



# OXFORD DESK REFERENCE TOXICOLOGY

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OXFORD DESK REFERENCE

# Oxford Desk Reference

# Toxicology

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## Fluoroacetate (sodium fluoroacetate)

### Background

**Sodium fluoroacetate** was selected by screening more than a thousand compounds for rodenticidal action during World War II and introduced into use in the USA in 1946. 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 *Dichapetalum cymosum*, a South African plant known to be poisonous to farm animals.

### Toxicokinetics

**Fluoroacetate** is absorbed rapidly from the gastrointestinal tract and is widely distributed to tissues. **Fluoroacetate** is then hydrolysed rapidly, fluoroacetyl CoA is formed, a toxicologically significant quantity of fluorocitrate is synthesized and key intracellular processes are disrupted. Some **fluoroacetate** is excreted unchanged in the urine.

### Mechanisms of toxicity

The toxicity of **fluoroacetate** stems from its similarity to acetate, which has a pivotal role in cellular metabolism. **Fluoroacetate** combines with co-enzyme A to form fluoroacetyl CoA, which can substitute for acetyl CoA in the tricarboxylic acid cycle where it reacts with citrate synthase to produce fluorocitrate (Figure 9.5). A metabolite of one of the four possible stereoisomers of 2-fluorocitrate inhibits aconitase, thereby halting further progression of the cycle. As a consequence, energy production is reduced and intermediates of the tricarboxylic acid cycle subsequent to the citrate cycle are depleted.

Among these is oxoglutarate, a precursor of glutamate which is not only an excitatory neurotransmitter in the central nervous system but is also required for efficient removal of ammonia via the urea cycle. Increased ammonia concentrations have been observed in experimental **fluoroacetate** poisoning and may contribute to the incidence of seizures. Glutamate is also required for glutamine synthesis and glutamine depletion has been observed in the brains of **fluoroacetate**-poisoned rodents. Reduced cellular oxidative metabolism contributes to a lactic acidosis. Inability to oxidize fatty acids via the tricarboxylic acid cycle leads to ketone body accumulation and worsening acidosis while lowered ATP concentrations inhibit high energy-consuming reactions such as gluconeogenesis.

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

Citrate and **fluoroacetate** are known calcium chelators. Hypocalcaemia is therefore to be expected in **fluoroacetate** poisoning and both animal and clinical data support hypocalcaemia as a mechanism of **fluoroacetate** toxicity. It is possible that fluorocitrate-induced seizures are

due, at least in part, to calcium being complexed in the spinal cord.

### Clinical features

**Sodium fluoroacetate** poisoning is most common after ingestion. However, systemic toxicity may also occur after inhalation and eye exposure. It is poorly absorbed through intact skin, but may be absorbed through breaks in the skin. Skin and eye exposure may also produce local effects.

Nausea, vomiting and abdominal pain are common within 1 hour of ingestion. Sweating, apprehension, confusion, and agitation soon follow. Both tachycardia and bradycardia have been described. More serious arrhythmias, including supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and asystole, have been reported. Non-specific ST and T-wave changes are common, the QT may be prolonged and hypotension may develop.

Seizures are the main neurological feature and may recur, occasionally over a period of days. Consciousness becomes progressively impaired within a few hours of poisoning leading to coma that may persist for several days. Cerebellar dysfunction has been observed.

Serum calcium concentrations have been measured in relatively few cases of human poisoning. In one study, the initial mean total serum calcium concentrations did not differ significantly between seven fatalities and 31 survivors of poisoning. However, later in the course of their hospital stay, 57% of those who died were hypocalcaemic compared with only 36% of survivors ( $p < 0.01$ ).

Less common features of **fluoroacetate** poisoning include nystagmus, chewing movements of the jaws, carpopedal spasms, reversible oliguric or non-oliguric renal failure in the absence of hypotension, metabolic acidosis, and increased transaminase activity.

Long-term sequelae have been reported. Cerebellar ataxia lasting for at least 18 months was reported in one patient; memory disturbances and depressive behaviour which resolved were also seen in this patient. Tetraplegia, cogwheel rigidity, grand mal epilepsy, cortical blindness, and divergent strabismus were seen in another patient 9 years after exposure; these features were attributed to cerebral hypoxia at the time of ingestion.

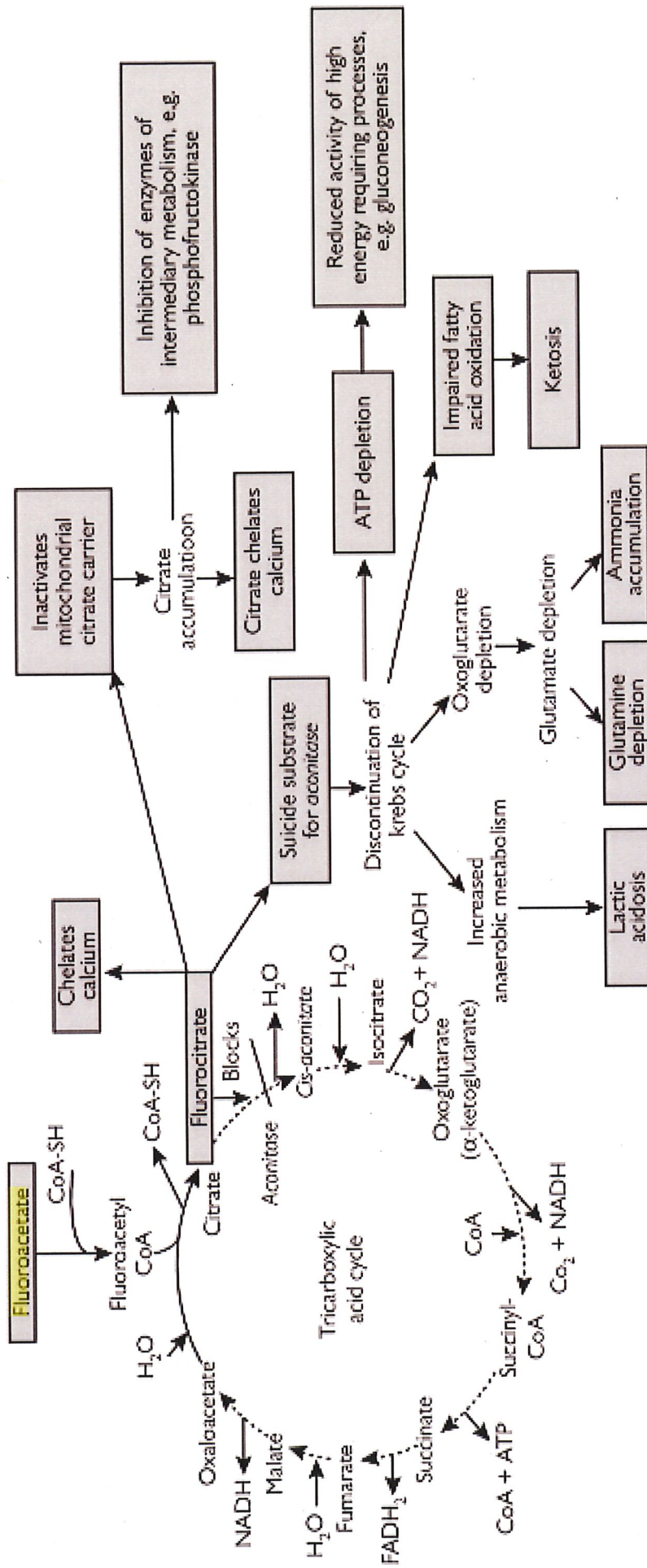
Hypotension, acidaemia, and raised serum creatinine concentrations have been identified as the most sensitive predictors of a fatal outcome, though ventricular arrhythmias, refractory hypotension and secondary lung infections are the main causes of death.

The lethal dose for humans is estimated to be 2–10 mg/kg.

### Management

If the patient presents within 1 hour of ingestion of a potentially toxic amount of **fluoroacetate**, gastric lavage may be performed, or activated charcoal may be given as it binds **fluoroacetate**, though there is no evidence that lavage or charcoal alters the clinical course.

- The plasma/blood glucose concentration should be measured urgently and hypoglycaemia corrected if found with 10% dextrose.
- If severe hypotension supervenes, rapid administration of intravenous saline 0.9% and a vasopressor such as



**Fig 9.5** Mechanisms of fluoroacetate toxicity. ATP: adenosine triphosphate; CoA-SH: coenzyme A; FADH<sub>2</sub>: reduced flavin-adenine dinucleotide; NADH: reduced nicotinamide-adenine dinucleotide. Reproduced from Springer, *Toxicological Reviews*, 25, 2006, pp. 213–219. Sodium fluoroacetate poisoning. Provedfoot AT et al., with kind permission from Springer Science + Business Media B.V.



norepinephrine 40 micrograms [base]/mL by intravenous infusion at an initial rate of 0.16–0.33 mL/minute, (for children 1 month–18 years give an intravenous infusion at a rate of 20–100 nanograms [base]/kg/minute; max 1 microgram [base]/kg/minute), adjusted according to response, may be necessary.

- Control of convulsions using an intravenous benzodiazepine is clearly vital, as is the establishment and maintenance of a clear airway and adequate ventilation. Give intravenous diazepam 10 mg (child 300–400 micrograms/kg) or lorazepam 4 mg (child 100 micrograms/kg). If repeated convulsions occur, phenytoin 20 mg/kg (max. 2 g) by slow intravenous injection or infusion (with blood pressure and ECG monitoring), at a rate not exceeding 1 mg/kg/minute (max. 50 mg per minute); for a child 1 month–12 years, 20 mg/kg at a rate not exceeding 1 mg/kg/minute (max. 50 mg per minute) as a loading dose.

Metabolic acidosis that is not secondary to hypoxia during seizures 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.

Though the importance of calcium concentrations in fluoroacetate poisoning is uncertain, the serum calcium should be measured in any patient with severe poisoning and hypocalcaemia should be corrected if it is found.

A number of substances, including ethanol (which inhibits fluorocitrate production), acetate (which is thought to supplement the tricarboxylic acid cycle and to enter cells readily and compete with fluoroacetate for binding to acetyl CoA) and sodium succinate (which is thought to supplement the tricarboxylic acid cycle), alone and in combination, have been assessed experimentally but none has yet been employed in man.

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