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Acute Toxicity of Ingested Fluoride

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Abstract

This chapter discusses the characteristics and treatment of acute fluoride toxicity as well as the most common sources of overexposure, the doses that cause acute toxicity, and factors that can influence the clinical outcome. Cases of serious systemic toxicity and fatalities due to acute exposures are now rare, but overexposures causing toxic signs and symptoms are not. The clinical course of systemic toxicity from ingested fluoride begins with gastric signs and symptoms, and can develop with alarming rapidity. Treatment involves minimizing absorption by administering a solution containing calcium, monitoring and managing plasma calcium and potassium concentrations, acid-base status, and supporting vital functions. Approximately 30,000 calls to US poison control centers concerning acute exposures in children are made each year, most of which involve temporary gastrointestinal effects, but others require medical treatment. The most common sources of acute overexposures today are dental products – particularly dentifrices because of their relatively high fluoride concentrations, pleasant flavors, and their presence in non-secure locations in most homes. For example, ingestion of only 1.8 ounces of a standard fluoridated dentifrice (900–1,100 mg/kg) by a 10-kg child delivers enough fluoride to reach the 'probably toxic dose' (5 mg/kg body weight). Factors that may influence the clinical course of an overexposure include the chemical compound (e.g. NaF, MFP, etc.), the age and acid-base status of the individual, and the elapsed time between exposure and the initiation of treatment. While fluoride has well-established beneficial dental effects and cases of serious toxicity are now rare, the potential for toxicity requires that fluoride-containing materials be handled and stored with the respect they deserve.

As is true of virtually all substances to which humans are exposed, including water, oxygen and table salt, exposure to high amounts of fluoride can cause adverse effects. It is a toxicological axiom that such effects are due to the level of exposure to the substance, not to the substance itself. Compared to the first half of the 20th century, cases of serious fluoride toxicity are uncommon today. At that time, sodium fluoride was used as a pesticide and rat poison and commonly found in homes, hospitals and elsewhere. Because sodium fluoride powder resembles flour, powdered sugar, baking powder, sodium bicarbonate and similar products, there were many accidental poisonings. Sodium fluoride was also used in a large number of suicides [1].

Table 1. Details of 3 deaths caused by ingestion of fluoride-containing dental products

Age	Body weight, kg	Sex	Dose, mg/kg	Comment	Reference
27 months	not reported	M	3.1–4.5[1]	ingested <100 0.5-mg fluoride tablets; death occurred 5 days later	Dukes [8]
3 years	12.5	M	16	ingested <200 1.0-mg fluoride tablets; vomited; death occurred 7 h later	Eichler et al. [7]
3 years	not reported	M	24–35[1]	swallowed 4% SnF_2 rinse solution; vomited; death occurred 3 h later	Church [6]

[1] Calculated using the 3rd and 97th percentiles for body weight of 3-year-old boys.

One of the most remarkable accidental poisonings occurred at the Oregon State Hospital [2]. About 10 gallons of scrambled eggs were mistakenly prepared with 17 pounds of sodium fluoride instead of powdered milk. There were 263 cases of acute poisoning, of which 47 were fatal. It was not possible to estimate the amounts of fluoride that were ingested by those affected, but the well-known signs and symptoms developed rapidly. Extremely severe nausea, bloody vomiting and diarrhea occurred almost immediately. General collapse accompanied by pallor, weakness, shallow breathing, weak heart sounds, wet cold skin, cyanosis and equally dilated pupils soon followed. When these signs were pronounced, death almost always occurred within 2–4 h. When death was delayed for up to 20 hours, muscle paralysis, carpopedal spasm and spasm of the extremities occurred. More recent reports of serious acute toxicity have indicated that muscular and cardiovascular problems are related to electrolyte imbalances, particularly severe hypocalcemia and hyperkalemia [3, 4]. A progressive, mixed respiratory and metabolic acidosis develops as kidney function and respiration fail.

Doses Causing Serious Toxicity: Rationale for the Probably Toxic Dose

Based on the sketchy information that could be gathered after the mass poisoning at the Oregon State Hospital, Lidbeck et al. [2] thought the acute lethal dose of fluoride was over 100 mg/kg. Hodge and Smith [1] estimated that the 'certainly lethal dose' was between 32 and 64 mg/kg or 5–10 g of sodium fluoride for a 70-kg person. Dreisbach [5] estimated the lethal dose at 6–9 mg/kg. These different estimates probably were due in large part to uncertainty about the amounts of fluoride that were actually ingested by the victims.

Church [6], Eichler et al. [7] and Dukes [8] did not attempt to estimate the acute lethal dose, but did present dosages in their case reports (table 1). The case described by Dukes [8] was unusual because of the small dose and the length of time from ingestion to death. A 27-month-old child ingested an unknown number (but fewer than 100) of 0.5-mg fluoride tablets and experienced respiratory failure. With treatment, the boy's condition improved, but he died 5 days after ingesting the tablets. The amount of fluoride ingested was approximately 50 mg, and the dose was estimated

at between 3.1 and 4.5 mg/kg. A 3-year-old boy died in a hospital after ingestion of about 200 1.0-mg fluoride tablets [7]. This child vomited immediately, seemed to recover completely, but then collapsed and died 7 h after the swallowing the tablets. The ingested dose was approximately 16 mg/kg. The case described by Church [6] was a 3-year-old boy who swallowed 4% stannous fluoride rinse from a small cup in a dental clinic. The child vomited immediately, had a convulsive seizure and died 3 h later. The ingested dose was estimated at between 24 and 35 mg/kg, but the absorbed dose was lower because of vomiting.

The report by Eichler et al. [7] also described 108 non-fatal cases of fluoride toxicity in children, most of whom had ingested fluoride tablets. As the ingested dose increased from less than 0.5 mg/kg to 'more than 5.0 mg/kg', the percentage of patients with symptoms increased from 15 to 71. The symptoms included nausea, vomiting and fatigue. One child died as described above. *Based on this report and those of Dukes [8] and Bayless and Tinanoff [9], it is concluded that the probably toxic dose (PTD) for fluoride is 5.0 mg/kg. The PTD is defined as the minimum dose that could cause serious or life-threatening systemic signs and symptoms and that should trigger immediate therapeutic intervention and hospitalization.* This does *not* mean that doses lower than 5.0 mg/kg should be regarded as innocuous.

Treatment

The treatment for serious or potentially life-threatening cases of acute fluoride toxicity must attempt to minimize absorption from the GI tract, increase urinary excretion and maintain the vital signs within levels compatible with life [1, 3, 4, 9]. If vomiting has not occurred, it should be induced unless the patient is unconscious (to avoid aspiration into the lungs). Because of the strong affinity of calcium for fluoride, absorption can be slowed and reduced by the oral administration of 1% calcium chloride or calcium gluconate or, if these solutions are not available, as much milk as can be tolerated. These actions should be taken as soon as possible because fluoride is rapidly absorbed from the stomach and intestines. At the same time, the hospital should be informed that a case of fluoride toxicity is in progress so that appropriate therapeutic interventions are in place when the patient arrives. Expeditious treatment is essential because severe cases often progress rapidly toward death.

In cases of life-threatening toxicity, which must be judged by the clinical signs and symptoms because the exact amount of fluoride ingested, i.e. the dose, is almost never known, an airway and intravenous line should be established immediately upon arrival at the hospital. Blood samples should be obtained upon arrival and then hourly for the measurement of serum fluoride, blood pH and gases, and serum chemistry – including calcium and potassium in particular. Intravenous administration of calcium gluconate to prevent hypocalcemia, glucose to reverse hyperkalemia, and sodium lactate or sodium bicarbonate to minimize acidosis and increase urinary flow and pH in order to increase the urinary excretion rate of fluoride should be given as required. Oxygen therapy, artificial respiration, electrocardiac conversion and hemodialysis may be required. These various measurements and treatments should continue until the vital signs have stabilized and the serum chemistry values have normalized for at least 24–48 h.

Sources of Fluoride

As discussed above, the acute dose of fluoride that may cause serious systemic toxicity is 5 mg/kg (11 mg/kg of sodium fluoride). This is called the 'probably toxic dose' (PTD). It is obvious that optimally fluoridated water (ca. 1.0 mg/l) cannot cause acute toxicity since 5 liters of water would have to be ingested for every kg of body weight.

Accidental overfeeds resulting in water fluoride concentrations sufficient to cause acute toxicity, however, have occurred.

One example involved kidney patients in a hemodialysis center [3]. Approximately 1,000 gallons of hydrofluorosilicic acid accidentally leaked into the public drinking water supply, which increased the fluoride concentration to a peak of 30 ppm. Two days later, the concentrations were lower but still elevated, and 8 patients undergoing hemodialysis developed gastrointestinal symptoms. During dialysis 1 patient developed pressure-like chest pain, difficulty breathing, nausea, vomiting, sweating, diarrhea and numbness in the right arm. The dialysis procedure was interrupted, the symptoms gradually improved and the patient went home. However, 14 h later the difficulty in breathing returned. On the way to the hospital the patient had cardiopulmonary arrest, but was successfully resuscitated despite severe hyperkalemia (10.5 meq/l; normal 4.0–5.5 meq/l) and a markedly elevated plasma fluoride concentration (0.4 mg/l; normal 0.02–0.04 mg/l). Another 1 of the 8 dialysis patients was found dead at home.

Another example occurred in 1992 in Hooper Bay, a small village in Alaska near the Bering Sea [10]. The water supply for the 470 residents was a single tank from which water was obtained and carried home for domestic use. One weekend, the water fluoridation equipment failed, resulting in a peak concentration of 150 ppm. Approximately 296 residents experienced several of the less severe symptoms listed above (nausea, vomiting, abdominal cramps). One woman was evacuated by air after 2 days of vomiting and diarrhea. Upon arrival at the hospital her serum calcium was 5.2 mg/dl (one half normal) and her serum fluoride was 9.1 mg/l (400 times normal). She recovered after several days of treatment, but her brother was found dead at home after prolonged vomiting and diarrhea. He had attempted to remain hydrated by continuing to drink the water. His postmortem serum calcium was 4.9 mg/dl. It was estimated that he had consumed 17.9 mg/kg during the course of the day.

Tragic examples such as these are rare today, but less severe episodes are not. Thousands of calls involving suspected or actual fluoride overdoses are made to US poison control centers each year and, up until 2005 when the publication of the annual reports ended, they were compiled and published in the *American Journal of Emergency Medicine* [11]. Table 2 shows a summary of the 2000–2003 data. Among the more than 30,000 reports for which a medical outcome was recorded in each year, approximately 7,250 were classified as 'none'. A 'minor' medical outcome means that there were some symptoms, but they were minimal (nausea, vomiting, dizziness) or required no treatment. A 'moderate' outcome means that the symptoms were more severe, more prolonged or more of a systemic nature and that some treatment was usually required. A 'major' outcome means that the patient survived, but the toxicity was life-threatening and/or resulted in residual disability.

In each of the 4 years, approximately 80% of the reports made to poison control centers involved toothpastes or mouthwashes (categories D and E) and nearly 90% involved young children. Between 394 and 471 were treated in a health care facility each year. Approximately 1,400 cases were classified as 'minor' or 'moderate' and 1–4 cases as 'major' each year, and there was 1 death, a suicide reported in the 2002 publication. These figures indicate that the most commonly used fluoride-containing dental products are sources of potential toxicity.

Fluoride Exposure from Dental Products

Table 3 shows the fluoride concentrations in several dental products, the amounts that are usually used, and the amounts that contain the PTD (5 mg/kg). The data indicate that there is little or no danger of systemic toxicity when the products are

Table 2. Fluoride-related reports made to US poison control centers (2000–2003)

Year	Category	Reports	Treated in health care facility	Medical outcome				
				none	minor	moderate	major	death
2000	A	3,681	191	1,028	337	15	1	0
	B	158	17	51	6	0	0	0
	C	2,637	90	578	58	3	0	0
	D	22,291	360	5,505	1,262	46	0	0
	E	2,073	34	520	78	5	0	0
	Total	30,840	692	7,682	1,741	69	1	0
2001	A	3,635	179	947	306	19	0	0
	B	484	49	99	11	4	0	0
	C	2,176	99	529	34	3	0	0
	D	22,790	391	5,014	1,328	38	4	0
	E	2,179	32	464	77	2	0	0
	Total	3,1264	750	7,053	1,756	66	4	0
2002	A	3,730	169	911	274	7	0	0
	B	354	20	61	12	1	1	0
	C	2,364	89	429	45	1	0	0
	D	24,089	411	4,852	1,218	40	1	1
	E	2,557	60	532	93	2	0	0
	Total	33,092	749	6,785	1,642	51	2	1
2003	A	3,541	139	809	233	11	0	0
	B	250	37	70	14	2	0	0
	C	2,437	80	483	42	5	0	0
	D	24,812	405	5,413	1,337	44	1	0
	E	3,401	43	751	72	2	0	0
	Total	34,441	704	7,526	1,698	64	1	0

Categories: A = electrolytes and minerals; B = adult vitamins; C = pediatric vitamins; D = fluoride toothpaste; E = fluoride mouthwash. See Watson et al. [11].

used in the usual amounts and as recommended. Rulings by the US Consumer Product Safety Commission (CPSC) that require child-resistant caps for fluoride mouthwashes and most prescriptions for dietary fluoride supplements have reduced the risk of systemic toxicity from these products. These child-resistant caps, however, are not 'child proof' and 'should be regarded as your last line of defense' [12]. As indicated in table 3, however, these products are sometimes ingested in excessive amounts. Unsupervised children may drink mouthwash from the bottle, eat toothpaste from the tube or tablets from the bottle. An 18-ounce bottle of 0.05% NaF mouthwash (510 ml) contains 124 mg of fluoride, an amount 2.37 times more than the PTD for a 10-kg child. Thus, ingestion of 7.6 ounces (215 ml) could cause serious toxicity. Although the mouthwash labels

Table 3. Fluoride contents of dental products and their relationships to the PTD

Product	Concentration of salt fluoride			Amount of product and fluoride usually used		Amount of product containing the PTD for child weighing	
	%	%	ppm	product	fluoride	10 kg	20 kg
Mouthwash							
NaF	0.05	0.023	230	10 ml	2.3 mg	215 ml	430 ml
NaF	0.20	0.091	910	10 ml	9.1 mg	55 ml	110 ml
SnF_2	0.40	0.097	970	10 ml	9.7 mg	50 ml	100 ml
Dentifrice							
NaF	0.22	0.10	1,000	1 g	1.0 mg	50 g	100 g
MFP	0.76	0.10	1,000	1 g	1.0 mg	50 g	100 g
Topical gel							
NaF (APF, tray)	2.72	1.23	12,300	5 ml	61.5 mg	4 ml	8 ml
SnF_2 (brush)	0.40	0.097	970	1 ml	0.97 mg	50 ml	100 ml
NaF tablet							
0.25 mg	–	–	–	1/day	0.25 mg	200 tabs	400 tabs
0.50 mg	–	–	–	1/day	0.50 mg	100 tabs	200 tabs
1.00 mg	–	–	–	1/day	1.00 mg	50 tabs	100 tabs

PTD = 5 mg/kg i.e. the amount of ingested fluoride that could cause serious or life-threatening systemic effects and that should trigger immediate therapeutic intervention and hospitalization; MFP = sodium monofluorophosphate; APF = acidulated phosphate fluoride. The average body weights of 1-year-old and 6-year-old children are approximately 10 and 20 kg, respectively.

in the USA are required by the Food and Drug Administration to specify that children under the age of 6 years should not use a fluoride mouthwash, they do have access to them in many homes. Dentifrices are available in tubes containing up to 8.2 ounces (232 g) so a 1,000-ppm product contains 232 mg of fluoride. Ingestion of only 1.76 ounces (50 g) by a 10-kg child provides enough fluoride to reach the PTD. As for fluoride tablets, the American Dental Association guidelines state that up to 480 0.25-mg tablets, 240 0.50-mg tablets, and 120 1.0-mg tablets may be prescribed per household [13]. These numbers of tablets and amounts of fluoride contained in them exceed the PTD for both 10-kg and 20-kg children. All of these products should be kept out of the reach of small children and secured with child resistant caps.

Topical acidulated phosphate fluoride (APF) gels and foams contain fluoride at a concentration of 12.3 mg/ml (12,300 ppm). APF treatments are rarely given to 1-year-old children, but they may be given to 2-year-old children (average body weight 12.4 kg). If maxillary and mandibular stock trays are loaded with 5 ml of gel in each tray, then 123 mg of fluoride would be placed in the mouth, which exceeds the PTD for a 2-year-old by a factor of 2, so swallowing one half of the applied gel would reach the PTD. The currently recommended procedure for APF gel

treatments minimizes the amount of gel that is likely to be swallowed and it should be followed. The recommendations are: (1) use the minimum amount of gel required to cover the teeth; (2) use no more than 2 ml of gel in each stock tray; (3) if custom-made trays are used, then use only 5–10 drops of gel in each tray; (4) seat the child in an upright position with the head inclined slightly forward to discourage swallowing; (5) use a saliva ejector throughout the procedure; and (6) allow the child to expectorate for 30 s after the procedure. When this procedure is used, the risk of even temporary stomach irritation due to swallowing is minimal. It is also worth noting that, while the APF foams have the same fluoride concentration as the gels, much less fluoride is placed in the patient's mouth because much of the volume is occupied by air [14].

Whitford et al. [15] reported that, when in an acidic solution, the threshold fluoride concentration that produces histological and functional damage to the canine stomach mucosa is between 19 and 95 mg/l or 1.0 and 5.0 mmol/l. It should be noted that the pH of APF products is approximately 3.5. The pK of hydrofluoric acid (HF) is 3.4, so nearly 50% of the fluoride in the gel or foam exists as undissociated HF (ca. 6,000 mg/l), a molecule that is very irritating to the stomach mucosa and at a concentration far above that known to damage the stomach mucosa. Unless care is taken to reduce swallowing even small amounts, nausea and vomiting may occur.

Products intended for self-application at home may also cause damage to the stomach. Spak et al. [16] examined the histological effects of a 0.42% fluoride gel (4,200 mg/l) with a pH of 6.5. Ten subjects added 1.5 g of the gel to each custom-made maxillary and mandibular tray (a total of 12.6 mg of fluoride) for a 5-min topical application. The average amount of fluoride not recovered from the mouth was 5.1 mg or 40% of the amount applied which was due to using more than the recommended volume for custom-made trays. None of the subjects experienced nausea, but endoscopic examination 2 h after the gel treatment revealed mucosal petechiae or erosions. Biopsies of the mucosa showed histological changes, including dilation of the gastric pits, localized losses of surface epithelium and bleeding, in 9 of the 10 subjects.

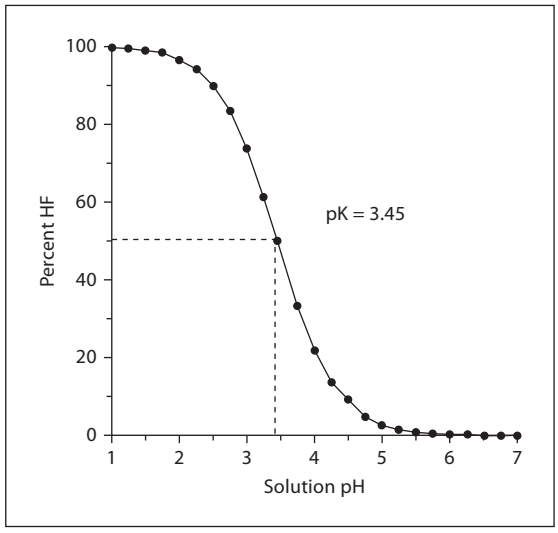

Fig. 1. Relationship between the pH of a solution and the percentage of fluoride that exists as HF.

Effects on the Stomach

Following the ingestion of a large amount of fluoride, or a relatively small amount in a small volume (i.e. a high concentration), the first organ to be affected is the stomach. The contents of the stomach have a distinctly acidic pH. Between meals the pH is usually between 2 and 4, while during and for 1–2 h after meals it is between 1 and 2. Figure 1 shows the relationship between the pH of a solution and the percentage of the total amount of fluoride in the solution that is combined with hydrogen ions to form HF, a weak acid whose pK_a is 3.45. The Henderson-Hasselbalch equation is used to calculate the relative concentrations of

ionic fluoride and HF at different pH values. The equation is:

$$pH = pK + \log([F^-]/[HF])$$

When the pH of the stomach contents is 4.0, 22% of the fluoride is in the form of HF. When the pH is lower than 2.0, more than 95% is in the form of HF. HF is a highly diffusible and permeating molecule that diffuses down its concentration gradient to cross cell membranes and epithelia including the stomach mucosa, a tissue that is relatively impermeable to most other ingested substances [17]. Upon entering the gastric mucosa where the pH is close to neutrality, HF dissociates immediately to release fluoride and hydrogen ions. In sufficiently high concentrations, these ions can disrupt the structure and function of the stomach [18–20].

It is important to understand that the effects of fluoride on the stomach are dependent on the *concentration* of fluoride (actually the HF concentration as discussed below) in contact with the mucosa, not on the ingested dose (i.e. mg/kg). For example, if 0.5 liters of water containing 5 mg of fluoride (10 ppm or 0.5 mmol/l) were ingested, it is unlikely that even the mildest of symptoms would be felt and there would be only minimal or no adverse effects on the stomach. If, however, 5 ml of water containing 5 mg of fluoride (1,000 ppm or 52.6 mmol/l) were ingested, nausea and perhaps vomiting and dizziness would be experienced by many people. In each case the same amount of fluoride would have been ingested, but the effects would be quite different. In fact, following the systemic absorption of fluoride, the toxic effects on internal organs are also dependent on the tissue concentration of fluoride but, because the concentrations in these organs are almost never known, the dose for systemic effects is usually expressed in terms of body weight (mg/kg).

The effects of pH on the gastric effects of fluoride were tested using in situ experiments with dogs [21] (fig. 2). Through a midline abdominal incision, a portion of the stomach from the greater curvature with its gastrosplenic blood supply intact was mounted in a two-compartment Lucite chamber with the mucosal surface facing upwards as described by Moody and Durbin [22]. The septum of the chamber divided the tissue into two halves of equal surface area (14.2 cm^2) so that control and test solutions could be placed side-by-side on the mucosa. This permitted a comparison of ion fluxes across the mucosa as well as direct observation of any gross changes that might occur.

The mucosa on one side of the chamber was exposed to a saline solution with or without 10 mmol/l sodium fluoride (190 ppm) at a pH of 6.2 for 22 15-min collection periods. At this pH, only 0.2% of the fluoride is in the form of HF. The mucosa on the other side was exposed to a saline solution acidified with 0.1 N HCl (pH 1.6) also with or without 10 mmol/l sodium fluoride. At this pH, 98.6% of the fluoride is in the form of HF. The solutions without fluoride served as the negative control solutions. The fluxes of water (determined by changes in the concentration of ^{14}C-inulin) and sodium, potassium and hydrogen ions were not affected by 10 mmol/l fluoride when the solution pH was 6.2 and the gross appearance of mucosa remained normal throughout the 5.5-hour study.

In contrast, the water and ion fluxes increased immediately upon exposure to the pH-1.6 solution containing 10 mmol/l fluoride. The water, sodium and potassium fluxes were positive, i.e. they were directed from the mucosa into the test solution. The hydrogen ion fluxes, however, were negative, i.e. directed into the mucosa, which indicated that HF was diffusing down its concentration gradient from the solution in the chamber and thus carrying hydrogen and fluoride ions into the tissue. When the mucosa was repeatedly exposed to the control solution (without fluoride) after the exposures to 10 mmol/l fluoride, the fluxes were reduced slightly but they did not

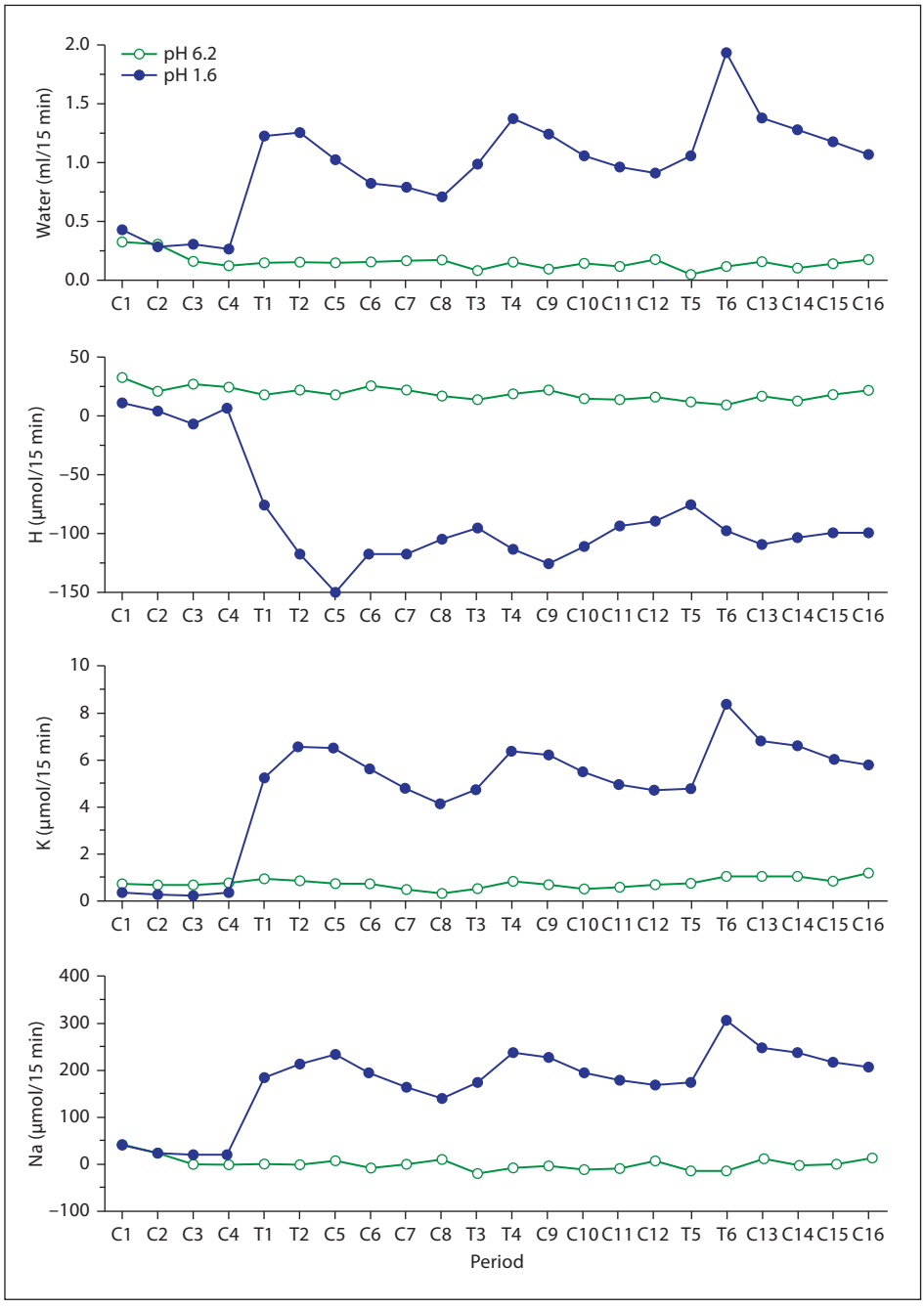

Fig. 2. Effects of solution pH (6.2 or 1.6) on water and ion fluxes from the gastric mucosa of the dog in response to exposure to sodium fluoride. The control solutions (labeled C1–C16) contained no fluoride. The test solutions (labeled T1–T6) contained 10 mmol/l sodium fluoride. Fresh solutions were placed on the mucosa every 15 min.

return to the baseline values. Further, there was an obvious increase in the secretion of mucus followed by swelling (edema) and localized areas of hemorrhage within the first few minutes after placing the pH-1.6 solution containing fluoride on the mucosa. These findings made it clear that changes in the structure and function of the gastric mucosa are caused by exposure to high concentrations of HF, and that equally high concentrations of ionic fluoride are without such effects.

Using the same model, experiments were done to determine the threshold HF concentration for gastric toxicity [15]. The solution used on the control side contained 50 mmol/l sodium chloride in 0.1 N HCl (pH 1.6). The same solution was used on the test side but also contained fluoride in the form of HF at 1.0, 5.0 or 10.0 mmol/l. The water and ion fluxes throughout the 4-hour study (16 15-min collection periods) and the gross and histological appearances on the control side were normal. On the test side, exposure to the solution containing 1.0 mmol/l fluoride as HF produced small but statistically non-significant increases in the fluxes and only minor changes in the appearance of the mucosa. However, all fluxes increased significantly upon exposure to the solution containing 5.0 mmol/l HF. Mucus secretion increased as did the redness and swelling of the mucosa. Subsequent exposure to the 10.0 mmol/l HF solution caused these effects to increase. Upon microscopic examination, the thickness of the surface mucus layer and the epithelium were greatly reduced. In some sections, evidence of surface cell exfoliation was seen indicating cell degeneration and necrosis. It was concluded that the threshold concentration for adverse effects of fluoride in a strongly acidic solution, i.e. HF, is more than 1.0 mmol/l (19 ppm) but less than 5.0 mmol/l (95 ppm). This explains why swallowed APF gel is damaging to the gastric mucosa and should be avoided. The total fluoride concentration (i.e. ionic fluoride plus HF) is 1.23% or 647 mmol/l (12,300 ppm) and, at pH 3.5, the HF concentration is 305 mmol/l (6,104 ppm).

Factors That Influence Toxic Effects

Chemical Compound

The compounds of fluoride vary greatly with respect to their solubilities. Very insoluble compounds such as calcium fluoride, cryolite (Na_3AlF_6), hydroxyfluorapatite and fluorapatite are poorly absorbed from the GI tract. Because of this their LD_{50} values, as determined in studies with laboratory animals, are much higher than those of highly soluble compounds such as sodium fluoride, fluorosilicic acid (H_2SiF_6) and sodium fluorosilicate (Na_2SiF_6), the three compounds that are commonly used to fluoridate drinking water at low fluoride concentrations.

The highest fluoride concentrations to which most people are regularly exposed are found in certain dental products, particularly dentifrices which typically contain 1,000–1,500 mg /kg fluoride. The compounds most often added to dentifrices are sodium fluoride and disodium monofluorophosphate or MFP (Na_2PO_3F). The fluoride in MFP is covalently bonded to the phosphorus. Its release from MFP is slow in water and dentifrices, but rapid in the presence of phosphatases found in the intestine, plasma and internal organs [23]. This was demonstrated in an experiment with 2 groups of rats that were given fluoride intravenously (2.0 mg/kg) as sodium fluoride or MFP [24]. Three blood samples were collected at 10, 30 and 60 min after administration of the doses. The plasma fluoride concentrations in the 2 groups were virtually identical, which indicated the complete hydrolysis of fluoride from MFP prior to the 10-min blood collections.

Based on the time courses of plasma concentrations, however, there is evidence that the absorption of orally administered fluoride when given as MFP is somewhat slower than that from sodium fluoride [23]. The delayed absorption and lower peak plasma fluoride concentrations appear to be due to the limited amount of phosphatase activity in the stomach compared to the intestine. There are, however, no significant differences in

the percentages of the doses that are ultimately absorbed systemically. The limited phosphatase activity in the stomach was also indicated in a study with humans by Müller et al. [25]. The subjects ingested sodium fluoride or monofluorophosphate tablets for 1 week. The gastric mucosa was then examined with a gastroscope. No significant damage was found in the MFP group, but acute hemorrhages and free blood were found in the NaF group.

The relative absence of gastric phosphatase activity also explained the lack of functional and structural effects of MFP on the canine mucosa [21]. Using the same split-chamber method described above, the mucosa on one side of the chamber was exposed to 10 mmol/l F as NaF and to 10 mmol/l MFP on the other side for two 15-min periods. The immediate effects on the NaF side included large increases in the fluxes of water, sodium and potassium, increased mucus secretion and increased mucosal swelling and redness. None of these effects occurred on the MFP side except for a slight and transient increase in the potassium flux.

Theoretically, the lower peak plasma fluoride concentrations could reduce the acute toxicity of MFP compared to sodium fluoride. In their study with rats, Shourie et al. [26] reported that the 24-h LD_{50} doses for these two compounds were 75 and 36 mg/kg, respectively. In their study with mice, Lim et al. [27] reported LD_{50} values of 94 and 44 mg/kg, respectively. These findings were used to support the increase of the total fluoride amount as MFP above the limit established by the American Dental Association (260 mg total fluoride per tube of dentifrice). More recent studies, however, could not confirm such differences. In their study with rats, Gruninger et al. [28] reported LD_{50} values of 102 and 98 mg/kg for MFP and sodium fluoride – with mice the values were 54 and 58 mg/kg, respectively. In their study with rats, Whitford et al. [29] reported LD_{50} values of 84.3 and 85.5 mg/kg for MFP and sodium fluoride. Based on these results, the authors stated that '. . .professional organizations and regulatory agencies should not endorse the policy of adding greater amounts of fluoride, as MFP, to dental products based on the concept that fluoride in the form of MFP is less hazardous than that in the form of NaF'.

Age

Maynard et al. [30] and Mornstad [31] reported that, compared to adult laboratory animals, young laboratory animals are more resistant to the acute toxic effects of fluoride. It is not known whether this is true for humans but there is reason to think that it is. As mentioned earlier, the systemic effects of acute exposures to high doses of fluoride are directly related to the concentrations in plasma and the target organs. The rate of removal of fluoride from plasma and the target organs depends almost entirely on the rates of uptake by calcified tissues, which contain 99% of the fluoride in the body, and excretion in the urine. Therefore, any factor that increases these rates should reduce the severity of the acute toxic effects.

Miller and Phillips [32] fed 3 groups of rats a diet with the same fluoride concentration for 4.5 months. The rats in 1 group began consuming the diet when they were weaned (21 days of age) while 2 other groups started at 9 or 20 weeks of age. At the end of the 4.5-month feeding periods, the bone fluoride concentrations were inversely related to the age at which the rats entered the study – the younger rats had higher concentrations. Similar results were reported by Zipkin and McClure [33] and Suttie and Philips [34] who used rats and by Weidmann and Weatherell [35] who used rabbits.

Whitford [21] used dogs of different ages (4 weeks, 6 months and several years) and infused isotonic solutions containing sodium fluoride intravenously for 20 min and then the infusion pump was turned off. Blood samples were collected 12 times over 6 h. Each dog received the same dose in terms of body weight (5.0 mg/kg). The

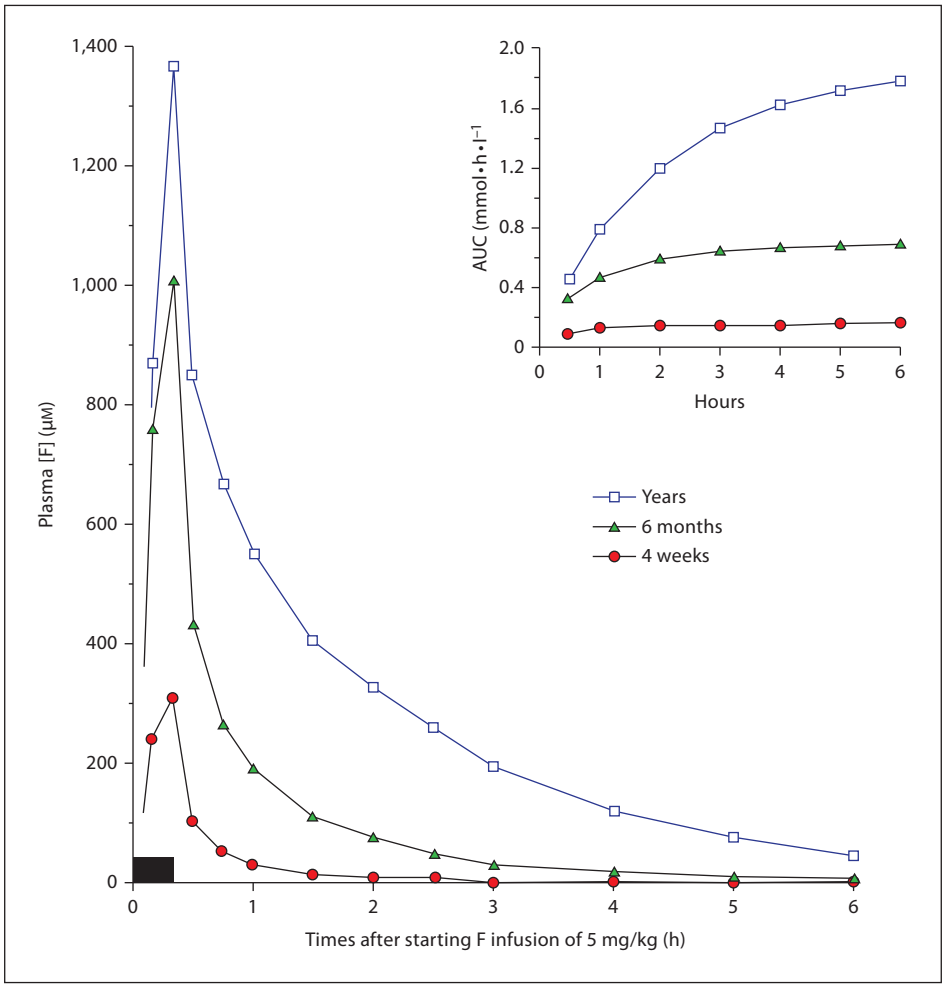

Fig. 3. Effect of age, or stage of skeletal development, on arterial plasma fluoride concentrations in dogs. The cumulative areas under the plasma-time curves (AUC) are shown [21].

peak plasma fluoride concentrations were 305, 1,004 and 1,367 μmol/l, respectively, and the areas under the time-plasma concentration curves were markedly higher in the older animals as well (fig. 3). Similar results were found in a study with rats that were 23 days or 6.5 months of age [21].

These age-related differences in plasma fluoride concentrations were due almost entirely to a greater rate of fluoride uptake by the bone of younger animals, and not to differences in urinary excretion. The results appear to be explained by the fact that the crystallites in developing bone are loosely organized and not compacted as in mature bone; thus, providing a much greater surface area for the rapid uptake of fluoride.

Acid-Base Status

There is a considerable body of evidence showing that the rates of fluoride absorption from the GI tract and excretion in the urine, as well as the

distribution of fluoride across the membranes of individual cells, are all dependent on pH gradients [21]. These observations are best explained by the fact that wherever there is a pH gradient across an epithelium or cell membrane separating two adjacent fluid compartments, there will also be a difference in the HF concentrations. In cases of distribution across cell membranes, HF, a highly diffusible and permeating molecule, will rapidly diffuse down its concentration gradient until the HF concentrations in the extracellular and intracellular compartments are equal. The result is that the concentration of ionic fluoride will be higher in the more alkaline compartment which, in nearly all tissues, is the extracellular fluid.

The magnitude of the pH gradient across cell membranes can be increased by alkalinizing the extracellular fluids which can be done, for example, by hyperventilating or the administration of sodium bicarbonate or sodium lactate. These actions increase extracellular pH more than intracellular pH [36]. Consequently the extracellular concentration of HF falls to a greater extent than that in the intracellular compartment which causes HF to diffuse from cells into the extracellular fluids. Thus the intracellular concentration of fluoride is reduced, thereby lowering the effects of fluoride on intracellular enzymes and transport systems. Further, the rate of fluoride absorption from the GI tract is inversely related to the pH of the stomach contents while the rate of urinary fluoride excretion is directly related to the pH of the renal tubular fluid. For all these reasons, it would be expected that the acute toxic effects of fluoride would be reduced by increasing the pH of the extracellular fluids and urine.

This expectation was confirmed in two studies with rats. The effects of pre-existing acid-base disturbances on acute fluoride toxicity [37] and of alkalosis imposed during the development of acute fluoride toxicity [38] were tested. In each study, fluoride was infused intravenously until death occurred. In the former study, acidosis or alkalosis was established before fluoride exposure by the oral administration of ammonium chloride or sodium bicarbonate, respectively. In the latter study alkalosis was established by the intravenous infusion of sodium bicarbonate with or without acetazolamide (Diamox®) during fluoride exposure. In each study, the alkalotic animals tolerated significantly higher fluoride doses and survived twice as long while the fluoride infusions continued. They also maintained higher blood pressures, heart rates, glomerular filtration rates and renal clearances of fluoride at any given plasma fluoride concentration. They died with significantly higher plasma fluoride concentrations and lower tissue-to-plasma fluoride concentration ratios. It was concluded that metabolic alkalosis, whether present before fluoride exposure or imposed during the development of toxicity, favorably influenced the clinical course and that establishing an alkalosis and a more alkaline urinary pH should be added to the therapeutic regimen.

Conclusion

As used in this chapter, acute toxicity means adverse effects that occur within a short period of time following the oral administration or ingestion of a single dose of fluoride or multiple doses within a few hours. The stomach – where the effects range from some degree of nausea to abdominal pain, bloody vomitus and diarrhea – is the first organ affected, with those latter effects signaling impending systemic effects that should be regarded as potentially fatal. Serious systemic toxic effects may occur when the amount ingested reaches the PTD of 5.0 mg/kg. It is difficult, however, to know the exact amount that was ingested, so estimations about the degree of toxicity and judgments about what actions and treatments should be taken typically depend on the early clinical signs and symptoms.

Today the most common sources of significant amounts of ingested fluoride available to most persons are fluoride-containing dental products

(tables 2, 3). Compared to the frequency with which these dental products are used, cases of acute toxicity are exceedingly rare. In the US, for example, it can be reasonably estimated that fluoride dentifrices are used at least once each day by at least 200 million people and that fluoride mouth rinses, dietary supplements and professionally applied topical products are used thousands of times each day. By comparison, only about 700 persons, most of whom were young children, were treated in a healthcare facility each year from 2000 through 2003, and fewer than 100 experienced moderate or major health outcomes (table 2). The use of child-resistant caps on fluoride mouth rinse bottles and most fluoride supplement containers, warning labels on toothpaste boxes and tubes, and rational recommendations for the safe use of professionally applied products have contributed to the safe use of these products.

Nevertheless, ingestion of excessive amounts of fluoride, whether accidental or intentional, does occur and moderate and major health outcomes can follow. It is for this reason that healthcare personnel, as well as parents, should be familiar with the characteristics of acute fluoride toxicity, the sources of potentially toxic doses and how to limit access to them especially by children, the amounts of ingested fluoride that can cause harmful effects, and what to do in case of overexposures. This chapter is a source of such information.

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