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Sodium Fluoroacetate Poisoning

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Abstract

Sodium fluoroacetate was introduced as a rodenticide in the US in 1946. However, its considerable efficacy against target species is offset by comparable toxicity to other mammals and, to a lesser extent, birds and its use as a general rodenticide was therefore severely curtailed by 1990. Currently, sodium fluoroacetate is licensed in the US for use against coyotes, which prey on sheep and goats, and in Australia and New Zealand to kill unwanted introduced species.

The extreme toxicity of fluoroacetate to mammals and insects stems from its similarity to acetate, which has a pivotal role in cellular metabolism. Fluoroacetate combines with coenzyme A (CoA-SH) to form fluoroacetyl CoA, which can substitute for acetyl CoA in the tricarboxylic acid cycle and reacts with citrate synthase to produce fluorocitrate, a metabolite of which then binds very tightly to aconitase, thereby halting the cycle. Many of the features of fluoroacetate poisoning are, therefore, largely direct and indirect consequences of impaired oxidative metabolism. Energy production is reduced and intermediates of the tricarboxylic acid cycle subsequent to citrate are depleted. Among these is oxoglutarate, a precursor of glutamate, which is not only an excitatory neurotransmitter in the CNS but is also required for efficient removal of ammonia via the urea cycle. Increased ammonia concentrations may contribute to the incidence of seizures. Glutamate is also required for glutamine synthesis and glutamine depletion has been observed in the brain of fluoroacetate-poisoned rodents. Reduced cellular oxidative metabolism contributes to a lactic acidosis. Inability to oxidise fatty acids via the tricarboxylic acid cycle leads to ketone body accumulation and worsening acidosis. Adenosine triphosphate (ATP) depletion

results in inhibition of high energy-consuming reactions such as gluconeogenesis. Fluoroacetate poisoning is associated with citrate accumulation in several tissues, including the brain. Fluoride liberated from fluoroacetate, citrate and fluorocitrate are calcium chelators and there are both animal and clinical data to support hypocalcaemia as a mechanism of fluoroacetate toxicity. However, the available evidence suggests the fluoride component does not contribute.

Acute poisoning with sodium fluoroacetate is uncommon. Ingestion is the major route by which poisoning occurs. Nausea, vomiting and abdominal pain are common within 1 hour of ingestion. Sweating, apprehension, confusion and agitation follow. Both supraventricular and ventricular arrhythmias have been reported and nonspecific ST- and T-wave changes are common, the QTc may be prolonged and hypotension may develop. Seizures are the main neurological feature. Coma may persist for several days. Although several possible antidotes have been investigated, they are of unproven value in humans. The immediate, and probably only, management of fluoroacetate poisoning is therefore supportive, including the correction of hypocalcaemia.

Sodium fluoroacetate (figure 1) was selected by screening >1000 compounds for rodenticidal action during World War II[1] and it was introduced in the US in 1946 as a rodenticide. It was, and still is, referred to as 1080, the laboratory reference number it was given during its assessment. Fluoroacetic acid was isolated in 1944 from *Dichapetulum cymosum*, a South African plant known locally as Gifblaar, that was known to be poisonous to farm animals[2] and has been identified as the toxic agent not only in *Dichapetalum cymosum* but also in 13 other *Dichapetalum* species. It has also been found in many poisonous plants native to Brazil, South and West Africa and Australia,[3,4] and in low concentrations in tea leaves and guar gum.

The considerable efficacy of sodium fluoroacetate against target species is offset by comparable toxicity to other mammals and, to a lesser extent, birds and its use as a general rodenticide was therefore severely curtailed by about 1990.

Currently, sodium fluoroacetate is licensed in the US for use against coyotes, which prey on sheep and goats, and in Australia and New Zealand to kill unwanted introduced species. It is also used in Mexico and Israel.[5] New Zealand is the largest user of sodium fluoroacetate.[5] Sheep and goats are protected by livestock protection collars ('toxic collars'). Coyotes attempting to kill collared livestock are likely to puncture the collars and hence be poisoned by sodium fluoroacetate.

1. Epidemiology

Acute poisoning with sodium fluoroacetate is uncommon. When describing a single case in 1955, Brockmann et al.[6] commented that 22 cases of acute poisoning with sodium fluoroacetate, including 16 deaths, were included in a memorandum from the Communicable Disease Center of the United States in 1952, while only two cases[7,8] had been reported in the medical literature. Over the following years, other single cases were published.[9-16] Reports containing larger numbers also appeared. In the 10 years during 1971–81, 111 exposures to sodium fluoroacetate were reported to the National Poison Center of Israel. Thirty were due to a single incident involving children, none of whom developed features of poisoning. Of the remaining 81 cases, three died.[17] Most recent reports have originated from China with five cases in Taipei during 1975–81,[18] and 38 in Taiwan during 1988–93.[19] However, there have also been reports of fluoroacetate poisoning in other countries. Application to control rats in a South American steel mill resulted in several workers becoming seriously ill[20] and illegal manufacture, importation and use were blamed for a large number of cases, including three fatalities, treated in Vietnam in 2002.[21]

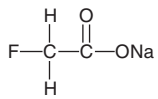

Fig. 1. Sodium fluoroacetate.

2. Mechanisms of Action

2.1 Aconitase Inhibition

Fluoroacetate was probably the first substance whose toxicity was shown clearly to depend on metabolic activation or 'lethal synthesis' as the original researchers, led by Rudolf Peters, termed the process.[22-25] Its extreme toxicity to mammals and insects stems from its similarity to acetate, which has a pivotal role in cellular metabolism. Fluoroacetate combines with co-enzyme A (CoA-SH, figure 2) to form fluoroacetyl CoA, which can substitute for acetyl CoA in the tricarboxylic acid cycle and reacts with citrate synthase to produce fluorocitrate. A metabolite of one of the four possible stereoisomers of 2-fluorocitrate,[26] (−)-erythro-2-fluorocitrate, inhibits aconitase, thereby halting further progression of the cycle (figure 2).[27] However, the isomer inhibits aconitase only after a series of conversions initiated by aconitase

itself. This involves defluorination and hydroxylation of (−)-erythro-2-fluorocitrate to generate 4-hydroxy-trans-aconitate as the actual aconitase inhibitor.[28] Rather than 4-hydroxy-trans-aconitate competing with citrate for the active site of aconitase, its affinity for the enzyme is so strong that it is bound in preference to the natural substrate even when present in only low concentrations.[27]

The manifestations of fluoroacetate poisoning are mainly direct and indirect consequences of impaired oxidative metabolism. Energy production is reduced and intermediates of the tricarboxylic acid cycle subsequent to citrate cycle are depleted. Among these is oxoglutarate, a precursor of glutamate, which is not only an excitatory neurotransmitter in the CNS but is also required for efficient removal of ammonia via the urea cycle. Increased ammonia concentrations have been noted in experimental fluoroacetate poisoning[29] and may contribute to the incidence of seizures.[30] Glutamate is also required for glutamine synthesis and glutamine depletion has been observed in the brains of fluoroacetate-poisoned rodents.[31] Reduced cellular oxidative metabolism contributes to a lactic acidosis.[32,33] Inability to oxidise fatty acids via the tricarboxylic acid cycle leads to ketone body accumulation and worsening acidosis.[32,34] Adenosine triphosphate (ATP) depletion results in inhibition of high energy-consuming reactions such as gluconeogenesis.[35] Invasive haemodynamic studies in a woman poisoned with sodium fluoroacetate have supported the suggestion that hypotension persisting despite correction of hypovolaemia and inotropic support, is the result of decreased systemic vascular resistance and increased cardiac output secondary to local inhibition of the tricarboxylic acid cycle in vascular epithelium and metabolic acidosis.[36]

2.2 Mitochondrial Citrate Carrier Inactivation

Fluoroacetate poisoning is associated with citrate accumulation in several tissues, including the brain.[37] This is partly due to aconitase inhibition, for which citrate is the normal substrate.[37] However, fluoroacetate also inactivates the mitochondrial membrane citrate carrier[38,39] and increases cellular citrate concentrations, thereby disrupting several enzyme systems including the key regulatory enzyme of glycolysis, phosphofructokinase. This in turn blocks glucose utilisation resulting in hyperglycaemia in experimental fluoroacetate poisoning.[30] Hypoglycaemia may also ensue as a consequence of glycogen depletion.[30] Poor glycaemic control does not appear, however, to be a significant problem in fluoroacetate poisoning in humans.

2.3 Hypocalcaemia

There are both animal and clinical data to support hypocalcaemia as a mechanism of fluoroacetate toxicity. Rats showed a significant ($p < 0.05$) reduction in calcium concentrations within 2.5 hours of being poisoned and the only one of four dogs that had a 'conspicuous' reduction of its calcium (14% between 3 and 4 hours post-poisoning) after being given intravenous fluoroacetate 150 μg/kg was also the only one to convulse.[40] Others have

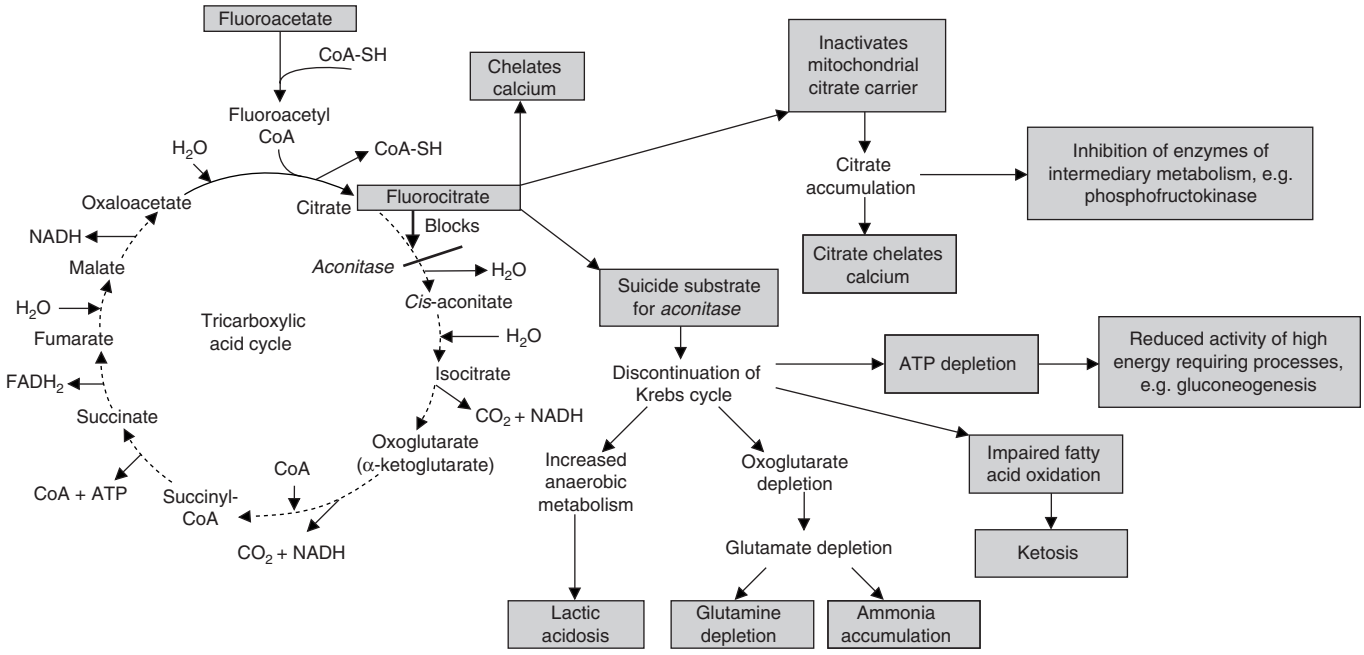

Fig. 2. Mechanisms of fluoroacetate toxicity. **ATP** = adenosine triphosphate; **CoA-SH** = coenzyme A; **$FADH_2$** = the reduced form of flavin-adenine dinucleotide; **NADH** = the reduced form of nicotinamide-adenine dinucleotide.

suggested that fluorocitrate-induced seizures are due, at least in part, to complexing of calcium in the spinal cord.[41] Similarly, mean ionised serum calcium concentrations in cats fell from 1.08 to 0.65 mmol/L 80 minutes after exposure and their survival was significantly prolonged by treatment with calcium chloride.[42] The same Israeli workers found that mean ionised calcium concentrations fell from 1.09 to 0.79 mmol/L after 40 minutes and that there was a good correlation between the lowest concentrations and prolongation of the QT interval.[43]

Fluoride ions, citrate and fluoroacetate are known calcium chelators. The bond between fluoride and carbon is believed to be the strongest carbon can form with any element.[3] Despite this, there is evidence that defluorination of sodium fluoroacetate occurs *in vivo*[44,45] and is mainly mediated via anionic proteins with glutathione transferase activity.[30] However, the resulting fluoride concentrations are far below those encountered in acute fluoride poisoning[45] strongly suggesting that the fluoride component of sodium fluoroacetate contributes very little, indeed if any, to hypocalcaemia. The latter must, therefore, be due to citrate and fluoroacetate.

3. Toxicokinetics

Data on the toxicokinetics of fluoroacetate are limited and derived almost entirely from animals. The compound appears to be absorbed rapidly from the gastrointestinal tract and widely distributed to tissues. Eason et al.[46] observed peak plasma concentrations in possums and rabbits 0.5–0.75 hours after ingestion and at 2.5 hours in sheep. The partitioning ratio of fluoroacetate between erythrocytes and plasma has been estimated to be 1 : 2.4 in mice.[47] Absorbed fluoroacetate is then hydrolysed but, being highly soluble in water, some is excreted unchanged in the urine. Eason et al.[46] found that some 34% of fluoroacetate was excreted unchanged in urine and faeces. In mice, some is also metabolised to at least seven different metabolites. Since features of toxicity appear as quickly as plasma concentrations are attained, metabolism to fluorocitrate must be comparably rapid. Elimination in rabbits and mice is faster than in sheep, goats and possums;[47,48] the plasma half-life in sheep being of the order of 11 hours[48] and as short as 1.1 hours in rabbits.[49]

It has been stated that fluoroacetate is poorly, if at all, absorbed through intact skin[46,50] but absorbed via the respiratory mucosa.[46] Evidence to substantiate these statements has not been found.

4. Clinical Features

4.1 Acute Toxicity

The classification of toxicity proposed by Chenoweth and Gilman in 1946[51] was based on a series of experimental poisonings. In general, they found that both the cause of death and features observed varied by species. The four categories that they proposed were:

- class I, where the main effects are on the heart;
- class II, where both the heart and the CNS are involved;
- class III, where the main effect is on the CNS;
- class IV, where there is an atypical response typified by slow shallow breathing and a slow heart rate.

Sherley[52] has cast doubt on the value of this classification because of the similarities of features of poisoning in different species and because neurological involvement is far more common than previously inferred. Although the experimental classification of Chenoweth and Gilman[51] is of little relevance to human poisoning, it does stress the main effects of fluoroacetate are on the heart, CNS and autonomic nervous system.

Although many authors have described a so-called 'latent period', based on experimental studies conducted by Chenoweth,[53] the delay between the onset of features and ingestion is short and of the order of 0.5–3 hours in humans. During this period, hydrolysis of fluoroacetate to fluoroacetyl CoA occurs, a toxicologically significant quantity of fluorocitrate is synthesised and disruption of key intracellular processes ensues, which results in the features of exposure. There is, therefore, no more of a delay than with the majority of toxins.

Ingestion is the major route by which fluoroacetate poisoning occurs. The oral dose of fluoroacetate sufficient to be lethal to most humans is 2–10 mg/kg.[5] Nausea, vomiting and abdominal pain are common within 1 hour of ingestion. Sweating, apprehension, confusion and agitation soon follow. Both tachycardia[9,12,13,36] and bradycardia[8] have been described as have premature cardiac contractions.[6,8,19] More serious arrhythmias, including supraventricular tachycardia,[6,21] atrial fibrillation,[19] ventricular tachycardia,[19,21] ventricular fibrillation[8,11,19,21] and asystole,[11,13] have been reported. Nonspecific ST- and T-wave changes are common,[19] the QTc may be prolonged[6,19] and hypotension may develop.[19,36] Seizures are the main neurological feature and may recur,[8,9,11,13,21] occasionally over several days. Consciousness becomes progressively impaired after a few hours leading to coma that may persist for several days.

Less common features include nystagmus,[7] chewing movements of the jaws,[6] carpopedal spasms,[6] reversible oliguric or non-oliguric renal failure in the absence of hypotension,[18] meta-

bolic acidosis[15,16,18,19,36] and increased transaminase activity.[18,36] Cerebellar dysfunction was present in the acute phase of poisoning in a 15-year-old girl whose CT brain scan showed evidence of diffuse cerebral atrophy 1 week after ingestion of the compound.[12]

The suggestion that repeated exposure to sodium fluoroacetate was the cause of renal failure in a 59-year-old professional pest controller who never handled the substance without wearing protective equipment or knowingly ingested it[10] is considered unproven on grounds of the analytical methods used[54] and the interpretation of the alleged concentrations of the pesticide in his urine.[55,56]

Despite reports of clinical features suggestive of hypocalcaemia and animal studies demonstrating the potential importance of hypocalcaemia in the toxicity of fluoroacetate,[43] serum calcium concentrations have been measured in relatively few cases of human poisoning. Taitelman et al.[57] reported ventricular tachycardia, ventricular fibrillation and convulsions in a 17-year-old man who had QT prolongation and a serum calcium concentration of 1.6 mmol/L. Administration of calcium chloride reduced the QT interval from 400 to 330 milliseconds. Their other patient, a girl aged 16 years, had multiple premature ventricular beats and a long QT interval; intravenous calcium chloride returned the electrocardiograph to normal. Chi et al.[19] found that the initial mean total serum calcium concentrations did not differ significantly between seven fatalities and 31 survivors of sodium fluoroacetate poisoning. However, later in the course of their hospital stay, 57% of those who died were hypocalcaemic compared with only 36% of survivors ($p < 0.01$).

Deaths have been recorded.[6,7,17,19,21,36] Ventricular arrhythmias, progressive hypotension, unresponsive to treatment, and secondary lung infections have been the main causes.

4.2 Long-Term Sequelae

Survival, even from serious intoxication, is usually associated with complete recovery.[8,9] However, cerebellar ataxia present in the acute phase persisted long term in a teenage woman and was attributed to the direct effects of the compound on neurones and impaired ability to metabolise glucose.[12] A young man with severe poisoning as manifested by coma lasting 10 days, repeated seizures and one episode of ventricular fibrillation lasting 10 minutes, experienced grand mal epilepsy, cortical blindness, divergent strabismus, tetraplegia and cogwheel rigidity 9 years later.[11] These features were considered the result of cerebral hypoxia. Similarly, two boys were left with severe neurological impairment after resuscitation from cardiac arrest complicating fluoroacetate ingestion.[13,21]

5. Management

Sodium fluoroacetate poisoning is a serious condition. Hypotension, acidaemia and raised serum creatinine concentrations have been identified as the most sensitive predictors of a fatal outcome.[19] Although several possible antidotes have been investigated, they are of unproven value in humans. The immediate, and probably only, management of fluoroacetate poisoning is therefore supportive, including the correction of hypocalcaemia.

5.1 Supportive Care

Gastric lavage may be carried out if the patient presents within 1 hour of ingestion of a potentially toxic amount. Alternatively, activated charcoal may be given. It binds fluoroacetate[58] but there is no evidence that it benefits the course of poisoning. Colestipol was more effective in animal studies[58] but has not been assessed in human fluoroacetate poisoning. The patient is best managed in an intensive care area so that serious features of poisoning can be treated optimally and without delay. Rapid administration of intravenous fluids should be given together with a vasopressor, such as norepinephrine (noradrenaline), if severe hypotension supervenes. Control of convulsions using a benzodiazepine intravenously is clearly vital, as is the establishment and maintenance of a clear airway and adequate ventilation. Metabolic acidosis requires correction with intravenous sodium bicarbonate. Arrhythmias other than ventricular fibrillation should only be treated if causing peripheral circulatory failure. Renal failure should be managed conventionally.

5.2 Correction of Hypocalcaemia

Though the importance of calcium concentrations in human fluoroacetate poisoning is uncertain, it would be prudent to measure the serum calcium in any patient showing serious toxicity due to this compound and to correct hypocalcaemia if it is found. Calcium chloride supplementation prolonged survival in fluoroacetate-poisoned cats,[42] but calcium gluconate was of no value in poisoned mice.[59] It is possible that the discrepancy was related to measuring total, rather than ionised, calcium concentrations in the latter study. Isolated clinical reports suggest calcium is helpful in reducing muscle over-activity,[6] including 'tetanic convulsive movements'[8] and particularly if arrhythmias such as ventricular fibrillation develop.[57]

5.3 Antidotes

A number of substances, including ethanol (ethyl alcohol),[60] acetate,[42,61] sodium succinate[59] and sodium 2-ketoglutarate,[59] alone and in combination, have been assessed in animals for

possible antidotal activity to sodium fluoroacetate. The rationale underlying their use varies. The oxidation of ethanol leads to increased blood acetate concentrations and inhibition of fluorocitrate production.[53,60] Acetate, sodium succinate and sodium 2-ketoglutarate are intended to supplement the tricarboxylic acid cycle and, therefore, their efficacy depends on the unproved presumption that they will reach mitochondria after administration.

5.3.1 Ethanol

The efficacy of ethanol in animals is variable and depends on the species being studied and the interval between poisoning and its administration.[60] Mortality among fluoroacetate-poisoned mice, guinea pigs and rabbits was reduced significantly if about 800 mg/kg of ethanol was administered subcutaneously as a 10% ethanol solution in normal saline within 30 minutes of poisoning. The most striking effects were obtained in mice when ethanol was given within 10 minutes of poisoning.[60] The claim that ethanol was effective in a single clinical poisoning[14] cannot be supported.

5.3.2 Acetate

Acetate, the least toxic source of which is monoacetin (glycerol monoacetate), is thought to enter cells readily and compete with fluoroacetate for binding to acetyl CoA. It was effective in animals,[42,61] though it was no more so than calcium and of no additional value when given in combination with calcium.[42]

It was recommended in 1985 that 500mL of 10% acetamide in 5% dextrose should be administered intravenously over 30 minutes followed by 200mL 4-hourly.[62] In 1982, the WHO is said to have recommended glycerol monoacetate 0.5 mg/kg by intramuscular injection every 30 minutes for 12 hours.[62] Another possible regimen for monoacetin in humans is based on studies in monkeys[61] and entails giving 0.1–0.5mL of a 60% solution of glycerol monoacetate/kg diluted to a concentration of <1% prior to intravenous administration. All these approaches remain unsubstantiated.

5.3.3 Sodium Succinate

Sodium succinate 240 mg/kg was ineffective in reducing the mortality in fluoroacetate-poisoned mice,[59] whereas the administration of sodium succinate 240 mg/kg and calcium gluconate 130 mg/kg within 15 minutes of fluoroacetate administration was highly protective.[59] In contrast, higher doses (360 or 480 mg/kg) of sodium succinate and the same dose of calcium gluconate resulted in loss of antidotal effect[59] for reasons that are not clear.

5.4 Newer Experimental Approaches

Two principal ways of developing effective therapies for fluoroacetate poisoning have been proposed.[30] Firstly, competitive inhibition of the fluoroacetate interaction with CoA and fluorocitrate interaction with aconitase and, secondly, increasing the availability of intermediates subsequent to aconitase in the tricarboxylic acid cycle, to enable the cycle to continue. The authors claim that their approach, which is not yet published fully, showed a marked reduction in mortality in female rats.

6. Biological Monitoring

Sampling should be undertaken at the end of the work day and ideally also on the last working day of a 'series' in order to increase the chances of detecting the maximum concentrations of fluoroacetate,[5] care being taken to avoid contamination from working clothes. The biological exposure index for fluoroacetate is 15 μg/L.

7. Conclusion

Sodium fluoroacetate is highly toxic. Although the mechanisms of fluoroacetate toxicity have been understood for more than four decades, no satisfactory treatment regimens have yet been developed to treat poisoning due to sodium fluoroacetate.

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