A Case Report

Fluoride Toxicity from Oral Medicament

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Abstract

The beneficial effects of fluoride on human oral health are well studied. There are numerous studies demonstrating that a small amount of fluoride delivered to the oral cavity decreases the prevalence of dental decay and results in stronger teeth and bones. However, ingestion of fluoride more than the recommended limit leads to toxicity and adverse effects. In order to update our understanding of fluoride and its potential toxicity, we have described the mechanisms of fluoride metabolism, toxic effects, and management of fluoride toxicity. The main aim of this review is to highlight the potential adverse effects of fluoride overdose and poorly understood toxicity. In addition, the related clinical significance of fluoride overdose and toxicity has been discussed.

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INTRODUCTION

Fluoride is the 13th most abundant element present in the earth's crust. It belongs to the halogen group of elements and is found naturally in water, soil, animals, and plants Water fluoridation is the most successfully adopted method (5-7). Fluoride delivery methods and related sources of dietary fluoride are:

Fluoridated water, beverages, and tea. Water is an important media for fluoride delivery. Fluoride exists either naturally or added during water fluoridation (8-11). Recommended optimal level of fluoride in drinking water is 0.7 mg/l; however, fluoride concentration in water varies based on geographical areas.

Fluoride containing dentifrices such as toothpaste, professionally used varnishes/ gels, and mouth rinses. Fluoride tooth pastes are available as low fluoride (500ppm), standard fluoride (1100-1500 ppm) and high fluoride toothpaste (>1500 ppm).

Fluoride is added in different forms to toothpastes and mouth rinses such as sodium fluoride (NaF), mono-fluorophosphate (MFP), or stannous fluoride (SnF) (14, 15). The mouth rinses have an advantage over toothpastes because of their low viscosity that results in better delivery to least accessible areas of the teeth such as pits and fissures and interproximal areas (7, 16, 17). Fluoridated milk including formula milk for infants and table salt fluoridation (7, 17). Fluoride delivery through milk fluoridation is not efficient as compared to other fluoride delivery methods. This is due to fluoride's tendency to form insoluble complexes with calcium, which makes fluoride absorption difficult.

a) Fluoride releasing dental materials. Some of these biomaterials not only release fluoride but also have a property to recharge them with fluoride once fluoride from other sources is available into the oral cavity. Commonly available fluoride releasing materials are glass ionomer cements (GICs), dental resin composites, compomers (modified dental composites), silicate cement, giomers, elastomeric rings and fluoride delivering mucoadhesive devices (18-21). The suggestive mechanisms for the beneficial effects of fluoride include following mechanisms (22).

a) Fluorapatite (FA) formation on tooth surface by substitution of hydroxyl with fluoride ion in the hydroxyapatite (HA). FA decreases the solubility of HA and makes the dental enamel more resistant to dissolution from the acid that is produced by the pathogenic bacteria.

b) Inhibition of enzyme enolase, which results in a reduction in lactic acid formation.

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Even though the beneficial effects of fluoride on dental health are well-established, it is very crucial to regulate the amount of fluoride intake. In addition to naturally or artificially fluoridated water, fluoride is available in a number of dental products and materials as mentioned earlier. Therefore, fluoride consumption at elevated levels may lead to a range of detrimental effects. The aim of this review is to highlight the potential adverse effects of fluoride overdose and poorly understood toxicity. In addition, the related clinical significance of fluoride overdose and toxicity has been discussed.

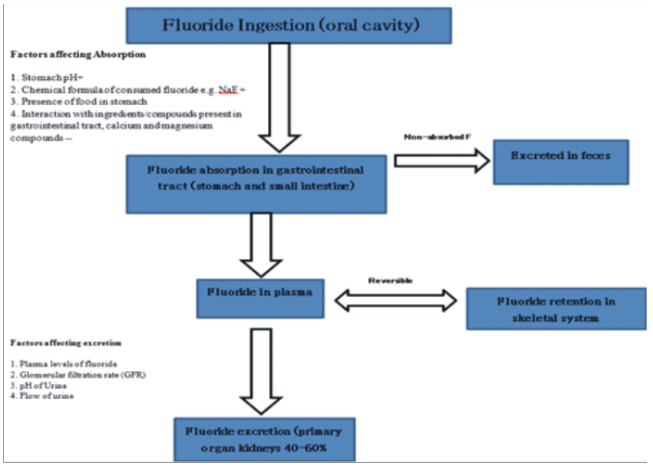

Figure 1. Summary Of Absorption, Metabolism, And Excretion Of Fluoride Following Oral Intake

Fluoride absorption, metabolism, and excretion

Fluoride is consumed commonly through the oral cavity and absorbed through the gastrointestinal tract. Other less common routes of fluoride absorption are inhalation and dermal absorption (23, 24). The principal sources of fluoride are fluoridated water and fluoride containing dental products. The absorption of fluoride starts through the stomach and upper part of the small intestine (1, 25).

In the stomach, the absorption of fluoride depends on the pH of the stomach while in the small intestine fluoride absorption is pH independent and absorption is through facilitated diffusion (26). Fluoride absorption depends on numerous factors such as stomach pH, the chemical formula of consumed fluoride, presence of food in the stomach, interaction with other food ingredients present in gastrointestinal tract, aluminum, calcium, and magnesium compounds (23).

The unabsorbed fluoride is defecated through feces while the absorbed fluoride is distributed rapidl y through the circulation into the intracellular and extracellular fluids and is retained only in the mineralized tissues of the body.

The fluoride uptake by mineralized tissues is more efficient in growing children and progressively declines with age. Retention of fluoride in the mineralized tissues of the body is reversible; fluoride is released back slowly when the fluoride level in plasma falls (25, 27).

Fluoride in the plasma is capable of crossing the placenta and is found in placental and fetal tissues. The placenta plays a regulatory role by the accumulation of excess fluoride, which protects the fetal tissues from excess fluoride intake (25).

Absorbed fluoride is deposited from serum into mineralized tissues while the remaining is excreted primarily into the urine and to a lesser extent into feces, sweat, saliva, and breast milk.

The excretion of fluoride through the urinary system depends upon several factors like plasma levels of fluoride, glomerular filtration rate (GFR), pH of the urine, and its flow (25, 28). The summary of the fluoride absorption, metabolism, and excretion is summarized in Figure 1.

Toxic effects of fluoride

Excessive ingestion of fluoride may cause toxic and harmful effects. It is important to note that the major source of fluoride toxicity remains oral hygiene products. According to fluoride poisoning

data collected by the American Association of Poison Control (AAPC), tooth paste ingestion remains the main source of toxicity followed by fluoride containing mouth washes and supplements (Table 1). The highest proportion (more than 80%) of the cases of fluoride toxicity was reported in children below the age of 6 (29).

Toothpaste	**68%**
Mouth rinses	**17%**
Fluoride supplements	**15%**

Table 1.Percentage of reported cases of fluoride toxicity (29)

These reported toxicities are due to the fact that the swallowing reflex in children is not completely developed and fluoride toothpastes are flavored, which results in voluntary toothpaste swallowing (30). Alternatively, a variety of flavors added to toothpastes may inspire young children to ingest it. Chewing stick (miswak) is another option that is natural and there are no reports of fluoride toxicity from miswak (31). The optimum beneficial dose of fluoride and the fluoride minimal risk levels are summarized in Table 2. These given doses are based on limited data reported in the literature and even at lower than the mentioned doses there are reports of toxic and lethal effects.

The possible mechanisms of fluoride toxicity are (29):

(a) As the fluoride comes in contact with mois ture this results in the formation of hydrofluoric acid and this acid formation results in burning of tissues due to low pH.
(b) Inhibition of nerve impulse or nerve function is due to the fact that calcium forms chemical complexes with fluoride leading to hypocalcemia and ultimately results in inhibition of physiological nerve functioning.
(c) Cellular poisoning results due to inhibition of enzymes required for the physiological functioning of cells.
(d) Hypocalcemia and hyperkalemia result in electrolyte

imbalance and eventually result in disturbances in cardiac rhythm.

(e) Fluoride is one of the most reactive elements. In the case of a toxic amount of fluoride in the body, fluoride attacks oxygen and disrupt the metabolism resulting in the production of hydrogen peroxide as a product. In addition, fluoride results in excessive production of free radicles that disrupt the antioxidant formation (23). The toxicity of fluoride due to excessive ingestion is classified into acute toxic effects and chronic effects (Figure 2).

Acute toxic effects

Acute fluoride poisoning although occasionally reported, however, may be fatal. Acute fluoride toxicity usually occurs due to the accidental consumption of fluoride solution or fluoride salts wrongly perceived as sugar solution or powdered eggs (33). The symptoms of acute fluoride toxicity depend upon the type and chemical nature of the ingested compound, the age, and the elapsed time between exposure and the beginning of management (34). For instance, NaF is more toxic as it is more soluble and releases more amounts of fluoride compared to calcium fluoride (CaF) that is a less soluble compound (28). The acute toxic dose range is 5-8 mg/kg body weight. In the case of acute fluoride toxicity, one or a combination of the following symptoms such as gastric disturbances (nausea, vomiting occasionally with blood, abdominal pain, diarrhea, weakness, and hypocalcemia) are observed.

Important doses of fluoride	
Optimal dose of fluoride (for children & adults)	**0.05 - 0.07 mg F/kg body weight**
Toxic dose of fluoride (for children & adults)	**5 mg F/kg body weight**
Lethal dose of fluoride (children)	**16 mg F/kg body weight**
Lethal dose of fluoride (adults)	**32 mg F/kg body weight**

Table 2. Summary of the important doses of fluoride (29, 30, 32)

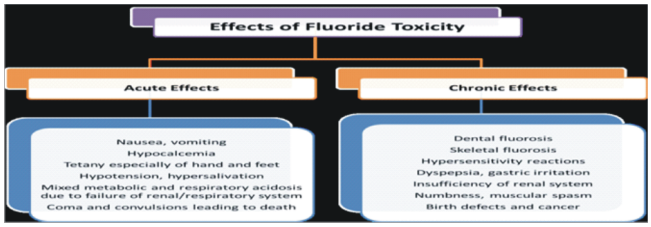

Figure 2. Classification of toxic effects due to excessive ingestion of fluoride

Chronic toxic effects

Chronic toxicity of fluoride is more common than acute toxicity. The effects of chronic ingestion of fluoride depend not only on the duration and dose but also on several other factors such as nutritional status, renal function, and interactions with other trace elements (24, 28).

Dental fluorosis

The association between excessive ingestion of fluoride and dental mottling (fluorosis) was initially discovered over a century ago by Frederick Sumner McKay a practicing dentist in Colorado Springs area and G. V. Black (22). Dental fluorosis is the most sensitive and the earliest indicator of chronic fluoride toxicity (1). Although fluoride is an important element for caries prevention, the chronic intake of fluoride greater than 1 mg/l or 0.1 mg/kg daily during the period of tooth development interferes with the process of enamel and dentin formation and leads to dental fluorosis (1, 35, 36).

The mechanism of dental fluorosis is very complex and not fully understood. The excess amount of fluoride impedes normal enamel maturation and the dental enamel formed is hypomineralized with more surface and subsurface porosity in comparison with normal enamel. In dentine due to excessive fluoride during dentin formation, the dentinal tubules have an irregular distribution and the lumina of the tubules become narrow and disrupted (36, 37). Clinically, the appearance ranges from mild opaque white to brown mottling of enamel associated with pits and enamel fracture in both deciduous and permanent dentitions, and the lesions are generally symmetrical bilaterally (28, 38, 39). The severity of dental fluorosis not only depends on excessive consumption of fluoride but al so on the timing and duration of excessive fluoride consumption, the plasma concentration of fluoride, type of fluoride consumed, renal function, and genetic factors (36).

Therefore, in order to prevent fluorosis the following measures should be instituted:

i. The fluoride level in the drinking water should be regulated between 0.5 to 1 ppm as suggested by the World Health Organization (5).
ii. Low fluoride dentifrices (500 ppm) are indicated for children living in fluoridated areas (35).
iii. Supervised brushing and a smear layer of low fluoride toothpaste should be applied on the brush (40).

Following these precautionary measurements, the chances offluorosis and related lesions will be reduced.

Skeletal fluorosis

Chronic fluoride exposure at more than the recommended levels either by ingestion, inhalation, or a combination of both results in skeletal fluorosis. This condition is characterized by an increase in bone mass and density because of deposition of excess fluoride within the bone matrix (24). The primary phase of skeletal fluorosis is associated with symptoms such as sporadic pain, joints stiffness due to fluoride deposition with resultant difficulty in mobility, kyphosis of back bone, tingling sensation, muscle weakness, and fatigue. The advanced stage of skeletal fluorosis is linked with signs of arthritis and osteoporosis in long bones, spinal cord compression and calcification of ligaments with resulting neurological defects and muscle wasting (41).

Radiographically, skeletal fluorosis may appear as osteosclerosis and calcification of ligaments (24 , 27). The neurological symptoms that occur because of fluoride

toxicity are due to abnormal bone outgrowths (1). Primary symptoms of skeletal fluorosis usually occur in fluoride doses greater than 4 mg/l. While the crippling skeletal fluorosis is rare and is associated with intake of water with fluoride level greater than 10 mg/l, it results in a remarkable limitation of joint movements, and deformities of major joints and spine leading to neurological problems (10, 27, 28). The severity of skeletal fluorosis depends on the amount of water intake, quality of water, renal disease, and dietary factors for instance calcium rich diet, which has a protective effect and prevents toxic effects of fluoride on bones (1, 27).

Fluoride/ kilogram body weight*	Treatment
< 5.0 mg/kg	1. Oral administration of soluble calcium (milk) to relieve GIT symptoms 2. Observe for a few hours 3. Induced vomiting not required.
> 5 mg/kg	1. Require hospital admission 2. Use emetic to empty the stomach. However, if the patient has depressed gag reflex for instance in the case of babies (<6 months old), Down's syndrome, or mental retardation, endotracheal intubation should be performed before gastric lavage. 3. Oral administration of soluble calcium (e.g. milk, calcium lactate, or gluconate solution). 4. Keep under observation for a few hours.
>15 mg/kg	1. Immediate hospital admission 2. Immediate stomach emptying and gastric lavage 3. Begin cardiac monitoring and be prepared for cardiac arrhythmias 4. Intravenous administration of 10% calcium gluconate solution 5. Electrolytes (calcium and potassium) should be monitored and corrected as required 6. Maintenance of adequate urine output by diuretics if required 7. General supportive measures for shock

Table 3.Summary of treatment protocol for fluoride overdose (48)

* Average weight/age: 1–2 years= 10 kg; 2–4 years= 15 kg; 4–6 years= 20 kg; 6–8 years= 23 kg

Basis of the treatment

The management of fluoride toxicity consists of:

i. The fluoride toxicity case must be evaluated immediately for the type and amount of ingested fluoride. The minimum optimal dose likely to cause toxicity and requiring therapeutic intervention has been set at 5 mg/kg of body weight. Regarding the chemical type, NaF and hydrogen fluoride are more soluble, resulting in faster absorption. On the other hand, CaF and magnesium fluoride are the less soluble fluoride compounds and absorption may be relatively slow (29).

ii. Milk has a proven role in reducing the absorption of fluoride (rich in calcium which has a fluoride binding effect). Further absorption can be minimized using, calcium gluconate, calcium lactate, or milk of magnesia and aluminum, which form insoluble complexes that decrease the absorption of fluoride.

Therefore, calcium containing compounds are used in acute fluoride toxicity (25,40). Gastric lavage is recommended instead of an emetic agent because of the danger of aspiration of gastric contents and burning of the esophagus due to hydrofluoric acid present in the stomach (40).

iii. Alkalization of the body fluids results in the faster removal of the ingested fluoride from the body fluids because of the faster flux of fluoride out of the cells and its elimination into the urine (25).

iv. Supporting the vital signs by oxygen therapy, artificial respiration, and hemodialysis are highly recommended. These measures should be continued until the stabilization of vital signs and serum chemistry (25).

CONCLUSION

The beneficial role of fluoride for the maintenance of good oral health has been known for many decades and strongly evidenced by scientific research. However, it must be emphasized that tooth decay (dental caries) is not caused by fluoride deficiency and fluoride supplementation will never reverse the active or gross carious lesions. Since the level of safety of fluoride is low, products that contain a high level of fluoride should be stored and used according to the recommendation and should be monitored by a qualified dental professional especially in children and pregnant women.

In children, the swallowing reflex is not very well developed and the fluoride containing dental products are flavored hence increasing the possibility of a child to consume an excessive dose of fluoride. In areas with high fluoride levels in the drinking water, alternative dental products with low fluoride levels should be prescribed and monitored.

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