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REVIEW ARTICLE

Updates on toxicology of Aluminum Phosphide and different management protocols

Mohamed Abd-Elfatah Abd-Allah[1], Ahmed A. Abdalla[1*], Nedaa Ali Mohamed[1], Mohamed Musad Rady[1], Ahmed A Farrag[1], Gamal Abd el Nasser[1], Kareem Salama[1], Yara M. Elfakharany[2]

[1] Fourth year medical student, faculty of medicine, zagazig university, Zagazig, Sharkia, Egypt.
[2] Assistant professor of clinical toxicology faculty of medicine zagazig university, Zagazig, Sharkia, Egypt.

[*]Corresponding author:
Ahmed A. Abdalla
E-mail:
dr.chibiyaro@gmail.com

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ABSTRACT

Background: Aluminum phosphide (ALP) is a poisonous chemical used to fumigate stored grains. Despite its severe toxicity, there is no antidote and only supportive measures are used. Aluminum phosphide causes mitochondrial damage and oxidative stress. We want to clarify incidence of ALP-toxicity in Egypt and globally, its consequences on various organs, and therapy options. The medical community must be informed of the increased risk of ALP-toxicity and the additional consequences seen in new patients. We examined PubMed, Cochrane, and Scopus databases to search for all ALP-toxicity consequences and decide the bes t option to be taken in acute AIP-toxicity and its sequelae. **Conclusion:** The growing market availability of AIP makes it an easy option for self-harm or perhaps murder. Due to the absence of a precise antidote, affected people die quickly. It's important for the medical staff to be aware of the increasing danger of ALP-toxicity and the new complications observed in the new cases.

Key words: Aluminum phosphide, incidence, mechanism of action, investigations, prognosis, elimination.

1.INTRODUCTION

Pesticide usage has boosted the quantity and quality of agricultural products in various developed countries. These substances, on the other hand, may cause significant acute and chronic poisoning. Throughout 300,000 people die each year from pesticide poisoning around the globe [1]. Aluminum phosphide is a major insecticide, rodenticide, and fumigant in underdeveloped nations but its toxicity and fatality is highly common for example, it accounts for around 68 percent of all poisoning fatalities in the Indian subcontinent, with the bulk of cases being attributed to phosphide consumption, especially among agricultural workers [1 & 2].

ALP toxicity is induced by the release of phosphine gas, which inhibits oxidative phosphorylation and causes cell hypoxia and circulatory failure [3]. Liberated phosphine is a very poisonous gas that causes respiratory irritation as well as considerable systemic damage. All systems are affected such as cardiovascular, pulmonary, GIT, musculoskeletal, CNS, and urogenital systems [4 & 5]. There is currently no antidote for its poisoning. According to several researches, magnesium sulphate, N-acetyl cysteine (NAC), glutathione, vitamin C and E, beta-carotenes, coconut oil, and melatonin may all assist to reduce phosphine's oxidative effects [2].

In this study we discuss the incidence of ALP poisoning, its mechanism of toxicity, pathophysiology, clinical manifestation, and management of ALP toxicity. We have chosen this topic because of its health risks and its danger of using.

2. INCIDENCE AND MODE OF TOXICITY

ALP poisoning is a prevalent method for suicide in most of developing countries such as North India, Iran, and Egypt . [6]. ALP poisoning is becoming more common in Egypt, and poison control centers are seeing an increase in cases [7]. Between May 2015 and April 2017, Egyptian research was conducted and there were 60 patients in the study, 49 of them were men and 11 of whom were women. The most common symptoms were

hypotension, cardiogenic shock, and palpitation, which accounted for 83 percent, 80 percent, and 70 percent of cases, respectively. Ninety percent of the patients had abnormal ECG readings, and 72 percent of the patients showed metabolic acidosis. The mortality rate in the most recent research was 92 percent. Cardiogenic shock, ECG arrhythmias, and metabolic acidosis all have a dismal prognosis when it comes to ALP poisoning. [7]

Phosphine gas (PH3) is the active pesticide component of ALP, and it is readily absorbed by inhalation, ingestion, and skin or mucosal contact [5]. Accidental or suicide ingesting is the most common method of exposure. It may also occur because of eating food that has been exposed to aluminum phosphide during preparation [5].

Chemistry:

Phosfume, Phostoxin, Quickphos, Alphosm, and Delicia are just a few of the brand names for aluminium phosphide (ALP) [1]. In Egypt , the common name is celphos (fig1). A three-gram pill may produce roughly one gramme of phosphine gas when it comes into contact with water. Phosphine gas is colourless, combustible, and has a rotten fish odour. [8] To minimise spontaneous combustion, the tablet should also include ammonium carbamate in a 56:44 ratio of AIP to ammonium carbamate, such that when the ALP tablet comes into contact with water, it produces phosphone, ammonia, and CO2. [9]. ALP has a fatal dosage of 150-500 ppm in a typical 70-kg adult. Air phosphine levels of 50 ppm in the workplace is completely dangerous to one's health, while 400-600 ppm might result in death in 30 minutes.[1]

3. TOXICOKINETICS AND TOXICODYNAMICS

Toxicokinetics:

Although aluminum phosphide absorption via the skin is uncommon, it may be absorbed through damaged skin and cause systemic poisoning. Inhalation of phosphine, which is generated by the action of water on metal phosphides, is another method of exposure [10]. Metal phosphide hydrolysis on the skin might result in the formation of gaseous phosphine, which could be inhaled and absorbed. After intake, a little quantity of zinc phosphide enters the liver and kidneys, where it is hydrolyzed into phosphine and zinc ions. It also makes its way to the brain. [11]

When metal phosphide is consumed, phosphine gas is produced, which is quickly absorbed throughout the gastrointestinal system, enters the bloodstream, and is transported in part to the liver through the portal vein. It's also quickly absorbed by the lungs. The majority of phosphine is eliminated intact in expired air after peak exposure, while the remainder is oxidised to phosphite and hypophosphite ions and expelled in urine. [11]

Mechanism of Toxicity:

The specific method by which phosphine causes death in humans has yet to be discovered. Despite this, phosphine inhibits mitochondrial respiration in cells Leading to cellular hypoxia. Also, it inhibits cytochrome oxidase with producing an oxidative stress by forming extremely reactive hydroxyl radicals and other reactive oxygen species (ROS). Phosphine also reduces oxygen intake, causing tissue damage. There might be direct toxicity to the adrenal and cardiac myocytes, resulting in a drop in blood pressure. Furthermore, phosphine is linked to decreased blood flow to essential organs. The entire generation of ATP (adenosine triphosphate) has decreased. Multiorgan system failure occurs with severe poisoning. Phosphine converts ferric iron to ferrous iron, allowing iron to be released from its protein-bound state. This behavior has the potential to exacerbate oxidative stress-related damage. The toxicity of phosphine is explained by all these processes. [12]

4. MANAGEMENT OF ALP-TOXICITY

4.1: clinical picture

The signs and symptoms of ALP poisoning occur within few minutes (10- 15 minutes), and are dependent on the dosage, route of entry, and time since toxin exposure. Those that lived had either taken a very little quantity, the pill had been expired, or the phosphine gas had dissipated due to air exposure. [13]. Patients usually experience airway discomfort and shortness of breath after breathing small volumes of phosphine gas. Dizziness, fatigue, chest tightness, headache, nausea, vomiting, diarrhea, ataxia, numbness, paresthesia, tremor, muscular weakness, vision disturbance, and jaundice are all possible symptoms. The patient may experience acute respiratory distress syndrome (ARDS), heart failure, cardiac arrhythmias, convulsions, and coma after inhaling large volumes of the gas, as well as late indications of hepatotoxicity and nephrotoxicity. [14] Cardiac toxicity, cardiac dysfunction, and circulatory failure are the major causes of death in ALP poisoning, all of which result in cardiomyocyte death [1].

4.1.1: Myocardial toxicity:

The heart is the main organ attacked by ALP toxicity. Cardiovascular problems such as refractory hypotension, dysrhythmia, and congestive heart failure occur within 12 to 24 hours of ALP exposure [4]. Cardiomyocytes, which make up approximately 75% of heart tissue, are critical for cardiac circulation. Mitochondria, as essential organelles, are abundant in

cardiomyocytes and essential for contractile function by creating ATP via the oxidative phosphorylation process.

The heart is particularly prone to oxidative damage due to its high O2 intake, limited antioxidant system, and high metabolic activity. Tissue hypoperfusion and intracellular acidosis may cause cardiac dysfunction [15]. Furthermore, cardiac suppression and resistive hypotension are two common side effects of ALP poisoning. ALP-induced cardiac toxicity is exacerbated by the production of free radicals, especially oxidative stress, and Reactive oxygen species (ROS), both of which cause Lipoperoxidation (LPO) to increase [16]. However, by inhibiting antioxidant enzymes and producing superoxide radicals, no bioavailability is lowered, resulting in increased neutrophil adherence to coronary arteries and vasoconstriction [17].

4.1.2: Respiratory toxicity:

Pulmonary edema, respiratory failure, and acute respiratory distress syndrome are examples of respiratory complications. Additionally, the most common pulmonary complications of AlP intoxication were congestion, hemorrhage, atelectasis, capillary vasodilation, and alveolar wall thickening [18]. When AlP is mixed with aqueous solutions, the immediate release of phosphine gas causes rapid absorption of phosphoric acid through the lungs, causing alveolar membrane damage [6].

4.1.3: Hepatotoxicity:

Manifestations of liver damage are usually less severe, the precise reason is unknown. Transient increases in serum aspartate and alanine aminotransferase are a more prevalent finding [19]. The most common histological findings in the liver at autopsy in cases of lethal phosphine poisoning are cytoplasmic vacuolization of hepatocytes and sinusoidal congestion. Nuclear fragmentation and sinusoidal clusters of polymorphonuclear leukocytes have also been reported in the liver [20].

4.1.4: Acid-base and electrolyte Imbalance.

ALP toxicity, which may be primary or after vomiting, is connected to electrolyte problems, including hypokalemia. The release of catecholamines may potentially have a function [21]. ALP poisoning has also been linked to hyperkalemia, hypo-, and hypernatremia, all of which have been associated with a greater death rate. [22].

The second deadly consequence of acute poisoning is severe metabolic acidosis. The major cause might be cytochrome C oxidase deficiency or broad tissue hypoperfusion. Sodium bicarbonate administration is used to fix it, but the prognosis is still dismal. [23].

4.1.5: Gastrointestinal manifestations

Toxic manifestations generally appear within minutes after consumption. Because ALP is corrosive and oral intake is the most common route of poisoning, gastrointestinal symptoms are often the first and most prevalent. [1]

Hematemesis, vomiting, and epigastric discomfort are the first signs of ALP consumption. Endoscopy shows esophageal and stomach corrosive lesions, severe gastric erosions, and duodenal erosions. [13]

Esophageal strictures or fistulas are common. Dysphagia is a typical late side effect. Unusual consequence reported in survivors of Aluminum phosphide poisoning is fistulous connection between the oesophagus and airway tract (esophagobronchial and esophagotracheal fistula). The proposed mechanism involves severe inflammation and corrosion of the esophageal and tracheobronchial walls as a result of localized phosphine gas release caused by localized tablet entrapment or impaction in the esophageal mucosa. It's especially important to remember in individuals who have dysphagia. If left untreated, aspiration and subsequent lung infections may cause serious morbidity and even death. [24]

4.1.6: Neurotoxic manifestations

ALP exposure has been linked to a decrease in cytochrome in the brain, with the exception of cytochrome b, as well as neuronal lipid peroxidation damage and changes in antioxidant synthesis, all of which have serious consequences for nervous system structure and function. [25].

Headache, irritability, disorientation, changed mental state, anxiety, and acute hypoxic encephalopathy are all symptoms of the nervous system. Ataxia, tremors, and convulsions are all frequent symptoms.

Unless there are major abnormalities, like as hypoxia or hypotension, these signs and symptoms are rarely visible. [1].

Due to arrhythmia, conduction interference, cardiac injury, peripheral vasodilation, and severe vomiting with fluid loss, persistent shock may ensue within 3-6 hours after administration, resulting in sleepiness, disorientation, and coma. [26]

4.1.7 :Intravascular hemolysis

To our knowledge, only a few cases of phosphide poisoning have resulted in intravascular hemolysis; two of these cases had a deficit in the enzyme glucose 6 phosphate dehydrogenase (G-6-PD), while the other had a normal G-6-PD enzyme level [27].

ALP directly damages blood vessels and the RBC membrane; it can also cause hemoglobinemia and intravascular hemolysis via producing free radicals

which in turn causes oxidative stress. Met-Hb is formed after exposure to substances that oxidize ferrous hemoglobin to ferric form. Another reason for multiple organ failure after ALP poisoning could be the reduction of Methemoglobin capacity to transport enough oxygen to tissues. Clinical methemoglobinemia manifestation are proportional to the degree of methemoglobin. Changes in the colour of blood and skin may occur at levels up to 20%. Hypoxia manifests itself as neurologic and cardiac symptoms when levels climb beyond 20%. Levels of more above 70% are typically lethal. Hemolysis can also occur as a result of metabolic acidosis, a common symptom of ALP poisoning. Despite the fact that hemolysis is a rare symptom of ALP poisoning, it is critical to detect because of the dangerous consequences [28].

4.1.8 :Uncommon findings

In addition to methemoglobenima, microangiopathic hemolytic anemia, pancreatitis, acute adrenocortical insufficiency with hemorrhage or necrosis, acute tubular necrosis, ascites, myocardial infarction, rhabdomyolysis, and disseminated intravascular coagulation are all unusual symptoms in ALP poisoning. [21]

4.1.9 :Chronic poisoning

Chronic phosphine exposure causes cough, dyspnea, chest pain, fatigue, decreased appetite, and epigastric pain, which is frequent among people that work in silos. Toothaches, edema, and necrosis in the mandible can all be caused by low-level phosphine exposure. Chronic cutaneous exposure to 0.4 mg L-1 phosphine gas might cause skin congestion and sensitivity [1].

4.2: investigation

Sinus tachycardia, ST segment abnormalities, inverted T wave, myocardial infarction, AV block (specifically right bundle branch block), and complete heart block are all common ECG changes. If the patient survives the first 24 hours, ECG changes will normalize in 10-25 days. Pulmonary edema, pleural effusion, and sub-pericardial bleedings are typically seen on chest x-rays. A blood sugar level test reveals hypoglycemia, which can be caused by gluconeogenesis, glycogenolysis, or adrenal insufficiency. Arterial blood gases (ABG) or Venous blood gases (VBG) assay reveals metabolic acidosis or a combination of metabolic acidosis and respiratory alkalosis. Liver and kidney function tests are some of the most common tests for Alp poisoning [1] & [23]. Serum electrolytes may show hypo-or hypermagnesemia which are linked to Cardiotoxicity and massive myocyte destruction. Levels of sodium and potassium in the blood can be high or low. Low levels of white and red blood cells are shown by a complete blood count (CBC). Methemoglobinemia and intravascular hemolysis may be detected. Biochemical indicators such as creatine phosphokinase (CPK), creatine kinase myocardial band (CK-MB), and Troponin-T have been associated to ALP-induced myocardial injury in some instances [28]. However, some sources show that these biomarkers change after ALP poisoning, but these markers are unreliable, according to studies conducted by Soltaninejad and her colleagues [27]

4.3: treatment of ALP poisoning

Treatment should begin right once after obtaining a short history and doing a clinical examination, rather than waiting for a confirmation diagnosis. All medical staff examining the patient should wear a full-face mask and latex gloves. Keep in mind that small-pore masks will not protect you against PH3 exposure. [1]

4.3.1: Stabilization of the patient: Airway and breathing:

The airway is patent if the patient answers in a normal voice. If left untreated, a closed airway may swiftly lead to cardiac arrest. Any health care worker, regardless of setting, may perform a head-tilt and chin-lift treatment to open the airway as needed. With the correct apparatus, suctioning the airways to eliminate obstructions is achievable. If breathing is insufficient, assisted ventilation is required. If a bag mask is available, trained workers should use it. [29]

Circulation:

The capillary refill time and pulse rate may be monitored in any situation. Looking at the skin might reveal circulatory problems. Color changes, sweating, and a decreased level of consciousness are all signs of reduced perfusion. If a stethoscope is available, a heart auscultation should be performed. As quickly as possible, blood pressure readings and electrocardiography monitoring should be performed. Hypotension is a life-threatening condition. Hypovolemia may be mitigated by putting the patient in a supine position and raising the patient's legs. An intravenous line should be set up as soon as possible, and saline should be supplied. [29]

4.3.2: Decontamination:

Face and eyes should be washed. Throw away the vomit since it may contain PH3 and represent a danger to others. In the instance of inhalational exposure, the patient should be removed from the contaminated garments as soon as possible and his or her skin region cleansed, following the required measures. [1]

a-Gastric lavage:

Potassium permanganate ($KMnO_4$) (1:10.000) is recommended for gastric lavage since it oxidizes

PH3 to nontoxic phosphate. [30]. SanaeiZadeh has also said that potassium permanganate may be a potent oxidant and has described instances of hemolysis and methemoglobinemia after ALP poisoning that were originally treated with potassium permanganate stomach lavage. [31]. It is hypothesized that gastric lavage with oil such as Paraffin oil 50ml forms a protective barrier surrounding injured stomach mucosa, inhibiting the absorption of PH3 gas. We can use 80 ml olive oil, or 60 ml oil of turpentine, or 100 mL of almond oil to dissolve one gram of phosphorus [32].

The efficacy of paraffin oil and sodium bicarbonate was assessed in a recent randomized controlled trial, and results recommended the usage of both of them in the gastric decontamination of ALP patients as they significantly reduced manifestations and associated complications. [33]

ALP is not decontaminated using activated charcoal since its molecular weight is just 58 Daltons, which is less than the adsorption characteristics of AC. Furthermore, whether the AC adsorbed numerous ALP molecules do not ensure that aluminum atoms retain their weak connections with phosphors. [34]. After acute ALP poisoning, water-based treatments should not be utilized for stomach decontamination. Using vegetable oils for gastric lavage or castor oil to limit increased PH3 release. [35]

4.3.3: Elimination:

a. coconut oil

Researchers believe that its most probable mechanism of action is preventing the systematic absorption of the phosphine released from the ingested tablets by lining the stomach wall. [36] Seven ALP-poisoned patients with severe hemodynamic circumstances were given a gastrointestinal lavage with diluted potassium permanganate, coconut oil, and sodium bicarbonate in addition to supportive treatments. Because four of the seven patients lived, the authors concluded that coconut oil may be an effective treatment in the absence of a particular antidote. Nonetheless, the lack of an effect group may be seen as a constraint that should be considered when evaluating results. [3]

b. Antioxidants:

Vitamin E has been suggested as a therapy for those who have been poisoned by ALP. A 21-year-old man who ate a 3-g ALP pill was effectively treated with a combination of standard treatments and antioxidants such as vitamin C, vitamin E, and N-Acetyl Cysteine. [37].

Vitamin E, given at 400 mg twice a day via intramuscular (IM) route with other supportive therapies to ALP-poisoned subjects, was able to lower the requirement for mechanical breathing (30 vs. 62%) and the fatality rate (15 vs. 50%) as compared to controls in the randomized controlled trial that included 36 ALP-intoxicated patients. [37].

c. lipid sink theory

It's thought that PH3 might also have lipid soluble property so we could use IV lipid emulsion to counter its toxic effects according to the "lipid sink" theory, which argues that a lipid soluble toxin may be sequestered inside the lipid emulsion, limiting its impact site concentration and toxicity, is utilized to create intra-lipid emulsion. [31]

4.3.4: Symptomatic and supportive:

Because there is no known cure for ALP poisoning, the core of therapy is symptomatic and supportive care. The timing has a significant impact on the prognosis. Patients should be given 100% oxygen and should be treated for fluid and electrolyte imbalances. Serum calcium and magnesium levels, as well as liver and kidney function tests, are required. Treat any seizures as usual and provide general supportive care with a focus on fluid balance. Chemical pneumonitis may result in pulmonary aspiration, and subsequent bacterial pneumonia need antibiotic treatment. Bronchodilators should be evaluated in conjunction with cardiac and electrolyte monitoring when bronchospasm is present, since arrhythmia or hypokalemia may be accelerated. [1], [23]

Adrenal insufficiency may occur as a result of shock, thus a hydrocortisone infusion is given, as in the case described by Katwal, 2021, in which a 17-year-old girl took 6 g (2 tablets) of ALP pills with suicide intent was successfully managed. Despite the fact that ingestion of 150–500 mg of ALP is associated with a 70–100% mortality rate, this person survived despite severe metabolic acidosis, acute renal failure, refractory shock, and ventricular tachycardia. [23]

Reports regarding the use of magnesium sulfate in ALP poisoned patients were rather contradictory. Generally, its usage was preferred as long as magnesium levels were measured regularly to avoid hypermagnesemia. Nano particles were also targeted in research. Magnesium nanocarriers were reported to improve heart rate (HR), blood pressure (BP), and reduce lipid peroxidation. [36]

If severe acidosis occur, dialysis is considered [9]. Sodium bicarbonate at a dose of 50-100meq/8hrs is used if bicarbonate level is <15meq/l. [38]

Aggressive cardiopulmonary support is recommended for critical patients, using extracorporeal membrane oxygenation (ECMO) to oxygenate blood and remove carbon dioxide using circuits outside the body. This prevents end-organ damage and works toward increasing the

survivability of patients in the first critical hours. But patients should be selected carefully due to the various complications of this intervention ranging from bleeding and infection to limb ischemia. [39]

Prognosis:

At admission, hypotension, significant ECG abnormalities, low blood pH, low serum bicarbonate, and hyperglycemia might be utilized to identify individuals at increased risk of ALP mortality. The frequency of vomiting episodes and the degree of hypotension experienced by a patient after ingestion are the strongest indicators of the patient's prognosis. It has nothing to do with the dosage of the drug. Refractory shock, aspiration pneumonitis, anaemia, metabolic acidosis, electrolyte shortage, coma, acute hypoxia, gastrointestinal hemorrhage, and pericarditis are the complications that associated to a poor prognosis. [40]

Figure (1): commercial name of Aluminum phosphide in Egypt (Celphos)

CONCLUSION

The increased availability of AIP in markets makes it an easy choice for self-harming or even for murdering people. As a fumigant, ALP is widely used in agricultural and other purposes. On the other hand, it is a highly toxic substance that can either be ingested or inhaled leading to toxicity. First, it affects and corrodes the gastric mucosa and then absorbed into the bloodstream leading to systemic toxicity which, in turn, affects the heart and can even cause acute respiratory distress syndrome (ARDS). The specific method by which phosphine causes death in humans has yet to be discovered. Despite this, phosphine inhibits mitochondrial respiration in cells Leading to cellular hypoxia. Also, it inhibits cytochrome oxidase with producing an oxidative stress by forming extremely reactive hydroxyl radicals and other reactive oxygen species (ROS). Phosphine also reduces oxygen intake, causing tissue damage. Extreme metabolic acidosis was also noticed. Furthermore, ALP can cause damage to the vascular walls and RBC membrane either directly or through inducing ROS. Gastric lavage is the first acceptable line for treatment of ALP toxicity. N-Acetyl cysteine (NAC) and glucagon were prescribed for the myocardial manifestations. Administering corticosteroids helps relieve adrenocortical lacking. Affected patients have a very high mortality rate due to the lack of a specific antidote. To be able to produce an antidote, researchers need formal experimental studies on the toxicokinetics of ALP on animals, firstly, then on humans.

RECOMMENDATIONS

- governments should raise awareness about the severity of aluminum phosphide toxicity.
- strict rules should be set to manage ALP sales and supervise its usage.
- Find alternative ways other than aluminum phosphide usage for preservation of wheat
- early intervention in case of ALP toxicity and early management of cardiogenic chock improve prognosis.

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