RODENTICIDES

Kramer R.E. and Baker R.C.
Department of Pharmacology and Toxicology, University of Mississippi Medical Center, U.S.A.

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Summary

A rodenticide is defined as any compound used to kill rodents or other small animals. They are widely used, and as a class encompass a disparate group of compounds with differing structures and mechanisms of action.

Rodenticides can be subdivided into inorganic and organic compounds. Inorganic rodenticides include agents such as arsenic salts, thallium, phosphorus, zinc phosphate and barium salts. They are considered highly toxic, exhibiting single-dose oral LD50
values for rats of 50 mg kg\(^{-1}\) or less, based on the ingestion of the commercially available product and including both active and inert ingredients. The estimated lethal dose for inorganic rodenticides ranges from 1 mg kg\(^{-1}\) for elemental phosphorus, 3-7 mg kg\(^{-1}\) for sodium monofluoroacetate, to 13-14 mg kg\(^{-1}\) for sodium fluoroacetamide and thallium. The mechanisms of toxicity for the inorganic rodenticides is as variable as the agents. Thallium interacts with sulphhydryl moieties within mitochondria, interfering with oxidative phosphorylation. Likewise, arsenic inhibits the activity of a variety of enzymes through binding to sulphhydryl groups. Fluoroacetate derivatives disrupt the Kreb’s cycle by serving as competitive substrates. Both barium and strychnine act, directly or indirectly, to block motor neuron activity, and phosphorus causes severe local irritation and burns followed by gastrointestinal, hepatic and renal dysfunction.

Organic rodenticides include fluoroacetate derivatives, thiourea-based agents, derivatives of vitamin D, short- and long-acting anticoagulants, red squill, norbormide and strychnine. Of these, pyriminil is designated as being highly toxic, with an estimated fatal dose of 5 mg kg\(^{-1}\). Its primary mechanism of toxicity appears to be interference with nicotinamide metabolism, resulting in dysfunction in a number of tissues including the central and peripheral nervous systems, the heart and the pancreas. \(\alpha\)-Naphthylthiourea, which causes acute pulmonary toxicity, and vitamin D-based rodenticides, which cause hypercalcemia with predictable sequelae, are considered moderately toxic; oral LD\(_{50}\) values for commercially available preparations range between 50-500 mg kg\(^{-1}\). Some other organic rodenticides are designated as having low toxicity with LD\(_{50}\) values in excess of 500 mg kg\(^{-1}\). Norbormide appears to be selectively toxic to rats. It causes vasoconstriction through a norbormide-specific receptor on rat vascular smooth muscle, and there have been no reported cases of systemic toxicity to norbormide in humans. Red squill is a glycoside and, as such, causes both cardiotoxicity and convulsant effects. Bromethalin uncouples oxidative phosphorylation. Concomitant depletion of cellular ATP has functional consequences on all cell types, but effects within the central and peripheral nervous systems are most pronounced. Although bromethalin has a reported LD\(_{50}\) in rats of 2 mg kg\(^{-1}\), the potential for bromethalin poisoning in humans is considered to be low. Warfarin and its more-long acting counterparts are anticoagulants, and death ultimately results from internal hemorrhage.

In the light of the mechanisms of action of many of the rodenticides, it is of no surprise that they are not selectively toxic to rodents. Variable toxicities to humans and other non-target species have been described. In relation to toxicity to humans, some groups of people are at greater risk than others from exposure to rodenticides. Exposure to rodenticides, particularly the more toxic agents, is an occupational hazard for pest control applicators. Intentional poisoning with rodenticides in cases of suicide (attempted or otherwise) or homicide have been reported. Individuals who abuse alcohol or other drugs, as well as people who suffer psychological disorders may be more prone to unintentionally ingest rodenticides for one reason or another. Likewise, children and the elderly may be more susceptible to the adverse effects of intentional or unintentional exposure to rodenticides.

In the United States, most human toxicities involve accidental poisoning of children, typically children younger than 6 years old. There are relatively few deaths, however,
and the deaths that do occur as a result of poisoning with known rodenticides are attributable to strychnine or the long-acting anticoagulants. Although the latter are considered to have only a low potential for toxicity in humans, they are available commercially for residential use. Thus, children are more likely to be exposed to the long-acting anticoagulant rodenticides than they are to more toxic agents with a more restricted use. Also repeated ingestion, in combination with their prolonged action, can be problematic in children.

The rodenticides have been described extensively in the scientific literature. Although limited in some cases, information regarding their physical properties, practical considerations in relation to their use as bait, mechanisms of action, and appropriate therapeutic intervention in cases of human toxicity is available. This review represents a compilation of that material. However, it should not be considered complete in and of itself. The reader is encouraged to consult the primary references as well as other reports for greater detail. Additional information can also be obtained from any number of textbooks on the principles of toxicology and the medical management of the poisoned patient.

1. Introduction

Rats and mice, when unchecked, can have a significant socioeconomic impact on humans. The control of rodent populations comprises an important component of post-harvest food protection, notably of grain and cereal crops. The ability of rats as well as other rodents to serve as vectors for human disease also brings the animals into the realm of public health. In settings in which sanitation is compromised and rats and humans are in close contact, reduction (if not complete eradication) of rodent populations is obligatory for effective prevention and containment of disease.

A variety of products have been designed specifically to kill rats and mice. These products, or rodenticides, consist of a wide range of inorganic and organic chemicals with diverse structures, mechanisms of action, effectiveness, and toxicities to non-target species including humans. Some rodenticides occur naturally in plants, whereas others are derived synthetically. In some cases, a metabolic process or a biochemical characteristic unique to the rat is targeted in an effort to diminish toxicity to other animals. For most rodenticides, however, the site and mechanisms of action are common across animal phyla and between species. Thus, with the use of most rodenticides, secondary poisoning to non-target species can be significant. Such non-specific toxicity associated with some agents has led to their application in the control of other small animal pests; for example, opossum, squirrels, moles, gophers, birds, bats, as well as small mammalian carnivores such as coyotes and foxes. It also increases the concern about potential toxicity to humans.

For any rodenticide to be effective, it must be accepted by the target species. Ideally, the rodenticide is lethal in a single dose and has a high lethal efficiency within the population. Long-term control also requires that the rodent population as a whole does not develop resistance to the poison. Characteristics of the ideal poison are only partially met by most rodenticides. The first is often achieved by mixing the rodenticide with food. Unfortunately, this tactic makes the poison attractive to other animals and, in
domestic settings, to children. Learned avoidance and development of tolerance continue to drive the development of rodenticides with different mechanisms of action to maintain effective control of commensal rodent populations. For the most part, complete eradication of rodents or other pests is impractical. The best that can be hoped for is stabilization of an acceptable population through the use of a combination of methods, often utilizing a number of different rodenticides.

The potential hazard associated with the use some rodenticides can be offset to some extent by application strategy (location, presentation), and the relative dosages at which toxicity develops between target and non-target species. In some cases, the immediate physiological response (e.g., regurgitation) to ingestion of the chemical or an adjuvant in the formulation can minimize poisoning to non-target species while maintaining effectiveness in rats. In the case of humans, restrictions on the use of highly toxic rodenticides to licensed applicators or appropriate government officials figure prominently in reducing the frequency of unintentional poisoning. For those rodenticides that are readily available “over-the-counter”, knowledge about proper handling and potential toxicities are equally important.

2. Fluoroacetate Derivatives

2.2. Sodium Monofluoroacetate

Sodium monofluoroacetate (SMFA or compound 1080) is a highly toxic single dose rodenticide. It is the sodium salt of fluoroacetate, a compound which occurs naturally in a number of poisonous plants throughout the world (e.g., *Acacia* and *Leguminosae* (Australia), *Dichapetalaceae* (South Africa), and *Palicourea* (South America). Sodium monofluoroacetate is highly effective against all types of rodents, and is used in some countries for the control of exotic vertebrate pests such as cats, opossums, rabbits and foxes. It is applied as single-lethal-dose baits or as a toxic collar on the prey of targeted pest. Oral LD$_{50}$ values in mice and rats are 2-3 mg kg$^{-1}$, and those in other mammals are between 0.03 mg kg$^{-1}$ and 1 mg kg$^{-1}$. The oral LD$_{50}$ for sodium monofluoroacetate in humans is estimated at 0.7-5 mg kg$^{-1}$. Poultry, with an LD$_{50}$ of 10-30 mg kg$^{-1}$, are less sensitive to sodium monofluoroacetate than are mammals. Due to its toxicity, sodium monofluoroacetate is best used in settings where the potential for secondary poisoning of non-pest species is minimal or where public access can be controlled. In some countries, including the U.S., the application of sodium monofluoroacetate is strictly controlled, and its use is restricted to licensed exterminators or Public Health officials.

Because of its chemical stability, water solubility and high toxicity, there is concern for the potential of sodium monofluoroacetate to contaminate ground water and to persist in the environment. In addition, sodium monofluoroacetate that leaches into soil from bait can be taken up and accumulated by plants, posing a risk of secondary poisoning to herbivores. However, in biologically active systems, the window for toxicity to sodium monofluoroacetate is relatively narrow. Fluoroacetate was rapidly absorbed by grass with peak levels being achieved within 3 days. However, it was just as rapidly degraded or otherwise eliminated from the plant. Absorption and elimination of fluoroacetate by broadleaf plants was somewhat slower; plant levels of fluoroacetate were maximal after 10 days, and elimination was complete by 24 days. The half-life of fluoroacetate in
biologically active water has been estimated at 1 day or less to as long as 6 days, depending on temperature and specific conditions. Fluoroacetate can undergo microbial metabolism in water and soil to glycolate or fluorocitrate. Glycolate is relatively nontoxic (oral LD$_{50}$ in rats is about 2g kg$^{-1}$), whereas fluorocitrate is thought to mediate the toxicity to sodium monofluoroacetate in mammals. In comparison to fluoroacetate, fluorocitrate has a comparable half-life in aquatic systems and a lower oral toxicity. Fluoroacetate in uneaten bait is degraded through microbial action.

Sodium monofluoroacetate is readily absorbed if ingested or inhaled. It can also be absorbed through broken skin, but it is not absorbed through intact skin. Clearance of fluoroacetate varies between species. Studies in rats indicate that fluoroacetate is retained in tissues for several days. The half-life of sodium monofluoroacetate in sheep and goats, respectively, is 10.8 and 5.4 hours, whereas its half-life is less than 2 hours in mice and 1.1 hours in rabbits. The concentrations of fluoroacetate in tissues are only 25-50% of those in plasma, and fluoroacetate appears to be cleared somewhat faster from tissue than from plasma. In studies using sodium [2-$^{14}$C]fluoroacetate, distribution of the isotope was accompanied, at least in liver and kidney, by accumulation of fluorocitrate.

The primary mechanism of toxicity to sodium monofluoroacetate is inhibition of the Krebs cycle and depletion of energy stores. In mammalian cells, fluoroacetate is converted to fluoroacetyl-CoA and then to fluorocitrate. Fluorocitrate, in turn, can inhibit aconitase, preventing the conversion of citrate to isocitrate. It can also inhibit the translocation of citrate across the mitochondrial membrane. Although only about 3% of a dose of sodium monofluoroacetate appears to be converted to fluorocitrate, these actions account for the depletion of energy stores – especially in heart, liver, kidney and brain – as well as the accumulation of citrate associated with sodium monofluoroacetate poisoning. Fluorocitrate mimics sodium monofluoroacetate in precipitating hypocalcemia as well as toxicity within the central nervous and cardiovascular systems. Although fluoroacetate is metabolized to products other than fluorocitrate, there is little evidence that other metabolites contribute to sodium monofluoroacetate toxicity. Similarly, fluoroacetate can undergo defluorination in the liver, but its toxicity is independent of its fluoride content or the concentrations of free fluoride obtained.

Symptoms often present within 30-180 minutes after the ingestion of sodium monofluoroacetate. The delay is attributed to the time required for fluoroacetate to be converted to fluorocitrate. Once symptoms begin, they are severe and widespread, presenting as respiratory, neurologic, gastrointestinal, cardiovascular and electrolyte disturbances. Manifestations of toxicity in the central nervous system and cardiovascular system, however, may be most apparent. The general response to sodium monofluoroacetate poisoning includes nausea, vomiting and abdominal pain initially, followed by respiratory distress and then signs of central toxicity. Toxicity within the central nervous system is reflected in agitation, apprehension, loss of consciousness, seizures, coma and respiratory failure. Muscle spasms and stupor are also common, and animals that die of monofluoroacetate poisoning show a characteristic hyperextension of the extremities. Cardiovascular symptoms commonly consist of hypotension and sinus tachycardia. The hypotension is associated with decreased peripheral vascular resistance, which is unresponsive to inotropic therapy and volume expansion,
suggesting a direct toxic effect of fluoroacetate on the vasculature. Tachycardia may progress to dysrhythmia marked by nonspecific T-wave and ST-T segment irregularities, then to supraventricular or ventricular tachycardia and, finally, to ventricular fibrillation and sudden cardiac arrest. Metabolic acidosis, hypocalcemia and hypokalemia are common, and acute renal failure with frank uremia can occur. Hypotension, increased plasma creatinine and metabolic acidosis were the most predictive indicators of poor prognosis and mortality in sodium monofluoroacetate poisoning.

There is no known antidote for sodium monofluoroacetate poisoning, but some therapeutic steps have been advocated on the basis of studies in experimental animals. In general, treatment is nonspecific and supportive. Repeated gastric lavage and catharsis seem empirically useful because of enterohepatic recycling of fluoroacetate, but there is no evidence of their effectiveness. Evidence to support the use of activated charcoal as an initial step to remove unabsorbed fluoroacetate is also lacking. Attempts to identify a substrate that would compete with, or by-pass, the inhibition of citrate metabolism caused by fluoroacetate indicated that glycerol monoacetate was the most beneficial in mice, rats, rabbits, dogs and monkeys. Glycerol monoacetate was also less acutely toxic than was either glycerol diacetate or glycerol triacetate. Ethanol, alone or in combination with glycerol monoacetate, was effective against fluoroacetate poisoning in mice and rats. But, the usefulness of ethanol as an antidote to fluoroacetate poisoning in humans is questionable, since it had no beneficial effect in monkeys. A combination of calcium gluconate and sodium succinate decreased mortality to sodium monofluoroacetate in mice, although neither was effective alone. Hypocalcemia contributes to the neural and cardiovascular effects caused by fluoroacetate, and administration of calcium chloride to sodium monofluoroacetate-poisoned cats prolonged survival. In contrast, calcium chloride augmented toxicity to sodium monofluoroacetate in monkeys. Sodium acetate, digoxin, sodium chloride and potassium chloride also enhanced sodium monofluoroacetate toxicity, presumably by exacerbating existing hypernatremia, hyperkalemia or metabolic acidosis. General recommendations for the management of a sodium monofluoroacetate-poisoned patient following these observations consist of intramuscular administration of glycerol monoacetate at hourly intervals, continued monitoring of cardiac function, control of seizures with an anticonvulsant such as diazepam or pentobarbital, and avoidance of cardiac glycosides, calcium, potassium, sodium, bicarbonate and excess acetate. It is important to note that these recommendations have not been evaluated in controlled clinical settings.

2.3. Fluoroacetamide

Fluoroacetamide (compound 1081) is a fluoroacetate derivative that is slightly less toxic and somewhat slower in onset than is sodium monofluoroacetate. Its intraperitoneal LD$_{50}$ in mice is 85 mg kg$^{-1}$ compared to 18 mg kg$^{-1}$ for fluoroacetate. The mechanism of action of fluoroacetamide appears to be identical to that of sodium monofluoroacetate. That premise is based on the observations that fluoroacetamide undergoes deamination to fluoroacetate in vivo and that whole body citrate levels increase subsequent to fluoroacetamide administration. Not surprisingly, the symptoms of fluoroacetamide poisoning mimic those of fluoroacetate poisoning. Thus, interventions appropriate for
the management of the sodium fluoroacetate-poisoned patient apply equally to the management of fluoroacetamide poisoning. Regulations for the use of fluoroacetamide parallel those governing the use of sodium monofluoroacetate.

2.3. 1,3-Difluoro-2-propanol

1,3-Difluoro-2-propanol (DFP) is the major (70%) active component of the pesticide gliflor; the remainder is 1-chloro-3-fluoro-2-propanol. Gliflor is used widely as a rodenticide in some countries and is being evaluated in others as a potential replacement for sodium monofluoroacetate. The oral LD₅₀ for gliflor in rats is about 46 mg kg⁻¹. Although 1,3-difluoro-2-propanol is not strictly a derivative of fluoroacetate, the signs of its toxicity and its apparent mechanism of action are similar to those caused by sodium monofluoroacetate.

1,3-Difluoro-2-propanol can undergo conversion to fluorocitrate in vivo and in vitro through a series of reactions initiated by an NAD⁺-dependent alcohol dehydrogenase. The resulting product, 1,3-difluoroacetone, undergoes a cytochrome P450-mediated defluorination and an acetyl-CoA-mediated decarboxylation to fluoroacetyl CoA. Finally, fluoroacetyl CoA is converted to fluorocitrate. Following administration of 1,3-difluoro-2-propanol to rats, citrate concentrations in the kidney increased coincident with fluoride and fluorocitrate concentrations. Increases in citrate and fluorocitrate concentrations caused by 1,3-difluoro-2-propanol were comparable to, but slower in onset than, the increases caused by sodium monofluoroacetate.

Increases in renal citrate and fluorocitrate concentrations caused by administration of 1,3-difluoro-2-propanol, but not those caused by sodium monofluoroacetate, were markedly attenuated by pretreatment of rats with 4-methylpyrazole. The protective effect of 4-methylpyrazole may reflect an inhibition of malate dehydrogenase. In any event, these observations raise the possibility of 4-methylpyrazole being an effective antidote for 1,3-difluoro-2-propanol poisoning without the introduction of significant additional toxicity. In that light, 1,3-difluoro-2-propanol may be a useful alternative for sodium monofluoroacetate in the control of rodents and other vertebrate pests.

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Biographical Sketches

Robert E. Kramer  received a Doctor of Philosophy Degree from The University of West Virginia (Department of Physiology) in 1976. His dissertation research focused on endocrine regulation of hepatic
and adrenocortical mixed function oxidases. His postdoctoral training was related to intracellular signaling within the adrenal cortex with emphasis on the regulation and expression of steroidogenic cytochrome P450 enzymes. His research focuses on the mechanisms of action of steroidogenic agonists and the modulation of those actions by environmental factors. A topic of current interest is the effects of organophosphorus pesticides on cytochrome P450 isozymes in the liver and in extrahepatic tissues. Presently, Dr. Kramer is a Professor of Pharmacology and Toxicology at The University of Mississippi Medical Center, Jackson, Mississippi.

Rodney C. Baker received a Master of Science Degree (nutrition) from Utah State University in 1970. His thesis addressed the interaction between diet protein quantity or quality and the metabolism of organochlorine pesticides. He received a Doctor of Philosophy Degree in 1974 from North Carolina State University (physiology/toxicology). His research project was directed toward elucidating the mechanism of piperonyl butoxide action. Dr. Baker’s postdoctoral training was in the area of lipid biochemistry. His research activities have centered on the interaction of various classes of drugs and xenobiotics on lipid metabolism and disruption of phospholipid dependent intracellular signal transduction processes. Dr. Baker is currently a Professor of Pharmacology and Toxicology at The University of Mississippi Medical Center, Jackson, Mississippi.