Fluoride metabolism when added to salt

Summary

The purpose of this review is to present the general characteristics of the metabolism of fluoride particularly as it occurs when ingested with fluoridated salt. Following the absorption of salt-borne fluoride from the stomach and intestines, its metabolism is identical to that of water-borne fluoride or other vehicles containing ionized fluoride. Because fluoridated salt is almost always ingested with food, however, absorption from the gastrointestinal tract may be delayed or reduced. Reports dealing with this subject have shown that fluoride absorption is delayed and, therefore, peak plasma concentrations are lower than when fluoride is ingested with water. The amount of ingested fluoride that is finally absorbed, however, is not appreciably affected unless the meal is composed mainly of components with high calcium concentrations. In this case, the extent of absorption can be reduced by as much as 50%. Fluoridated salt is also ingested less frequently than fluoridated water. Data are presented to show that the dose size and frequency of ingestion have only minor effects on fluoride retention in the body and on the concentrations in plasma, bone and enamel. Finally, calculations are presented to show that the risk of acute toxicity from fluoridated salt is virtually non-existent.

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Introduction

Figure 1 shows the major features of fluoride metabolism (for a detailed review see Whitford 1996). Following its absorption from the stomach and upper small intestine, which is rapid and extensive, fluoride is carried in plasma for distribution throughout the body. Plasma is considered the central compartment because it is this fluid into which and from which fluoride must pass for its distribution and elimination. It readily migrates across cell membranes of nearly all soft tissues which have steady-state tissue-to-plasma concentration ratios which range from 0.5 to 0.9. Exceptions to this are brain and fat which have considerably lower ratios and kidney which has a higher ratio because fluoride is concentrated in the tubular fluid (Whitford et al. 1979). Fluoride is secreted from plasma into ductal saliva at a concentration

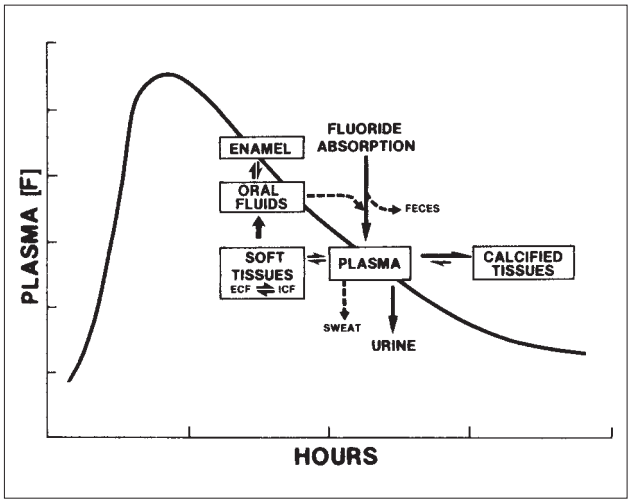

Fig. 1 The general features of fluoride metabolism.

that is about 75% of that in plasma so that, except during sleep, saliva is a continuous source of low concentrations of fluoride for dental plaque and enamel (EKSTRAND 1977; WHITFORD et al. 1999).

Following the ingestion of soluble fluorides such as NaF and KF, the peak plasma concentration typically occurs within 30–60 minutes but it may be delayed if ingested with a meal. The peak concentration is followed by a rapid decline due to rapid uptake by calcified tissues and excretion in the urine. These are the major metabolic fates of fluoride. At least 99% of the fluoride in the body is found in calcified tissues, mainly bone where it is strongly but not irreversibly bound. Approximately 50% of the fluoride ingested each day is excreted in the urine although it may be as low as 10–20% or as high as 60–70%, depending on several factors including age and urinary pH. Among the halogens, the excretion of fluoride by the kidneys is unusually rapid. Its renal clearance from plasma typically ranges from 25–50 ml/min which is several orders of magnitude higher than that of other halogens. The clearance of fluoride is positively related to tubular fluid pH indicating that reabsorption from the renal tubules occurs as the highly diffusible and permeating molecule, HF. Thus, factors that influence urinary pH will also affect the excretion of fluoride. Such factors include the composition of the diet, certain metabolic or respiratory disorders, alkalinizing or acidifying drugs and residence at high altitude. There is no evidence showing that fluoride excretion is related or linked to the excretion of sodium or chloride (WHITFORD et al. 1976).

When compared to fluoridated water, the ingestion of fluoridated salt has several distinguishing features that could potentially alter the quantitative aspects of fluoride metabolism: (1) In contrast to fluoridated water, fluoridated salt is almost always ingested with a snack or meal. Thus the rate and extent of absorption from the gastrointestinal tract could be reduced. (2) Salt is ingested less frequently than water so that somewhat more fluoride tends to be ingested at one time. This raises the possibility that the frequency and size of the dose could alter the overall metabolism of fluoride when ingested with salt. (3) A third and related issue is the fact that salt particles tend to segregate according to size in the container (shipping sack or salt shaker) such that smaller particles with higher fluoride concentrations preferentially accumulate at the bottom. This raises a question about the possibility of acute adverse effects. The main purpose of this review is to discuss these possibilities.

Effect of ingesting fluoride with food

A popular method for determining the effect of ingesting fluoride with food on its absorption is to compare the pharmacokinetics with those that occur when it is ingested with water under fasting conditions. The parameters most often measured are the peak plasma fluoride concentration (C_{max}), the time when the peak plasma concentration occurs (T_{max}) and the area under the time-plasma concentration curve (AUC) which is usually determined using the trapezoidal rule. Delays in T_{max} indicate slower absorption and, for equivalent fluoride doses, they are always associated with lower peak concentrations. The extent of absorption (bioavailability) is determined by dividing the AUC when fluoride is ingested with food by the AUC when it is ingested with water which typically approaches 100% in fasting persons. The urinary excretion of fluoride can also be used to estimate the extent of absorption. That subject is discussed by MARTHALER & SCHULTE (2005) elsewhere in this publication.

Table I shows T_{max} and percent absorption values determined in four different studies. As the standard for comparison, these two variables were determined in fasting subjects after a few milligrams of fluoride had been ingested in an aqueous solution as NaF or disodium monofluorophosphate (MFP, Na_2PO_3F). The absorption data under fasting conditions was assumed to be 100%. Remarkably similar reductions in absorption of 25–30% were observed in the four studies when fluoride was ingested with milk or baby formula. When fluoride was ingested with a high-calcium breakfast (milk, cheese and yoghurt), absorption was further reduced to 46% of the fasting value (EKSTRAND & EHRNEBO 1979). The authors attributed these effects to the formation of insoluble calcium fluoride and to trapping of fluoride within coagulated milk and milk products in the GI tract.

T_{max} was further delayed but quite different values for absorption were reported when breakfast included milk and an otherwise low-calcium breakfast consisting of rolls, butter, bacon, jam and coffee or tea prepared with deionized water. The reduced

Tab. I Summary of four studies showing the effects of ingesting fluoride in baby formula or milk with or without food on the time to reach peak plasma fluoride concentration (T_{max}) and the percent of fluoride absorbed from the GI tract.

Reference	F Ingested with:	T_{max}, minutes	% Absorbed
EKSTRAND & EHRNEBO (1979)	Water*	30	100
	Milk	Delayed**	74
	Milk, cheese, yoghurt	Delayed	54
SPAK et al. (1982)	Water*	30	100
	Milk	Delayed	72
	Baby formula	Delayed	76
TRAUTNER (1989)	Coffee*	34	100
	Milk	85	72
	Low-Ca breakfast	107	101
	Milk with low-Ca breakfast	114	87
TRAUTNER & EINWAG (1989)	Water*	43	100
	Milk	68	70
	Milk with low-Ca breakfast	91	99

* Subjects were fasting. ** T_{max} values were not specified numerically but the graphs clearly showed that they were delayed.

absorption observed when fluoride was ingested with milk alone did not occur. Instead the inhibitory effect of milk was partially (Trautner 1989) or even completely abolished (Trautner & Einwag 1989). The authors attributed these observations to a reduction in the transit of chyme through the stomach and intestine which, they said, "allows F to become liberated from bound forms and coagulation products by digestive processes."
Based on these reports it can be concluded that the ingestion of fluoride with a meal slows its absorption and C_{max} but has little effect on the amount that is ultimately absorbed unless the meal is mainly composed of foods rich in calcium. This is in agreement with other reports of the effect of calcium on the bioavailability of fluoride. Jowsey & Riggs (1978) reported that the administration of calcium carbonate with fluoride reduced fluoride absorption by an average of 22% in human volunteers as judged by plasma fluoride concentrations. In a 30-day metabolic balance study, rats were fed a diet containing nutritionally adequate (0.4% by weight) or high (1.4%) amounts calcium (Whitford 1994). Although fluoride intake did not differ significantly between the groups, fecal fluoride excretion was more than twice as high and plasma and bone fluoride concentrations were 41% and 59% lower in the high-calcium group, respectively.
An important question related to this issue is this: For a given amount of intake regardless of the vehicle (e.g. water or salt), is the cariostatic effectiveness of fluoride affected if its absorption into the systemic circulation is somewhat reduced on a chronic basis? Although there is evidence for the role of fluoride incorporated into enamel during its development or post-eruptively (Marthaler 1979; Chow 1990; Groeneveld et al. 1990), it is generally agreed that the cariostatic effect of fluoride is largely due to its concentration in the oral fluids, especially in dental plaque. Whole saliva is the major vehicle for the delivery of fluoride to plaque. Thus the concentration of fluoride in plaque depends mainly on the concentration in whole saliva. Fluoride secreted from the systemic circulation by salivary glands into the oral cavity has a concentration about 75% of that in plasma and rarely exceeds 0.05 ppm. The author is not aware of a publication showing the fluoride concentrations in whole saliva (or plaque) associated with eating foods seasoned with fluoridated salt but it can be safely assumed that they are many times higher than 0.05 ppm. For these reasons, it appears that the answer to the question is "no" or "not by much."

Effect of dose size and frequency

The possibility that the metabolic characteristics of fluoride might be influenced by the dose and frequency of fluoride ingestion was evaluated in a chronic study with rats (Whitford et al. 1991a). The rat is an appropriate model for fluoride metabolism in humans (Whitford et al. 1991b).
Female Sprague-Dawley rats (n = 26) were randomly assigned to four groups and fed low-fluoride food (1 ppm) throughout the study. Group A served as the untreated control and received no additional fluoride. Group B had free access to water containing fluoride at 25 ppm (as NaF) while Groups C and D received distilled water. The amount of fluoride consumed with water by Group B rats was measured daily. This amount was administered to the rats in Groups C and D by stomach tube once per day and three times per day, respectively, including weekends for six weeks.
Fluoride intake with food and water was measured twice each week. Urine and feces were also collected twice each week and analyzed. From these data total intake and the balance and percent retention (balance/intake) of fluoride were calculated. At the end of the study aortic blood, mandibular incisor enamel and the distal epiphysis of the femur were collected for analysis. The administration of fluoride in drinking water or by stomach tube was stopped 16 hours before the animals were killed so that the plasma concentrations would not be significantly influenced by the last fluoride exposures but, instead, they would reflect the fluoride concentration in the exchangeable compartment of bone (Taves & Guy, 1979).
Table II shows the results. All values in Groups B, C and D were significantly higher than those in Group A. Among Groups B, C and D all values fell within reasonably narrow ranges although some statistically significant differences were found. The plasma, femur and enamel concentrations were higher in Groups C and D than in Group B, significantly so for plasma and femur. These higher concentrations were due to greater fluoride absorption (data not shown) which was explained by the fact that rats eat and drink mainly during the night. That is, Group C and D rats received their water-borne fluoride by stomach tube during the daytime when the consumption of food is low. Group B rats, however, consumed most of their water-borne fluoride along with food during the nighttime hours which would have reduced absorption.
The results of this study, the only one of its kind known to us, indicate that the dose and frequency of exposure have only minor effects on the balance and tissue concentrations of fluoride. It can be reasonably concluded, therefore, that these variables would also be similar among humans whose major sources of exposure are fluoridated water or fluoridated salt.

Tab. II Fluoride intake, balance, percent retention and tissue concentrations in rats given fluoride at different frequencies for six weeks.

Group	Intake	Balance	% Retention	Fluoride Concentration		
				Plasma	Femur	Enamel
A	21.2 ± 0.8	14.3 ± 0.4	67.5 ± 2.0	0.39 ± 0.02	50.5 ± 2.2	24.6 ± 3.0
B	836[a] ± 12	655[a] ± 16	78.3[a] ± 1.4	3.18[a] ± 0.15	1052[a] ± 49	210[a] ± 13
C	907[b] ± 14	697[b] ± 19	76.8[a] ± 1.6	3.86[b] ± 0.20	1202[b] ± 33	228[a] ± 6
D	844[a] ± 8	700[b] ± 10	82.9[b] ± 0.9	3.87[b] ± 0.25	1226[b] ± 40	248[a] ± 10

Data expressed as mean ± SE. Units: Intake and balance, µg/24 h/2 rats; plasma [F], µmol/l; femur and enamel, mg/kg dry weight. ANOVA compares Groups B, C and D. Values in a column with the same superscript are not significantly different at $p < 0.05$.

Potential for acute toxicity

We determined the fluoride concentrations in 250-ppm Swiss salt after passing it through sieves with known openings ranging from 600 to 180 µm. Several analyses of the salt that passed through the 180 µm sieve gave concentrations in the 600–700 ppm range, while the salt that did not pass through the 600 µm sieve had concentrations below 100 ppm. For the sake of this discussion let us assume that the salt at the bottom of the sack or salt shaker has a concentration of 1,000 ppm (mg/kg).

Based on case reports describing serious acute toxic events due to the ingestion of fluoride tablets or solutions, of which three resulted in the death of children, the 'probably toxic dose' or PTD of fluoride has been set at 5 mg F/kg of body weight (Whitford 1996). The PTD is "the minimum dose that could cause serious or life-threatening systemic signs and symptoms and that should trigger immediate therapeutic intervention and hospitalization." In the extreme case of a 1-year-old child with the average body weight of 10 kg, the PTD would be 50 mg which would be contained in 50 g of 1,000-ppm salt. It can be concluded, therefore, that the risk of reaching the PTD by ingesting fluoridated salt is virtually non-existent.

Zusammenfassung

Ziel dieser Übersicht ist die Darlegung allgemeiner Charakteristika des Fluoridstoffwechels, insbesondere bei Zugabe von Fluorid zum Salz. Nach der Adsorption aus Magen und Darm ist der Stoffwechsel von mit Salz aufgenommenem Fluorid identisch zu jenem aus Wasser oder andern Vehikeln. Da fluoridiertes Salz fast ausnahmslos mit der Nahrung aufgenommen wird, kann die Absorption aus dem Gastrointestinaltrakt verzögert oder vermindert vor sich gehen. Diesbezügliche Berichte belegen eine verzögerte Absorption, weshalb Spitzenkonzentrationen später auftreten und niedriger sind als bei Fluoridaufnahme aus Wasser. Die Menge des schlussendlich absorbierten Fluorids ist aber nicht wesentlich vermindert, es sei denn, die Nahrung enthalte Komponenten mit hohen Kalziumkonzentrationen. In diesem Falle kann die Resorption bis zu 50% vermindert sein. Unter Umständen wird fluoridiertes Salz weniger häufig konsumiert als fluoridiertes Wasser. Daten zeigen, dass die Höhe der Dosis und die Häufigkeit der Ingestion nur eine geringe Wirkung auf Retention von Fluorid im Körper und auf die Konzentrationen im Plasma, Knochen und Schmelz haben. Zum Schluss zeigen Berechnungen, dass ein Risiko akuter Toxizität durch fluoridiertes Salz praktisch nicht existiert.

Résumé

L'objet de cet exposé est de présenter les traits caractéristiques du métabolisme du fluorure, en particulier quand il résulte de l'ingestion de SF. Celui-ci étant presque toujours ingéré avec la nourriture, son absorption par l'appareil gastro-intestinal peut être retardée ou réduite. Des examens faits à ce sujet ont démontré que si l'absorption de fluorure est alors retardée, la concentration maximum de plasma est moindre qu'à la suite de l'ingestion de fluorure avec de l'eau. La quantité de fluorure ingérée qui est finalement absorbée n'est toutefois pas sensiblement affectée, sauf quand un repas se compose surtout de constituants à haute concentration de calcium. Dans ce cas, le degré d'absorption peut être réduit de 50%. SF est ingéré moins fréquemment que le fluorure transporté par l'eau. Il existe des données indiquant que le volume du dosage et la fréquence de l'ingestion n'ont qu'un effet sans importance sur la rétention du fluorure dans le corps et sur sa concentration dans le plasma, l'ossature et l'émail. Finalement, nous présentons des calculs démontrant que le risque d'une toxicité importante causée par le SF est virtuellement inexistant.

References

Chow L C: Tooth-bound fluoride and dental caries. J Dent Res 69 (Spec Iss): 595–600 (1990)

Ekstrand J: A micromethod for the determination of fluoride in blood plasma and saliva. Calcif Tiss Res 23: 225–228 (1977)

Ekstrand J, Ehrnebo M: Influence of milk products on fluoride bioavailability in man. Eur J Clin Pharmacol 16: 211–215 (1979)

Groeneveld A, Van Eck A A M J, Backer Dirks O: Fluoride in caries prevention: Is the effect pre-or post-eruptive? J Dent Res 69 (Spec Iss): 751–755 (1990)

Jowsey J, Riggs B L: Effect of concurrent calcium ingestion on intestinal absorption of fluoride. Metabolism 27: 971–974 (1978)

Marthaler T M: Fluoride supplements for systemic effects in caries prevention. In: Johansen E, Taves D R, Olsen T O (Eds): Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium #11, Westview Press, Boulder, Colorado. pp 33–59 (1979)

Marthaler T M, Schulte A G: Monitoring salt fluoridation programs through urinary excretion studies. Schweiz Monatsschr Zahnmed 115: 679–684 (2005)

Spak C J, Ekstrand J, Zylberstein D: Bioavailability of fluoride added to baby formula or milk. Caries Res 16: 249–256 (1982)

Taves D R, Guy W S: Distribution of fluoride among body compartments. In: Johansen E, Taves D R, Olsen T O (Eds): Continuing Evaluation of the Use of Fluorides. AAAS Selected Symposium #11, Westview Press, Boulder, Colorado. pp 159–185 (1979)

Trautner K: Influence of food on relative bioavailability of fluoride in man from Na_2FPO_3-containing tablets for the treatment of osteoporosis. Int J Clin Pharmacol Ther Toxicol 27: 242–249 (1989)

Trautner K, Einwag J: Influence of milk and food on fluoride bioavailability from NaF and Na_2FPO_3 in man. J Dent Res 68: 72–77 (1989)

Whitford G M: Effects of plasma fluoride and dietary calcium concentrations on GI absorption and secretion of fluoride in the rat. Calcif Tiss Int 54: 421–425 (1994)

Whitford G M: The Metabolism and Toxicity of Fluoride, 2nd edition (Ed: Myers H M). S Karger, Basel (1996)

Whitford G M, Pashley D H, Stringer G I: Fluoride renal clearance: a pH-dependent event. Am J Physiol 230: 527–532 (1976)

Whitford G M, Pashley D H, Reynolds K E: Fluoride tissue distribution: short-term kinetics. Am J Physiol 236: F141–148 (1979)

Whitford G M, Birdsong-Whitford N L, Augeri J M: Fluoride balance and tissue concentrations: effect of dose frequency. Proc Finn Dent Soc 87: 561–569 (1991a)

Whitford G M, Biles E D, Birdsong-Whitford N L: A comparative study of fluoride pharmacokinetics in five species. J Dent Res 70: 948–951 (1991b)

Whitford G M, Thomas J E, Adair S M: Fluoride in whole saliva, parotid ductal saliva and plasma in children. Arch Oral Biol 44: 785–788 (1999)