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Acute Zinc Phosphide Poisoning: Diagnosis and Management

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Abstract:

Zinc phosphide is a dark grey, crystalline compound. It is used as a rodenticide against such small mammals as mice, rats and squirrels. Upon ingestion, it gets converted to phosphine gas in the stomach, which is subsequently absorbed into the bloodstream through the stomach and the intestines and gets captured by the liver and the lungs. Phosphine gas inhibits cytochrome *c* oxidase which results in formation of highly reactive oxygen compounds leading to tissue injury, particularly those with a high oxygen demand (brain, lungs, liver, and kidney). Clinical symptoms are circulatory collapse, hypotension, shock symptoms, myocarditis, pericarditis, acute pulmonary edema, and congestive heart failure. Zinc phosphide poisoning is a significant cause of morbidity and mortality among socioeconomically low and especially in developing countries. The diagnosis of zinc phosphide poisoning depends on history, clinical examination and laboratory findings including ABG, liver and kidney functions,CBC and cardiac enzymes. Management of Zn_3P_2 is supportive and symptomatic as there is no specific antidote.

Keywords: Zinc Phosphide, Poisoning, Diagnosis, Management.

Introduction:

Zinc phosphide is a rodenticide that has been used since 1940 in agricultural, urban and industrial environments. Since 1985, there are specific restrictions in the regulations, guidelines and standards on its use as a pesticide. It is even prohibited in several countries **(1).**

Zinc phosphide is cheap, easily available, and a highly potent rodenticide. Mortalities due to accidental, suicidal, and homicidal exposure to zinc phosphide have been reported in Eastern countries **(2).**

The increasing rate of mortality is due to uncontrolled marketing, the cheapness of zinc phosphide and lacking knowledge on social media about it **(3).**

Zinc phosphide is an inorganic compound that is used in pesticide products as a rodenticide. The International Union of Pure and Applied Chemistry (IUPAC) chemical name is trizinc diphosphide and the Chemical Abstracts Service (CAS) registry number is 1314-84-7**(4).**

Zinc phosphide is an inorganic compound that combines phosphorus with zinc. It is one of the commonest rodenticides, that is black smooth powder or gray crystalline compound **(5).**

It is synthesized by direct combination of zinc and phosphorus. It is a slow acting rodenticide as compared to aluminum phosphide **(4).**

$6\ Zn + P_4 \rightarrow 2\ Zn_3P_2$

Zinc phosphide reacts with the acid of the stomach or its water content leading to the release of phosphine gas (PH_3) **(6).**

$Zn_3P_2 + 6\ HCL \rightarrow 3\ ZnCL_2 + 2\ PH_3$

$Zn_3P_2 + 6\ H_2O \rightarrow 2\ PH_3 + 3\ Zn(OH)_2$

- ✓ **Route of exposure**

Oral

The zinc phosphide oral toxicity (LD_{50}, lethal dose that kills 50% animals) is 60–70 mg/kg for sheep. For several rodent species, the LD_{50} is in the range of 20–40 mg Zn_3P_2 /kg body weight **(7).**

The U.S. Environmental Protection Agency (USEPA) considered zinc phosphide to be highly toxic via oral exposure **(8).**

Dermal

The dermal LD_{50} in rabbits was determined to be 2000-5000 mg/kg, so zinc phosphide is considered to be low in toxicity based on these results **(4).**

Eye irritation tests performed with zinc phosphide on rabbits resulted in discharge, swelling of the eyelid and eye surface tissue, and some redness in the conjunctiva. The U.S. EPA considered zinc phosphide to be very low in toxicity for eye irritation **(8).**

Researchers applied zinc phosphide to the skin of rabbits to determine if it is a skin irritant. Zinc phosphide was found to be non-irritating **(9).**

Inhalation

The U.S. EPA considered inhalation of zinc phosphide highly toxic **(8).**

- ✓ **Dose**

The ingestion of 4-5 g of (Zn_3P_2) (55-70 mg/kg) is potentially lethal with a high mortality rate between 37-100% **(10).**

- ✓ **Causes of death**

Zinc phosphide toxicity is associated with a high mortality rate, which can range from 37–100% **(2).**

Refractory hypotension, heart failure, cardiotoxic shock and severe metabolic acidosis lead to the death of the patient. Most deaths occur within the first 12 to 24 h, usually due to cardiovascular collapse **(1).**

- ✓ **Diagnosis of zinc phosphide poisoning:**

The diagnosis of zinc phosphide poisoning depends on history, clinical examination and laboratory findings **(11).**

The patients can be assessed clinically by various scoring systems. For example, the poison severity score (PSS), which is an international standardized score designed specifically for clinical evaluation of intoxicated cases **(12).**

It is a valuable score in the evaluation of metal phosphide poisoning **(13).**

All patients should be subjected to thorough history taking (personal and medical history and data related to poisoning) and clinical assessment using the PSS **(12),** as follows:

- None: no symptoms or signs related to poisoning.
- Minor: mild, transient, and spontaneously resolving symptoms.
- Moderate: pronounced or prolonged symptoms.
- Severe: severe or life-threatening symptoms.
- Fatal: death.

1- Laboratory investigations

❖ **Arterial blood gas (ABG)**

The analysis and monitoring of arterial blood gas (ABG) is an important process in the follow-up of acid-base balance and oxygenation in high-risk and critically ill patients **(14).**

Metabolic acidosis, or mixed metabolic acidosis and respiratory alkalosis are frequent in zinc phosphide poisoning **(15).**

Hosseinian et al. (16) considered severe metabolic acidosis as a predictor of mortality in zinc phosphide poisoning.

❖ **Blood glucose level**

Both hyperglycemia and hypoglycemia have been reported as clinical features of phosphide poisoning. Hypoglycemia may be persistent and severe. Hypoglycemia was the clinical feature of zinc phosphide poisoning, particularly in severe cases and in patients who died **(5).**

❖ **Liver function tests**

Hepatic functions including the determination of liver enzymes, such as aspartate aminotransferase (AST or SGOT), alanine transaminase (ALT or SGPT), and alkaline phosphatase (ALP), should be monitored daily.

Furthermore, studies have demonstrated that the levels of ALT and AST as two important hepatic enzymes might be elevated during Zn_3P_2 poisoning **(17).**

Besides, phosphides could induce hepatotoxicity that could be manifested by hepatomegaly and elevated hepatic transaminases. The residual hepatotoxicity and even fatal liver failure are reported following acute Zn_3P_2 toxicity **(5).**

According to **Mashali et al. (18)** elevation of liver enzymes could be predicted if:

- The amount ingested > 3.5 sachets
- Time till hospitalization > 5 h
- Poison Severity Score (PSS) > 1
- AST >50 U/L
- ALT >82 U/L

Kidney function tests

Elevated creatinine and low glomerular filtration rate (GFR) levels indicated moderate kidney impairment **(10).**

❖ **Serum electrolytes**

Electrolytes should be monitored daily **(17).**

The laboratory tests showed low calcium and potassium levels in zinc phosphide poisoning **(10).**

❖ **Complete blood count (CBC)**

Low white blood cell count (WBC) has been reported in zinc phosphide poisoning **(10)**, also intravascular hemolysis, thrombocytopenia and disseminated intravascular coagulopathy **(19)**.

❖ **Troponin I level**

Cardiac troponins are the most appropriate biomarkers for diagnosis of cardiac injury as acute toxic myocarditis; as they are normally found in the blood in small undetectable concentrations but in the case of heart muscle injury, troponins are released in high concentrations and the higher its concentration, the more damage there is, for this reason, cardiac troponins are considered specific and highly sensitive markers of myocardial injury and cardiac toxicity **(20).**

Heart is a significant target organ of metal phosphides toxicity as they affect the cardiac and vascular tissues in the form of direct myocardial tissue damage, hypoperfusion, myocarditis, pericarditis, arrhythmias and elevated cardiac biomarkers **(21).**

Significant elevation of troponin is an indicative of injury to the myocardium. A small elevation of troponin I (but a normal CK-MB level) may indicate a microscopic zone of myocardial necrosis (microinfarction), truly elevated troponin I levels have also been documented in tachyarrhythmia and myocarditis **(22).**

Khater and Sarhan, (23) showed that direct myocardial injury in zinc phosphide poisoning was evidenced by the finding of increased serum cardiac troponin I.

❖ **Measurement of plasma total antioxidant capacity (TAC):**

Total antioxidant capacity refers to the overall antioxidant status in the biological samples. It is one of the most important bioanalytical measures of oxidative stress in the body **(24).**

Initial TAC and troponin I levels in patients with acute metal phosphides poisoning could be useful in predicting development of oxidative damage and cardiotoxicity that may reduce mortalities and improve outcome

among these poisoned patients**.** Metal phosphides induced oxidative stress which was detected by TAC decrease **(20).**

- **Phosphine (PH3) detecting tests (Silver nitrate screening test):**

It is a chemical qualitative color test that was done to detect phosphine (PH3) in stomach contents **(13).**

Soltaninejad et al. (25) indicated that PH3 detection with silver nitrate test is the commonest and most valuable in clinical and forensic tests that can be done on bio samples such as stomach content and expiratory air and is sensitive enough to detect very low concentrations of PH3 as 0.05 mg L-1(0.05 ppm).

Positive silver nitrate screening test was more prominent in non-survivors than survivors and this may be due to the fact that non-survivors usually ingest higher amounts of the poison hence more concentration of PH3 in the stomach content **(13).**

- **Oxidative stress markers (Superoxide dismutase, Catalase activity, Malondialdehyde)**

Zinc phosphide induces oxidative stress. It inhibits the activity of catalase (CAT) and superoxide dismutase (SOD). It elevates malondialdehyde (MDA) levels in cardiac tissues **(26).**

- ✓ **Superoxide dismutase (SOD)**

Superoxide dismutase is a group of important metalloenzymes that act as a defense mechanism against oxidative stress, it catalyzes the superoxide (O_2^-) radical into ordinary molecular oxygen (O_2) and hydrogen peroxide. Superoxide is a product of oxygen metabolism and, if not regulated, causes many types of cell damage **(27)**.

- ✓ **Catalase activity(CAT)**

Catalase is one of the necessary antioxidant enzymes that minimize oxidative stress and restore tissue viability by acting on ROS such as cellular hydrogen peroxide (H2O2) and changing it into water (H2O) and oxygen (O2) **(28)**.

- ✓ **Malondialdehyde (MDA)**

Malondialdehyde is one of the end products of the lipid peroxidation process due to the reaction of oxygen with unsaturated lipids in lower PH which is expected in the case of oxidative stress. The qualification of the process of lipid peroxidation is mainly done by measuring aldehydes, such as MDA **(29).**

- **ECG evaluation and monitoring**

Patients included in a study by **Khater and Sarhan, (23)** had dysrhythmias, in the form of wide complex ventricular tachycardia, atrial fibrillation, diffuse ST segment elevation or abnormal repolarization in the form of (inverted T wave). The presence of electrocardiographic abnormalities predicted mortality.

2 –Imaging or others

Abdominal x-ray is required for the presence of radiopaque substances **(30).**

Zinc is a radio-opaque metal, which may enable the visualization of this toxic material. Plain abdominal radiography: a powerful tool to prognosticate outcome in patients with zinc phosphide poisoning**.** Positive abdominal imaging was an indication for aggressive management so, immediate abdominal radiography can help stratify patients into high- or low-risk groups and determine treatment strategies **(31).**

✓ **Management of zinc phosphide poisoning (Figure 1):**

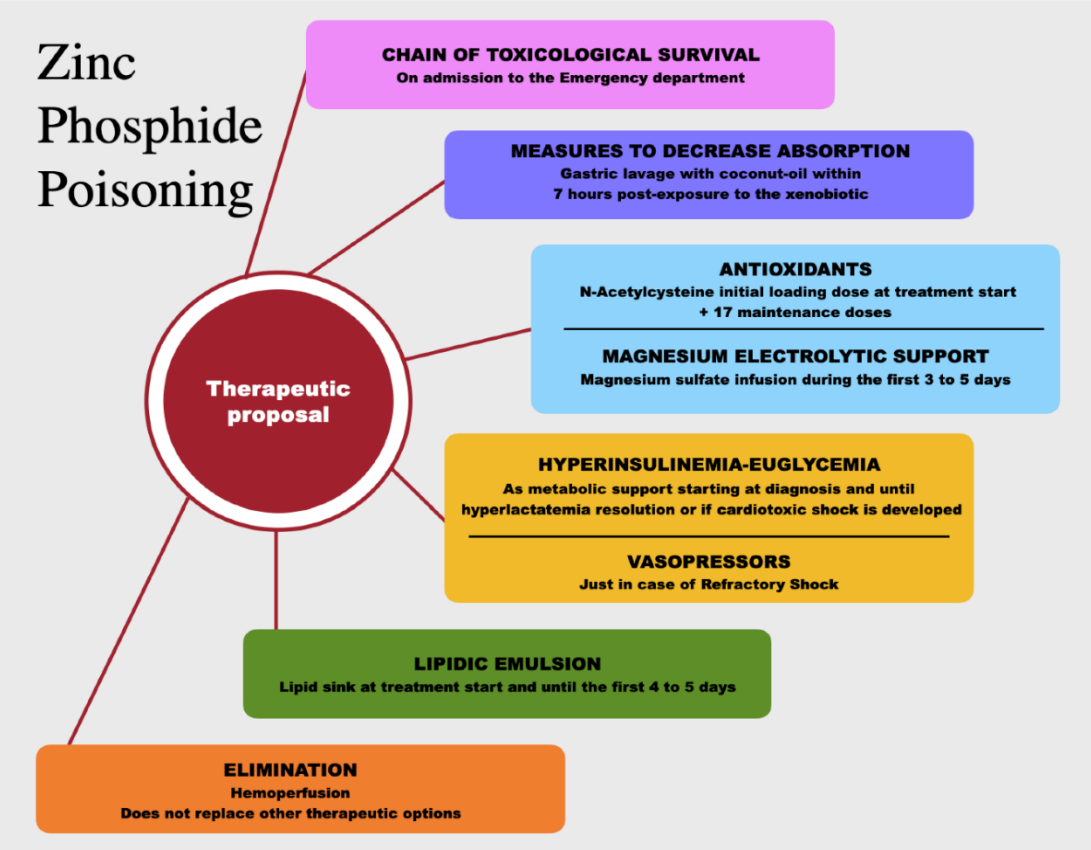

Fig. (1): management of zinc phosphide poisoning **(1).**

Zinc phosphide poisoning may be asymptomatic initially or with mild clinical symptoms that may gradually worsen. Therefore, hospitalization and obtaining a history and a careful physical examination should be considered **(30).**

Treatment of Zn_3P_2 is supportive and symptomatic as there is no specific antidote **(10).**

- **Stabilization of patients**

Making an early diagnosis is very important and starting treatment as early as possible. The first thing to assess is the toxicological survival chain, which includes the medical approach to the airway, breathing and circulation (ABC) **(32).**

Keeping patent airway and adequate ventilation in cases of loss of airway protection reflexes; the anticipated risk of bronchial aspiration or as management of intoxication related to crises seizures, severe agitation or delirium; or ventilatory or oxygenation failure **(33).**

They usually require advanced airway management and invasive ventilation with positive pressure due to acute respiratory distress syndrome, refractory shock, hypoperfusion-induced coma, hemodynamic instability or acute pulmonary edema, which may occur secondary to pulmonary vasodilatation and alveolar fluid extravasation. Therefore, we do not rule out early airway protection in the setting of an intoxicated patient with a predictably severe course **(1).**

Treating shock if present to maintain adequate circulation **(11).**

Installation of a peripheral venous line or central venous access (if required), fluid resuscitation with crystalloid solutions and vasopressors may be required in appropriate circumstances **(34).**

The administration of sodium bicarbonate as an adjuvant treatment and its benefit in metabolic acidosis is controversial considering that the main cause of metabolic acidosis secondary to this xenobiotic is a consequence of tissue hypoperfusion, and thus, it should be limited mainly to pH < 7.0 **(1).**

- **Decontamination Measures and Absorption Reduction**

Gastric lavage with coconut oil in combination with sodium bicarbonate is suggested to decrease the conversion of phosphide to phosphine since the acid increases this conversion. The mechanism of action of coconut oil is not clear, but it can form a layer around the gastric mucosa that inhibits the release of phosphine gas due to its physicochemical properties (high in saturated free fatty acids) and it was also described to accelerate gastrointestinal motility and help to remove the toxic compound from the digestive tract **(1).**

The use of activated charcoal is challenging; however, it is recommended that a dose of activated charcoal should be given to poisoned patients as soon as they are received by the emergency department (ED) **(17).**

GIT decontamination with polyethylene glycol (PEG) should be considered in the presence of radiopaque substances **(30).**

- **Antioxidants**

Oxidative stress and the production of oxygen free radicals (ROS) mediate the mechanism of phosphine toxicity; therefore, using antioxidants such as N-acetylcysteine (NAC) (with a loading dose of 140 mg/kg and a maintenance dose of 70 mg/kg for 17 doses), glutathione, melatonin, vitamin C, vitamin E and carotenes may be beneficial and limit toxicity **(1).**

N-acetylcysteine has been shown to prevent organ toxicity including hepatotoxicity by serving as a glutathione (GSH) precursor or GSH restorer and has also proved beneficial in Zn_3P_2 poisoning**.** The use of alpha-lipoic acid (ALA) in Zn_3P_2 poisoning could be beneficial based on its antioxidative and chelating properties **(10).**

Thus, different studies pointed to NAC as a promising antidote in the management of acute Zn_3P_2 poisoning **(18).**

Tehrani et al. (35) also found that plasma total antioxidant capacity value significantly increased in NAC treatment group.

Vitamin C (ascorbic acid) is a water-soluble vitamin that is necessary for normal growth and development. When ascorbic acid interacts with a reactive and possibly harmful free radical, it donates two electrons, the reactive free radical is reduced and an ascorbyl free radical is formed in its place. As compared to other free radicals, ascorbyl radical is relatively stable with a half-life of 5–10 seconds and is fairly unreactive. This property explains why ascorbate may be a preferred antioxidant in zinc phosphide poisoned patients **(26).**

Alpha-lipoic acid (ALA) is an antioxidant and a natural coenzyme present in every cell and it has been used as medicine in the treatment of diabetic and alcohol-induced liver cirrhosis The use of ALA in Zn_3P_2 intoxication could be beneficial based on its antioxidative and chelating properties **(10).**

- **Magnesium sulfate**

Myocytes are highly susceptible to oxidative stress, which leads to a reduced ejection fraction of the left ventricle and subsequently heart failure can occur. Therefore, the correction of electrolyte alterations and the acid–base balance that limits the arrhythmogenic potential must be a priority and immediate. Improvement was reported due to its membrane stabilizer and antioxidant effects **(1).**

- **Hyperinsulinemia–Euglycemia Therapy (HIET)**

Hydrocortisone and hyperinsulinemia–euglycemia therapies were administered to severely poisoned patients with zinc phosphide who developed shock **(5).**

Insulin has been known to have positive cardiac inotropic properties since the 1930s, although the mechanism is not fully understood. The use of high doses of insulin together with glycemic support, known as hyperinsulinemia–euglycemia therapy (HIET) **(36).**

In 2008, it was introduced as a possible treatment for aluminum phosphide poisoning by Hassanian-Moghaddam **(32).**

For a toxin such as phosphine, which induces myocardial depression in up to 60% to 100% of cases, HIET can restore the hemodynamic state to normal, increasing cardiac contractility and improving tissue perfusion **(1).**

Hyperinsulinemia–Euglycemia Therapy provides metabolic support to the alterations associated with cardiotoxic shock. It increases both glucose uptake and pyruvate dehydrogenase activity, which improves lactate oxidation, limiting metabolic acidosis **(32).**

The vasodilator property of insulin can occur in systemic, coronary and pulmonary vasculature, and thus, it is not considered a vasopressor. The mechanism is probably due to the activation of the enzyme inositol triphosphate kinase (PI3K), which increases the activity of endothelial nitric oxide synthase. Coronary vasodilation makes it possible to improve tissue perfusion, thus improving cardiac contractility **(37).**

When regular insulin is administered intravenously, an immediate peak plasma concentration is obtained. The onset and peak of the cardiovascular effects of insulin occur between 15 to 40 min after administration and the duration of the effect is 3 to 6h **(38).**

The reported adverse effects of high doses of insulin are hypoglycemia, hypokalemia, hypomagnesemia and hypophosphatemia. However, if they occur, it is not an indication to suspend treatment since it restores them to their normal values and adversity is resolved; therefore, they should be closely monitored by measuring serum phosphate, magnesium and glucose every 6 h **(1).**

The initial dose of insulin is 1 IU/kg in bolus and the glucose supply is calculated at 0.5 g/kg; if glucose is less than 200 mg/dL, an initial bolus of glucose solution (1 mL/kg of solution glucose 50%) should be previously administered. When starting this treatment, it is necessary to monitor serum glucose every 15–30 min; after the glycemia goals are maintained, monitoring will be less frequent, spacing it every hour and then every 4 h **(39).**

- **Intravenous Lipid Emulsion (ILE)**

Intravenous lipid emulsion (ILE) was introduced in 1960 as an energy substrate because it contains essential fatty acids, and it was administered parenterally as a nutritional supplement in seriously ill patients **(40).**

It's mechanism of action in phosphine intoxication is not defined, however, several mechanisms are described:

(1) The original theory of a "lipid sink", which is based on the high lipid solubility of the toxicant, where it sequesters lipophilic compounds in an expanded intravascular lipid phase, allowing the lowest serum concentration to generate a concentration gradient, removing the tissue agent and reducing its concentration, effect and toxicity at the site of action and in critical organs, such as heart and brain **(34).**

(2) A metabolic effect by increasing the energetic substrate to the myocyte and a direct cardiotonic effect on cardiotoxicity, improving cardiac function **(41).**

(3) The cardioprotective action of long-chain fatty acids in ILE was found to involve Ca^{2+} homeostasis and rescue signaling pathways that regulate the opening of the mitochondrial permeability transition pore (mPTP), which restores mitochondrial Ca^{2+} levels **(1).**

Possible adverse effects may occur such as hematologic effects (intravascular hemolysis, disseminated intravascular coagulation), renal effects (acute kidney injury), pulmonary effects (hypoxia, acute lung injury, respiratory distress syndrome), acid–base imbalance effects (metabolic acidosis), vascular effects (deep vein thrombosis, phlebitis), hypersensitivity and allergic adverse effects, fat overload syndrome (hypertriglyceridemia, lipemia, hyperamylasemia, pancreatitis, cholestasis) and immunological effects (susceptibility to infections) **(42).**

- **Supportive and symptomatic treatment**

Intravenous fluids, vasopressors, sodium bicarbonate ($NaHCO_3$) infusion, antiemetics, antispasmodics, H_2 blockers, and proton pump inhibitors **(18).**

The toxic effects of phosphine on myocytes and the adrenal gland, in addition to fluid loss can induce circulatory collapse and refractory shock. Therefore, minimally invasive continuous hemodynamic monitoring and echocardiography can help to guide treatment **(34).**

Norepinephrine and epinephrine are the initially recommended options. Dopamine and dobutamine are vasoactive agents with greater affinity for beta receptors and are, therefore, associated with a greater arrhythmogenic potential **(43).**

Cardioversion, the use of a temporary pacemaker or the installation of a balloon pump, and veno-arterial extracorporeal membrane oxygenation (VA ECMO) therapy for mechanical circulatory support should be considered as therapeutic options in patients with cardiotoxic shock refractory to vasopressors and in medical units where the resource is available **(44).**

Hemodialysis should be considered in the case of fluid overload and renal failure **(1).**

Conclusion

Zinc phosphide is highly toxic rodenticide with a high mortality rate between 37-100%.

The clinical scores (APACHE II and REMS) are effective tools for prediction of severity and the need for ICU admission, and APACHE II was more effective than REMS, though REMS proved to be more applicable owing to its simplicity and less time consuming.

Troponin I, TAC and CPK-MB respectively are good predictors for severity and need for ICU admission in acute (Zn_3P_2) poisoning.

Recommendations

More policies are needed to restrict the availability and sale of zinc phosphide to limit the magnitude of the problem, and further researches to find specific antidote is highly recommended.

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