]	6.7 (1.73) [0.081]	1.7 (0.58) [0.572]	7.6 (2.35)[3] [0.018]

[1] $I(T,x) = (\alpha_0 + \alpha_{1,2})\ T^{-(\beta 0 + \beta 1,2)}$ (see text), $\bar{x}$ denotes the mean and $\bar{Z}$ denotes mean z-score; t-values is round parentheses, p-values in square parentheses.

[2] Significant from 0 at 1 % level.

[3] Significant from 0 at 5 % level.

($P < 0.05$ for T*).

Positive energy balance, induced by oral energy supplementation, had no effect on retention, elimination of the iodine or the duration of effectiveness of oral iodized oil.

Changes in weight, weight-for-height and subcutaneous fat mass did not effect retention, elimination or duration of effectiveness (results not shown). However, a decrease in midupper-arm circumference was found to increase iodine retention ($\alpha_1 > 0$), slow down elimination ($\beta_1 < 0$), and increase the duration of effectiveness from 12.2 to 18.2 weeks ($P < 0.05$).

Discussion and conclusions

Weight-for-height, indicative of wasting, revealed only a marginally significant relationship with the efficacy of orally administered iodized oil at 5 % level ($P = 0.08$).

Table 3 The statistical relationship between initial energy balance, goiter, urinary iodine concentration and alterations in midupper arm circumference (MUAC) and the retention, elimination and duration of effectiveness of oral iodized oil, Ntcheu, Malawi[1]

	Energy balance	Goiter	Urinary iodine	Alterations in MUAC
α_0				1.30 (5.86)[2]
α_1	1.52 (7.49)[2]	0.08 (0.11)	1.47 (5.19)[2]	-0.98 (1.70)
α_2	0.57 (0.83)	1.64 (4.93)[2]	-0.56 (1.02)	0.02 (0.11)
β_0				0.47 (8.57)[2]
β_1	0.51 (11.19)[2]	-0.15 (1.10)	0.48 (7.39)[2]	-0.11 (1.28)
β_2	0.11 (0.91)	0.61 (8.85)[2]	-0.08 (0.45)	0.02 (0.54)
R^2	0.17	0.20	0.14	0.16
T_1	14.8 (12.01)[2]	10.6 (8.73)[2]	15.7 (7.97)[2]	18.2 (7.94)[2]
T_2	15.6 (6.22)[2]	25.4 (3.92)[2]	8.5 (2.07)[3]	12.2 (7.85)[2]
T_2-T_1	0.8 (0.31) [0.75]	14.7 (2.52)[3] [0.025]	-7.2 (1.58) [0.115]	-6.0 (2.14)[3] [0.031]

[1] $I(T,x) = (\alpha_0 + \alpha_{1,2})\ T^{-(\beta 0 + \beta 1,2)}$ (see text); t-values is round parentheses, p-values in square parentheses.

[2] Statistically significant at 1 % level, Students t-test.

[3] Statistically significant at 5 % level, Students t-test.

However, children with a relatively large subcutaneous fat mass were found to retain significantly more iodine than those with relatively little subcutaneous fat. Initial height, indicative of stunting, and the initial midupper-arm circumference (MUAC), indicative for energy-protein malnutrition when low, were not found to effect iodine retention, elimination or the duration of effectiveness of oral iodized oil. So far, little is known about possible storage sites of iodine, other than the thyroid, after oral iodized oil administration in human beings. Reichel et al (16) studied the absorption of Lipiodol in the lymph of cats using X-ray photographs and concluded that the uptake and metabolism of iodized oil from the gut was analogous to that of other dietary fats. Further, increased concentrations of iodine had been found in body fat of rabbits, rats and mice after oral administration of iodized oil and iodofat which is a preparation of sodium salts of iodized

fatty acids (17,18). From the results of our study it is apparent that significant quantities of iodine are stored in the subcutaneous fat and that it plays an important role in duration of effectiveness of orally administered iodized oil.

Groen (19) reported increased iodine retention in adults gaining weight after oral administration of triacylglycerol esters of iodized fatty acids from poppy-seed oil. In our study using ethyl esters of iodized fatty acids from poppy-seed oil, weight gain or weight loss and changes in subcutaneous fat mass in children affect neither retention nor elimination of iodine after an oral dose. This may be due to the difference in chemical properties of the two types of iodized oil, their routes of absorption, storage sites and subsequent metabolic pathways. Of the glyceryl esters of iodized fatty acids used by Groen, 91 to 98 % was absorbed as neutral fat in normal persons. After absorption some of the iodized oil is oxidized and some is stored in the body. Absorption of ethyl esters of iodized fatty acids may be more rapid and may occur via a different mechanism and at a different site than neutral fat (triacylglycerol). This may account for the difference in the duration of effectiveness between the ethyl esters and the triacylglycerol esters of iodized fatty acids from poppy-seed oil reported in an earlier study (14). Once absorbed, ethyl esters may be less readily taken up by adipose tissue and become subject to more rapid oxidation. The iodine released will be taken up by the thyroid gland. The rate of iodine uptake by the thyroid will depend on the iodine status of the subject.

The initial midupper-arm circumference was not found to play a role in iodine retention. However, a decrease in midupper-arm circumference during the study was observed to enhance significantly the duration of effectiveness of orally administered iodized oil significantly. A possible explanation for this finding may be that iodine is also stored in muscle tissue (approximately 50 % of the body mass) and that, when muscle is being broken down, iodine is slowly released into the plasma. From the plasma it can either be taken up by the thyroid or it can be excreted in the urine. In iodine-deficient subjects it may be expected that most of the iodine released by protein turnover would be taken up by the thyroid thus prolonging the duration of effectiveness. For those who do not need to utilize protein for energy supply the iodine would remains in the muscle tissue and will not become readily available to the thyroid. Gebre Medhin et al (personal communication) observed that subjects on a slimming diet, given iodized oil (ethyl esters of iodized fatty acids) demonstrated a longer duration of effectiveness of the orally

administered iodized oil than non-slimming subjects after receiving the iodized oil. In our study, general weight loss and the reduction of subcutaneous fat did not contribute to prolonging the duration of effectiveness, but a reduction in midupper-arm circumference did. The prolonged duration of effectiveness for slimming subjects as observed by Gebre Medhin et al may therefore also be the result of protein breakdown rather than the reduction in subcutaneous fat mass.

In this study goitrous subjects retained more iodine after oral dosing with iodized oil than non-goitrous subjects which resulted in a difference in the duration of effectiveness being approximately 15 weeks. This increase in iodine uptake in goitrous subjects may be explained by an increase in the thyroidal iodine clearance rate which is known to occur when the thyroid gland mass is increased in order to compensate for iodine deficiency (20,21). In addition a significant increase in iodine elimination was observed in our study. Although no apparent negative side effects of the administered dose of iodine (480 mg) were observed or reported in our study it is reasonable to assume that the increased elimination of iodine may be the result of a mechanism in the thyroid gland to adjust its iodine content to its upper limit of iodine concentration in the process of size reduction (normalization) or overcoming mild hyperthyroidism. The initial urinary iodine concentration did not reveal an effect on iodine retention.

From the results in this study it is apparent that subcutaneous fat tissue and muscle tissue are important for the storage of iodine after oral dosing with iodized oil. In the scope of increasing the duration of effectiveness of oral iodized oil administration, it is worthwhile to consider these findings when planning an iodine prophylaxis program using oral iodized oil. In developing countries, where the nutritional status of its people is known to fluctuate as a result of seasonality, oral iodized oil should be given at the end of the post-harvest season.

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6 Methods for estimating the prevalence of iodine deficiency after oral dosing with iodized oil

Carina A. Furnée, Frits van der Haar, Clive E. West and Joseph G.A.J. Hautvast

Abstract

A cumulative frequency distribution (CFD) of individually assessed durations of effectiveness of orally administered iodized oil can be described by either a concave-shaped function or a sigmoid-shaped function. These functions describe the rates at which urinary iodine concentrations drop below a level associated with moderate iodine deficiency after oral iodized oil administration for subjects with different characteristics. For oil A (ethyl esters of iodized fatty acids) the CFD converged to unity (100%) faster than for oil B (triacylglycerol esters of iodized fatty acids). The number of non-responders to oral iodized oil was significantly higher for oil A (11.1 %) compared to oil B (3.1 %). For 8, 9 and 10-y-old girls and for consumers of raw cassava the CFDs converged to unity faster than for boys of the same age and those who do not consumed raw cassava, respectively.

Introduction

Iodine deficiency is notoriously difficult to quantitate in an objective way. Therefore, it is hard to compare studies carried out at different places by different research investigators working in the field at different time intervals. Further, it is often impossible to study thyroid function, to closely define thyroid status and to obtain information on iodine intake. Consequently, iodine status and nutrition are generally evaluated by indirect indicators. Daily urinary iodine excretion is the most precise index of iodine status as the amount of iodine excreted in the urine corresponds to the level of iodine intake to maintain pre-existing iodine stores in the body (1). Iodine concentration is mostly measured in casual urine samples. Despite a large daily variation in iodine concentration as measured in these samples it remains an efficient index for evaluating

iodine supply, especially when an average iodine concentration can be calculated from two or more casual urine samples per individual taken on consecutive days (2). In a previous study we have shown that at group level the average retention of iodine, the iodine elimination rate and the duration of effectiveness can be calculated for orally administered iodized oil using a model (3). The parameters which describe this model are calculated from the urinary iodine concentrations of casual urine samples taken at regular intervals after oral iodized oil administration. A duration of effectiveness can be calculated per individual. The cumulative frequency distribution these individually assessed durations of effectiveness offers information about the rate at which the subjects become iodine deficient again, based on their urinary iodine concentration, after an oral dose of iodized oil. In this study methods are proposed to assess a continues relationship between duration of effectiveness and time. Subsequently, the rate at which subjects who have received either ethyl esters of iodized fatty acids from poppyseed oil or triacylglycerol esters of iodized fatty acids from poppyseed oil are compared. A distinction in the duration of effectiveness of the two types of oil had been established at group level in previous work (3). In addition, the effect of raw cassava consumption is studied because of its role in the etiology of iodine deficiency (4,5) and the impact of the male and female sex is considered as the prevalence of goiter was found to be unequally distributed over the two sexes (2).

Materials and methods

Subjects

Apparently healthy school children, 8, 9, and 10-y-old from four schools in Ntcheu District, Malawi, were selected to participate in the study (n = 486). 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. All children were examined by a medical assistant from Ntcheu District Hospital. Children with a significantly enlarged liver or spleen, indicating a clinical condition of disease which may interfere with fat or protein metabolism, or with a midupper-arm circumference < 15.5 cm, indicating energy-protein malnutrition, were excluded from the study. The thyroid gland was graded by palpation as recommended by the World Health Organization (6). For all subjects the goiter grading

was done by the same person, before and 10 months after oral iodized oil administration, who was not aware of the different treatment schedules. The grading was checked by one of the authors. In case of doubt the lowest goiter grade was recorded.

Children with mixed intestinal parasites were treated with appropriate medication two weeks prior to receiving the iodized oil and admitted to this study. Subjects with single intestinal parasite infestations, who received a split dose of iodized oil, neutral poppy seed oil or a carbohydrate rich drink immediately prior to oral iodized oil administration are not considered in this study. From the remaining group of children (n = 244) the subjects were randomly allocated by age and sex to four different treatment groups. The control group (n = 197), received a single dose of 1 mL oil A (Lipiodol UF, 490 mg iodine/mL, Laboratoire Guerbet, Aulnay-sous-Bois CEDEX, France) which is comprised of iodized fatty acids containing 490 mg iodine; an other group (n = 37) received a single dose of 1.25 mL oil B (Oriodol, 540 mg iodine/mL, Laboratoire Guerbet) which is comprised of triacylglycerol esters of iodized fatty acids containing 675 mg iodine. The doses were administered orally using dispensers (Englass Dispensing Devices, The English Glass Co. Ltd., Leicester, England) delivering 1.0 mL (oil A) or 1.25 mL (oil B).

All subjects were visited in their homes (households) by two field workers to verify the date of birth, place of birth, sex and to obtain information on the consumption of raw cassava using a food frequency table and three standardized portion sizes of cassava root (75, 150 and 300 g). The main caretaker of the subject was asked whether the subject consumed raw cassava, what size the portions of cassava are on average and how often the subject consumed raw cassava. Those who ate raw cassava at regular intervals were classified as cassava consumers. All others were considered as non-consumers.

Study design

The data of 234 subjects were eligible for analysis as they had received either a single dose of oil A or oil B, were free of intestinal parasites and data were available of urinary iodine concentrations from two or more periods of urine collection. In addition, information had to be available on the subjects cassava consumption habits.

Measurement of urinary iodine excretion was based on the concentration of iodine

in casual urine samples as it was not possible to collect 24-h samples. Samples were collected during morning hours at school under supervision of field assistants. The iodine status per subject, at baseline, was determined from the average iodine concentration in urine samples collected on two consecutive days before iodized oil administration. Subsequent values were based on the average iodine concentration in urine samples collected on three consecutive days during the 4th, 8th, 20th, 40th and 44th week after oral iodized oil administration (2).

Urinary analysis

The 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 prior to laboratory analysis. Iodine concentration in urine was assayed following alkaline digestion using the Sandell-Kolthoff reaction (7-9) adapted for use with a micro titre plate reader (Thermomax, Molecular Devices Corporation, Palo Alto CA, USA) coupled to a personal computer equipped with special software (*Softmax*, Molecular Devices Corporation). All samples were assayed in duplicate. When measurements differed by > 10% from their mean, the analysis was repeated. The precision and sensitivity of the procedure were 0.004 and 0.04 μmol, respectively. The recoveries of standard iodate and iodide were 100 and 97 %.

Statistical analysis

Depletion of the iodine stores after oral iodized oil administration, measured as the urinary iodine concentration in casual urine samples taken at regular time intervals, can be described by a model (3):

$$I_i(T) = \alpha_i T^{-\beta i},$$

where I = urinary iodine concentration;
T = time in weeks;
α_i = iodine retention capacity;
β_i = iodine elimination rate;
i = individual subject.

This can also be expressed as a log-linear relationship between urinary iodine concentration and time:

$$\ln I_i(T) = \ln \alpha_i - \beta_i \ln T$$

Given estimates a_i and b_i of α_i and β_i respectively, per subject, the individual duration of effectiveness T_i^* can be calculated as follows:

$$T_i^* = (a_i/I^*)^{1/bi}$$

Where I^* is set at 0.40 μmol I/L urine representing the level below which subjects are regarded as suffering from moderate iodine deficiency (10). By assessing the model-based duration of effectiveness for each individual subject (T_i^*) and sorting them in ascending order it is possible to plot a cumulative frequency distribution (CFD) of T_i^* against time. Prior to statistical analysis a continuous relation is sought to describe the CFD of T_i^* against time using standard techniques as described by Snedecor and Cochran (11). Such a continuous relationship facilitates the evaluation of the efficacy of oral iodized oil, based on the duration of effectiveness, in populations with different characteristics. Further, information can be obtained about the percentage of non-responders to oral iodized oil administration. In the subsequent analysis the efficacy of oil A and oil B are compared based on the rates at which the urinary iodine concentration of the subjects drop below 0.40 μmol/L subjects after oral dosing with iodized oil as calculated using the appropriate curve function for their respective CFD of T_i^*. The same technique is used to compare the efficacy of oral iodized oil in boys and girls and in subjects who had or had not consumed raw cassava.

Results

Per study group the mean weight, height, midupper-arm circumference and the sum of four skinfolds with their respective standard deviations, the prevalence of total goiter and the median urinary iodine concentration at base-line have been given in **Table 1.** All groups were comparable with regard to the nutritional indicators and urinary iodine concentration. For the girls the total goiter percentage was higher. There was no

Table 1 Nutritional status, urinary iodine concentration and the prevalence of total goiter in the different study groups, Ntcheu, Malawi[1]

	Oil A	Oil B	Cassava	No cassava	Boys	Girls
n	207	32	30	109	113	126
Weight, kg	25.6 (3.6)	25.1 (3.5)	25.3 (3.4)	25.8 (3.8)	25.4 (3.8)	25.6 (3.8)
Height, cm	128.2 (7.3)	128.0 (7.6)	128.2 (7.5)	128.2 (7.5)	127.6 (7.5)	128.6 (7.4)
Midupper-arm, cm	18.2 (1.4)	18.2 (1.3)	18.0 (1.2)	18.3 (1.5)	17.8 (1.2)	18.6 (1.5)
Skinfolds, mm	19.8 (6.8)	19.5 (3.5)	19.0 (4.9)	20.5 (8.1)	17.5 (3.2)	21.7 (8.3)
Total goiter, %	62.0	56.1	62.7	63.8	52.6	69.6
Urinary iodine, μmol/L[2]	0.16 [0.11, 0.26]	0.16 [0.12, 0.26]	0.16 [0.11, 0.26]	0.15 [0.11, 0.27]	0.15 [0.11, 0.26]	0.16 [0.11, 0.25]

[1] Mean, standard deviation given in round parentheses.
[2] Median, 25th and 75th percentile given in square parentheses.

difference in cassava consumption between the boys and girl. The boys and girls were equally distributed in all study groups.

A concave shaped Inverse Polynomial (IP) curve (11):

$$p(T^*) = [1 + \sigma / (T^* + \gamma)]^{-1}; \sigma, \gamma > 0$$

was found to describe the CFD function of t_i^* against time in general (**Figure 1**) and for those who had received oil A specifically (**Figure 2**). However, the Gompertz-curve (sigmoid shaped):

$$p(T^*) = \exp[-\sigma \exp(-\gamma T^*)]; \sigma, \gamma > 0$$

which is not symmetrical about the point of inflexion (11) was found to fit the CFD

Figure 1 Incidence of iodine deficiency in total sample (n = 239) after oral dosing with iodized oil for controlling iodine deficiency for school-aged children, Ntcheu, Malawi

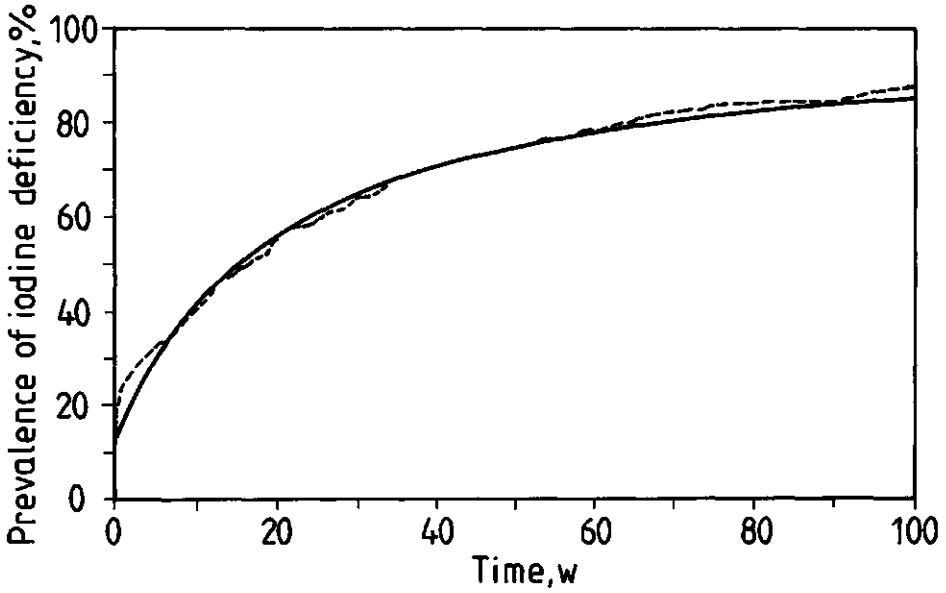


Figure 2 Incidence of iodine deficiency after oral dosing with iodized oil for controlling iodine deficiency for school aged children (n = 207) who had received oil A, Ntcheu, Malawi

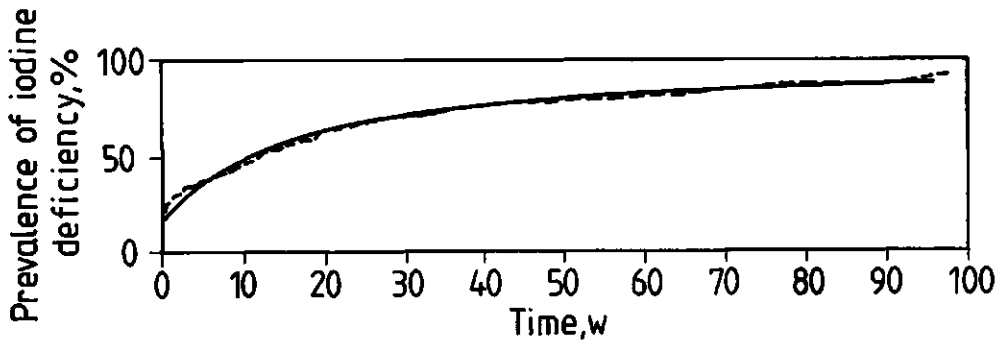
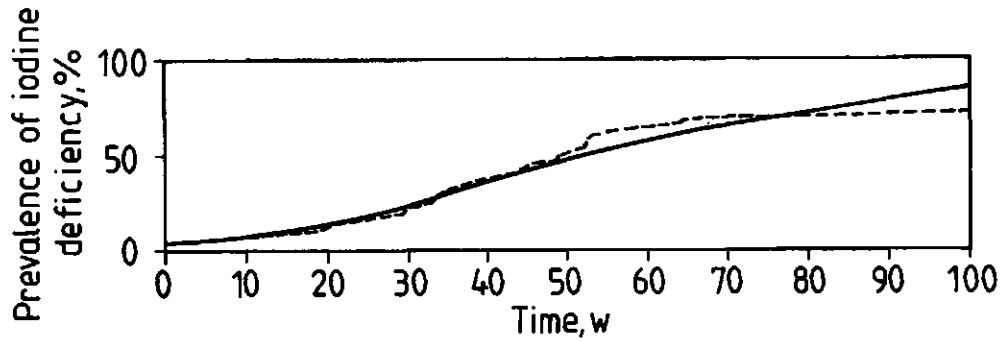


Figure 3 Incidence of iodine deficiency after oral dosing with iodized oil for controlling iodine deficiency in school aged children (n = 32) who had received oil B, Ntcheu, Malawi



function best for those who had received oil B (**Figure 3**).

The two curve functions, which fit their respective CFD, can be used to assess the prevalence of iodine deficiency at any time after oral dosing with iodized oil provided that the curve function fits the CFD properly. It can be expected that a CFD function which can be described by the Gompertz curve (oil B) is a sign of improved efficacy of oral iodized oil as it approaches unity (100 %) much slower than the IP curve for oil A does.

The number of individuals in the sample, the number of non-responders, the type of curve that fits the CFD functions, the estimated values of σ and γ , $\bar{\sigma}$ and $\bar{\gamma}$

Table 2 The parameters for describing cumulative frequency distributions of the estimated duration of effectiveness of oral iodized oil for controlling iodine deficiency of school aged children with different characteristics, Ntcheu, Malawi[1]

	N	n_0	Curve[2]	Parameters		$\bar{R}^2$
				$\bar{\sigma}$	$\bar{\gamma}$	
All subjects	239	24	IP	17.93 (47.28)	2.70 (17.91)	0.967
Oil A	207	23	IP	13.32 (40.94)	2.25 (16.84)	0.971
Oil B	32	1	Gompertz	3.742 (32.31)	0.032 (26.40)	0.971
Cassava consumption	130	12	IP	16.04 (39.19)	2.30 (13.65)	0.976
No cassava consumption	109	12	IP	19.77 (31.06)	3.21 (12.26)	0.970
Boys	113	12	IP	19.09 (49.64)	1.84 (11.52)	0.985
Girls	126	12	IP	16.11 (23.87)	2.23 (16.85)	0.969

[1] Students t-values are given in parentheses.
[2] See text for description of the curves.

respectively, that describe shapes of the respective CFD functions for subjects with different characteristics have been summarized in **Table 2.** In addition, the corresponding squares of multiple correlation coefficients adjusted for the number of parameters estimated ($\bar{R}^2$) have been given for each curve that fits the CFD. The percentage of non-responders to iodized oil was 10.4 % in the total group. For those subjects who had received oil B the percentage of non-responders was 3.1 % which is significantly lower than for those who had received oil A (11.1 %). For all other groups the percentage of non-responders were distributed between 9.2 and 11.8 %.

In **Table 3** the estimated times (w), per study group, are given at which 25 %, 50 % and 75 % of the subjects have urinary iodine concentration below 0.40 μmol/L again after oral dosing with iodized oil using the parameters $\bar{\sigma}$ and $\bar{\gamma}$ **(Table 2)** that describe the curve that fits each specific CFD of T_i^* per study group best.

The CFD of T_i^* for subjects who had or who had not consumed raw cassava are both characterized by IP curves (Figures not shown). For subjects who had eaten cassava the IP curve converges to unity (100 %) faster than the IP curve for subjects who had not eaten cassava. This implies that the duration of effectiveness of oral iodized oil is reduced by the consumption of cassava. The cassava consumers reach a prevalence of 50 and 75 % of urinary iodine concentrations below 0.40 μmol/L in a shorter period of time than those who did not consume raw cassava (**Table 3**). The difference in the duration of effectiveness being 2.9 and 10.3 weeks respectively. At group level cassava consumers were found to retain the iodine better than those who had not consumed cassava, but the elimination rate of iodine was also significantly increased for cassava consumers. The estimated mean durations of effectiveness of oral iodized oil at group level were 16.8 and 21.0 weeks for cassava consumers and non-cassava consumers respectively (data not shown).

The CFD of T_i^* and thus the IP curve for boys approaches 1 (100%) more slowly than for girls (Figure not shown). This indicates that the duration of effectiveness of iodized oil is longer for boys than for girls. For the girls a prevalence of 25, 50 and 75 % of urinary iodine concentrations below 0.40 μmol/L is reached in a shorter period of time than for the boys (**Table 3**) the difference in time being 2.4, 4.4 and 10.3 weeks respectively. At group level the boys were found to retain iodine significantly better than girls although their iodine elimination rate was slightly lower. The estimated mean **Table**

3 Estimates of the prevalence of iodine deficiency, as measured by urinary iodine concentration, after oral dosing with iodized oil for school aged children with different characteristics using cumulative frequency distributions of individually assessed durations of effectiveness[1]

	Time, in weeks, after oral dosing with iodized oil at which 25, 50 and 75 % of the subjects have their urinary iodine concentration dropped below 0.40 μmol/L		
	25%	50%	75%
All subjects	3.3 (0.11)	15.2 (0.30)	51.1 (1.04)
Oil A	2.2 (0.10)	11.1 (0.25)	37.7 (0.89)
Oil B	31.4 (0.78)	53.2 (1.42)	81.0 (2.41)
Cassava consumption	3.1 (0.13)	13.7 (0.32)	45.8 (1.12)
No cassava consumption	3.4 (0.19)	16.6 (0.50)	56.1 (1.74)
Boys	4.5 (0.13)	17.3 (0.31)	55.4 (1.06)
Girls	2.1 (0.19)	12.9 (0.51)	45.1 (1.83)

[1] SE are given in parentheses.

durations of effectiveness at group level were 20.6 and 16.8 weeks for boys and girls respectively (data not shown).

Discussion and conclusions

In this study we have shown that the cumulative frequency distribution (CFD) of the individually assessed duration of effectiveness of orally administered iodized oil can be described by either a concave function (IP-curve) or a sigmoid function (Gompertz-curve). Both curves describe a relationship between the duration of effect and time, therefore they can be used to estimate the prevalence of iodine deficiency in a population at any time after oral dosing with iodized oil. From our data it appears that in case of a poor efficacy of orally administered iodized oil, as with oil A, the CFD of the individually assessed duration of effectiveness is concave shaped and is thus characterized by an IP curve. By an improved duration of effectiveness the CFD of the individually assessed duration of effectiveness takes the shape of the sigmoid function and it therefore

best characterized by the Gompertz curve as for oil B in this study. The difference in the efficacy of the two types of iodized oil was already established in a previous study (3). An oil type in which the iodized fatty acids are present as triacylglycerol esters (oil B) was found to be retained better than a type of oil in which the iodized fatty acids are present as ethyl esters (Chapter 3). We did not measure faecal excretion of iodine after oral dosing with iodized oil therefore we were unable to pronounce upon a distinction in the absorption of the two types of oil. However, the difference in retention of the two types of oil is likely due to a difference in the absorption mechanism of ethyl esters and triacylglycerol esters from the intestine although oil B contained 27 % more iodine. This notion is supported by the fact that in the present study the percentage of non-responders is much higher for those who had received oil A than for those who received oil B.

For consumers of raw cassava an increased retention of iodine was observed. However, the elimination of iodine after oral dosing with iodized oil was also increased and to such an extent that the duration of effectiveness of oral iodized oil was shorter compared to those who did not consume raw cassava. In accordance with these findings the prevalence rate of iodine deficiency, based on urinary iodine concentration, was higher for those who consumed raw cassava. Cassava contains a cyanogenic glycoside linamarin, which is converted primarily to thiocyanate in the body. It is suggested that cassava consumption plays a direct role in causing endemic goiter as thiocyanate progressively reduces the thyroid function by accelerating the loss of iodine from the gland (4). In a previous study an increased retention of iodine after oral dosing with iodized oil was also observed for goitrous subjects (Chapter 5). Further, an increase was observed for the iodine elimination although this did not result in a decrease in the duration of effectiveness of the orally administered iodized oil as observed for consumers of raw cassava. For goiter the increased retention can be explained by an increased activity of the iodine trapping thyroid pump (12,13). The increased iodine elimination rate in goitrous subjects can be explained by a mechanism in the thyroid gland itself to eliminate excess iodine which was initially taken up as a result of the increased thyroidal iodine clearance rate (14). In the present study the prevalence of total goiter was the same for those who did and did not consume raw cassava which may be due to age. It may be expected that for those subjects who consume raw cassava the thyroidal iodine clearance rate is increased to compensate for the accelerated loss of iodine from the thyroid gland

due to presence of thiocyanate. This would explain the increased retention of iodine after oral dosing with iodized oil for the subjects who consumed raw cassava in this study. Although some iodine will be lost from the thyroid due to a mechanism in the thyroid gland itself to eliminate excess iodine, the increased iodine elimination rate for raw cassava consumers may primarily be explained by the impact of thiocyanate on the thyroid function. In this study we have shown that in populations where raw cassava is consumed oral iodized oil will need to be administered more frequently than in areas where no raw cassava is consumed in order to maintain an effective iodine prophylactic measure.

The 8, 9, and 10-y-old girls in this study showed a significantly increased prevalence rate of iodine deficiency after oral dosing with iodized oil compared to the boys of the same age group in this study. In this study more girls were found to suffer from goiter than boys. With regard to the results of a previous study (Chapter 5), in which the duration of effectiveness of oral iodized oil was increased for goitrous subjects, it was expected that the prevalence rate of iodine deficiency after oral iodized oil administration would have been lower for girls than for boys. However, the opposite was observed and may possibly be explained by age-related changes in thyroid hormone production (T_4 and T_3) and changes in the concentration of plasma proteins that carry the thyroid hormones in the plasma. Thyroxine-binding globulin (TBG), T_4 and T_3 have been found to drop slightly between 1 and 15 years (15), and thyroxine-binding prealbumin (TBPA) has been found to increase during this period of life (16,17). Further, estrogens have been found to increase the serum concentrations of TBG which results in an increase in serum total thyroxine and in a decrease of T_4 and the fractional turnover of this hormone (18-20). Opposite effects have been observed for androgenic hormones (18). It may be possible that the rate of age-related changes in thyroid hormone production and their availability are different for 8 to 10 years old boys and girls. However, we did not collect blood samples in this study to investigate the proposed explanations for the difference in efficacy of oral iodized oil between boys and girls. Further research, using appropriate indicators, is needed to obtain information on the role of hormones in the effectiveness of iodine prophylaxis.

With a minimum of three observation per individual it is possible to compare the efficacy of oral iodized oil, measured as the decline of urinary iodine concentration in

casual urine samples with time (3). It may be worthwhile to reconsider studies on the effectiveness of oral iodized oil which have been carried out in the past in order to make them comparable. Using the models as proposed in this paper it is now possible to estimate the prevalence of iodine deficiency after oral dosing with iodized oil. They will be helpful for evaluating iodine supplementation programs using oral iodized oil. Knowledge about the impact of factors that influence the efficacy of oral iodized oil will contribute to identifying people at risk for iodine deficiency despite prophylactic measures taken. An additional advantage of the methods proposed for estimating the efficacy of oral iodized oil is that those people who do not respond to oral iodized oil, in terms of adequate urinary iodine concentrations, can be identified. For research purposes this group may be useful in providing additional information on factors that influence the efficacy of oral iodized oil.

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7 General discussion

Endemic goiter is easy to prevent. For developed countries and a number of developing countries this confident remark has been fully justified by subsequent experience. Many countries have been using prophylactic iodine for quite some time and the incidence of iodine deficiency disorders has notably declined in these countries. Despite available and feasible methods to combat iodine deficiency, using mainly iodized salt or iodized oil, approximately 1,000 million people, of which the majority reside in developing countries, receive insufficient iodine and suffer from its consequences (1).

Presently most countries have met political agreement on implementing iodization programmes and are in the process of planning them. Ideally the method of choice for controlling iodine deficiency is salt iodization. This method is justified when the production or import of high quality iodized salt is centralized and liable to quality control. Furthermore, the networks for commercial salt distribution should be extensive and the price of iodized salt should be cheap. Many developing countries will have to tackle technical, geographical or political problems before they can successfully implement iodized salt programmes (2). As long as salt cannot be used as a fortification vehicle, oral iodized oil is ideally suited for immediately attacking the problem of IDD.

Iodized oil can be given either by injection or orally. The duration of effectiveness of injected iodized oil exceeds that of oral iodized oil by far and may thus appear to be the most convenient and effective method for iodized oil administration. However, there are a number of shortcomings attached to injecting iodized oil. Although the chances for local inflammatory reaction at the injection site are trivial, it is a painful experience to receive the iodized oil intramuscularly. In order to minimize the complications associated with injecting the medical team should be thoroughly trained in aseptic techniques and skills. To diminish the chances of spreading highly infections diseases either disposable syringes and needles are needed or equipment should be available to ensure proper sterilization of the instruments. Fielding the injection team which includes salaries, food, lodging and transport will greatly contribute to the additional costs of an iodized oil injection program. Against the rather high expenses are the benefits of a procedure which

may protect the population for 3 to 5 years.

Oral iodized oil, either as capsules or by using a dispenser, can be administered by any responsible person such as a primary health care worker or a school teacher. Besides the cost of iodized oil, import expenses, if any, and transportation, if an existing distribution network of medical goods does not exist, the expenses of an oral iodized oil program are substantially reduced. Despite a high variability in the duration of effectiveness (3-8), oral iodized oil has been winning ground since 1974.

It is quite complicated and often impossible to obtain data on the actual iodine intake in most populations. For most nutrients the intake can be calculated using food composition tables. However, the iodine content of food and water is know to vary to such an extent that this method does not apply to its intake. Therefore, iodine status is often evaluated by indirect indices of which daily urinary iodine excretion is considered the most precise (9). As it is often very difficult to obtain accurate collection of 24-h urine samples it has been proposed that the ratio between the concentration of iodine and creatinine in casual urine samples be used to assess the iodine supply of populations (10-12). The value of this ratio rests upon the assumption of a constant excretion of creatinine each day. However, in a recent study, carried out among Malawian school children with a median urinary iodine concentration of 0.16 μmol/L, we observed large inter and intra individual variations in daily urinary creatinine concentration. Furthermore, the ratio between urinary iodine and creatinine correlated significantly with the creatinine excretion. Thus we have concluded that the iodine-creatinine ratio in casual urine samples is an unsuitable indicator for evaluating iodine status (Chapter 2 of this dissertation). Despite a high variation in daily iodine excretion the assessment of iodine concentration in causal urine samples remains a valuable method to evaluate iodine status. We have suggested that calculating an average iodine concentration of casual urine samples collected on consecutive days per individual enhances the precision of this index.

The efficacy of oral iodized oil is determined as a combination of the retention of iodine in the body and the rate of iodine excretion in the urine. A model can be used to describe the urinary iodine excretion pattern over time after oral iodized oil administration thus allowing for the assessment of the duration of effectiveness and to study factors which may affect the retention and elimination of iodine (Chapter 3 of this dissertation).

Cumulative frequency distributions of individually assessed durations of

effectiveness very conveniently describe the prevalence rate of iodine deficiency, based on urinary iodine concentrations, after oral iodized oil adminstration. Models can be used to describe these cumulative frequency distributions which may be very useful when evaluating oral iodized oil programmes for controlling iodine deficiency (Chapter 6 of this dissertation). An additional advantage is that information can be obtained on the number of non-responders. For research purposes this groups of non-responders may be useful in providing more information on factors that influence the efficacy of orally administered iodized oil

In general oral iodized oil has been used without consideration of factors that may affect the absorption of iodized oil and the retention and elimination of iodine. From experience it is clear that the efficacy of oral iodized oil often leaves much to be desired. However, it must be kept in mind that the studies on the effectiveness of oral iodized oil have been carried out by different investigators at different geographical locations using different methods, indices and time schedules. This makes it impossible to draw a univocal conclusion on the effectiveness of oral iodized oil.

In the study described in Chapter 3 we have shown that a single dose of an iodized oil in which the iodized fatty acids are present as triacylglycerol esters (675 mg iodine) has a duration of effectiveness of approximately one year whereas the duration of effectiveness of iodized oil (490 mg iodine) which consists of a mixture of ethyl esters of iodized fatty acids, lasted only 3-4 months. The former, which is cheaper to produce, is more viscous than the latter but quite suitable for oral use both as capsules and from a dispenser.

From the results of our study on the impact of intestinal parasites we found that the effectiveness of iodized oil (ethyl esters of iodized fatty acids) was greatly improved by treating these infestations. For *Entamoeba histolytica* it appears that anti-parasitic therapy is imperative when iodized oil is administered orally since we found no effect of iodized oil in untreated subjects (Chapter 4 of this dissertation). This observation is almost certain due to a decreased absorption but systemic factors may also be involved. The question remains by which mechanism *Entamoeba histolytica*, a parasite of the colon, affects the absorption of the iodized oil since oil and fats, in general, are absorbed from the small intestine. Maybe ethyl esters, unlike triacylglycerol esters, are not absorbed from the small intestine but from the colon. In this case the influence of *Entamoeba*

histolytica may be overcome by giving an iodized oil preparation which consists of triacylglycerol esters of iodized fatty acids. However, more research is needed on the role of intestinal parasites of the small intestine on the effectiveness of such a type of iodized oil. This work should be extended to studies on the effectiveness of oral preparations of vitamin A.

Children with a relatively large amount of subcutaneous fat were found to retain the iodine from orally administered iodized oil better than those with little subcutaneous fat. Height-for-age, weight-for-height and midupper-arm circumference have no effect on either retention or elimination of iodine resulting in a significantly altered duration of effectiveness of oral iodized oil. No adverse effects were found for dramatic changes in nutritional status. In fact, a reduction in midupper-arm circumference was observed to increase the duration of effectiveness of iodized oil. From our study it appears that both fat and muscle tissue play an important role in the efficacy of orally administered iodized oil. In the scope of increasing the efficacy of oral iodized oil it is worthwhile to plan its distribution during that part of the year in which the people are relatively well fed. This in case the nutritional status of a population is liable to seasonal fluctuation.

Goitrous subjects were found to retain more iodine than non-goitrous subjects (Chapter 5 of this dissertation). This observation may be explained by the increased activity of the iodine pump which is known to occur when the thyroid is enlarged as a result of iodine deficiency (9). The partial autonomy of iodine trapping probably accounts for the persistent high uptake of iodine in human goiters after the administration of iodine supplements in general. The increase in iodine elimination in goitrous subjects may be the result of a intrathyroid mechanism to adjust its iodine content to its upper limit of iodine content.

In areas where cassava is consumed raw it may be necessary to plan a more frequent distribution of oral iodized oil as we found the prevalence rate of iodine deficiency after oral iodized oil administration to be higher for subject who had consumed cassava (Chapter 6 of this dissertation). Only the impact of raw cassava consumption was studied, but similar effects may be expected when other goitrogenetic factors are present (Chapter 1 of this dissertation). Planners of oral iodized oil programs should be aware of the impact of goitrogenetic substances on the duration of effectiveness.

In our study we also observed a statistically significant difference in the duration

of effectiveness of oral iodized oil between the old boys and girls. Further research, using appropriate blood parameters, is needed to explain this finding which indicates that girls, even when young, may need to receive oral iodized oil more frequently than boys.

Recommendations for the use of oral iodized oil

1. Oral iodized oil is extremely useful as an interim measure and in for controlling iodine deficiency as an interim measure until sufficient iodized salt is available to the whole population.
2. Oral iodized oil should consist of triacylglycerols of iodized fatty acids rather than ethyl esters of iodized fatty acids.
3. Oral iodized oil should be provided on an annual basis.
4. Oral iodized oil should be given towards the end of the post-harvest season. For Malawi this is in October.
5. The urinary iodine/creatinine ration is not an appropriate indicator to measure iodine status.
6. The median rather than the mean urinary iodine concentration should be considered when assessing iodine status at population level.
7. The evaluation of oral iodized oil programs can be improved by using the methods proposed in this dissertation.

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Summary

Iodine deficiency exists in areas where the soil has been depleted of iodine and the diet of the population consists predominatly of locally grown foods. Salt iodization is an inexpensive, highly effective means for preventing iodine deficiency. However, delays in achieving effective salt iodization in areas where iodine deficiency requires immediate attention demand an intermediate measure such as iodized oil given either by intramuscular injection or orally. Administration of iodized oil orally has practical advantages over intramuscular injections and has been used increasingly since 1974. However, the duration of effectiveness for orally administered iodized oil is much shorter, ranging from 6 months to two years, than for injected iodized oil.

The general aim of the studies described in this dissertation is to improve the effectiveness of oral administration of iodized oil in the controlling iodine deficiency. The specific aims are (1) to compare the duration of effectiveness of two types of oral iodized oil each containing the same dose of iodine given as a single dose. One type of oil (oil A) was initially developed for intramuscular injection and consisted of ethyl esters of iodized fatty acids. The second type of iodized oil (oil B) consisted of triacylglycerol esters of iodized fatty acids. (2) To compare the effect of splitting the dose of oil A into two equal portions and giving them on two consecutive days to the efficacy of the single dose of oil A; (3) to study the impact of treating intestinal parasitic infestations on the efficacy of orally administered iodized oil and; (4) to determine whether nutritional status, sex, energy balance and the consumption of raw cassava play a role in the retention and the elimination rate of iodine after oral dosing with iodized oil. In addition, the appropriateness of using the urinary iodine-creatinine ratio as an indicator for the iodine status was considered as all results are based on urinary iodine concentrations of casual urine samples. Further, methods are proposed to describe the urinary iodine excretion pattern over time after oral dosing with iodized oil.

The studies were carried out in Ntcheu District, Malawi, with 8, 9, and 10-y-old school children. All children were medically examined before the onset of the study, their thyroid gland was graded, the urinary iodine and creatinine concentration were

determined and weight, height, midupper-arm circumference and four skinfolds were measured. In addition, stool samples were examined microscopically for the presence of intestinal parasites. Those children with single intestinal parasitic infestations of either *Entamoeba histolytica, Ascaris lumbricoides* or hookworm were randomly selected to either receive anti-parasitic treatment either before or after oral dosing with iodized oil. All children with mixed infestations received anti-parasitic treatment before receiving iodized oil. These children were randomly allocated to receive either a single dose of oil A (490 mg iodine) or oil B (675 mg iodine), a split dose of oil A (2 x 245 iodine), a carbohydrate-rich drink immediately prior to receiving oil A, or neutral poppy seed oil (placebo). For follow up, anthropometric measurements were taken at two/three months intervals and their urinary iodine concentration was measured in three causal urine samples each taken on three consecutive days during the 4th, 8th, 20th, 40th and 44th w after oral dosing with iodized oil. All subjects were visited at their homes to verify the date of birth, sex and whether or not they consumed raw cassava.

All results are based on urinary iodine concentrations in casual urine samples. Due to large variations in day-to-day urinary iodine excretion it is often related to urinary creatinine. The inappropriateness of relating urinary iodine to urinary creatinine to correct for the large day to day variation in urinary iodine output was established in the study described in Chapter 2. In this study large inter and intra individual variations were observed for both the creatinine and iodine concentrations in two casual urine samples collected on consecutive days. Furthermore, the urinary iodine/creatinine ratio correlated significantly with the creatinine concentration. If creatinine were a suitable parameter to correct for variations in iodine excretion, no correlation would be expected. From these observations we concluded that the iodine/creatinine ratio in casual urine samples is an unsuitable indicator for evaluating iodine status. To compensate for the day-to-day variations in iodine excretion we suggest that an average iodine concentration be calculated from two or more casual urine samples each taken consecutive days.

Urinary iodine concentration reflects the mutual effects of the physiological mechanisms involved in iodine retention and elimination. In Chapter 3 a model is proposed which describes the urinary iodine excretion pattern, after oral iodized oil administration. In this model the efficacy of oral iodized oil is determined by the retention of iodine and its elimination rate. Subsequently, a duration of effect can be assessed

given a urinary iodine concentration of 0.40 μmol/L associated with moderate iodine deficiency (UNICEF/WHO/ICCIDD). The parameters, retention capacity and rate of elimination, that describe the model, were compared for subjects who had received either a single or split dose of oil A or a single dose of oil B. Compared to a single dose of oil A, the iodine retention of oil B was significantly higher. Although the iodine elimination rate was also increased for oil B the duration of effectiveness was significantly improved. The efficacy of splitting the dose of oil A into two equal amounts given on consecutive days did not improve compared to that of a single dose of oil A. The assessed duration of effectiveness was estimated to be 13.7, 9.9 and 55.2 weeks for a single dose of iodized oil A, a split-dose of oil A, and a single dose of iodized oil B, respectively. From this study we conclude that a single dose of oil type B, which consists of triacylglycerol esters of fatty acids, is much more effective compared to a single dose of oil A. Therefore oil B should be used for controlling iodine deficiency rather than oil A.

The effect of treating intestinal parasites (*Entamoeba histolytica* (cyst passers), *Ascaris lumbricoides* and hookworm) in general and for each parasite specifically on the efficacy of orally administered iodized oil type A for controlling iodine deficiency has been described in Chapter 4. Treating intestinal parasitic infestations in general increased the duration of effectiveness of oral iodized oil with approximately 2 months. Treating *Entamoeba histolytica* specifically improved the duration of effectiveness from 2.0 to 21.0 weeks ($p < 0.05$). In fact, it appears that the absorption of iodized oil is greatly disturbed for *Entamoeba histolytica* cysts passers. *Entamoeba histolytica* is a parasite of the large bowl, and fats and oil are absorbed from the small intestine. A possible explanation for the observed effect of this amoeba may be that ethyl esters of fatty acids are not absorbed from the small intestine from the colon. Therefore, the problem of decreased absorption may be overcome be giving an iodized oil preparation in which the fatty acids are present as triacylglycerol esters. In this case the impact of intestinal parasites of the small intestine such as *Ascaris lumbricoides* and hookworm will need to be reconsidered.

The relation between nutritional status and the efficacy of oral iodized oil for controlling iodine deficiency was established in Chapter 5. Children with a relatively high sum of skinfolds, indicative of a relatively large subcutaneous fat mass, were found to retain more iodine than subjects with little subcutaneous fat. The duration of effectiveness

was increased by approximately 8 weeks for those with a high sum of skinfolds compared to those with a low sum of skinfolds. Although the initial midupper-arm circumference, indicative of protein-energy status, revealed no effect on the efficacy of orally administered iodized oil, a reduction in midupper-arm circumference prolonged the duration of effectiveness. This observation suggests that iodine is also stored in muscle tissue. For goitrous subjects both retention and elimination of iodine were significantly increased. The duration of effectiveness was approximately 4 months longer for the goitrous subjects compared to those without goiter.

In Chapter 6 methods are proposed to assess the prevalence rate of iodine deficiency and the number of non-responders. In this study, frequency distributions of individually assessed durations of effectiveness, using urinary iodine concentrations, after oral iodized oil administration are considered for subjects with different characteristics. These methods were used to compare the efficacy of the two types of oral iodized oil and to compare the efficacy for boys and girls and for those who did or did not consume raw cassava. The prevalence rate for subjects who had received oil A increased faster than for those who had received oil B. The number of non-responders to oral iodized oil was lower for oil B (3.1 %) than for oil A (11.1 %). The prevalence of iodine deficiency increased faster for girls and for consumers of raw cassava than for boys and those who did not consumed raw cassava, respectively.

In Chapter 7, the results and conclusions are discussed and a number of recommendations to improve the efficacy of oral iodized oil and to facilitate its evaluation are given. In short, oral iodized oil is a suitable prophylactic measure until iodized salt is readily available. However, the preparation should consist of triacylglycerols of iodized fatty acids and is preferably given at the end of the post-harvest season on an annual basis. In case of limited sources girls should have priority in receiving the iodized oil.

For research purposes the median urinary iodine concentration should be considered rather than its mean. To correct for the highly variable output of iodine in the urine an average urinary iodine concentration, assessed in two or more casual urine sample taken on consecutive days per person, can be calculated. A hyperbolic function describes the urinary iodine excretion over time after oral dosing with iodized oil and requires a minimum of three observations at different time points for a relatively small number of subjects. Information on the prevalence rate of iodine deficiency and the

percentage of non-responders, based on urinary iodine concentrations, can be obtained using cumulative frequency distributions of individually assessed durations of effectiveness.

Samenvatting

Een tekort aan jodium in het menselijk lichaam komt voor in gebieden waar geen jodium meer in de bodem voorkomt en waar de bevolking hoofdzakelijk van lokaal verbouwde produkten leeft. De meest bekende aandoening ten gevolge van jodiumgebrek is een zwelling van de schildklier die zichtbaar is in de hals. Dit wordt krop of struma genoemd. Naast krop kan een tekort aan jodium het risico op miskramen, zuigelingesterfte en aangeboren afwijkingen verhogen. De ernstigste aangeboren afwijking is cretinisme (dwerggroei), dat gepaard gaat met doofstomheid, arm- en beenverlammingen en idiotie. De ernst van de lichamelijke en/of geestelijke onderontwikkeling is afhankelijk van de mate van jodiumgebrek.

Jodium deficiëntie kan gemakkelijk worden voorkomen door het gebruik van gejodeerd zout. In veel Derde Wereld landen is echter de verkrijgbaarheid van gejodeerd zout echter (nog) niet gegarandeerd. Ondanks dat er op het ogenblik overal ter wereld maatregelen worden getroffen voor de produktie van gejodeerd zout, blijft het de vraag of men daadwerkelijk op korte termijn hierover zal kunnen beschikken. Zolang de produktie en/of distributie van gejodeerd zout onvoldoende is, zullen andere middelen ter hand genomen moeten worden om dit gebrek te bestrijden. Het gebruik van gejodeerde olie is een goed alternatief en is reeds op grote schaal toegepast. Vroeger werd gejodeerde olie geïnjecteerd; een pijnlijke, kostbare, maar zeer effectieve maatregel die een paar jaar bescherming biedt tegen jodiumdeficiëntie. Later werd deze olie oraal toegediend in de vorm van capsules. Ondanks een veel kortere effectiviteitsduur werd deze methode van jodiumdeficiëntie-bestrijding populair omdat het goedkoper, veiliger en gemakkerlijker is dan injecteren.

De studies beschreven in dit proefschrift, trachten inzicht te krijgen in de faktoren die mogelijk van invloed zijn op de effectiviteit van oraal toegediende gejodeerde olie.

De specifieke onderzoeksdoelstellingen waren (1) het vergelijken van de effectiviteit van twee typen gejodeerde olie te vergelijken waarvan type A ethylesters van gejodeerde vetzuren bevat en type B triacylglycerolesters van gejodeerde vetzuren. Beide olieën zijn op basis van papaverzaad en bevatte ongeveer evenveel jodium per dosis; (2) het vergelijken van de effectiviteit van olie A wanneer deze als enkele dosis of in twee

keer de helft geven wordt op twee opeenvolgende dagen; (3) om de invloed van darmparasieten op de effectiviteit van oraal toegediende olie A vast te stellen; (4) om na te gaan of voedingsstatus, energie balans, het hebben van een vergrote schildklier en het consumeren van rauwe cassave van invloed zijn op de retentie en/of de uitscheidingssnelheid van jodium na orale toediening van gejodeerde olie A, en of bij jongens en meisjes verschillen optreden.

Het onderzoek vond plaats in het district Ntcheu in Malawi. De proefpersonen waren 8 tot 10 jaar oude schoolkinderen afkomstig van 4 lagere scholen. Voor toediending van de gejodeerde olie werden alle kinderen medisch onderzocht. Verder werden de grootte van hun schildklier vastgesteld, de jodium en creatinine concentraties werden in twee urine monsters bepaald, en gewicht, lengte, middenbovenarmomvang en de dikte van 4 huidplooien (biceps, triceps, subscapula en supra-iliaca) werden gemeten. Kinderen met een vergrote lever, een vergrootte milt of een middenbovenarmomvang kleiner dan 15,5 cm werden niet in het onderzoek opgenomen. Alle proefpersonen werden onderzocht op darmparasieten. Een kleine groep kinderen met slechts één soort darmparasiet werd pas na toediening van de gejodeerde olie (type A) behandeld tegen de soort darmparasiet. Alle andere kinderen werden, indien nodig, tegen hun darmparasieten behandeld twee weken vóór dat ze gejodeerde olie kregen en werden ingedeeld in verschillende behandelingsgroepen (olie A met 490 mg jodium, olie B met 675 mg jodium, 2 keer de helft van olie A op twee opeenvolgende dagen, een energie-rijk drankje vlak voor de toediening van olie A, of neutrale papaverzaad olie). Na toediening van de gejodeerde olie werden, met tussenpozen van 2/3 maanden, de anthropometrische metingen herhaald. Gedurende de 4de, 8ste, 20ste, 40ste en 44ste week werden per persoon drie urine monsters verzameld op drie opeenvolgende dagen. Van ieder monster werd de jodiumconcentratie bepaald.

Alle resultaten in dit proefschrift zijn gebaseerd op jodium concentraties in de urine. Omdat de jodiumuitscheiding een grote fluctuatie van dag to dag vertoont wordt deze vaak gerelateerd aan de concentratie van creatinine in het zelfde monster. De uitscheiding van creatinine in de urine wordt verondersteld constant te zijn en onafhankelijk van de jodium uitscheiding. Naar aanleiding van de resultaten van de studie, die beschreven is in hoofdstuk 2, werd besloten om de jodium/creatinine-verhouding niet te gebruiken aangezien de onafhankelijkheid van deze maatstaf niet

was gegarandeerd.

In hoofdstuk 3 wordt een model geïntroduceerd, dat het niet-linieare uitscheidingspatroon van jodium in de urine beschrijft tussen de 4 en 44 weken na toediening van de gejodeerde olie. Dit model is een hyperbool die de omgekeerd evenredige relatie beschrijft tussen de opname-capaciteit voor jodium en de snelheid, waarmee de jodium wordt uitgescheiden. Met behulp van dit model kan een effectiviteitsduur berekend worden voor een bepaald type olie of voor proefpersonen met een bepaald kenmerk. Hiervoor dient een waarde vastgesteld te worden voor een jodium concentratie in de urine die geassociëerd wordt met jodiumgebrek (0.40 μmol/L; door UNICEF, de Wereldgezondheidsorganisatie en ICCIDD (International Council for Control of Iodine Deficiency Disorders) vastgesteld voor middelmatig jodiumgebrek). Deze methode werd gebruikt om de effectiviteit te bepalen van olie A, olie B en voor olie A wanneer de dosis in 2 keer de helft werd toegediend. Uit het onderzoek bleek dat de opname-capaciteit voor olie B hoger is dan voor olie A en dat de uitscheidingssnelheid lager is voor olie B. De effectiviteitsduur voor olie B is 55.2 weken. Voor een enkele en een gedeelde dosis olie A is dat slechts 13.7 en 9.9 weken. De conclusie is dan ook dat alleen olie B in aanmerking dient te komen voor orale toediening. De effectiviteitsduur van olie A wordt niet verlengd door de dosis over twee opeenvolgende dagen te verdelen.

In hoofdstuk 4 wordt gekeken naar het effect van behandelingen tegen darmparasieten op de effectiviteit van olie type A. Het verschil in effectiviteitsduur tussen de behandelde en onbehandelde proefpersonen, ongeacht de darmparasieten soort, was ongeveer 2 maanden. In deze studie was het effect van het niet behandelen tegen *Enamoeba histolytica* opmerkelijk; de effectiviteitsduur van olie A bedroeg slechts 2 weken. Voor kinderen die wel behandeld waren tegen deze darm parasiet was de effectiviteitsduur 21 weken. Dit betekent dat deze amoebe waarschijnlijk de absorptie van olie A verstoort. *Entamoeba histolytica* houdt zich op in de dikkedarm. Gezien het feit dat de absorptie van vet plaats vindt in de dunne darm, zijn de resultaten voor wat deze amoebe betreft moeilijk te verklaren. Een mogelijke verklaring is dat de absorptie van ethylesters van vetzuren, zoals in olie A, niet vanuit de dunnedarm maar vanuit de dikkedarm plaatsvindt. Als dit inderdaad het geval zou zijn, dan kan dit probleem mogelijk opgelost worden door een gejodeerde olie te kiezen die uit triacylglycerolen bestaat, zoals olie B, aangezien de absorptie van triacylglycerolen plaatsvindt in de

dunnedarm. Het effect van *Ascaris lumbricoides* en mijnworm, beide parasieten van de dunnedarm, op de effectiviteit van olie B zal dan opnieuw onderzocht moeten worden.

In hoofdstuk 5 wordt de rol die de voedingstoestand van de proefpersonen speelt in de effectiviteit van gejodeerde olie ter bestrijding van jodium deficiëntie bestudeerd. Kinderen met relatief veel subcutaan vet hebben een verhoogde retentiecapacitieit en daardoor een langere effectiviteitsduur vergeleken met kinderen met subcutaan vet hebben. Gejodeerde vetzuren worden waarschijnlijk opgeslagen in het vetweefsel. Een afname in bovenarmomvang, een indicatie voor de eiwit-energie voedingstoestand, leidde tot een verlengde duur van effectiviteit. Dit suggereert dat jodium ook in het spierweefsel wordt opgeslagen. Naar aanleiding van deze resultaten is het advies dat gejodeerde olie het beste op een moment toegediend kan worden wanneer de voedingstoestand van de mensen optimaal is. Voor Malawi is dit aan het einde van het oogstseizoen, in oktober. De kinderen met krop bleken een veel hogere opname capaciteit voor jodium te hebben en, ondanks een eveneens hogere uitscheidingsnelheid, was de effectiviteitsduur ongeveer 4 maanden langer in vergelijking met kinderen zonder krop. De verhoogde opnamecapaciteit kan verklaard worden door een verhoogde activiteit van de schildklier om jodium op te nemen. Een mechanisme in de schildklier, om vervolgens van het jodiumoverschot af te komen, is waarschijnlijk verantwoordelijk de verhoogde uitscheidingssnelheid.

In de hierboven beschreven onderzoeken werden de patronen in jodiumuitscheiding voor kinderen met bepaalde karakteristieken vergeleken op groepsniveau. In hoofdstuk 6 wordt de effectiviteitsduur per individu berekend. Een frequentie verdeling van de individueel berekende duur van effectiviteit werd uitgezet tegen de tijd. Dit geeft informatie over de prevalentie van jodiumdeficiëntie op willekeurige tijdstippen na de behandeling. Op deze manier kon de effectiviteit van olie A worden vergeleken met die van olie B. Tevens kon hierdoor worden vastgesteld hoeveel proefpersonen geen baat hadden bij de behandeling. De prevalentie van jodium deficiëntie steeg aanzienlijk sneller voor de proefpersonen die olie A hadden toegediend gekregen. Het aantal proefpersonen dat geen baat had bij de behandeling was lager voor olie B (3.1 %) dan voor olie A (11.1 %). Voor meisjes en voor diegenen die rauwe cassava consumeren blijkt dat de prevalentie voor jodium deficiëntie sneller toeneemt dan voor jongens en voor diegenen die geen rauwe cassave eten. De conclusie luidt dat meisjes

meer jodium nodig hebben of frequenter gedoseerd moeten worden dan jongens. Hetzelfde geldt voor personen die rauwe cassave consumeren.

Tot slot worden in hoofdstuk 7 aanbevelingen gedaan om het gebruik van orale toediening van gejodeerde olie zo effectief mogelijk te laten plaatsvinden, en om de evaluatie van programma's, waarin gejodeerde olie oraal wordt toegediend, te vergemakkelijken. Als noodoplossing is gejodeerde olie uitermate geschikt voor oraal gebruik mits de olie uit triacylglycerolesters van gejodeerde vetzuren bestaat. Deze olie moet één maal per jaar toegediend worden, bijvoorkeur aan het einde van het oogstseizoen. Wanneer er onvoldoende gejodeerde olie beschikbaar moeten meisjes en vrouwen de voorkeur genieten boven jongens en mannen.

Voor evaluatie en onderzoeksdoeleinden is het beter om naar de mediaan van de jodiumconcentratie in urine te kijken in plaats van het gemiddelde aangezien de jodium-concentraties niet normaal verdeeld zijn. De jodium concentratie in de urine dient niet te worden gerelateerd aan de creatinine concentratie. Het probleem van dag tot dag variatie in de jodium concentratie van urine monsters kan ondergevangen worden door het bereken van een gemiddelde van monsters die op opeenvolgende dagen genomen zijn. De uitscheiding van jodium in de urine na orale toediening van gejodeerde olie kan gejodeerde olie kan beschreven worden door een wiskundige model. Met een minimum van drie meetpunten in de tijd kan van een relatief kleine groepen mensen de effectiviteitsduur worden berekend in een bepaalde populatie. De frequentie verdeling van de individueel berekende effectiviteitduur biedt de mogelijkheid om informatie te krijgen over de prevalentie van jodiumdeficiëntie op ieder gewenst tijdstip na toediening van de gejodeerde olie.

Curriculum Vitae

Anna Catharina Furnée was born in Ahwaz, Iran, on the 8th of March 1962. She obtained her V.W.O. diploma in 1982 after taking state exams. She started her study in Biological Health Sciences in 1984. During her years of study she had three major periods of practical training. The first one was on the subject of gas chromatography for detection of indoor air pollution and was carried out at the Department of Industrial Medicine of the University of Limburg. The second one was to obtain a degree in laboratory animal science at the University of Utrecht. The last practical period was spent at the Department of Biological Health Sciences on a project on the carcinogenetic properties of anti-oxidants used in foods to prolong shelf-life. In 1989 she graduated at the Faculty of Health Sciences of the University of Limburg. That same year she was enroled in the Ph.D. research program of the Department of Human Nutrition of the Wageningen Agricultural University, Wageningen, The Netherlands. She took a course in medical parasitology in 1990 at the Medical School of the University of Nijmegen and attended the 1992 Summer Conference of the New England Epidemiology Institute, Boston, USA.


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