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A COMPREHENSIVE REVIEW ON RODENTICIDE POISONING AND ITS MANAGEMENT

Ede Srilakshmi[1]*, Shaik Ujefa[1], Ganji Komali[1], Tadichetti Devi Priya[1], Bellapu Dhanush[2] and Padmalatha Kantamaneni[3]

[1]Pharm. D V Year, Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, Andhra Pradesh, India.

[2]Associate Professor, Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, Andhra Pradesh, India.

[3]Professor and Principal, Department of Pharmacology, Vijaya Institute of PharmaceuticalSciences for Women, Enikepadu, Vijayawada – 521108, Andhra Pradesh, India.

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***Corresponding Author**
Dr. Ede Srilakshmi
Pharm. D V Year, Department of Pharmacy Practice, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada – 521 108, Andhra Pradesh, India.

ABSTRACT

Developing countries, the most used agents for self-poisoning are agricultural pesticides, including rodenticides. These chemicals differ in their chemical composition, mode of action, toxic doses and lethal effects. Yellow phosphorus, phosphide metals (Aluminium phosphide, zinc phosphide) and anticoagulants like warfarin and super-warfarin are the most commonly used rodenticides in India. Phosphorus is the most prevalent and deadly poison among these rodenticides, especially after 3–4 days of ingestion as liver injury develops. The type and dosage of poison taken, the absence of a known antidote for some rodenticides, and the length of time between exposure and treatment all have an impact on the result.

KEYWORDS: Rodenticide poisoning, Yellow phosphorus, Metal phosphides, Anticoagulants.

INTRODUCTION

In developing agrarian nations, poisoning is mostly preventable, most of the time leading to suicide and rarely resulting in accidental death. Rodenticide poisoning continues to be the

second most common poison ingested after organophosphorus poisoning.[1,2] Rodenticides, which are synthetic chemicals targeted to eliminate small rodents, are commonly referred to as "rat poisons." The typical targets for their use are household animals, such as mice, squirrels, gophers, and so forth.[3]

In almost every household, rodenticides are commonly available to protect stored grains from rodents. Because it is less expensive than other rodenticides on the market and easy to obtain. It is frequently consumed by people who are contemplating suicide or accidentally ingested by children due to its easy availability in every household. They come in blocks, powders, pastes, pellets, cereal baits, and other forms.[1,2] An ideal rodenticide is one that is profoundly poisonous to rodents in little amounts, non-harmful to non-target species and stays away from trap bashfulness and lure refusal.[3]

History

In the past, rodenticides were mostly made from inorganic chemicals like thallium and arsenic trioxide or from plants like strychnine. These days, they are made of synthetic organic compounds. Thallium, for instance, poses the same threat to humans as it does to rodents. However, their use is now restricted to reduce the risk of toxicity, particularly in humans.[1,6] However, if they are used improperly, they are still considered toxic. Children who consume rodenticides orally are the most common patients who present with rodenticide poisoning. Yellow phosphorus, phosphide metals (aluminium phosphide, zinc phosphide), and long-acting anticoagulants like warfarin and superwarfarins are the most commonly used rodenticides in India. Regardless, determining the substance consumed is the most significant aspect of history.[7]

Classification

The harmfulness is sorted by how much toxin expected to cause passing in half of these uncovered known as lethal dose 50 or LD 50. On product labels, the toxicity is indicated by signal words in some areas, including the United States: danger, caution, and warning. Based on toxicity rodenticides are classified as follows:

- **Highly toxic [Danger]:** LD 50 is 0-50mg/kg.

e.g.: strychnine, thallium, elemental phosphorus, metal phosphides, sodium monofluoroacetates, arsenic

- **Moderately toxic [Warning]:** LD 50 is 50-500mg/kg.

e.g.: Alpha-naphthyl thiourea, cholecalciferol

- **Less toxic [Caution]:** LD 50 is 500-5000mg/kg.

e.g.: warfarin, superwarfarins [brodifacoum, bromadiolone, chlorophacinone, difenacoum & diphacinone], bromethalin, red squill.[3,5]

These chemicals differ in their chemical composition, mode of action, toxic doses and lethal effects. As a result, the toxidrome generated by one rodenticide differs significantly from that generated by another.[4] Phosphorus is the most prevalent and deadly poison among these rodenticides, especially after 3–4 days of ingestion as liver injury sets. The type and dosage of poison taken, the absence of a known antidote for some rodenticides, and the length of time between exposure and treatment all have an impact on the result.[4]

In this article the most commonly available and frequently encountered rodenticides poisoning, were reviewing with their mechanism of action, clinical presentation and management as;

Rodenticides commonly used in india

➢ **Anti-Coagulants**

Warfarin was first employed as a rodenticide in 1948 by a biochemist by the name of Karl Link and his colleagues. It was later utilised in humans as an anticoagulant.[8] As rodenticides quickly acquire resistance to warfarin, the second generation of the 4-hydroxycoumarin class of anticoagulants, also known as super warfarin or long-acting anticoagulant rodenticides, has been utilised as a rodenticide due to their prolonged presence in the body and high potency.[9] Even after a single dose, they produced a strong anticoagulant effect for six weeks. As a result, it currently ranks among the worst toxins.

Mechanism of action

Since warfarin is a known anti-metabolite of vitamin k, it prevents the conversion of inactive vitamin k to its active form by inhibiting the epoxide reductase enzyme, which is helpful in vitamin k regeneration. This inhibits the synthesis of vitamin k dependent clotting factors [II, VI, IX, & X]. Repeated dosages, however, are necessary to maintain maximum inhibition of active vitamin K production, which leads to high prothrombin levels, depletion of vitamin K dependent clotting components, and internal bleeding that may be fatal. Bleeding only happens when a factor's level falls by more than one-fourth of its initial value. The

mechanism of action of super warfarin is like that of warfarin but is 100 times more potent than warfarin.[10]

The average half-lives of clotting factors that depend on vitamin K:

- Prothrombin [II] – 41 hours
- Stable factor [VII]- 6.2 hours
- Christmas factor[IX]- 13.9hours
- Stuart factor [X] – 16.5 hours [11]

Laboratory findings

- Prothrombin time
- International normalised ratio [INR]
- Activated plasma thromboplastin time [APTT]
- Complete blood count
- Liver function test
- Measurement of vitamin k dependent clotting factors [10]

Differential diagnosis

- Haemophilia
- Vitamin k deficiency
- Disseminated intravascular coagulation [DIC]
- And other factors deficiencies, other causes of liver failure also ruled out.

Clinical presentation

Patient is asymptomatic right away after consuming the toxin but begins to exhibit symptoms 1-2 days later.12 After all the clotting factors are below 30% of normal, the symptoms of coagulopathy start to manifest 24 to 48 hours after intake.[13]

Symptomology of Long-Acting Anticoagulant Rodenticides [LAARs] poisoning in humans: The most widely recognized bleedings were mucosal draining like haematuria, gingival dying, epistaxis, and gastrointestinal dying.

After that, there is a mix of spontaneous bleeding, soft tissue hematoma, and intramuscular bleeding. Abdominal pain, flank pain, melena, fainting, loss of consciousness, intracranial

bleeding, headache, hematemesis, thrombosis, spontaneous abortion, and rectal bleeding are additional symptoms.

The haemorrhagic occasion generally normally connected with death was intracranial drain. Notably, intracranial haemorrhage was linked to 10 of the 14 deaths from case report data, or 71%; And only one of the ten cases of intracranial haemorrhage that were reported survived, or 10%. Brodifacoum was the most prevalent contaminant in this in-depth examination of LAAR exposures.[14,15] Brodifacoum has a half-life of 16 to 34 days, whereas warfarin has a half-life of 17 to 34 hours.[13] Brodifacoum's effects have been reported to last from 16 to 270 days after consumption. due to their slow elimination from the body, increased affinity for hepatic enzymes, and high lipid solubility.[16]

Management

It mostly depends on the time of presentation, the amount consumed, and bleeding symptoms. Gastric lavage, followed by an infusion of activated charcoal, vitamin k therapy, and a fresh frozen plasma transfusion in the event of severe active bleeding, are all options for poisoned patients' treatment. Crystalloids are used to treat acute bleeding episodes to replace lost blood.

Acute intake of less than one bait of super warfarin does not produce significant toxicity and they are simply managed. Without gastric lavage and no lab investigations is needed, unless bleeding occurs. If they ingest more than one bait, and present within 4 hours of ingestion as per detoxification protocol as follows.

- Gastric lavage followed by infusion of 1g/kg activated charcoal and 250 ml of magnesium citrate via nasogastric tube [magnesium citrate was used to prevent constipation after administration of activated charcoal].
- Administration of vitamin k1 via an intramuscular or oral route
- Intravenous vitamin k1 is avoided if possible due to risk of anaphylaxis.
- Finally, a transfusion of fresh frozen plasma in case of active bleeding.[16,17]

Vitamin k1 can be administered orally, subcutaneously, intramuscularly, or intravenously. But the most preferred rout in most cases is oral route.

Intravenous route is reserved for patients with life threatening bleeding in view of the rare case reports of potentially lethal anaphylactoid reactions after intravenous vitamin k1

administration.[18] Studies have shown benefit of therapeutic plasma exchange in children following anaphylactic reaction to vitamin k administered for brodifacoum poisoning.[19]

In contrast to typical dose of vitamin k used for warfarin reversal

- For non-bleeding patients: 1 – 5 mg /po
- For bleeding patients: 5 – 10 mg po/iv[20]

Therapeutic vitamin k doses for LAAR poisoning are 10-20 times higher. In addition, duration of treatment involves extended courses median of 140 days, range 28 – 790 days of high doses of vitamin k, with mean maintenance [po] dose of 100 mg daily [median 60mg, range 15-600mg]. Currently, the end point of vitamin k_1 therapy for super warfarin poisoning is determined by discontinuing the administration of vitamin k_1 and observe the patient for an elevation of INR after 48 hours.[13]

The timing of reducing vitamin k_1 dose, with subsequent discontinuing of therapy relies solely on serial clotting profile monitoring and doctors clinical experience.[21]

➢ **Phosphorus:**

The name "phosphorus" is derived from Greek, meaning "light-bearing".

Physical appearance: It generally exists in three different forms.

- **Yellow [or white] phosphorus:** This is yellowish, waxy, crystalline solid with garlicky odour. On exposure to air, it oxidises into whitish fumes of phosphorus pentoxide. It is luminescent and glows in the dark [phosphorescence].
- **Red phosphorus:** This is a reddish or brownish, amorphous, odour less substance. It is insoluble and relatively harmless since it is not absorbed from the GI tract.
- **Black phosphorus:** it is inert, nontoxic allotropic form of elemental phosphorus.[22]

Among these, yellow phosphorus is highly reactive and dangerous which is commonly used rodenticide which is generally available as paste.[7]

Yellow phosphorus poisoning

Yellow phosphorus, a protoplasmic poison is a potent hepatotoxin when ingested it directly causes tissue damage with local phosphoric acid and phosphorus pentoxide.

Fatal dose: 1mg/kg body weight

Toxicokinetic: It is rapidly absorbed from the gastrointestinal tract and the absorption is greatly enhanced by fatty vehicle. After absorption it is primarily distributed to liver, kidney,

intestinal mucosa, epidermis, follicles, and pancreas. Moderately distributed to lungs, myocardium, spleen and renal medulla. Low distribution to brain fat and muscle.[3]

Mechanism of action: The ingested toxin is absorbed by the gastrointestinal tract, causes corrosive damage by an exothermic reaction producing phosphoric acid, that causes direct tissue damage due to the production of free radicals against organic molecules. This in turn, will bring about changes in ribosomal function and protein synthesis, failure of regulation of blood glucose, and fatty degeneration of multiple organs such as liver, kidney, and brain.

In large doses it can cause shock and cardiovascular collapse since it is toxic to heart. Locally it produces irritation of skin and mucosa.[23]

Clinical manifestations: The early signs and symptoms may appear almost at once. The usual interval is 2 to 6 hours but, in rare cases, there may be a delay of 12 to 48 hours.[25] Mortality due to ingestion, range from 20-50%.[26] Initially nausea, vomiting, diarrhoea are the common symptoms that appear. A garlic odour on the breath may also be noted. Jaundice, hypoglycaemia and other features of hepatotoxicity and renal failure may be seen in severe cases.[23]

Poor prognosis indicators

i) Ingestion of more than 1mg/kg.
ii) Severe electrolyte disturbance.
iii) Mental status changes and prolongation of QT interval changes
iv) Greater than 10fold raise in alanine amino transferase
v) Severe coagulopathy
vi) Peak liver enzymes reached within three days of ingestion.[27]

Good prognosis indicators: Survival after 3 days and minimal elevation of LFT

Old literature describes course of poisoning in 3 stages:

Stage 1: Lasts hours to days after ingestion. Manifested as irritation of digestive tracts, may cause arrythmias and some neurological manifestations.

Stage 2: Digestive symptoms resolve, lasting for few days.

Stage 3: PATIENTS develop hepatic, renal & cardiac toxicities, mostly causing death. If recovery occurs it takes few weeks. However most death occurs as a result of fulminant

hepatic failure within first week. Some delayed death occurs between 5-8 days due to cardiotoxic. Few deaths only occur, if patient survive beyond this stage.[28]

Complications

- Bleeding manifestations
- Encephalopathy
- Hypotension
- Myocarditis
- Cardiogenic shock[29]

Management

Intial care

Basic life support such as protection of airway and circulatory status must be maintained. Complete blood count, liver function test, prothrombin time, international standardised ratio (INR), blood urea, serum creatinine, serum electrolytes especially of calcium phosphates, potassium levels should be done immediately after admission, should access intravenous line and frequent recording of vitals and cardiac monitoring should be done. Urine output should be recorded, if they complaint of irritation of eye, eye wash should be given with clean water immediately.

Gastric lavage with potassium permanganate (1:5000), which oxidises phosphorus into less toxic phosphoric acid and phosphates. Do not administer milk or any oily/fatty foods, since it will enhance the absorption of phosphorus. Vitamin k by iv drip [65 mg] slowly, to combat hypoprothrombinaemia.

Intravenous fluids used are

1. Isotonic saline and sodium lactate to treat shock, dehydration, and acidosis.
2. Glucose to combat hypoglycaemia.
3. Calcium gluconate for hypocalcaemia.

- Whole blood or fresh frozen plasma to correct coagulation defects.
- Steroids and inotropic support for shock.
- Anticonvulsants for seizures.
- Some investigations suggest the use of N- acetylcysteine (NAC) in patients with stage 1 phosphorus toxicity.

A dose regimen of 150 mg/kg in 200 cc D5W for 15 minutes, followed by 50 mg/kg in 500 cc D5W for 4 hours, and then 100 mg/kg in 1000 cc D5W for 16 hours is recommended. It is presumed that NAC may be effective in preventing progression of liver damage when given in stage 1 of the illness.[22]

- Haemodialysis rapidly improves the electrolyte disturbance such as hyperphosphatemia, hyperkalaemia, and hypocalcaemia. However, it significantly reduces mortality by 50% thus exchange transfusion was beneficial.[24,30]

➢ **Phosphides**

Phosphides such as zinc and aluminium phosphides are the most common agents of rodenticide poisoning in India. They are popular rodenticides because they are very effective, usually inexpensive, and leave no toxic residue on grain. Aluminium phosphide is available as dark yellow or dark grey crystals, while zinc phosphide is available as a grey crystalline powder.

Mechanism of action

Phosphides react with hydrochloric acid and water to release phosphine gas. The reaction is far stronger with acid than water. Pure phosphine is usually a colourless and odourless gas. Phosphine inhibits cytochrome - C oxidase, an essential enzyme in mitochondrial oxidative phosphorylation resulting in widespread organ damage due to cellular hypoxia. The organs with the greatest oxygen requirements appear to be especially sensitive to damage include brain, kidney, heart, and liver.[3,22]

Toxicokinetic

Once phosphine is released in stomach, enters the blood stream, reaches the liver, kidney, and brain. Most of phosphine is excreted unchanged by the lungs while some of it is changed to phosphite and hypophosphite ions that are excreted in urine.

Investigation

- Chest x-ray for identifying pulmonary toxicity.
- Abdominal x-ray for opacities in gut.
- Liver function tests, urea, creatinine, electrolytes should be measured.

Clinical manifestations

- It causes severe mucosal irritation, manifested as nausea, vomiting and abdominal pain within 15 minutes of ingestion of aluminium phosphide and 30minutes after ingestion zinc phosphide. There may be a garlic odour in the breath of these patients.
- These features are rapidly followed by circulatory collapse, hypotension, myocarditis, pericarditis, acute pulmonary oedema, and congestive heart failure.
- Echocardiography in these patients often reveal global hypokinesia of the left ventricle and depressed ejection fraction. ST–T changes and arrythmias are seen on the electrocardiogram.
- Acute renal failure, jaundice, transaminitis progressing to acute liver failure, and disseminated intravascular coagulation are also common.
- Respiratory distress is invariably present with cyanosis, and cold, clammy skin.
- However neurological manifestations are rare, but seizures and coma are recorded in expired patients. Hypokalaemia and hypoglycaemia can also occur frequently post poisoning.
- Following inhalation, chest tightness, headache, giddiness, lethargy, convulsions, and delirium may be seen.
- Circulatory failure is an important cause of death. Majority of death occurs after 24 hours of ingestion, may be delayed up to 2 weeks, which was mainly reported due to myocardial damaged.

Management

Treatment is mainly supportive and symptomatic. Emesis is not to be induced. Though there is often intense thirst, do not administer water [Since whatever phosphide still remain in stomach will react with it, releasing phosphine].

Stomach wash is contra indicated while activated charcoal can be administered, it should be mixed with sorbitol [not with water), using 240 ml for every 30 grams. However, some authorities recommend the performance of gastric lavage as well as administration of activated charcoal using aqueous solutions.

Sodium bicarbonate, water, and even milk are all attempted as lavage agents. After lavage, phosphine gas is emitted in lavage solution and stools, hence they must be cleaned and

disposed properly to prevent inhalation exposure to health care workers by providing proper face masks.

Presently the suggested measures include following

- Management of circulatory shock with iv fluids (4-6 litres cover 6 hours) while monitoring the central venous pressure and / or pulmonary wedge pressure.

Dopamine can be given iv at a dose 4-6mcg/kg/min (max 10 mcg/kg/min).

- Management pf respiratory distress with 100% humidified oxygen, intubation and assisted ventilation.
- Management of metabolic acidosis with $NaHCO_3$ 50mEq/15 min [until the arterial bicarbonate rises above 15 mmol/L].
- Control of convulsions with anticonvulsants.

Diazepam – 5 to 10 mg/kg iv over 2 to 3 minutes [adults]

0.25 to 0.4 mg/kg iv over 2 to 3 minutes [child] or

Phenytoin – 10 to 15 mg/kg iv at 30 to 50 mg/min [adult or child] or

Phenobarbitone – 12 to 15 mg/kg iv in 60 ml of normal saline at 25 to 50 mg/min [adult /child]

- **Magnesium sulphate therapy**

Which is beneficial in management of cardiac arrhythmias. Conventional antiarrhythmic drugs such as digoxin and lidocaine are ineffective.

$MgSO_4$ is given iv as a 3 grams bolus, followed by 6g infusion over 24 hours for 5 to 7 days. Alternatively, 1 gram can be given iv to begin with, followed each hour by the same dose for 3 consecutive hours, and then 1g every 6hours for 5 days.

- Ranitidine 50 mg iv 8^{th} hourly to counter the epigastric pain[22] or Injection Proton pump inhibitors (PPI's) like Pantoprazole, Rabeprazole, Esomeprazole, etc., are replaced now-a-days the ranitidine, because of its severe hepatotoxicity effect. When a patient complaints of epigastrium pain and vomiting a combination of antiulcer drugs like PPI's add with antiemetics domperidone, metoclopramide or ondansetron etc.

CONCLUSION

Rodenticide poisoning continues to be the 2^{nd} common poison ingested after organophosphorus poisoning. Rodenticides, are synthetic chemicals targeted to eliminate small rodents, are commonly referred to as "rat poisons", made with synthetic inorganic

chemicals like thallium and arsenic trioxide and/or plant like strychnine. Children who consume rodenticides orally are the most common patients, who present with rodenticide poisoning. Yellow phosphorus, phosphide metals (aluminium phosphide, zinc phosphide) and anticoagulants like warfarin and super-warfarin's are the most used rodenticides in India.

The most common symptoms routinely noticed in clinical practice were nausea, vomiting, abdominal pain and giddiness, under laboratory investigations patient biochemical parameters show elevation in liver functions, coagulation profile, electrolytes abnormalities. On examination poisoned cases were present with asymptomatic at initial days based on the type of substance within couple of days cardiopulmonary functional abnormality will develop like change in pulse rate, respiratory depth, cardiogenic shock may be possible in severe cases which leads to death eventually. Rodenticide poisoning doesn't have any antidote or counteracting drugs, so based on the symptoms in individuals' treatment may vary widely. In general, alkalising agents, anticonvulsants, antiulcer agents, antiemetics, in suspected or arrhythmic management magnesium sulphate was useful, but only few cases were showed positive response. In this study we concluded that rodenticide poisoning management requires indeed research to develop significant therapeutic strategies to reduce mortality globally.

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