THE PHARMACOLOGY OF RODENTICIDES

S. A. PEOPLES, School of Veterinary Medicine, University of California, Davis, California

The compounds used as rodenticides are tremendously varied in their chemical structure and mechanism of action. With a few exceptions, these agents are generally poisonous to all animals, including man, and a great deal of study has been directed to their toxicity in animals other than rodents. However, the development of new compounds as Norbormide and certain antifertility drugs which are highly selective in their action may justify the hope that the ideal rodenticide free of secondary toxic hazards will soon be available.

Until this happy announcement is made, a review of the pharmacology of the older compounds is in order to enable us to understand the limitations on their effectiveness and hazard. The tremendous chemical variety of the compounds precludes any obvious systematic grouping of the compounds for discussion so that I have arbitrarily divided them into Inorganic, Organic, and Fumigants. The discussion of each one is limited to the primary pharmacological mechanism of the toxic action and will only briefly mention interesting but non-essential side effects.

ORGANIC AGENTS

The Anticoagulants

The discovery that dicoumarol was the active agent in the hemorrhagic disease caused by spoiled sweet clover has led to the synthesis of two series of compounds derived from coumarin (Dicoumarol, Coumachlor, Warfarin) and 1, 3 indandione (Pindone or Pival). These chemical compounds differ in solubility, rate of absorption and duration of action but not in their basic mechanism of action. Their basic chemical structure is sufficiently similar to vitamin K that they competitively interfere with its conversion to prothrombin in the liver. When the prothrombin level falls below a critical level, clotting cannot occur and the tiny hemorrhages throughout the body become major ones and the animal literally bleeds to death.

To be most effective the dose should be administered over several days although a single massive dose may be effective. Certain strains of rats have been shown to have a natural resistance to this type of drug. (1) Preexistant liver damage would increase the potency of this compound and vitamin K would act as an effective antidote.

Alpha naphthyl thiourea - Antu

This compound, although insoluble in water, is readily absorbed from the intestinal tract. It has a specific effect on the capillaries of the lungs leading to the rapid development of pleural effusion and pulmonary edema. This results in anoxia and ends in respiratory failure.

Repeated sublethal doses in rats leads to the development of tolerance so that resistance to several lethal doses is developed.

All animals are susceptible to Antu but the lethal doses differ widely.

	LD mg/Kg
rat	3
dog	10
pig	25
horse	30
cow	50
cat	75
fowl	2500

Sodium Fluoroacetate (1080) and Fluoroacetamide (1081) and Methyl Fluoroacetate.

These are the most potent rodenticides known, being toxic to all animals in doses under 1mg/Kg. Their mechanism of action is identical and indirect. The compounds enter the citric acid cycle exactly as does acetate, resulting in the formation of fluorocitric acid which blocks the enzyme aconitase, thereby blocking the TCA cycle. Since this cycle is of basic

importance to all tissues, widespread functional changes occur in all organs but most particularly the heart and the central nervous system. In the rat, both changes occur simultaneously, giving rise to tetanic convulsions and cardiac irregularities and ultimate failure.

The course of the poisoning is rapidly fatal and there is no known antidote.

Strychnine Sulfate

This alkaloid is a potent poison with a dose of 1mg/Kg being lethal for most animals. It is not absorbed from the stomach and failure of the stomach to empty will delay the onset of symptoms.

Its poisonous action is entirely on the spinal cord by lowering the threshhold for stimulation of spinal reflexes. It removes the inhibition exerted by the Renshaw cells over the motor cells in the spinal cord so that they can be stimulated by weak afferent impulses. A poisoned animal will go into tetanic convulsions by a touch, flashing lights or a loud noise.

Death results from anoxia due to breath holding while in the convulsive state. C.N.S. depressants are used as antidotes but are rarely successful.

Red Squill (Urginea Maritima)

The dried bulb of the plant contains the cardiac glycoside scillaroside, which has the same pharmacological properties as other digitalis-like glycosides. The compound acts directly on the heart muscle to first slow the rate and then produce ventricular irregularities culminating in cardiac standstill. In the rat, there is apparently an additional action on the C.N.S. resulting in convulsions, the mechanism of which is not known. This also occurs with other digitalis like compounds.

The presence of high levels of oxalic and tannic acid in the crude drug cause most animals to reject it and to vomit when it is ingested. This effectively prevents poisoning those animals which can vomit, an ability lacking in the rat.

Norbormide (RATicate, SHOXIN)

This compound is unique in that it has a lethal dose of 5 - 15 mg/Kg in rats and essentially no toxicity for the cat, dog, chicken, duck, primates, sheep or swine. This selective toxicity is unparalleled in pharmacology and as yet no basis for it has been found.

Roszkowski (2) made the initial studies on this compound and found that the basic mechanism of its action was directly on the smooth muscle of peripheral vessels causing them to constrict irreversibly, resulting in widespread ischemia leading to death. The receptor sites in the muscle are not the same as for other vasoconstrictors such as epinephrine, and one must postulate that they exist uniquely in the rat.

CHEMICAL STERILANTS

The attempt is being made to develop drugs which will temporarily or permanently sterilize the male or female rat. Since this will be the subject of an extensive report in this symposium, it will not be discussed here except to note that R.V. Ericsson (3) reported that 3 chloro-1, 2 propanediol caused permanent lesions in the genital tract of male rats blocking the passage of sperm. Furthermore, it did not affect or only temporarily so such animals as the mouse, rabbit, monkey, guinea pig, and ram.

Chlorinated Insecticides

Compounds such as dieldrin, DDT and endrin have been found lethal to mice, but not rats when dusted along their path ways. Presumably, they lick their feet and absorb cumulatively a toxic dose. The action of these compounds is similar in that it produces stimulation of all parts of the central nervous system, particularly the motor nerves. This results in ataxia, convulsions and death from asphyxia.

The mechanism of action is not well understood but the current theory is that all parts of the nerve cell are stimulated. The treatment of poisoning, which is rare in pets, domestic animals and man, is the judicious use of sedatives and anesthetics.

INORGANIC RODENTICIDES

Zinc Phosphide

This compound reacts with water in the gastrointestinal tract to produce the gas Phosphene which readily enters the blood stream and is distributed throughout the body. In lethal doses there is hemolysis, resulting in hemolytic icterus and the blocking of the kidney with the liberated hemoglobin. There is also gastrointestinal irritation as evidenced by vomiting, colic, and diarrhea in most animals. The observation of the occurrence of convulsions may be explained on terminal C.N.S. anemia.

Thallium sulfate

This compound is lethal to most animals in doses of 10-20 mg/Kg. Its mechanism of action is not completely understood but it apparently reacts with the free-SH groups in such essential proteins as enzymes thereby producing widespread damage in most organ systems.

In acute poisoning there is gastrointestinal irritation, motor paralysis and death from respiratory failure. If a lower or repeated sublethal doses are taken, characteristic reddening of the skin of the face and abdomen with alopecia will develop. Pathological changes occur in most organs involving perivascular "cuffing" around blood vessels and degenerative changes in the brain, liver and kidney.

Barium carbonate

This compound is insoluble in water but readily dissolves in the stomach to release the free barium ion which is rapidly absorbed and distributed throughout the body. It then reacts with specific receptors in the smooth muscle of the gastrointestinal tract which go into a violent spasm. It also reacts with the smooth muscle of the arterioles which constrict, causing an acute increase in blood pressure. However, it is the effect on the cardiac muscle which probably results in death.

Phosphorus (Yellow)

This is an extremely dangerous compound in that it can catch fire spontaneously and direct contact on the skin will produce burns that heal very slowly. Its mechanism of action is not fully understood. It produces severe gastrointestinal irritation which can produce shock from circulatory failure. With lower doses there is profound destruction of the liver and kidney, resulting in death.

All animals are susceptible to this poison and there is no effective antidote.

White Arsenic - Arsenic Trioxide

This is the oldest of all poisons and still in use. It is practically tasteless, insoluble in water and very stable in baits. It causes death by acute irritation of the gastrointestinal tract resulting in bloody diarrhea and secondary shock. If the animal survives long enough there is destruction of liver tissue resulting in jaundice and mental depression.

Poisoning with low doses in animals and man can be successfully treated with B.A.L. (1, 2 Dithiopropanol) given intramuscularly. This ties up the arsenic in a way that makes it non-toxic and readily excreted.

FUMIGANTS

Carbon Monoxide

This gas is poisonous in low concentrations to all animals. It acts by combining with the hemoglobin to form a stable compound thereby reducing the oxygen carrying capacity of the blood. Death is due to tissue anoxia with the depression of the respiratory center the cause of death. If death does not occur, the animal will recover without residual tissue damage.

It is hazardous in that it has no odor or color to warn of dangerous concentrations.

Methyl Bromide

This compound is a heavy gas which has no warning odor. Its mechanism of action is not known but it is thought to slowly release hydrobromic acid in the cells of the lung and nervous system. High concentrations result in acute pulmonary congestion and death. With low concentrations the effects are delayed with the onset of convulsions as well as respiratory irritation.

Hydrogen Cyanide

This gas is the most rapidly fatal of all poisons and effects all animals. It is rapidly absorbed and distributed to all body cells causing them to stop using oxygen. The mechanism of this action is the inactivation of the iron-containing enzymes in the cells, cytachrome oxidases, without which all cell energy transfer ceases. The symptoms and signs of poisoning are the effects of the functional failure of organ systems, such as convulsions and cardiac failure with death occurring in a matter of minutes.

SUMMARY

An attempt has been made to briefly describe the essential mechanisms of action of some common rodenticides. A list of recent books on this subject is included in the bibliography which will supply more detailed information than could be given in this paper.

BIBLIOGRAPHY

1. Laboratory investigations of resistance to Warfarin of Rattus Norvegicus from Montgomeryshire and Shropshire. Drummond, D. C., Wilson, E. J. Ann. of Applied Biol 1968 61:303-12.
2. The Pharmacological properties of Norbormide, a selective rat toxicant. Adolph P. Roszkowski. J. of Pharmacol. and Exper. Therap 1965 149:288-299.
3. Chemosterilants. R. V. Ericsson. Chemical and Engineering News 1969 47:39
4. Handbook of Pest Control. Fifth Ed. Arnold Mallis MacNair-Dorland Co. 101 West 31st St., NYC, NY.
5. Progress in Chemical Toxicology. Vol. 4, 1969. Abraham Stolman. Academic Press. NYC, NY.
6. Veterinary Toxicology. Second Ed. 1970. R. P. Radeleff Lee and Febiger, Phila., Pa.