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Estimation of the fraction of an ingested dose of fluoride excreted through urine in pre-school children

Alberto Villa, Gabriela Salazar, Mireya Anabalón and Lorena Cabezas
Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile

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Abstract – *Objective:* To determine the fraction of an ingested fluoride dose of 1 mg in 50 mL orange juice that is excreted through the urine (FUEF) of children aged 3–5 years. *Methods:* Eighty-eight controlled determinations involving 24-hour urinary collections from a total of 48 children were carried out during consecutive control and test days. Net fluoride urinary excretion due to the ingested dose was calculated as the difference between the total amount of fluoride excreted by each child on test and control days. *Results:* Excretion of the fluoride ingested from the single fluoride dose presented an average value of 30.7% (95% CI: 28.9–32.5%). No significant associations were found between individual FUEF values with either anthropometrical variables or urinary pH values. The average FUEF value found in the present study lies between previously reported values for infants and young adults. The epidemiological usefulness of the FUEF values in estimating daily fluoride dose in pre-school children is discussed.

Key words: fluoride excretion; fluoride monitoring; urinary fluoride

Alberto E. Villa, INTA, Universidad de Chile, Casilla 138–11, Santiago, Chile
Tel/fax: (+56-2) 221 2249
e-mail: avilla@uec.inta.uchile.cl

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The relationship between the prevalence and severity of enamel fluorosis and an excessive ingestion of fluoride (F) during early childhood has been clearly demonstrated (1). In order to determine how much F is excessive as an average chronic ingestion from birth to 6–8 years old it is usual to estimate the total daily fluoride intake (TDFI) in terms of body weight. Several reports have dealt with this kind of estimation after typical market-basket surveys of the frequency of ingestion of such foods and beverages by children in certain age groups (2–6). More recently, TDFI values were estimated through the duplicate diet method (7–9). A comparison is then made of the TDFI data and the so-called optimal dose range of values repeatedly quoted as 0.05–0.07 mg F/kg body weight (3, 5, 10). The origin and appropriateness of the optimal dose of ingested fluoride have been recently reviewed (2, 11).

This approach to the estimation of TDFI values presents several limitations: a) most of the studies related to the estimation of TDFI ranges were carried out in North America (2–7, 11) and some in Europe (12, 13) and New Zealand (8, 9). Thus, these ranges are not necessarily applicable to other situations such as those occurring in developing countries where dietary habits, water consumption and use of fluoridated dental products may be different; b) the varying degree of F absorption from the gastro-intestinal tract from different foods, beverages and fluoridated dental products adds to the uncertainty when relating TDFI values for young children to eventual enamel fluorosis in their permanent dentition; c) the different values of TDFI leading to a certain degree of enamel fluorosis suggested by different reports (2, 12–15) indicate imprecise estimations, which in turn lead to uncertainties when trying to establish the safety of cer-

tain fluoride exposures for a given community; d) continuous changes in patterns of F ingestion might limit the value of previously determined values of TDFI for certain communities; and e) the experimental work involved in determining minute amounts of fluoride in a great number of foods, beverages and other items is often cumbersome and costly.

In spite of the above limitations, the TDFI approach is still considered useful (2, 11), although other methods based on F urinary excretion measurements might prove at least as good as the TDFI approach, being both easier to perform and physiologically more meaningful (16–20).

Several studies attempted to establish relationships between fluoride exposure and urinary F concentrations in groups of subjects. Urinary fluoride concentrations have been used to monitor F exposure of workers in aluminium smelters (21–23), and empirical associations between optimal concentrations of fluoride in tap water and urinary fluoride concentrations have also been used in earlier studies (24, 25) based on the apparent similarity of both values when fluoride levels in potable water were higher than 0.5 mg/L (26, 27). More recently, measuring the rate of urinary fluoride excretion was recommended as an adequate method for monitoring fluoride intake in children consuming either fluoridated salt or fluoridated water (18), and there is one report dealing with 24-h urine collection in an effort to estimate fluoride intake among 4-year-old children from Sri Lanka and England (16). Rates of F urinary excretion are currently being used to monitor several fluoridation programmes (28–31).

In order to establish useful associations between any fluoride urinary excretion related parameter and daily fluoride intake among pre-school children it would be necessary to assess the fraction of F that is excreted through the urine from the TDFI under usual conditions of ingestion. In addition, data on fractional fluoride urinary excretion from an ingested dose for this age group are lacking. For young adults, this fractional value has been quoted as ''approximately'' 50% (18, 32) although the range of experimental values reported in several pharmacokinetic studies is 41–47% (33–36) depending on certain metabolic conditions. More recently, an average value of 16.7% was determined for the fractional urinary excretion of fluoride (FUEF) among infants 37–410 days old (37). A previous study used results from a dog model to estimate a range of FUEF values for children (32). In spite of the usefulness that the estimation of the fractional urinary fluoride excretion in pre-school children would have, only scarce information on the experimental determination of this value is available (38, 39).

Previous assessments of FUEF in infants (37) and in young adults (33–36) were carried out under single and multiple dose conditions. Values of the fractional urinary excretion of F from the usual sources of fluoride may differ under stable F intake conditions and have still not been determined for different age groups, with the exception of a recent study on infants carried out on a limited number of subjects (40).

Taking into account all the above information, and the recommendations previously made on the need to determine FUEF in pre-school children (32, 41), this paper reports on the fractional urinary excretion of fluoride from a single ingested dose, in children aged 3–5 years, comparing it with previously reported values for other age groups.

Material and methods

The study protocol was approved by the Ethics Committee of INTA, University of Chile. Informed consent was obtained from the authorities and personnel in charge of the children (''tías'') at ''Hogar Las Nieves'', a privately funded institution that takes care of orphans and abandoned infants and young children who live permanently at the institution facilities. This institution is located in Santiago, the capital city of Chile (500–700 m above sea level), with adjusted fluoride concentration (0.6 mg/L) in its potable water. Studies reported in this paper were conducted in April (early autumn) and October (mid-spring) 1997. Tap water samples were frequently taken at the participating institution, and their fluoride concentrations were determined in our laboratory.

Subjects

Fifty-six children aged 34–61 months at the beginning of the studies (March 1997) were clinically examined by a paediatrician and found to be healthy. Their height and weight were recorded every month. Forty-eight children (25 girls and 23 boys), whose weights and heights were within ±1 Z-score relative to the mean values for growth curves adapted by the Chilean Ministry of Health from international standards (42), were included in the present study. The selection of the sample was

made with the aid of the "Epinut anthropometry" program from the Epi Info 6.04a package.

Preliminary activities

Several meetings were held with the "tías" to instruct them on the experimental procedure to be followed and to obtain their co-operation before the experimental work was initiated. Two preliminary separate test-study days were carried out to learn what problems could arise with urine sampling, to get acquainted with the children, and to obtain preliminary data on daily fluid consumption, children's habits, fluoride concentration of urine samples and urinary pH values.

Study design

For 1 week prior to each assessment and during control and test days, the milk intake of participating children consisted of flavoured UHT pasteurised whole milk (low fluoride content) at breakfast and the afternoon (5 p.m.) meal, instead of the currently used powdered milk prepared with tap water. Direct tap water consumption was replaced by powdered orange juice (pH 2.9), freshly prepared with distilled water from our laboratory. Orange juice was offered to participating children every 2 to 3 h (50–100 mL). Foods served at lunch and dinner were prepared as usual. During the same period children brushed their teeth according to their usual schedule, i.e. after breakfast, lunch and dinner, but non-fluoridated toothpaste Dentoxyl®, kindly provided by Laboratorios Master (Chile), was used throughout. Control and test days lunches were identical and so were the dinner menus. Tea is never served at the institution. Fresh or canned fish and sea food were not included in the control and test day diet.

Fluoride concentrations of tap water during the week prior to both studies (April and October 1997) as well as those of the test and control days were in the range 0.57–0.62 mg/L. Due to the study design, the contribution of F from tap water to the daily F ingestion of participating children during control and test days was mainly indirect, i.e. through the preparation of foods served at lunch and dinner. The F concentrations of solid items of food were not determined, but the meals did not include any component known to contain significant amounts of fluoride. Within the frame of the present study, this preparatory low-F intake period was considered to be adequate for two reasons: 1) during the test day, the addition of a fluoride dose of 1 mg (see procedure section) to the usual F intake from drinking water (0.6 mg/L), the inadvertent swallowing of fluoridated toothpaste and food prepared with fluoridated water might have been considered unnecessarily high for this age group; 2) the experimental uncertainty of FUEF assessment was lessened because the difference between F intake on the test day and the previous, control day was high.

Procedure

Two separate assessments were carried out. Forty-two children were included in the first, on 9 and 10 April, with almost the same low and high ambient temperatures (8–18°C). The second assessment included 46 children on 22 and 23 October (10–21°C). Forty children included in the first study also participated in the second one. Each assessment was carried out during two consecutive days at the Hogar Las Nieves facilities. The children continued their usual recreational and educational activities under the guidance of their "tías". During each study, two female members of our research team (LC and MA) were permanently present to supervise urine sample collection and handling. Children were constantly instructed and supervised by their "tías" to void their urine only in their individual wide-necked plastic flasks, labelled with a coloured, easily recognisable individual sticker. Urine collection (control day) started after mid-morning voiding (10–10:30 a.m.) and flask 1, containing all of the urine collected up to 5:30 p.m., was closed and brought to our laboratory, where volume and pH of each individual sample were immediately determined, while an aliquot (50 mL) was frozen until F assessment was carried out within the next 48 h. Flask 2 contained all individual urine voiding from 5:30 p.m. until 10 a.m. of the following (test) day. Flask 2 (control day) was closed at 10 a.m., 2.5 h after breakfast and 2 h before lunch, when 1 mg F was given in 50 mL of orange juice to every child. Fluoridated orange juice was prepared by diluting a 100 mg/L Orion standard solution (Orion catalogue no 96–0000 Waltham, MA, USA) to obtain a final F concentration of 20 mg/L. Samples of the fluoridated juice were carefully analysed in triplicate prior to its ingestion. From then on, all individual urine voidings from each child were collected following the same pattern as previously described for the control day (flasks 3 and 4). Collection of urine ended after the mid-morning urine sample (about 10 a.m.) on the third day had been collected. All of the flasks contain-

ing urine samples were kept permanently closed in a refrigerator until they were brought to the laboratory.

Chemical analyses

The F concentrations of water, milk, orange juice and urine samples were determined in triplicate by a previously described technique (43) using a fluoride ion selective electrode (Orion model 96–09) connected to an Orion model 940 digital pH/mV meter.

Calculations

In the control studies, the amount of fluoride excreted in the first 7 h after the mid-morning void (flask 1) was determined by multiplying the F concentration of each sample by the corresponding volume, and the same procedure was followed for urine samples from the consecutive 17-h period (flask 2). Adding up the amounts of fluoride from both flasks represents the total amount of daily excreted fluoride. The rate of urinary excretion of fluoride was computed by dividing the corresponding amounts of F by each time interval (7, 17, and 24 h). The same procedure was followed for urinary F excretion during the test day, after administering the fluoride dose. For each child, the urinary excretion attributable to the F dose was calculated as the total (24-h) quantity of fluoride excreted on the test day minus the total (24-h) amount of fluoride on the control day. Determination of the net amount of fluoride excreted during the first 7-h period after intake of the dose was similarly computed. Finally, the individual fractional urinary excretion of fluoride was determined dividing the net amount of F excreted attributable to the dose by the dose itself. Average values of the retention of fluoride from the fluoride supplement were estimated for the 7- and 24-h time intervals by subtracting the corresponding net amounts of fluoride excreted through the urine for each individual from the ingested dose (assuming 100% absorption). These net amounts of retained fluoride were divided by the dose itself to estimate fractional fluoride retention.

Statistics

All data were entered into an IBM-compatible computer and were summarised using standard descriptive statistics with Epi Info 6.04 software package, and linear regression analyses were made with SAS/STAT software (SAS Institute, Cary, NC).

Results

Fluoride concentration of flavoured UHT whole milk served at breakfast and afternoon meals was lower than 0.02 mg/L. The orange juice served to participating children throughout these studies was prepared from powdered commercial products diluted with distilled water and their F concentration was in the range 0.04–0.08 mg/L. Fluoride concentration of the toothpaste used during these studies was lower than 5 μg F/g. The concentrations of fluoride in the orange juice given in the test days of the first and second studies were 19.4±0.3 mg/L and 19.0±0.4 mg/L, respectively. The average values were not significantly different, *t*-test; $P=0.20$. These fluoridated orange juices had a pH value of 2.90. The corresponding F doses administered to children in the test days of the first and second studies were derived from the above concentrations and found to be 0.97 and 0.95 mg, respectively.

Table 1 shows the mean and median values for age, weight and height of the sample, together with the associated standard deviations and 95% confidence interval for these variables. A preliminary analysis of the experimental data did not show significant differences for any urine-related variable when comparing April and October assessments. Thus, the averages from each pair of data from the 40 children who participated in both assessments were averaged and pooled with the individual results from the two and six children who participated once in either April or October. The statistical results from these 48 independent determinations are shown in Table 2. During the first 7

Table 1. Sample description

Variable	Values	April 1997	October 1997
Number	N	42	46
Age (months)	Mean	54	61
	SD	11	12
	Median	55	63
	95% CI	50.7–57.3	57.5–64.5
Weight (kg)	Mean	15.4	18.6
	SD	1.9	1.8
	Median	15.9	18.5
	95% CI	14.8–16	18.1–19.1
Height (cm)	Mean	100.5	103.5
	SD	7.1	7.3
	Median	101.5	104.5
	95% CI	98–103	101–105

Table 2. Fractional urinary excretion of fluoride

		Control day			Test day		
		10–17 h	17–10 h	10–10 h	10–17 h	17–10 h	10–10 h
Duration (h)		7	17	24	7	17	24
pH	Mean	6.69	6.65	6.67*	6.58	6.68	6.63*
	SD	0.29	0.34		0.40	0.34	
Volume (mL)	Mean	264	295	559	282	320	602
	SD	96	101	197	99	111	210
Urinary flow (mL/h)	Mean	37.7	17.4	23.3	40.3	18.8	25.1
	SD	13.7	5.9	8.2	14.1	6.5	8.8
F concentration (mg/L)	Mean	0.39	0.40	0.40*	1.27	0.45	0.84*
	SD	0.34	0.32		0.66	0.37	
Amount F excreted (μg)	Mean	110	119	229	385	141	526
	SD	105	113	218	114	88	202
Rate F excreted (μg/h)	Mean	15.7	7.0	9.5	55	8.3	21.9
	SD	15.0	6.6	9.1	16.3	5.2	8.4
FUEF** (%) (7 h)	Mean			28.5			
	SD			6.1			
	95% CI			26.8–30.2			
FUEF** (%) (24 h)	Mean			30.7			
	SD			6.4			
	95% CI			28.9–32.5			

* Estimated geometric mean.
** Fractional urinary excretion of fluoride from the ingested dose (see text for explanation).

h fluoride concentrations were approximately three times higher after intake of 1 mg fluoride, while during the subsequent 17-h period, the respective differences were negligible.

The fractional urinary excretion of fluoride (FUEF) was 28.5% (95% CI: 26.8–30.2%) during the first 7 h following the ingestion of the F dose and the integrated 24-h FUEF was 30.7% (95% CI: 28.9–32.5%). The two averages 28.5% and 30.7% were not significantly different: *t*-test; $P=0.09$.

Although, on an individual basis, amounts of fluoride excreted and other urine-related parameters were calculated by multiplying or dividing the corresponding individual data, the same calculations on the mean values of Table 2 are not necessarily identical due to the difference between arithmetic and geometric means.

Although it was not uncommon to observe variations of 0.4 to 0.5 units in the pH of urine samples collected during the 7- and 17-hour periods for the same subject on test and control days, no significant differences were found between average urinary pH values for all four time intervals (ANOVA; $F=1.00$; $P=0.40$). The same trend was also apparent when urine volumes for each time period for test and control days were considered.

Mean values of urinary F concentration in the two collection periods of the control day were not significantly different (*t*-test; $P=0.88$). During the control day, the average rate of fluoride excretion (micrograms/hour) was significantly higher in the first 7-h period than in the consecutive 17-h period (*t*-test; $P<0.001$). The average rate of F excretion in the time interval (7 h) immediately following the ingestion of the F dose on the test day was significantly higher than the corresponding value for the control day ($P<0.0001$), whilst there was no significant difference (*t*-test; $P=0.29$) between the rate of F excretion in the consecutive 17-h period when test and control days were compared.

Simple regression analyses did not show any significant relationship between individual FUEF values and either pH (for any time interval or combination of intervals), age, body weight or weight/height ratio ($r^2 \leq 0.1$, for all cases).

Discussion

Although the average FUEF value obtained using 24-h calculations is not significantly different from the corresponding 7-h average value, the former will be used in this discussion. However, the pres-

ent experimental data suggest that a 7-h period after F dose ingestion would be adequate in order to determine reliable average FUEF values for similar studies using the present experimental set-up. This latter finding is similar to those previously reported in infant studies (37, 40).

The average of approximately 30% for the fractional urinary excretion of fluoride from an ingested dose obtained in this study for children aged 3–5 years constitutes the first report of this value on the basis of a statistically meaningful sample (88 determinations in 48 children). A recent communication (39) reported a range of 23–39% for FUEF after a 0.5 mg F dose was ingested by eight children aged 5 years. These values seem to be consistent with the present data.

Previous studies (32, 44) have suggested that a lower fractional excretion of absorbed fluoride by young children than by adults is to be expected due to a greater capacity of children to deposit fluoride in hard tissues. In fact, an average FUEF of 17% was recently determined for infants within the age range 1.2–13.7 months (37). It is noteworthy that in this latter, well-controlled study, analyses of the individual values of FUEF for this age group did not show any significant relation to either age or body weight. A similar feature was found in the present study involving young children. However, when individual data from both reports together with corresponding individual data for young adults obtained in different studies (33–36) are combined, a significant linear relationship ($r^2=0.65$; $P<0.0001$) between FUEF and body weight is obtained. The best fit for all the individual points is described by the linear equation: FUEF(%)= 14.7+0.49×body weight (kg).

This seems to indicate that when relatively narrow ranges in the anthropometric variables are considered, variations within and between individuals in each ''narrow'' age group may not provide a sufficient basis for demonstrating a relation between FUEF values and such variables.

The previously mentioned linear relationship between FUEF values and body weight serves to point out that the data obtained in this study are consistent with previous data for other age groups under similar conditions, i.e. single-dose studies. However, its mathematical meaning must be interpreted with caution. First, it would be necessary to obtain additional data on other relevant age groups, e.g. adolescents, middle-aged and elderly subjects in order to obtain a more complete description of FUEF (or retention) values as a function of age. Second, the intercept and slope of the previous equation, while likely to be applicable for pharmacokinetic single-dose studies, would need substantial correction when excretion is used as a basis for estimating general or average level of fluoride intake in constant exposure situations (as a means of monitoring total fluoride intake level). Further studies will be necessary to elucidate these issues.

It can be argued that the preparatory low-F intake period outlined in the study design section – which might correspond to a low fluoridated area – causes a high retention of the ingested supplement. However, present data seem to be consistent with previously reported results, under similar experimental conditions (33–37).

As shown in Table 2 urinary pH values do not present wide variations. This is probably because the children were all offered the same meals over a long period. Thus, the present conditions were not adequate for identifying an association between FUEF values and urinary pH, such as those reported previously (32, 44).

Since experimentally determined FUEF values for young adults were the only ones available until recently, Whitford used data from a dog model study (32) in order to propose a tentative set of values for human body F retention and thence FUEF, by inference. The FUEF values thus predicted for 4–6-year-old children (22–29%) are remarkably similar to those obtained in the present study.

The above discussion suggests that the average FUEF value of 30.7% for a single dose obtained for 3–5-year-old children is reasonable and consistent with previous studies.

According to the experimental design used in this study the F dose was administered in orange juice (pH 2.9) 2.5 h after breakfast and 2 h before lunch. Under these conditions, it can be considered that F is 100% bioavailable (45). Therefore, the mean value of approximately 30% can be considered the average fractional F urinary excretion of a single absorbed dose for the age group studied.

The present data might also be compared with a study of 24-h urinary fluoride excretion in 4-year-old children in Sri Lanka and England (16) where the F concentration in drinking water was in the range 0.8–1.1 mg/L. Daily urinary volumes and urinary flows are reasonably similar for both studies. The average value of 526 μg/day for 24-h F urinary excretion following dose intake obtained in this study is also very similar to the corresponding values obtained in Sri Lanka and England (16).

However, both results were obtained under different F ingestion patterns. Children in Sri Lanka and England were studied under stable F-intake conditions and the current assessment was carried out as a single F-dose study.

As stated in the introductory section, in order to establish useful associations between any fluoride urinary excretion related parameter and daily fluoride intake among pre-school children it would be necessary to assess the fraction of F that is excreted through the urine from the TDFI under usual conditions of ingestion. Further studies are currently underway in order to fulfil this objective.

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