Fluoride Metabolism and Excretion in Children

Gary M. Whitford, PhD, DMD

Abstract

This paper compares fluoride pharmacokinetics (plasma, renal, and extrarenal clearances) and metabolic balances in healthy infants or children with those in young or middle-aged adults. Regardless of age, the removal of fluoride from the intra- and extracellular body fluids occurs almost exclusively by uptake in calcified tissues and excretion in the urine. While there can be considerable differences among individuals, the rates at which fluoride is cleared from plasma by calcified tissues and the kidneys in adults are approximately equal. The calcified tissue clearance of fluoride from plasma in children is substantially higher than that by the kidneys. This is due to the greater surface area of the loosely organized crystallites in the developing calcified tissues during growth. Thus, the balance of fluoride (total intake minus total excretion) is typically higher in children than in adults, but it can be positive or negative at any age. Positive balance occurs when chronic fluoride intake is sufficient to prevent plasma concentrations from declining. When positive, the fluoride content of the calcified tissues, which contain more than 99 percent of the body's fluoride, tends to gradually increase. Negative balance, which indicates net mobilization of fluoride from calcified tissues, can occur when plasma concentrations decline due to a reduction in the level of fluoride intake. [J Public Health Dent 1999;59(4):224-28]

Key words: fluoride, metabolism, pharmacokinetics, balance.

Most of our knowledge about the metabolism of fluoride derives from studies with healthy, adult laboratory animals or humans. [For a comprehensive review, see Whitford (1).] It is known that, in the absence of high concentrations of calcium or other dietary components that may form insoluble compounds with fluoride, about 75 percent to 90 percent of ingested fluoride is absorbed from the gastrointestinal tract. The half-time for absorption is approximately 30 minutes, so that peak plasma concentrations typically occur about 20 to 40 minutes after ingestion. Fluoride is not bound to proteins or any other components in plasma nor to cell membranes or subcellular structures. It is, however, present in the intracellular fluids of soft tissues, where its concentrations exhibit a steady-state relationship with the concentration in plasma. This means that, while the intracellular concentration in any given soft tissue (except kidney) is lower than in plasma, it changes rapidly and in proportion to that in plasma. Thus, the tissue-to-plasma concentration ratio remains relatively constant over time.

Fluoride is removed from the body fluids almost exclusively by calcified tissue uptake and renal excretion. As a general rule for healthy adults, approximately 40 percent of the fluoride ingested each day becomes associated with calcified tissues within 24 hours, while the remainder is excreted in the urine. Approximately 99 percent of the fluoride in the body is found in calcified tissues, where most of it is strongly, but not irreversibly, bound. The rate at which fluoride is removed from plasma by bone is strongly dependent on the stage of skeletal development, it being greater in the developing skeleton than in the mature skeleton. This difference in removal rate is probably true also for developing teeth; however, direct evidence is lacking. The higher clearance by the developing skeleton is due largely to the presence of more numerous, loosely organized bone crystallites, which provide a greater surface area for fluoride uptake than is found in the mature skeleton.

The renal clearance of fluoride is much higher than that for other halogens. In the adult human, it is typically in the 30 to 50 mL/min range, whereas the clearances for chloride, iodide, and bromide are normally less than 1.0 mL/min. Data from most studies with laboratory animals and humans indicate that the renal clearance of fluoride is directly related to urinary flow rate and/or pH. The pH-dependence is consistent with the hypothesis that fluoride is reabsorbed from the kidney tubules in the form of the weak acid, hydrogen fluoride (HF, pK_a=3.4). The rate of fluoride absorption from the stomach shows a similar pH dependence.

The purpose of this paper is to provide a summary and comparison of the metabolic characteristics of fluoride in different age groups. While the literature for infants and young children is smaller than that for adults, there is sufficient data upon which to base several conclusions and to make comparisons with adults.

Pharmacokinetics

The pharmacokinetics of any substance deals with the time course of its concentrations in the various body fluids and excreta. This area of investigation is important because the actions or effects of any substance, including fluoride, are nearly always a function of the concentration at the tissue level. The most important pharmacokinetic features of fluoride are the plasma, renal, and extrarenal clearances. The unit for any clearance is "volume per time" and is usually expressed as mL/min. The clearance of fluoride from plasma, for example, is the volume of plasma from which fluoride was removed each minute. It is calculated using plasma concentrations at known time points after administration and the appropriate equations (2). Because plasma is a subset of the extracellular fluid and the concentra-

Send correspondence to Dr. Whitford, Department of Oral Biology, School of Dentistry, Medical College of Georgia, Augusta, GA 30912-1129. E-mail: gwhitfor@mail.mcg.edu. Paper as presented at the Dietary Fluoride Supplement Workshop, Chicago, IL, January 31–February 1, 1994.

tions of fluoride in the extra- and intracellular fluids change rapidly and proportionately, the plasma clearance is undoubtedly very close, if not identical, to the clearance of the ion from the total body water.

The removal of fluoride from plasma occurs almost entirely by renal excretion and skeletal (extrarenal) uptake. Thus, it is generally accepted that the sum of the renal and extrarenal clearances is equal to the plasma clearance of fluoride. As in the case of plasma, the renal clearance of fluoride can be determined empirically if the amount of fluoride excreted in the urine and the plasma concentrations during the urine collection are known. The extrarenal clearance cannot be determined directly, but is calculated as the difference between the plasma and renal clearances.

The literature contains several publications indicating that the quantitative features of some aspects of fluoride metabolism and pharmacokinetics change as a function of age. Lawrenz et al. (3), Miller and Phillips (4), Zipkin and McClure (5), and Suttie and Phillips (6) all concluded that the amount of fluoride taken up by the skeleton is inversely related to age. Whitford and Pashley (7; also see Whitford [1]) administered a fixed dose of fluoride by constant intravenous infusion (5 mg/kg over 20 min) to dogs of different ages and measured the plasma fluoride concentrations for 6 hours. The peak plasma concentration in the 4-week-old puppy was 308 µmol/L, while in the oldest dog (>4 years) it was 1,370 µmol/L. The six-hour area under the time-plasma concentration curve was 10.6 times higher in the oldest dog. Similar results were obtained when rats of different ages were studied (1).

The results from the only longitudinal study of fluoride pharmacokinetics were reported originally in an abstract by Ekstrand and Whitford (8) and more fully in later publications (1,9). The study started with six weanling dogs that were studied at frequent intervals for the next 18 months. The dog has been shown to be a good model for fluoride pharmacokinetics in the human (10). From the time of weaning to the cessation of growth at about 1 year of age, the plasma clearance of fluoride declined exponentially from 27 to 4 mL/min/kg body weight. During this period, the plasma clearance declined by 50 percent about every 80 days; however, during the remainder of the study the half-life was much longer (ca. 400 days). These marked changes in the plasma clearance were almost entirely attributable to changes in the extrarenal clearance of fluoride. During the first few weeks of the study, the extrarenal clearance was about 25 mL/min/kg, at nine months it was 7 mL/min/kg, and at the end of the study it had fallen to about 2 mL/min/kg. Thus, the extrarenal clearance—which for practical purposes is equivalent to the retention of fluoride in the body—accounted for at least 90 percent of the plasma clearance at the time of weaning, whereas at the end of the study it accounted for only about 50 percent of the plasma clearance. The renal clearance of fluoride showed little change throughout the study and averaged 2.1 mL/min/kg.

Table 1 shows renal clearance data from two studies, one with 4- to-18-year-old children undergoing water diuresis, with normal kidney function and stratified according to glomerular filtration rate (GFR) (11), and one with adults in two widely separated age groups (12). The children, who were not stratified further into smaller age groups, were studied without the administration of fluoride; the adults received 22.6 mg fluoride orally as sodium fluoride. It is important to note that the GFR and fluoride renal clearance data were adjusted to 1.73 m^2 of body surface area (BSA) in each study. This adjustment explains the high values for GFR and fluoride renal clearance in the children who would have had a smaller BSA. The average BSA values for the two groups of adults were stated by Jeandel et al. (12), so that the unadjusted clearance values could be calculated, although not by Spak et al. (11). Thus, direct comparisons of the actual clearance values reported in these two studies cannot be made.

In both studies, the renal clearance of fluoride was proportional to GFR. This relationship suggests that plasma and tissue fluoride concentrations should be proportional to GFR on a chronic basis. The plasma fluoride concentration was slightly higher in the 4- to-18-year-old group with the lowest GFR; however, there was no difference between the two groups in the study by Jeandel et al. (12), even though the GFR of the older group was lower by 40 percent. The lack of a difference in plasma fluoride between the two groups is not in agreement with results from several other studies and may have been due to analytical difficulties often encountered when concentrations below the limit of sensitivity of the fluoride electrode (ca. 1 µmol/L) are analyzed. In the study with children, the fractional fluoride clearances (C_R/GFR, i.e., the percent of fluoride filtered into the renal tu-

TABLE 1
Comparison of Fluoride Renal Clearances in Children and Adults

Age (Years)	Sample Size	$[F]_P$ (µmol/L)	GFR (mL/min)	C_R (mL/min)	C_R/GFR (%)
Spak et al. (11)					
4–18	4	1.2	145	50	34
		±0.3	±3	±9	±7
4–18	24	1.2	111	45	40
		±0.2	±10	±10	±9
4–18	10	1.4	87	31	37
		±0.2	±5	±9	±10
Jeandal et al. (12)					
21–26	12	0.7	93	59	64
		±0.3	±20	±25	±25
61–75	15	0.7	57	47	82
		±0.4	±21	±19	±46

Data expressed as mean ±SD. Glomerular filtration rate (GFR) and fluoride renal clearance (C_R) are adjusted to 1.73 m^2 body surface area.

TABLE 2
Plasma, Renal, and Extrarenal Fluoride Clearances in Infants and Young Adults

Age	*n*	GFR (mL/min)	F Clearance (mL/min)			GFR (mL/min/kg)	F Clearance (mL/min/kg)		
			Plasma	Renal	Extrarenal		Plasma	Renal	Extrarenal
Ekstrand et al. (15)									
37–410 days (control)	20	15.3 ±5.9	—	4.44 ±2.33	—	1.95 ±0.35	—	0.57 ±0.21	—
37–410 days (0.25 mg F)	20	15.2 ±5.0	49.5 ±11.8	8.1 ±2.0	41.4 ±10.4	1.96 ±0.35	6.8 ±2.0	1.1 ±0.3	5.7 ±1.9
Ektrand et al. (2)									
22–25 years (adidotic)	5	—	148 ±25	61.5 8.1	86.3 ±21.3	—	2.00 ±0.33	0.87 ±0.11	1.21 ±0.22
22–25 years (alkalotic)	5	—	207 ±31	97.8 ±10.4	109.2 ±20.7	—	2.83 ±0.17	1.38 ±0.19	1.54 ±0.18

Data expressed as mean ±SD. Dashes indicate that the data were not reported.

bules that was actually excreted in the urine) fell within a fairly narrow range regardless of GFR, so that 60 to 66 percent of the filtered fluoride was reabsorbed. These data suggest that the fractional tubular reabsorption of fluoride in children is independent of GFR, a finding different from that reported by Jeandel et al. (12). This difference between the renal handling of fluoride by children and adults, if real, is of potential importance and should be confirmed by additional research.

As shown in Table 1, the fluoride renal clearances reported in the two studies were not markedly different. As noted above, one reason for this is that the data were adjusted for BSA. Another possible reason is that the children had high urinary flow rates induced by the oral administration of water. Several studies have shown a direct relation between flow rate and fluoride clearance (13,14). Therefore, the renal clearance values for the children probably would have been lower had the subjects not been undergoing a water diuresis.

Table 2 shows data from two other pharmacokinetic studies, one with infants (15) and one with young adults (2). The actual (mL/min) and body-weight-adjusted clearances are shown. In each study, the subjects were studied under two conditions. The infants were studied before (control) and after the oral administration of 0.25 mg of supplemental fluoride. The plasma and extrarenal clearances could not be determined in the control portion of the study because the plasma fluoride concentrations were not changing, a requirement for kinetic analysis. The adults were studied while in the acidotic state, induced by the ingestion of ammonium chloride, and the alkalotic state induced by the ingestion of sodium bicarbonate. The purpose of altering acid-base balance was to determine whether the dependence of fluoride renal clearance on urinary pH in rats (16) also occurred in humans. As shown in Table 2, it did.

The removal of fluoride from plasma was three to four times faster in the adults than in the infants (Table 2). The renal clearances were 7.5 to 22 times higher in the adults; however, the extrarenal clearances were only two to two-and-a-half times higher than in the infants. These relative rates indicate that the extrarenal clearances in infants were proportionately much greater than in the adults, a fact made clear by the data adjusted for body weight. In agreement with the data from the longitudinal study with dogs discussed above, these data show that the plasma and extrarenal clearances were significantly higher in the infants than in the adults, while there was little difference between the renal clearances.

One unusual finding in the study with infants was that the fluoride renal clearances were about twice as high after the 0.25 mg supplement had been administered (Table 2). The authors discussed this observation, but commented that the explanation was not known. A dose-dependent effect on the renal clearance of fluoride has not been reported previously and there is no apparent physiological mechanism to account for the finding. It may have been due to the fact that the plasma fluoride concentrations (range=0.5 to 1.1 μmol/L; average=0.8 μmol/L) during the control studies were at or below the limit of sensitivity of the fluoride electrode (1 μmol/L), which often results in an overestimation of the true concentration. When such low concentrations are encountered, the accuracy of the analyses can be increased significantly by using a preparatory method such as the HMDS-facilitated diffusion method developed by Taves (17).

Other data from the study with infants (15) are worthy of comment. During the control studies, when fluoride intake was only from milk or formula and very low, the urinary excretion of fluoride exceeded fluoride intake in 13 of the 20 subjects, indicating that they were in a negative fluoride balance. In contrast, fluoride intake always exceeded excretion when the infants were given supplemental fluoride. The average intake was 36.6 μg/kg/5 h; the average urinary excretion was 7.65 μg/kg/5 h.

The most likely explanation for the major effect of the level of intake on the excretion of fluoride can be found in the dynamic relation between the concentrations of the ion in the extracellular fluid pool and the exchangeable pool in calcified tissues (1). According to this theory, there is a fixed ratio between these concentrations in an individual under given conditions, so

TABLE 3
24-hour Fluoride Balances in Infants as a Function of Fluoride Intake

Type of Feeding	F Intake, μg	Excretion, μg			Balance	
		Urine	Feces	Total	μg	%
Breast milk	19	28.4	2.7	31.1	−12.1	−64
Breast milk	15	26.0	1.9	27.9	−12.9	−86
Breast milk	6	32.3	0.9	33.2	−27.2	−453
Breast milk	8	49.7	0.8	50.5	−42.5	−531
Breast milk	5	15.6	0.1	15.7	−10.7	−214
Mean	10.6	30.4	1.3	31.7	−21.1	−270
SD	6.1	12.4	1.0	12.5	13.7	213
Formula fed	891	427	5	432	459	52
Formula fed	905	325	32	357	548	61
Formula fed	595	265	7	272	323	54
Formula fed	902	344	6	350	552	61
Formula fed	1,012	343	49	392	620	61
Mean	861	341	20	361	500	58
SD	157	58	20	59	115	4

Data from Ekstrand et al., 1984. Age range: 8–28 weeks.

TABLE 4
24-hour Fluoride Balances in Infants With or Without 0.25 mg F Supplement

Regimen	Age (Days)	Weight (kg)	Intake (μg/kg/d)	Total Excretion (μg/kg/d)	Balance, %	
					Total Intake	Supplement
A: fluoride from diet only	291	9.29	20.5	17.5	12.5	—
	±120	±1.18	±4.2	±2.3	±13.8	
B: fluoride from diet and 0.25 mg	230	8.51	46.0	24.0	47.1	68.1
supplement given with meal	±70	±0.64	±5.2	±6.0	±14.7	±14.8
C: fluoride from diet and 0.25 mg	229	8.31	48.9	23.2	52.3	73.0
supplement given 1 h before meal	±92	±1.39	±8.1	±3.8	±6.7	±6.0

Data from Ekstrand et al. (15). Data expressed as mean ±SD (n=8–12).

that when plasma fluoride concentrations decline, as occurs when intake is relatively low, the ion is mobilized from calcified tissues and becomes available for urinary excretion. When plasma fluoride concentrations increase, net uptake into the exchangeable pool of calcified tissues occurs to maintain the fixed ratio of concentrations. Although the actual levels of fluoride intake during the weeks or months prior to the study were not reported, this explanation implies that fluoride intake by the infants during the control studies was lower than it was prior to the studies and that it was higher when the fluoride supplements were given.

Balance Studies

The "metabolic balance" of a substance is the difference between the amount taken in from all sources and the amount excreted by all routes. If the intake is greater than the amount excreted, the balance is positive. If it is less, the balance is negative. Tissue concentrations and, in some cases, the effects of a substance are proportional to the balance. Although balance studies are labor-intensive and time consuming, they can provide important information about the overall physiological handling of a substance, as well as a means to assess the extent to which certain variables affect the process.

It is known that the balance of fluoride in infants and young children (18-21) and in adults (22) can be positive or negative. Table 3 shows some of the findings reported by Ekstrand et al. (20). Two groups of infants, 8 to 28 weeks of age born to mothers living in the same community, were studied. One group was fed breast milk, which had a fluoride concentration between 0.004 and 0.008 ppm, and the other was fed a formula diluted with drinking water containing fluoride at 1 ppm. The average 24-hour intakes by the groups were 10.6 μg and 861 μg, respectively, and the corresponding

excretions (urinary and fecal) were 31.7 μg and 361 μg. Thus, the breast-fed infants were losing at a net rate of 21.1 μg/d while the formula-fed infants were gaining at a net rate of 500 μg/d. Fecal fluoride excretion accounted for less than 12 percent of fluoride intake in each group, so that the findings were not due to differences in absorption from the gastrointestinal tract.

Ekstrand et al. (15) reported data from a balance study with four infants whose ages ranged from 9 to 60 weeks. Each subject was studied from one to four times under each of three regimens: A, no fluoride supplement; B, 0.25 mg fluoride supplement given immediately before a feeding; C, 0.25 mg fluoride given three hours after the last feeding and one hour before the next feeding. Fluoride absorption (defined as intake minus fecal excretion) under the three regimens was high and ranged from 89 percent to 96 percent so that, unlike the results from most studies investigating this subject, the influence of a meal on absorption was not statistically significant. Under regimen A, three of the 11 24-hour balances were negative while the other eight were relatively low. As shown in Table 4, the average balance under regimen A was 12.5 percent of the daily intake which was 20.5 μg/kg body weight. The results obtained under regimens B and C were similar and did not differ with statistical significance. All of the balances under regimens B and C were positive and ranged from 16 percent to 63 percent. The overall average (±SD) for regimens B and C was 50.3±10.6 percent. The authors calculated that the balances for the 0.25 mg fluoride supplements were 68.1 percent and 73.0 percent under regimens B and C, respectively.

Concluding Comments

Although there are no known age-related differences in the qualitative aspects of fluoride metabolism, there are quantitative differences. The rate at which fluoride is removed from plasma in infants and young children is several times faster than in adults when the data are factored by body weight or surface area. This difference appears to be due almost entirely to the greater surface area provided by the numerous and loosely organized crystallites in the developing skeleton. The extent to which developing teeth contribute to this effect is not known. The body-weight-adjusted or surface-area-adjusted renal clearance of fluoride appears not to change much from childhood to adulthood, but tends to decline in the later years of life, as do glomerular filtration rate and the renal clearances of most substances.

An abundance of data from metabolic balance studies show that the daily intake of fluoride can either exceed or be less than fluoride intake. Negative balances indicate that skeletal, and perhaps dental, stores of fluoride are being partially depleted. These periods of negative balance appear to occur most often when fluoride intake is reduced relative to that in the recent past. This phenomenon has obvious importance to clinical or public health measures designed to maintain or increase the fluoride concentrations of bones or teeth for preventive or therapeutic purposes. For example, the attempt to increase the fluoride content of developing teeth in utero by prenatal fluoride supplementation may be offset if the infant is breastfed because of the very low fluoride concentration in breastmilk (<0.01 ppm).

More research clearly is needed on the physiological handling of fluoride in infants and children, both those in good health as well as those with diseases or disorders that affect skeletal development or metabolism, renal function or acid-base balance. The body of information for very young, healthy children is growing, but there is virtually none for discrete age groups such as 4 to 6 years, 6 to 8 years, and so on. Data during periods of growth spurts, particularly around the time of puberty, might be particularly interesting.

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