Influence of Coffee on Fluoride Metabolism in Rats (43052)

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Abstract. **Concomitant intragastric administration of sodium fluoride and coffee resulted in a significantly higher (*P* < 0.01) plasma fluoride level than intake of the same amount of fluoride with water. The same result was obtained when coffee was substituted with an equivalent amount of caffeine. Comparison of plasma fluoride levels by total area under the curve of plasma fluoride concentration versus time indicated an almost 2-fold difference. Although the mechanism(s) is not known, it appears that caffeine is responsible for the present observation. This finding could help explain the variations in the incidence of dental fluorosis among people living in optimally fluoridated communities.** [P.S.E.B.M. 1990, Vol 194]

Caffeine, from natural sources, has been consumed and enjoyed by people throughout the world for centuries in the form of coffee and tea. It is also used, to a lesser extent, as a flavoring agent in baked goods, dietary desserts, pudding, and fillings and in candy. Therapeutically, caffeine has been used in infant apnea as a bronchial dilator and cardiac stimulant, in acne and other skin disorders, and for migraine headaches. It also occurs in a variety of over-the-counter products used as analgesics, diuretics, weight control aids, allergy relief preparations, and alertness compounds (1). Daily consumption per person in the United States is estimated at 210 mg, 75% of which is derived from coffee.

Ingested caffeine is rapidly absorbed, metabolized, and excreted in the urine as methylxanthine derivatives (2, 3). Within a few minutes after ingestion, caffeine enters all organs and tissues and after 1 hr is distributed in proportion to tissue water content (4–6). Rapid equilibrium is reached between mother and fetus and between blood and all tissues. The metabolic half-life of caffeine in the plasma and most organs is about 3 hr. In addition to metabolic conversion and urinary excretion, caffeine is also found in saliva, semen, umbilical cord blood, and breast milk (7–12).

The pharmacologic effects of caffeine ingestion in humans have been studied over the several decades. The actions of caffeine on metabolism and on the cardiovascular, respiratory, gastrointestinal, renal, and central nervous systems have been extensively investigated (13). Caffeine probably exerts most of its pharmacologic effects through antagonism of adenosine receptors, although inhibition of phosphodiesterases, reduction of extraneuronal uptake of catecholamines, and calcium mobilization is important (14–20).

Chronic subcutaneous injection of caffeine has been shown to increase urinary volume excretion as well as urinary excretion of calcium, potassium, sodium, inorganic phosphate, and magnesium (21). However, when caffeine was given in the rat's diet, only an increase in urinary calcium excretion was noted (22). Recently, it has been reported that maternal caffeine intake during pregnancy resulted in decreases in calcium, magnesium, and zinc content of fetal rat bone (23). In humans, it has been demonstrated that coffee consumption inhibits iron absorption (24). Furthermore, it has been reported that total urinary excretion of calcium, magnesium, sodium, and chloride increased significantly after caffeine intake, while zinc, phosphorus, potassium, creatine, and urinary volumes were unchanged (25). However, to the best of our knowledge, there has been no investigation on the effect of caffeine on fluoride metabolism.

One of the references linking coffee intake and fluoride overdose is the report on the 1979 incident of overfluoridation of drinking water in Annapolis, MD (26). Fluoride intoxication was recorded, through a series of surveys, to be less severe among coffee drinkers

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than drinkers of other beverages. A similar observation was reported in an overfluoridation of a school water system in Pennsylvania which occurred in June 1972. This was reported in a symposium (27) but no primary reference to it could be located. Students attending a school picnic vomited after drinking orange juice reconstituted with water, but none of the teachers who consumed only coffee made with the same water became ill. It was postulated that some components of coffee, such as caffeine, formed a complex with fluoride and caused it to be less available for absorption when ingested. It has been demonstrated that induction of dental fluorosis (28) and therapeutic treatment of osteoporosis patients with fluoride (29) are dependent on the fluoride level in the blood plasma. Therefore, the current studies on coffee consumption and fluoride metabolism could have important clinical ramifications.

Materials and Methods

Female Sprague-Dawley rats (250 ± 10 g) were housed, individually, in stainless steel cages in animal rooms maintained at a temperature of 23 ± 1°C and relative humidity of 40–80%. The rats were fed, *ad libitum*, Rodent Blox (Wayne Pet Food Division, Continental Grain Co., Chicago, IL) that contained 0.4% sodium and 0.5% chloride, based on ash weight, and tap water with a fluoride level of 37 μM. A 12-hr light cycle (6 AM to 6 PM) was maintained in the animal rooms. Under general anesthesia, with a cocktail that contained 15.63 mg of ketamin, 0.63 mg of acepromazine, and 3.13 mg of rompun in each milliliter of solution, a chronic jugular vein catheter was placed in each rat (30). These catheters exited dorsally behind the head and were filled up with heparinized normal saline solution (1000 IU heparin/30 ml of saline solution) to prevent clotting and blockage of the catheters. The animals were allowed 24 hr to recover from the surgical procedure before intragastric (ig) administration of the drugs. Groups of seven rats were surgically prepared as described to ensure that five rats were available for experimentation. These rats were weighed and given a solution of sodium fluoride (Fisher Certified ACS; Fisher Scientific Co., NJ) intragastrically at a dosage of 53 μmol fluoride/ml water/250 g body wt. Through the jugular vein catheter, 0.2-ml blood samples were collected in heparinized 1-ml plastic disposable syringes at 0, 20, 40, 60, 90, 120, 180, and 240 min after the intragastric doses. The blood samples were transferred to polyethylene microcentrifuge tubes, and plasma samples were removed and stored at 4°C for fluoride analysis, which was performed using the HMDS diffusion method (31, 32). A second group of rats was administered, ig, a sodium fluoride solution with coffee as solvent, at a dose of 53 μmol fluoride/ml coffee/250 g body wt. Timed blood samples were collected and plasma fluoride levels were determined as described before.

In a separate experiment, two groups of 24 rats were housed individually in plastic metabolic cages under identical environmental conditions as rats in the previous experiment. One group was dosed with 53 μmol fluoride/ml water/250 g body wt, while another group, with the same number of rats, was given 53 μmol fluoride/ml coffee/250 g body wt. Coffee was prepared with a Mr. Coffee coffee maker, using 55 g of Mountain Grown Folgers coffee (automatic drip) and 1500 ml of deionized water. Each milliliter of coffee prepared this way contained 3.8 μmol of caffeine and 0.013 μmol of fluoride. Urine samples were collected at 3, 6, and 24 hr after ig dosing and stored at 4°C for fluoride analysis the following day.

In order to determine whether the caffeine in coffee was responsible for the altered fluoride level in blood plasma, rats were each surgically prepared, as described before, and were given 26.5 μmol of fluoride dissolved in 1 ml of a solution containing either 0, 0.67, 1.34, 2.68, or 5.36 μmol of caffeine (Sigma Chemical Co., St. Louis, MO). Timed blood sampling and fluoride analysis was carried out as described. Student's t test was used to determine whether the differences between the control and treatment groups were statistically significant.

Results

The results in Figure 1 indicate that when sodium fluoride dissolved in water was administered ig to rats, it was initially absorbed very rapidly and the plasma fluoride level (42.2 μM) peaked during the first 20 min. Plasma fluoride levels decreased rapidly over the next 1 to 1½ hr, but average plasma fluoride levels remained significantly higher (6.5 μM) than the baseline level (0.8 μM) even 4 hr after the fluoride administration. The same initial response was observed when coffee with fluoride (NaF) added was administered ig to rats. However, when the same dose of NaF was co-administered with coffee, plasma fluoride levels remained higher during the experimental period of 4 hr than in those rats given fluoride with water. Comparison of fluoride levels under these two different conditions, using the trapezoidal rule of calculating the area under the curve of plasma concentration versus time from 0 to 4 hr (ΔAUC)0–4, indicates a 100% increase in fluoride in the plasma. Since the amount of fluoride present in 1 ml of coffee was less than 20 μg, it could not account for the difference that was observed.

The results in Table I showed that urinary excretion of fluoride was 31.1% less ($P < 0.02$) among rats dosed with fluoride in coffee, as compared with rats dosed with fluoride in water, during the first 3 hr following ingestion of fluoride. Such a reduction in fluoride excretion could partially account for the higher plasma

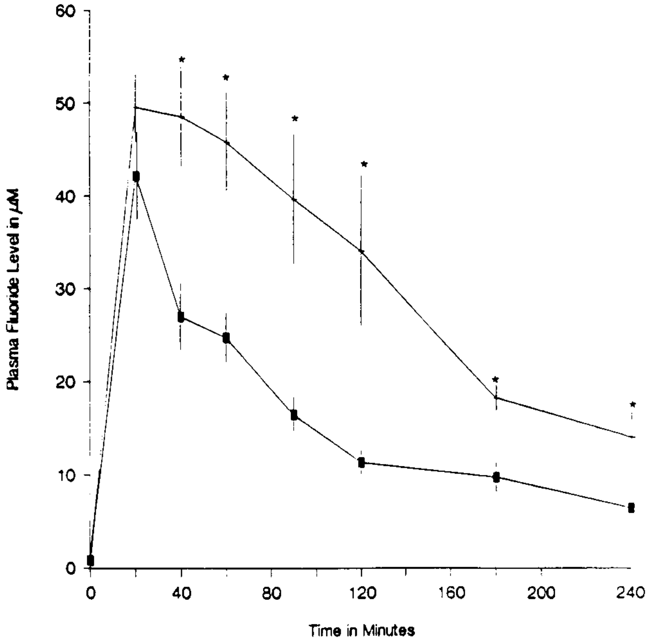

Figure 1. Plasma fluoride concentration curve of rats following administration of 53 μmol fluoride/ml water/250 g body wt (▮—▮); or 53 μmol of fluoride/ml coffee/250 g body wt (|—|). Each point represents the average value of five rats, with the standard error of mean indicated by vertical bars. *Indicates the value is significantly different from those treated with fluoride in water ($P < 0.01$).

fluoride concentration during the first 4 hr following ingestion of fluoride with coffee, as indicated in Figure 1. No difference in amount of fluoride excretion was observed for the remaining collection period. The 24-hr urinary fluoride excretion was about 13% less in the coffee group; however, the difference was not statistically significant.

A significant difference was also observed in the volume of urine excreted during the 24 hr following fluoride ingestion (Table II). Coffee exerted the well-known diuretic effect even at the present low dosage. Contrary to the plasma fluoride results, the diuretic effect of coffee was absent during the first 3 hr following ingestion of NaF-coffee solution. If fluoride excretion is influenced by the rate of urine excretion, then the plasma fluoride of rats in this treatment group might be even more pronounced in absence of the diuretic effect.

The effect of graded doses of caffeine on plasma fluoride levels of rats are shown in Figure 2. Plasma fluoride levels in all of the groups given caffeine were higher than those of the control animals which were not exposed to caffeine. The greatest effect of caffeine was observed in animals that were exposed to 0.67 and 1.34 μmol of caffeine. Plasma fluoride levels decreased as the rats were exposed to higher caffeine doses of 2.68 and 5.36 μmol; however, the plasma fluoride levels of these animals were still significantly greater than those of animals in the control group.

Discussion

Dietary caffeine has been reported to significantly increase urinary calcium excretion (33, 34). However, in the present study, urinary calcium excretion of the NaF-water group and the NaF-coffee group was the same. This could be due to the fact that a much lower level of caffeine (one hundredth) was administered to rats in this study as compared with the earlier study (22). Furthermore, in the present study caffeine was administered ig in one dose, while in the earlier study, caffeine was mixed with food and given *ad libitum.*

It has been reported that in an adult male human, 1.85 mmol of caffeine is needed to induce an increase in urine volume, i.e., 1.85 mmol/70 kg or 26 mmol/kg body wt (35). In newborn rabbits, diuretic effects were exhibited by animals given 51 μmol of caffeine/kg body wt (33). Rats in this study were exposed to 15 μmol of caffeine/kg body wt; however, even at this low dosage, a definitive diuretic effect was observed. Rats dosed with NaF in coffee excreted 30% more urine volume than rats dosed with fluoride in water.

In the present study, rats were dosed at the level of 52 μmol of fluoride/250 g body wt or 14.7 mmol of fluoride/70 kg body wt. Based on the metabolic body weight, this is equivalent to a dose of 2.8 mmol of fluoride/70 kg body wt in humans (36). Osteoporosis patients on fluoride therapy are given 22–110 mg NaF or 0.5–2.6 mmol of fluoride/day (29). Therefore, the fluoride dose used in this study is at the higher level of the usual therapeutic dose.

The increase in plasma fluoride level in the presence of coffee may be caused by an increase in gastric secretion, which would facilitate the formation of hydrogen fluoride, hence an increase in the rate of fluoride absorption (37). It could also be due to an increase in

Table I. Effect of Coffee on Fluoride Excretion following Intragastric Administration of NaF Solution

Treatment	Urinary fluoride (μmol)			
	0–3 hr	3–6 hr	6–24 hr	0–24 hr
NaF in water	3.38 ± 0.27[a]	2.62 ± 0.28	3.81 ± 0.42	9.67 ± 0.60
NaF in coffee	2.33 ± 0.29[b]	2.53 ± 0.32	3.76 ± 0.35	8.43 ± 0.58

[a] Mean ± SE.
[b] Value is significantly different from the control at $P < 0.02$.

Table II. Effect of Coffee on Urine Excretion following Intragastric Administration of NaF Solution

Treatment	Urine volume (ml)			
	0–3 hr	3–6 hr	6–24 hr	0–24 hr
NaF in water	0.78 ± 0.09[a]	1.03 ± 0.12	4.95 ± 0.53	6.76 ± 0.64
NaF in coffee	0.76 ± 0.12	1.35 ± 0.12	6.66 ± 0.53[b]	8.77 ± 0.62[b]

[a] Mean ± SE.
[b] Value is significantly different from the control at $P < 0.05$.

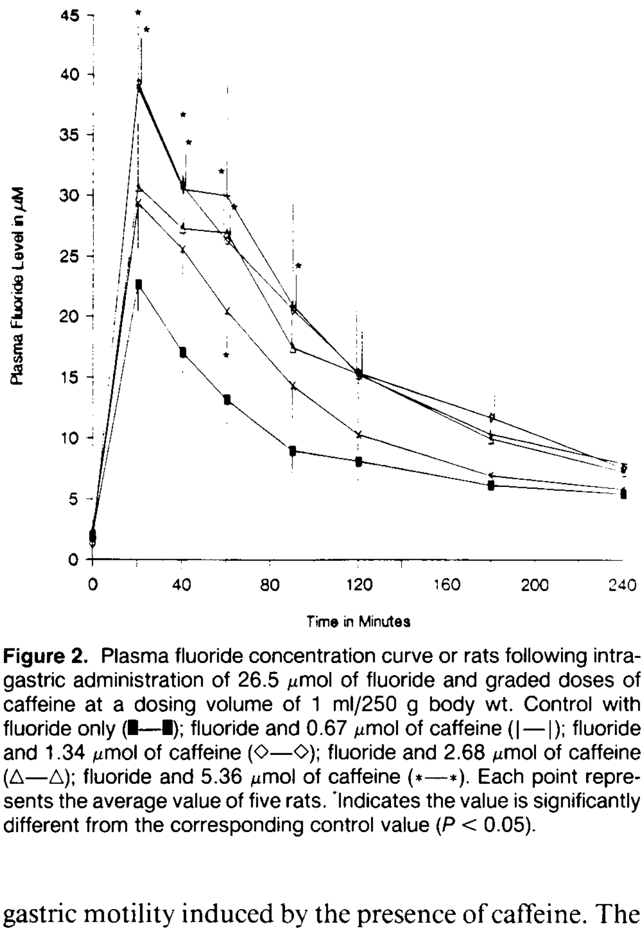

Figure 2. Plasma fluoride concentration curve or rats following intragastric administration of 26.5 µmol of fluoride and graded doses of caffeine at a dosing volume of 1 ml/250 g body wt. Control with fluoride only (■—■); fluoride and 0.67 µmol of caffeine (|—|); fluoride and 1.34 µmol of caffeine (◇—◇); fluoride and 2.68 µmol of caffeine (Δ—Δ); fluoride and 5.36 µmol of caffeine (*—*). Each point represents the average value of five rats. *Indicates the value is significantly different from the corresponding control value ($P < 0.05$).

gastric motility induced by the presence of caffeine. The reduction in urinary fluoride excretion of rats exposed to caffeine during the first few hours following ig fluoride administration could be the result of an increase in uptake of fluoride by skeletal tissues, which are known to be the major site where fluoride retained by the animal body is deposited or due to an effect of caffeine on renal function.

In order to determine if the effect of coffee on plasma fluoride level exhibited a dose-response relationship, the fluoride dose was reduced by half in the second study. Plasma fluoride levels of rats exhibit a similar response when coffee is substituted by caffeine (Fig. 2), which indicates that the active component of coffee could be the methylxanthines. It is not clear why plasma fluoride levels decreased at the higher caffeine doses of 2.68 µmol/250 g body wt and 5.36 µmol/250 g body wt. Caffeine is a weak base, therefore, the neutralizing effect against the gastric acidity would be insignificant even at the highest dose used in this study. A greater diuretic effect exerted by a higher dose of caffeine could result in an increase of fluoride excretion. Action of caffeine on the cardiovascular system is complex and sometimes antagonistic (20). The resultant effects depend upon the route of administration and the dose used. In addition, caffeine also affects the vascular and cardiac tissues. The role of any one or combinations of the pharmacologic effects of caffeine in the enhancement of plasma fluoride level is unknown.

It has been demonstrated that rats fed a diet deficient in chloride (0.02%) retained significantly more dietary fluoride than did rats fed diets containing either normal (0.1%) or five times normal chloride (38, 39). However, those were 6-week chronic studies, comparison to the present acute experiments is not feasible. Further studies are required to determine the exact mechanism(s) involved in the effect of caffeine on fluoride metabolism in rats. However, the present finding could offer an explanation to the recent reports on the increase in prevalence of dental fluorosis (40, 41), and variation of incidence of dental fluorosis among the population living in communities with optimal or below optimal levels of fluoride (42).

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