ACUTE POISONING WITH SODIUM FLUOROACETATE (COMPOUND 1080)

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Since the report of Kalmbach [1] on the rodenticide activity of fluoroacetate (compound 1080) this compound has been extensively used by government agencies, the armed forces, and privately employed exterminators. In spite of its high toxicity to all species, relatively few cases of human poisonings have been reported so far, none of which have ended fatally.[2] All of the victims took small, but unidentified, quantities of fluoroacetate. The toxic dose for human beings has not been established, but on the basis of animal studies it has been theorized as being approximately 5 mg. per kilogram of body weight. The case reported here ended fatally, pathological examination was performed, and the quantities of fluoroacetate in the organs were determined. For the experimental literature on fluoroacetate we may refer the reader to the recent reviews by Chenoweth [3] and by us.[4]

REPORT OF CASE

A white man, about 40 years of age, was found on Feb. 3, 1949, noon, in his bedroom at home in an unconscious state. He was admitted to the emergency ward with the information from his wife that he had probably taken sodium fluoroacetate.

Past History.—According to his wife, who had known him since birth, he never had any serious illness or operation until after being discharged from the Army after World War II. At this time he was hospitalized with battle fatigue for six months. He received shock treatment for "severe depression." He was discharged December, 1940, and readmitted from October to December, 1947. The diagnosis was manic depressive psychosis. His family was warned of danger of possible suicide. The family history was essentially negative.

Examination on Admission.—He was unconscious and had nystagmus of both eyes and slight muscular spasms. The heart rate was 92, rhythm was irregular, and no murmurs were heard. The abdomen was soft, and between muscle spasms peristalsis was heard.

Therapy and Course.—The stomach was lavaged and magnesium sulfate instilled. He was given a soft soap enema. Following this, nystagmus became pronounced and he had an epileptiform convulsion. For sedation, 2 grains (0.12 gm.) of phenobarbital (luminal®) sodium was given four times and 1/50 grain (1.2 mg.) of scopolamine hydrobromide. Blood pressure had fallen to 90/40 mm. Hg. Plasma was administered and three intracardial injections of 5 ml. of 1% procaine hydrochloride given. Oxygen was administered. Blood pressure rose to 120/180. Muscle spasms continued, perspiration became profuse, the face flushed, he frequently retched and occasionally opened his eyes, and frothing at the mouth occurred. At midnight blood pressure rose to 118/75, pulse 100, respiration 28, and temperature in the axilla 97; he was very restless. Because of excess mucus secretion 1/150 grain (0.4 mg.) of atropine sulfate was given and calcium gluconate was given intramuscularly. At 3 a. m. respiration was labored, and at 5 a. m. the patient was pulseless, ceased breathing, and was pronounced dead.

Pathological Examination.—The skin had a yellowish tint; the scleras were not markedly tinted. There was a small amount of tenacious mucus in the oral cavity. About 100 cc. of clear yellow fluid was found in the left pleural cavity. Numerous epicardial petechiae were mainly about the base of the heart and along the course of the coronary vessels. Two needle punctures were in the right ventricle near the septum. The myocardium was of average normal color and thickness. On standing the color changed to a coppery red color and it had a slightly mottled appearance as though there was interfascicular hemorrhage present. The endocardium and the valves showed no abnormalities. Coronary arteries were free of sclerosis and blood clot. No significant sclerosis was found in the aorta or arterial trunks, and the blood tended to remain fluid. Much diffuse dark red color was seen in the lungs. There were a few small petechiae on the diaphragmatic surface. The cut surfaces were dark red, and on pressure very little air or thick, sanguinous fluid could be expressed. There was intense congestion of the bronchial mucosa. A small amount of sanguinous mucus was in the bronchi.

Tan discoloration of the lower third of the esophageal mucosa was present, and many hemorrhagic partly confluent erosions were on the cardiac portion of the stomach. Toward the pylorus only the crests of the rugae were involved; there was no definite ulceration. The stomach contained about 100 cc. of dark brown fluid. Intense hemorrhagic erosions appeared on the crests of the duodenal mucosa. These became less numerous as the jejunum was approached and were not seen more than a foot beyond the ligament of Treitz.

On the cut surface of the kidneys a slight congestion of the arcuate vessels was observed. The bladder was distended with about 600 cc. of clear yellow urine. Many discrete and confluent petechiae were seen in the mucosa. The cut surface of the liver was more yellowish than usual. There was an irregular prominence of the sinuses suggesting irregular distribution of blood or extravasation. The gallbladder, spleen, and adrenals showed no pathological change on macroscopic examination.

There was a considerable quantity of subarachnoidal fluid of normal appearance present. The arachnoid was studded with whitish granules of 1 to 2 mm. in diameter, which resembled pacchionian granulations but were more widespread. On the floor of the fourth ventricle, immediately subjacent to the ependyma, there were several small petechia-like lesions.

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1. Kalmbach, E. R.: "Ten-Eighty." War-Produced Rodenticide, Science **102**: 232 (Aug. 31) 1945.

2. Gajdusek, D. C., and Luther, G.: Fluoroacetate Poisoning: Review and Report of Case, Am. J. Dis. Child. **79**: 310 (Feb.) 1950. Williams, A. T.: Sodium Fluoracetate Poisoning, Hosp. Corps Quart. (no. 1) **21**: 16 (Jan.-March) 1948. Wright, E. R.: Personal communication, cited in Hutchens, J. O.; Wagner, H.; Podolsky, B., and McMahon, T. M.: Effect of Ethanol and Various Metabolites on Fluoroacetate Poisoning, J. Pharmacol. & Exper. Therap. **95**: 62 (Jan.) 1949.

3. Chenoweth, M. B.: Monofluoroacetic Acid and Related Compounds, J. Pharmacol. & Exper. Therap. part 2, **97**: 383 (Dec.) 1949.

4. Harrisson, J. W. E.; Ambrus, J. L., and Ambrus, C. M.: Fluoroacetate (1080) Poisoning, to be published.

Microscopic Examination.—Ecchymoses was present in the epicardial fat, with diffuse venous congestion. Heart muscle seemed to be normal. There was a minimal degree of anthracosis in the lungs. Diffuse vasocongestion and scattered foci of alveoli showed endothelial proliferation suggesting passive congestion. In the bronchi there was marked hemorrhagic edema of the submucosa. There were foci of lymphocytes in the deeper tissues suggesting that there had been a chronic peribronchitis of a mild degree, probably existing for some time. There were a peribronchial node, slight anthracosis, and nodules of caseous tuberculous material with definite peripheral activity (lymphocytes, endothelial cells, and giant cells).

Atropic gastric mucosa was found in the stomach. Numerous erosions, without ulceration, were characterized as small submucosal petechial ecchymoses. There was diffuse tubular degeneration in the kidneys, affecting mainly the convoluted tubules and to a minor extent the collecting tubules and the loops of Henle. The convoluted tubules contained protein exudate. There was general vasodilation. The interstitial tissue was compressed so that it was hardly visible. The glomeruli seemed normal. There was slight, diffuse edema of the sinuses of the liver with some evidence of biliary stasis in the perilobular portions of the lobules and marked passive congestion of the splenic pulp.

In the adrenals there was marked lipoid vacuolization of the fascicular zone and partially of the reticular zone with occasional evidence of pyknosis. The medulla showed considerable evidence of antemortem degenerative changes. The pancreas was essentially normal. Occasional islets were seen in which there were cells with dense eosinophilic cytoplasm.

Adjacent to the substantia nigra there was diffuse vasodilatation with small to moderate sized extravascular hemorrhages. There were numerous small petecchial hemorrhages scattered through the corpora quadrigemina. There was evidence of bleeding both of fresh blood as well as blood that was present long enough to be split to hemosiderin in the phagocytic cells in the perivascular spaces.

TABLE 1.—*Calculated Quantity of Sodium Fluoroacetate in Organs of Patient*

Organ or Contents of Organ	Total Weight of Organ or Quantity of Material	Weight of Sample Tested	Fluorine, Mg. per Kilogram of Organ Weight	Fluorine Calculated to Sodium Fluoroacetate, Mg. per Kilogram of Organ Weight	Calculated Total Sodium Fluoroacetate in Organ, Mg.
Urine, from bladder	600 cc.	300 cc.	70.0	368.0	220
Liver	1,726 gm.	210 gm.	11.1	58.4	100
Brain	1,450 gm.	237.5 gm.	14.4	75.7	109
Stomach content	105 gm.	105 gm.	22.5	118.0	12.4
Kidney Right:	170 gm.	117 gm.	12.3	64.7	11
Left:	170 gm.				

TABLE 2.—*Fluorine in Normal Human Organs**

	Organ		
	Brain	Liver	Kidney
Organs from 2 adult males, Zdarek †	0.23-0.27	0.68-0.80	1.34-1.54
Individual organs from different adult males, Gautier and Clausmann ‡	3.07	2.13	0.95
Organs from 1 adult male, Roholm §	....	0.50	1.10

* Measured in milligrams per 100 gm. of dry weight.

† Zdarek, E.: Über die Verteilung des Fluors in den einzelnen Organen des Menschen, Hoppe Seyler's Ztschr. f. physiol. Chem. **69**:127 (Oct. 24) 1910.

‡ Gautier, A., and Clausmann, P.: Le fluor dans l'organisme animal: C. cerveau, glandes, muscles, sang, lait, excrétions, Compt. rend. Acad. d. sc., Paris **157**:94, 1913.

§ Roholm, K.: Fluorine Intoxication, Copenhagen, NYT Nordisk Forlag, 1937; Fluorschädigungen, Leipzig, Johann Ambrosius Barth, 1937; Fluorvergiftung, eine "neue" Krankheit, Klin. Wchnschr. **15**:1425, 1936; Fluor und Fluorverbindungen, in Heffter, A.; Heubner, W., and Schüller, J., editors: Handbuch der experimentellen Pharmakologie, Berlin, Julius Springer, 1938, vol. 7, p. 1.

Toxicological Examination.—Fluorine content of the organs and body fluid was determined according to the distillation method of Willard-Winter [5] using a thorium nitrate back titration, following preliminary ashing with an excess of calcium hydroxide to fix the fluorine. From these data the theoretical sodium fluoroacetate content was calculated. The results are shown in table 1. In table 2 the fluorine content of normal human organs is set forth on the basis of the literature.

COMMENT

A fatally ending case of fluoroacetate poisoning is presented. The clinical course suggests that in human beings the central nervous system as well as the cardiac effect of fluoroacetate are manifested. It is known from the experimental literature [6] that some species, such as rabbits, goats, horses, and spider monkeys, exhibit only cardiac symptoms; others, such as dogs, guinea pigs, and frogs, have only convulsions; and again others, including cats, pigs, chicks, and rhesus monkeys, show cardiac as well as central nervous system effects.

The pathological observations are essentially similar to those found by Foss [7] in acute intoxication with fluoroacetate of experimental animals. Human cases and animal intoxications with sodium fluoride exhibit pathological changes [8] indistinguishable from those seen when fluoroacetate is used. Since, however, sodium fluoroacetate is much more toxic than sodium fluoride, it seems likely that the above changes were caused mainly by fluorine, while the special biochemical actions of fluoroacetate produced no pathological changes of diagnostic significance. The death from fluoroacetate poisoning [6] seems to be due to the failure of the heart, exhaustion because of cramps of central origin, and probably toxic depression of the respiratory and vasomotor centers.

It is interesting that in the Langerhans' islands dense eosinophilic cytoplasm was seen. Although it is difficult to draw conclusions on the basis of one case, the observation may indicate a preservative action of fluoroacetate on the enzymic granules.

The distribution of fluoroacetate was relatively uniform in the organs tested. The high level in the urine indicates a rapid urinary excretion. This is in agreement with the findings of Ramsey and Clifford,[9] who found in poisoned rats an even distribution of fluoroacetate between brain, heart, liver, and kidneys. It is significant that in spite of the gastric lavage and the fact that death

5. Official Methods of Analysis of the Association of Official Agricultural Chemists, ed. 7, Washington, D. C., Association of Official Agricultural Chemists, 1950.

6. Chenoweth.[3] Harrisson.[4]

7. Foss, G. L.: Toxicology and Pharmacology of Methyl Fluoroacetate (MFA) in Animals, with Some Notes on Experimental Therapy, Brit. J. Pharmacol. **3**:118 (June) 1948.

8. Tappeiner, H.: Zur Kenntniss der Wirkung des Fluornatriums (Zum Teil unter Mitwirkung von Dr. N. Oblonsky), Arch. f. exper. Path. u. Pharmakol., Leipz. **25**:203, 1888-1889; Zweite Mittheilung über die Wirkungen des Fluornatrium, ibid. **27**:108, 1890. Heidenhain, R.: Neue Versuche über die Aufsaugung im Dünndarm, Arch. f. d. ges. Physiol., Bonn **56**:579, 1894. Hedström, H.: Skandinav. Vet. Tidsskr. **22**:55, 1932, cited by Roholm (see table 2 §). Dalla Volta, A.: Zur Kenntniss des Experimentellen Flurornatriumvengiftung, Deutsche Ztschr. f. ges. gerichtl. Med. **3**:242, 1924.

9. Ramsey, L. L., and Clifford, P. A.: Determination of Monofluoroacetic Acid in Foods and Biological Materials, J. A. Offic. Agr. Chemists **32**:788-797, 1949.

ensued about 17 hours after the ingestion of the poison, important quantities of the poison were found in the stomach. Brandl and Tappeiner [10] and Gadaskina and Shtessel [11] presented data on the excretion of fluoride through the gastrointestinal tract, and Charnot [12] described fluoride excretion in the bile. Thus it is possible that gastroenterohematic circulation of fluorine compounds exists. Because of these data and the high toxicity of fluoroacetate repeated gastric lavages seem to be advisable.

The total quantity of fluoroacetate recovered from the organs and body fluids tested was 465 mg. Since the patient weighed approximately 140 lb. (63.5 kg.), disregarding the fluoroacetate present in organs from which no sample was available for toxicological study, he ingested a minimum of 6 mg. per kilogram of fluoroacetate.

The therapy used in this case was essentially symptomatic: barbiturates to decrease convulsions, intracardial procaine hydrochloride to inhibit ventricular fibrillation, atropine sulfate to decrease bronchial mucus secretion, and plasma transfusion and oxygen to offset vasomotor and respiratory failure. Experimental studies have suggested the use of certain specific antidotes.[6] Of these monacetin was directed for the treatment of this case; however, it arrived too late to be employed.

SUMMARY

1. A case history of fluoroacetate poisoning has been described together with postmortem examination and chemical analysis of the fluoroacetate content of organs and body fluids.

2. It appears that there is no important difference between postmortem findings of sodium fluoroacetate and sodium fluoride poisoning. The additional biochemical effects of sodium fluoroacetate thus seem to have no pathological manifestation of diagnostic significance.

3. Because of indications of gastrointestinal excretion and reabsorption of fluorine compounds, repeated gastric lavages seem to be advisable.

4. Other therapeutic aspects are briefly discussed.

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10. Brandl, J., and Tappeiner, H.: Über die Ablagerung der Fluorverbindungen im Organismus nach Fütterung mit Fluornatrium, Ztschr. f. Biol. München u. Leipz. **10**: 518, 1891-1892.

11. Gadaskina, I. P., and Shtessel, T. A.: Resorption, Distribution and Elimination of Fluorine After Experimental Poisoning with Sodium Fluoride, J. Physiol. U.S.S.R. **19**: 1245, 1935.

12. Charnot, A.: Influence de quelque composés minéraux sur les effets toxiques du fluorure de calcium, Bull. Acad. de méd., Paris **120**: 224 (Oct. 18) 1938.

ELECTROENCEPHALOGRAPHIC CHANGES IN PROFESSIONAL BOXERS

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Since the days of the Roman gladiators, men have fought each other and other persons have watched. The sport of boxing, as it exists today, is largely the product of psychological forces that have not changed in essence for 2,000 years. It is the feeling of many persons that in spite of periodic criticism and the efforts to ban prize fighting, the sport will persist. Since it appears unlikely that athletic contests requiring physical contact will ever cease, the physician should attempt to safeguard the physical and mental health of the participants.

Much has been accomplished to protect the athlete in such sports as football and ice hockey, but protective measures for the amateur and professional pugilist have not kept pace. Jokl [1] in his monograph (1941), which is concerned with the medical aspects of boxing, recognized and deplored this situation, and he collected a wide variety of case material that was representative of possible sequelae due to boxing injuries. Raevuori-Nallinmaa [2] in a recent publication states his belief that the usual cause of death related to boxing is intracranial hemorrhage. Tragic and sobering though they be, deaths of this kind are relatively rare. More important, and certainly much commoner, are the mild psychic changes observed in a high percentage of boxers. These changes are due to brain damage, which is also responsible for the less frequently seen, so-called "punch-drunk" person, who is in fact in a state of traumatic dementia and reveals severe psychic and neurological abnormalities.

The syndrome of boxing encephalopathy is probably due to multiple concussion hemorrhages as well as to contusion and laceration of the brain. The "knockouts" and "technical or near knockouts" (representing states of commotio cerebri) are usually the result of a trauma that alters brain function. If the trauma is severe or is mild but repeated at intervals that do not permit the brain to return to normal functioning, permanent damage may result.

Many investigators have reported on the value of the electroencephalogram in the detection of brain injuries. Dow, Ulett, and Raff,[3] in doing electroencephalograms of persons immediately after injury, reported that a

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Mr. W. Asmus, Executive Director, and Mr. E. Bohn, Chairman of the State Athletic Commission of Colorado, assisted in the preparation of this study.

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1. Jokl, E.: The Medical Aspect of Boxing, Pretoria, S. Africa, J. L. Van Schaik, Ltd., 1941.

2. Raevuori-Nallinmaa, S.: Brain Injuries Attributable to Boxing, Acta psychiat. et neurol., supp. 60, p. 51, 1951.