TOXICOLOGY OF ω-FLUOROCARBOXYLIC ACIDS

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Summary

At this time we know thousands of organofluorine compounds and many of them are very toxic for humans (1). Mainly fluoroacetic acid and many other alifatic monofluoro compounds satisfied criteria of reliable poisons (2) and several these compounds were examined during the last war for possible use as chemical warfare agents (3-5). Author of this article hopes that more widespread knowledge of these very dangerous compounds may act as a deterrent to their illegal use and that concern may be stimulated in the search for more satisfactory methods of medical treatment.

KEY WORDS: ω-Fluorocarboxylic acids.

Historical development

Fluoroacetic acid was first prepared more than one hundred years ago (6). Its physicochemical properties were recorded, but without any note was made of its toxicity. Nevertheless, in 1930 fluoroacetic acid was prepared in Germany as a mothproofing agent (7). A general method for preparation of fluoroacetic acid and many its derivatives was elaborated in Poland (8) and in the

course of their pharmacological examination it became apparent that the fluoroacetates were extremely toxic to a wide variety of animals via common routes of administration (9). We mentioned that fluoroacetates were examined as candidates for chemical warfare agents (4), but were not used for this purpose. Different types of organofluorine compounds were developed as contact and/or systematic insecticides (10-12). Very effective insecticide was for instance sodium fluoroacetate (13). Because all organofluorine insecticides have appreciable mammalian toxicity, were lately exchanged by other types of insecticides (organochlorine compounds, organophosphates, carbamates, pyrethroids etc.).

Fluoroacetic acid

Shortly after findings of fluoracetic acid toxicity other compounds of this type were prepared and tested on the toxic effect. It was shown that many derivatives of fluoroacetic acid are also highly toxic, for example fluoroacetaldehyde (14) and even 2-fluoroethanol (14, 15), esters (2, 16-18), amides and others (19). Difluoroacetic acid as well as trifluoracetic acid were non-toxic (9).

Toxicology of fluoroacetic acid

The most outstanding feature of the toxicology of the fluoroacetates is the extraordinarily wide variation in response between different species of animals in regard both to sensitivity and symptoms (20, 21). An examination of the LD_{50} values listed in Table I. These differences in response are evident (2). The symptoms of poisoning equally varied, too. The major point of attack may be either the central nervous system or the heart (21) and the death may result from respiratory arrest following severe convulsions, cardiac failure with ventricular fibrillation or progressive depression of the central nervous system with either cardiac or respiratory failure as the terminal event (21, 22).

All these responses follow a long and essentially irreducible latent period after the administration of the fluoroacetate(2, 23). This latent period depends on species of the animal and also on the way of poison administration (2). In humans, the latent period is up to six hours (24-28). From a study of the case histories is evident that the major toxic effects of the fluoroacetate in man involve the central nervous system and the heart. Characteristic symptoms are epileptiform convulsions alternating with coma and depression associated very often with failure of respiration, cardiac irregularities, ventricular fibrillation and cardiac arrest. Death can result from cardiac arrest, asphyxia during a convulsion or respiratory failure and was observed in fifty percent of all cases of poisoning with fluoroacetate (29-32).

Table I

Toxicity of fluoroacetate in different species of animals

Species	LD_{50} (mg/kg)	Route of addministration [a]
Mouse	7	i.p.
Rat	5	i.p.
Guinea pig	0.35	i.p.
Rabbit	0.5	i.v.
Cat	0.2	i.v.
Dog	0.06	i.v.
Frog	150	s.c.
Sheep	0.3	o.
Horse	1.0	o.
Man	2-10[b]	o.

[a] Routes of administration: i.p. = intraperitoneal, i.v. = intravenous, s.c. = subcutaneous, o. = oral.
[b] The figure for man was extrapolated and should be accepted with considerable reserve.

Fluoroacetic acid as toxic principle of Dichapetalum cyanosum

A poisonous plant occurring in South Africa known here as gifblaar (*Dichapetalum cyanosum* (Hook), Engl., has long been known as one of the most deadly stock poisons. It is an underground shrub possessing branches, many of which attain great length and from which small shoots ascend to the surface, there giving rise to the tufts of green leaves and inconspicious flowers. Because of the very great depth to which the underground stems can penetrate, the plant sprouts early in the summer before the first rains when the grassland is still dry. Therefore green patches of gifblaar are very attractive to cattle. Unfortunately, this plant is very toxic for all animals. In cattle, symptoms of intoxication may appear within twelve hours after ingestion of the plant. The animal lies down and when standing, the front legs are held well forward and the hind legs tucked under the body. The heart action is increased, the pulse is soft and hardly perceptible. The respiration is increased and the animals sometimes moan et expiration. Furthermore there is a quivering of the muscles, especially those of the shoulder, and all the reflexes are exaggerated. Also salivation is increased and the animals get very dull and there are unable to rise. Death may occur as soon as twelve hours after the first symptoms appeared (33).

All the above work on toxicology proceeded without any knowledge of the toxic principle (34). In 1943 Marais isolated toxic principle in the form of its potassium salt (35) and early identified this compound as potassium fluoroacetate (36). Until this time, no naturally-occurring organic fluorine compound had been known. The biosynthesis of fluoroacetate *in situ* presents several interesting problems connecting with C-F link formation (37, 38).

The mode of toxic action of fluoroacetic acid

The toxic effect of fluoroacetate was enigmatic for a long time (39, 40). In 1947 Bartlett and Barron (41) suggested that fluoroacetate exerted its toxic action by inhibiting the conversion of acetate to "active acetate", now recognized as acetyl co-enzyme A, prior to its oxidation in the tricarboxylic acid cycle. Shortly afterwards, Kalnitsky and Barron (42) observed that citric acid accumulated markedly during experiments involving the action of fluoroacetate in rabbit kidney homogenates and Liébecq and Peters (43) occurred inhibitory effect of fluoroacetate on the tricarboxylic cycle. Up to this point, all biochemical experiments had been carried out *in vitro*, but in 1949 Buffa and Peters (44) made the important discovery that citric acid accumulation occurs also *in vivo*. At last the accumulation of citric acid has been found by many workers who occur it in different animals and animal tissues (45-49). Summarizing these findings it was apparent that citric acid accumulated due to blockade of citric acid oxidation in the tricarboxylic acid cycle and that fluoroacetate had no affect on the individual enzymes of this cycle. This apparent discrepancy was resolved by the suggestion of Liébecq and Peters (50) that fluoroacetate was converted to fluorocitric acid, and that the fluorocitric acid thus formed was the ultimate toxic agent (51). Such a conversion by enzymic synthesis of a non-toxic substance to a toxic one, is known as a "lethal synthesis".

It is commonly known that the acetate is activated by formation of acetyl-coenzyme A which occurs when free acetate and coenzyme A react in the presence of ATP. As shown in Fig. 1, the acetyl-coenzyme A is then incorporated into the tricarboxylic acid cycle so that it reacts with the enol form of oxaloacetic acid to produce citric acid, the first member of the cycle which is known also under the name of citric acid cycle or Krebs' cycle. By the chemical changes summarized schematically in Fig. 1, the citric acid formed is degraded through the agency of specific enzymes to carbon dioxide, water and oxaloacetic acid. The important step for fluoroacetic acid effect is formation of cis--aconitic acid from citric acid, since enzyme catalyzing this reaction, aconitase, is inhibited by fluorocitric acid (52-55). Fluoroacetic acid alone is non-toxic but in vivo forms fluorocitric acid which blocks cellular metabolism at the citrate stage. The inhibition of ATP formation reduces energy supply to cell, and thus causes cellular dysfunction or degeneration. All body cells are potentially affected, although with different sensitivity. Symptoms occur with a delay but lethal synthesis of fluorocitric acid leads to the irreversible cellular dysfunction, especially in CNS and circulatory system (31). Acute renal failure was found in many causes. Poisoning may be treated with monoacetin and acetamide. Health hazards are emphasized resulting from the exposure to fluoroacetate and necessity to follow strictly safety regulations (32).

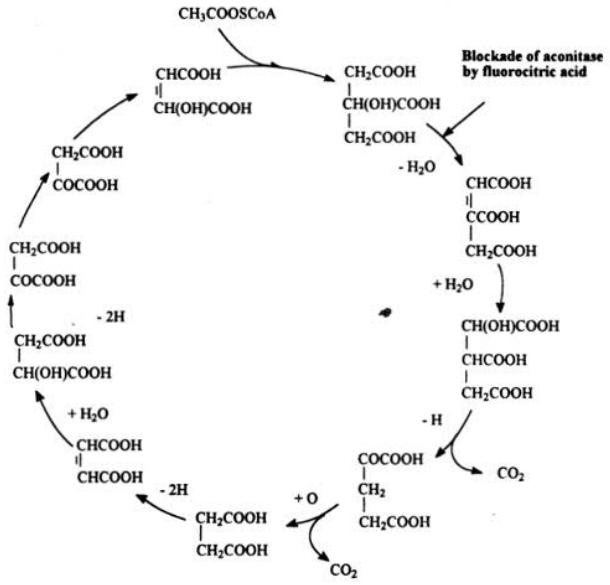

Fig. 1 The simplified tricarboxylic acid cycle (Krebs' cycle) and the place of the inhibition effect of fluorocitric acid on aconitase, if fluoroacetyl-coenzyme A is present.

ω-Fluorocarboxylic acids

Very interesting results were obtained when 3-fluoropropionic and 4-fluorobutyric acids were prepared. While 3-fluoropropionic acid was found to be non-toxic, 4-fluorobutyric acid was even more toxic than fluoroacetic acid. Also other ω-carboxylic acids were either toxic or non-toxic in dependence on the number of carbon atoms in their molecule (Table II) (56).

Table II

Toxicity of ω-fluorocarboxylic acids $F-(CH_2)_n-COOH$ for mice in intraperitoneal administration

n	LD_{50} (mg/kg)
1	6.6
2	60
3	0.65
4	>100
5	1.35
6	40
7	0.64
8	>100
9	1.5
10	57.5
11	1.25
17	5.7

The results may be summarized in the following generalization: if the total number of carbon atoms in the chain of ω-fluorocarboxylic acid $F-(CH_2)_n-COOH$ is even, the compound is toxic, whereas if

the total number is odd, the compound is non-toxic (Fig. 2) (57).

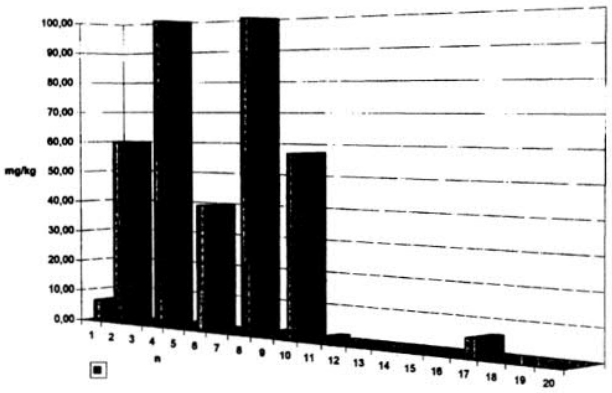

Fig. 2 Toxicity of ω-fluorocarboxylic acids F-$(CH_2)_n$-COOH. The dependece of LD_{50} values on the number of ethylene group (n) in molecule of ω-fluorocarboxylic acid.

The variation of toxicity depending on the number of carbon atoms was observed also in other groups of ω-fluoro-compounds, for example ω-fluoroalcohols (58), ω-fluoroaldehydes (59), ω-fluoroketones (60), esters of ω-fluorocarboxylic acids (57), an even ω-fluoroalkanes, ω-fluoroalkenes, and ω-fluoroalkynes (61).

The mode of toxic action of ω-fluorocarboxylic acids

As described earlier, one of the consequences of fluoroacetate poisoning is the accumulation of citric acid in various tissues. This accumulation was explained as a result of the biochemical conversion of fluoroacetate to fluorocitric acid, which is strongly competitive inhibitor of the enzyme aconitase and is responsible for the normal utilization of citric acid in living organisms. Since there is no evidence to suggest that the long-chain acids have any inhibition effect on aconitase, any fluoro-compound which results in marked citric acid accumulation may therefore be considered as metabolized to fluoroacetic acid, or, more precisely, to fluoroacetyl-coenzyme A. Because the metabolic degradation of fatty acids is realized in so called β-oxidation procedure (62), all fatty acids are degraded by the simultaneous removal of two-carbon fragments. If this process of β-oxidation is applied to the ω-fluorocarboxylic acids, it can be seen that all the toxic members (i.e. those containing an even number of carbon atoms) can form the very toxic fluoroacetic acid, whereas the non-toxic members (i.e. those containing an odd number of carbon atoms) can be degraded only as the non-toxic 3-fluoropropionic acid.

The toxicity of long-chain ω-fluoroacetic acids apparently behaves basically in the same way as fluoroacetate after initial degradation to fluoro-acetyl-coenzyme A. However, certain qualitative and quantitative differences have been reported. For instance, 4-fluorobutyric acid is more toxic and acts more rapidly than fluoroacetic acid, and the resultant distribution in the tissues of accumulated citric acid is different from the two compounds (63). Probably the most toxic ω-carboxylic acid is 8--fluorooctanoic acid, which is on a molar basis more than twenty times more toxic than fluoroacetic acid. Even 10-fluorodecanoic and 12--fluoro dodecanoic acids are more toxic than fluoroacetate. Comparative toxicity with fluoroacetic acid was found in 18-fluorostearic acid (64). It was evident that long-chain ω-carboxylic acids are a toxic principle similarly to fluoroacetic acid of some West Africa shrubs *Dichapetalum* species. That fruticose plant is a glabrous shrub occurring in Sierra Leona known as ratsbane (*Dichapetalum toxicarium*), formerly named *Chailletia toxicaria*, Don. The fruit of ratsbane was widely used for the destruction of rats and other animals, but in additio to this it was also used in some areas by the people to poison each other (65).

The relatively high concentrations of fluoroacetate were found newly also in other toxic plants, for example in *Arrabidea bilabiata (66)*, *Palicourea marcgravii (66, 67)*, Indian leguminous plant *Cyamopsis tetragonolobus (68)* or in Australian plant genus *Gastrolobium* (69).

Conclusions

Fluoroacetic acid as well as some ω-fluoro-fatty acids with even number of carbons produce toxic effects by metabolic conversion to fluorocitrate, inhibit Krebs' cycle and the formation of ATP, reduce energy supply to cells, and thus cause their dysfunction. Symptoms of poisoning begin after a latent period of one-half to several hours and death follows rapidly. Convulsions and arrythmia are common terminal signs. Fluoroacetic acid and its many derivatives are used for various purposes and make hazard for man. This acid, as well as higher ω-fluorocarboxylic acids, were found in some toxic plants.

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