

Plasma Fluoride Levels in Rabbits Acutely Poisoned with Sodium Fluoride¹ (36285)

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The ranges of plasma fluoride levels associated with the well-known fluoride effects (*e.g.*, mortality, kidney injury, growth depression, osteosclerosis) may well serve as exceptionally useful indices of the fluoride status of persons exposed accidentally or occupationally.

As a beginning in discovering these ranges, the plasma fluoride concentrations associated with acute lethal fluoride poisoning in rabbits have been determined. Previous studies are limited. Largent (1) reported whole blood levels in two acutely poisoned rabbits; Lopez (2) determined diffusible plasma fluoride concentrations in an extensive series of acutely poisoned rats. Human data comprise analyses of blood samples taken from individuals who died from acute fluoride poisoning; under such circumstances that magnitude of the dose is seldom known (3). This report describes the changes in plasma diffusible fluoride (F ion) concentration following the administration of acutely toxic oral doses in rabbits.

Methods. Female, New Zealand albino rabbits (Blue Spruce Farms, Altamont, New

York) weighing 2.0 to 2.5 kg, and maintained according to the ACP recommendations with Purina Rabbit Chow and tap water (1 ppm F) *ad lib.* were fasted for 48 hr prior to gavage with 0.1–0.2 *M* solutions of sodium fluoride in the doses shown in Table I. Blood samples (2–3 ml) were taken from a marginal ear vein at successively more distal sites, before treatment, 1 hr after dosing, and at intervals during the succeeding 24 hr. The plasma was immediately separated by centrifugation and frozen until analyzed. One of 2 ml aliquots of control plasma were analyzed and 25–200 μ l of plasma from poisoned rabbits using the Taves diffusion method (4) with two minor modifications: a) silicone stopcock grease furnished volatile silanes, and b) for convenience, the plasma was pipetted directly into the diffusion dish without prior separation of proteins.

Results. The pretreatment, acid-labile plasma fluoride (F ion) concentrations (Table I) ranged from 0.01 to 0.07 ppm (average 0.04 ppm). Total plasma fluoride determined independently (on large samples by ashing and distillation) gave practically the same average concentrations, namely 0.05 ppm F, showing that little or none of rabbit plasma fluoride exists in a bound form.

Plasma fluoride concentrations following dosing increased promptly to high values and, in nearly every case, declined thereafter with disappearance half-times of approximately 4 or 5 hr (Table I). The F concentrations in one hour plasma samples failed to increase consistently with dose. Following doses of 100 mg NaF/kg, the one hour F levels were 12 and 28 ppm in 2 rabbits; with 110 mg/kg—13 and 16 ppm; with 120

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TABLE I. Plasma Concentrations of Acid-Labile Fluoride in Parts per Million ($\mu\text{g F/ml}$).^a

Rabbit no.	Body weight (kg)	Dose (MgNaF/kg)	Pre-treatment	Plasma F (ppm); time (hr)								
				1	2	3	4	5	6	7-9	10-12	24-27
1	2.19	100	0.04	12	14	—	—	—	—	—	2.6	0.8
2	3.43	100	0.02	28	—	27	—	—	16	D ^b	—	—
3	2.11	110	0.04	13	—	—	—	5.2	—	—	3.6	—
4	2.21	110	0.06	16	—	—	6.1	—	—	—	3.2	—
5	2.49	120	0.02	17	17	—	13	—	9.1	7.8	—	1.0
6	2.27	120	0.07	15	13	—	10	—	—	—	4.3	—
7	2.83	120	0.03	28	24	—	13	—	10 D	—	—	—
8	2.48	120	0.05	18	16	18	—	18	D	—	—	—
9	2.00	130	0.01	19	15	—	—	7.2	—	—	—	—
10	2.23	130	0.02	21	—	13	10	—	—	—	—	—
11	2.27	130	0.03	24	19	—	16	—	9.1	—	4.0	—
12	2.15	130	0.04	29	26	—	14	—	12	—	D	—
13	2.21	140	0.04	18	14	—	8.6	—	5.3	—	2.5	0.6
14	2.37	140	0.02	18	13	—	8.6	—	7.8	—	—	—
15	2.37	140	0.03	19	16	—	—	16	13	D	—	—
16	2.21	140	0.03	31	32 D	—	—	—	—	—	—	—
17	2.27	140	0.07	30	35 D	—	—	—	—	—	—	—
18	2.22	140	0.04	41 D	—	—	—	—	—	—	—	—

^a Blood samples were drawn from fasted rabbits at the specified times after administration of a single dose of sodium fluoride by stomach tube.

^b D = Death.

mg/kg—in the range 15 to 28 ppm; with 130 mg/kg—19 to 29 ppm; with 140 mg/kg—18 to 41 ppm.

If the plasma F concentration at one hour equalled or exceeded 28 ppm (with two exceptions, rabbits No. 8 and 15), the rabbit died in 12 hr or less. The rabbits (with the same two exceptions) in which the one hour concentrations were 24 ppm or less survived for at least 24 hr.

All but two of the 12 rabbits surviving for 24 hr died in the succeeding 7 days. During this time the rabbits appeared ill and nasal discharge was frequently present; rectal hemorrhage was noted in one rabbit. Gross autopsy examinations of the rabbits dying within 12 hr revealed normal-appearing organs except for hemorrhagic areas of the stomach wall. Stomachs and ceca were not distended. No evidence of faulty intubation was encountered.

Discussion. The "lethal concentrations" in rabbits (≤ 28 ppm) were similar in magnitude to those in rats (≤ 10 to 12 ppm) (2). In two rabbits that died in 6 and 9 hr,

respectively (No. 8 and 15, Table I), plasma F levels never were observed to reach 20 ppm, and, for reasons unknown, the levels failed to decrease in the ensuing 4 hr as occurred with all other rabbits. The plasma concentration-time products exceeded those of rabbits surviving for 24 hr. The highest concentrations (Table I) are less than the single previously reported value, 51 ppm total F (whole blood), in a fatally poisoned rabbit given orally 500 mg NaF/kg (1). A surviving rabbit given 200 mg NaF/kg exhibited a plasma total F concentration of 9 ppm after 4 hr (1), in reasonable agreement with the data of Table I.

The promptness of the rise in plasma F levels (Table I) agrees with previous observations, mostly from studies using ^{18}F , *e.g.*, in sheep (5), rabbits (6), rats (2, 7), and in dogs (8). Absorption through the stomach mucosa (9) may account in part for the rapidity of absorption.

The cause of death in acute fluoride poisoning remains obscure (10). Catastrophic enzyme inhibition may block energy or other

vital cell systems. The *in vitro* activity of certain enzymes is reduced to one-half or less in the presence of 10^{-5} to 10^{-3} M fluoride (11); such concentrations were found in the plasma of the poisoned rabbits.

Summary. Following acutely toxic oral doses of sodium fluoride, plasma F levels (normal—0.01 to 0.07 ppm) promptly rose to high values; doses of 100 to 140 mg/kg gave one hour plasma F concentrations of 12 to 41 ppm. One hour plasma F values over 28 ppm were associated with death in 12 hr or less. Rabbits usually survived for at least 24 hr if 1-hr levels were less than 24 ppm.

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1. Largent, E. J., J. Ind. Hyg. Toxicol. 30, 92 (1948).
 2. Lopez, O. H., M. Sc. thesis, University of Rochester, Rochester, NY, (1970).
 3. Dodinval-Versie, J., Dodinval, P., and Andre, A., Ann. Med. Leg. 46, 155 (1966).
 4. Taves, D. R., Talanta 15, 1015 (1968).
 5. Perkinson, J. D., Jr., Whitney, I. B., Monroe, R. A., Lotz, W. F., and Comar, C. L., Amer. J. Physiol. 182, 383 (1955).
 6. Ericsson, Y., Acta Odontol. Scand. 16, 51 (1958).
 7. Ericsson, Y., Santesson, G., and Ullberg, S., Arch. Oral Biol. 4 (special supplement), 160 (1961).
 8. Carlson, C. H., Ph.D. thesis, University of Minnesota, Minneapolis, Minnesota, (1959).
 9. Crane, D. B., Stookey, G. K., and Muhler, J. C., J. Dent. Res. 40, 713 (1961).
 10. Caruso, F. S., Maynard, E. A., and DiStefano, V., "Pharmacology of fluorides, Handbuch der experimentellen Pharmakologie," Vol. 20, Pt. 2, Chap. 4. Springer-Verlag, Berlin, Heidelberg, New York, (1970).
 11. Wiseman, A., "Pharmacology of fluorides, Handbuch der experimentellen Pharmakologie," Vol. 20, Pt. 2, Chap. 2. Springer-Verlag, Berlin, Heidelberg, New York (1970).
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