

ARTICLE INFO

Date Received:
21/05/2021;
Date Revised:
27/08/2021;
Date Published Online:
31/12/2021;

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How to Cite:

Manouchehri A, Ghareghani S, Shamaei S, Nilechi M, Bossaghzadeh F. A review on Aluminum phosphide (Rice Tablets) Poisoning; From Exposure to the Applicable and New Strategies of Clinical Management. Adv. Life Sci. 8(4): 326-332.

Keywords:

Phosphine; Rice tablet; Aluminum phosphide; Human poisoning; Pesticide; Toxicity of ALP; Management strategies

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A review on Aluminum phosphide (Rice Tablets) Poisoning; From Exposure to the Applicable and New Strategies of Clinical Management

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Abstract

Rice tablets (especially aluminum phosphide) as a solid fumigant pesticide is one of the major areas of interest within the field of pesticide poisoning due to high fatality. It is commonly used in grain storage places including silos, warehouses, and grain transporting systems such as ships to control damages of pests and rodents. Unfortunately, it is considerably consumed for suicidal purpose in developing countries because of the ease of access. Aluminum phosphide (ALP) has been conceived as the most mortal one among others and accounts for many deaths each year. ALP toxicity is associated with phosphine gas liberation which is highly toxic and may cause various toxicities in all body organs, especially in cardiovascular and respiratory systems. As there is no certain antidote to prevent human's death, hence having thorough information about this pesticide is required. Thus, in this article physiochemical features of rice tablets, various toxicological, clinical/pathological impacts of ALP on human body and also applicable and new strategies of its managements have been highlighted. Eventually, gathering all published information about ALP intoxication till date demonstrated that restricted preventative measures plus early and improved management protocols can limit the organ injuries and mortality.



Introduction

Metal phosphides are one of the most widely used groups of pesticide agents used for safe storage and transportation of rice and grains in developing countries because of agricultural revolutions and pest controls [1]. Among all members belonging to metal phosphides including aluminum, magnesium, calcium, and zinc phosphite, aluminum phosphide (ALP) has been conceived as the most fatal one [2]. As it is readily available in low to middle-income countries (such as Asian markets), deliberate and accidental poisoning of this pesticide has been identified as the most lethal poisoning due to its high mortality [3].

In spite of the fact that the use of aluminum phosphide has been forbidden in many countries (such as Iran), it is sold illegally in some markets usually in the form of 3g tablets, which is referred to as rice tablet, with different brand names [4,5]. Although Most reports of ALP intoxication are associated with young adult populations from rural Asian areas, also there has been some phosphine poisoning reports in European countries including Germany [6,7], UK. [8], France [9], and Denmark [10] over the last three decades. In regard to large burden of pesticide and fumigant poisoning in developing countries (such as India and Iran), it is becoming extremely difficult to say that ALP poisoning happens accidentally. Self-poisoning by pesticides has become increasingly prevalent response due to ease of availability in some developing countries. Researchers have maintained that most of the self-harm cases do not plan to commit a suicide leading to die, but as they are unaware of destructive and deadly effects of some pesticides (such as ALP) have unplanned die [11]. However, it is worth to say that it seems phosphine poisoning predominantly occurs unintentionally in developed countries.

Methods

Search strategy and selection criteria

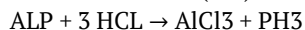
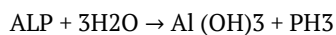
A literature search of this narrative review was conducted by key terms of "aluminum phosphide", "rice tablet", "human poisoning", "mechanism of ALP poisoning", "new strategies for treatment of ALP poisonings", "organ toxicity in ALP toxications", "routes of exposure to ALP" in Google Scholar and Pub Med databases and all the relevant articles were selected. The selected articles were reviewed for contents and the articles with duplicated information were excluded.

Discussion

Physio-chemical features of rice tablets

ALP, the active component of rice tablet, is a solid fumigant formulated by ammonium carbonate with

ratio of 56: 44% to prevent probable combustion of diphosphine gas (which is produced as a result of phosphine gas interactions with atmospheric moisture) during transportation or storage [12,13]. ALP interacts with atmospheric moisture and liberates phosphine gas which is the leading cause of rice tablet poisoning and death in pests and human as well [1]. Moreover, there is an evidence demonstrating that the release of phosphine gas elevates in acidic environments [3]. Equation of ALP reaction to moisture and hydrochloric acid:



The physical features of rice tablets are addressed in table 1.

Routes of Exposure and Toxicity Levels

According to numerous researches done by scholars, rice tablet toxicities originate from three main routes including (I) direct oral consumption, (II) inhalation of air containing phosphine, and hardly ever (III) absorption via skin or eyes. However, absorption through oral ingestion has been regarded as the most common cause of toxicity. In the literature on ALP poisoning, human lethal dose has been determined about 150- 500 mg (depending on the exposure of tablet to moisture and expiry date) [14]. Furthermore, the recommended workplace exposure limit for people working at ALP manufacturing industries, grain storage warehouses, and ships has been suggested to be below 0.3 ppm [15].

Mechanisms of Toxicity in Human Body

As soon as ALP contacts to the gastro-intestinal moisture and stomach hydrochloric acid, the release of phosphine gas (PH₃) occurs in gastrointestinal tract and cytochrome oxidase blocks and inhibition of oxidative phosphorylation begin. Hence, some sensitive organs requiring more oxygen including brain, kidney, heart, lungs and liver are more vulnerable to these toxic effects which may contribute to histopathological alters and cell death [3,16]. It certainly appears to be the case that the valence of hemoglobin hem component alters as a result of the cytochrome oxidase blocks. Moreover, it has been demonstrated that extra-mitochondrial liberation of free oxygen radicals and oxidative stress stemming from cytochrome oxidase blocks may lead to lipid peroxidation and protein denaturation of the cell membrane in several organs. So, any organ could be affected via ALP intoxication [17-19].

Acute Toxicity

Non-specific clinical features of ALP poisoning remain controversial, because it mainly relies on way of

Features	Definitions
Color	Usually gray (sometimes green or brown)
Shape	Round 3g tablets
Odor	Odorless or smells like rotten garlic
Brand names	Celphos, Quickphos, Phostoxin, Synsel, Phostek, phosfume, Talunex, degesch, Synfume, Delicia, and etc.

Table 1: Physical features of rice tablets

Routs of exposure	Acute toxicity signs	Ref.
Oral consumption	Nausea, diarrhea, vomiting, stomach pain, chills, convulsion, shortness of breath, headache, and coma	[20]
Acute inhalation	Headache, dizziness, nausea and vomiting, diarrhea, gastritis, fatigue, cough with sputum (green) moving difficulty and speaking.	[20]

Table 2: Different toxicity signs related to acute exposure to rice tablets

Type of Toxicity	Clinical toxicity signs	Ref.
Gastrointestinal toxicity	Early symptoms: vomiting, hematemesis, epigastric pain. Endoscopy recognition: Corrosive lesions of stomach and esophagus, duodenal erosions, severe gastric erosions, esophageal fistula or stricture Late complication: Dysphagia	[25-28]
Respiratory toxicity	Tachypnea, dyspnea, rhonchi and crepitation, pulmonary edema including respiratory distress syndrome, protein-rich or hemorrhagic pleural effusion	[29]
Hepatotoxicity	Transient increase in serum aspartate and alanine aminotransferase, hepatitis Post mortem recognitions: cytoplasmic vacuolization of hepatocytes, sinusoidal congestion, nuclear fragmentation, sinusoidal clusters of polymorphonuclear leukocytes	[30,31] [30]
Renal toxicity	Uremia, metabolic acidosis, acute tubular necrosis, oliguria, glomerulonephritis, acute adrenocortical insufficiency	[32,33]
Neurological toxicity	Cerebral anoxia, Dizziness, paresthesia, nystagmus, delirium, numbness, ataxia, seizures, changed sensorium, coma, Microscopic examination: degeneration of Nissl granule in brain cytoplasm	[34-36]
Cardiovascular toxicity	Chest pain, dyspnea, syncope, palpitation, congestive heart failure, myocarditis, pericarditis, arrhythmias (tachycardia), sub-endocardial infarction, pericardial effusion, cardiogenic shock, cardiomyopathy, refractory hypotension, raised systemic venous pressure, disseminated intravascular coagulation Post mortem recognition: myocyte vacuolation, neutrophilic infiltration, cell necrosis, myocardial fiber destruction	[22,37] [37]
Electrolyte and metabolic abnormalities	Metabolic acidosis, respiratory alkalosis and acidosis, dyselectrolyemia including hypokalemia, hyperkalemia, hypomagnesemia, hypernatremia, hyponatremia, hypoglycemia and hyperglycemia	[38-42]
Other toxicities	Methemoglobinemia, serositis, thyroiditis, rhabdomyolysis, microangiopathic hemolytic anemia,	[43]

Table 3: Various organ toxicity symptoms associated with ALP poisoning

NO.	Compound	Dose	Function	Ref.
1	Potassium permanganate + Activated charcoal	1:10,000 dilution 1g/kg of body weight	Oxidizing stomach phosphine gas to potassium phosphate and aluminum permanganate Neutralizing and reducing the ALP absorption in gastrointestinal system	[49]
2	Sodium bicarbonate solution	3-5%	Inhibition of ALP conversion to phosphine by reducing the acidity of stomach environment	[48]
3	Sodium bicarbonate + coconut oil	1:1	Vegetable oils provide a mechanical barrier over the gastric mucosa resulting in reduction of phosphide breakdown and prevention of phosphine absorption in systemic circulation	[50]
4	Sweet almond oil	-	Reduction in cholinesterase levels Providing a mechanical barrier over the gastric mucosa	[51]

Table 4: Common gastric lavage protocols used for rice tablets (ALP) poisoning

Type of measure	Measure/ substance	Effect on organ/body	Ref.
Antidote therapy	Magnesium supplementation	Stabilizing the cell membrane and decrease the lipid peroxidation as a result of free radicals of oxygen	[2,52]
Antidote therapy	N- acetylcysteine	Replenishing cellular glutathione and magnesium as an antioxidant, and also decreasing myocardial oxidative stress	[8,53]
Antidote therapy	Vitamin E	Reduction of mortality, diminishing the mechanical ventilation duration as an antioxidant	[54,55]
Respiratory Supportive care	Hyperbaric oxygen	Increasing survival time	[56]
Cardiologic Supportive care	Intra-aortic balloon pump	Treating the cardiogenic shock	[57]
Antidote therapy	Liothyronine	Ameliorating cardiac complications and also reducing oxidative stress as an antioxidant	[58]
Gastrointestinal Supportive care	Coconut/almond oil	Increasing survival rate by reducing ALP absorption in gastrointestinal system	[4,59]
Antidote therapy	Laurus nobilis L	Decreasing of oxidative stress and DNA damage as an antioxidant	[60]
Supportive care	Calcium chloride	Preventing dyselectroemia and hypocalcemia	[61]
Supportive care	sodium bicarbonate (intravenous)	Aggressive management of metabolic acidosis	[62]
Supportive care	Lipid emulsion (intravenous)	Entrapping the absorbed phosphine molecules	[63]
Renal supportive care	Hemodialysis	Preventing renal failure, fluid overload, and metabolic acidosis in patients with acute kidney injury	[62]
Antidote therapy	Sodium selenite	Diminishing the pulmonary and liver complications (in albino rats)	[64]
Antidote therapy	Vasopressin and milrinone	Cardio-protective impacts and ATP elevation (in rats)	[65]
Antidote therapy	Melatonin	Antioxidant activity, elevating ATP production, and preventing apoptosis (in rats)	[60]
Antidote therapy	Coenzyme Q10	Scavenging oxygen-derived free radicals, mitigating mitochondrial dysfunction, improving heart contractility	[66]

Table 5: Common Treatment used in ALP-poisoning managements

exposure, dose, and duration of exposure. Different clinical signs of acute toxicity relating to each exposure rout are listed in table 2.

Chronic Toxicity

Respiratory symptoms entailing chest pain, cough, mandibular necrosis (known as phossy jaw), and dyspnea frequently happens as a result of low-level respiratory poisoning in chronic mode. Besides, it has been reported that prolonged exposure to 0.4 ppm phosphine gas through skin can contribute to dermatitis alterations. This kind of intoxication may occur in storage facility workers [1].

Organ Toxicity

Earliest organs commonly involved in rice tablet poisoning are gastrointestinal and respiratory systems in oral and inhalational routs of exposure, respectively. however, there has been much discussion as to the ALP poisoning effects on various human organs and evidence seems to be supporting ALP rice tablets could be affected any organ [1].

Cardiovascular toxicity is the leading cause of High morbidity and mortality in patients with ALP poisoning. Electrocardiographic evidence shows that sinus tachycardia is the most common rhythm abnormality on electrocardiogram (ECG) in the first 3-6 hour. However, dysrhythmia, ST-T wave changes (6-12 hours) and arrhythmias occur respectively as the subsequent

complications [2,21-23]. In fact, Siwach et al. (1998) have been maintained that malignant arrhythmias such as supraventricular and ventricular tachycardia may involve 86.7 % cases (46.7% and 40% respectively). Moreover, 23.3% of ALP-poisoned patients are vulnerable to ventricular fibrillation, but arterial fibrillation may occur in 20% of them [24]. The most common clinical toxic impacts and symptoms of ALP on different organs including cardiovascular, respiratory, nervous, gastrointestinal, and renal systems etc. are addressed in table 3.

How to diagnose ALP poisoning?

ALP intoxication may be misdiagnosed because of metabolic abnormalities, inflammation and also sepsis, thus appropriate history and clinical suspicious are needed. According to the fact that other metal phosphides create the same symptoms in less intense, differentiation of ALP to others requires precise and detailed history and also biochemical testing by hydrochloric acid, ammonium hydroxide, and ammonium chloride [40,44]. Silver nitrate (0.1 NAgNO₃) saturated paper can be prescribed for diagnose of ALP poisoning in doubtful cases. If there is a phosphine in breath, silver nitrate paper will turn to black due to the silver phosphate formation. Furthermore, it can be diagnosed by heating gastric aspirated samples above 50°C in order that phosphine could be released above the flask. Then, these fumes can be detected by silver nitrate

papers [45,46]. It has been proved that quantitative methods are the most reliable ones for differentiation. With reference to this fact, gas chromatography with nitrogen phosphorus detector is the most sensitive and specific test which is accessible for phosphine detection [47].

Management/Treatment Strategies

There is no need for any confirmatory test to start the treatment of ALP-Poisoned patient and it should be done immediately after any clinical suspicious history, because early identification plays a key role when encountering to phosphine gas contributing to organ failure and further complications. ALP-poisoning managements can be categorized in the following 3 parts:

Reducing the Toxin exposure

The respiratory poisoned victims (which are mostly workers of ALP-related industries or warehouses and grain storage silos) should be transfer from the offending environment to outdoor. Besides, gut decontamination in the form of gastric lavage within the first hour of toxin ingestion plays a crucial role in poisoning management. There are two challenges with ALP (rice tablets) poisoning gastric lavage [48]: (I) water cannot be used for this situation due to the avoiding phosphine gas formation, (II) it is very important to protect the patient's air way from direct contact of stomach liquid containing acid and phosphine gas.

Various gastric lavage protocols have been suggested by scholars over the last three decades which are reported in table 4.

Increasing the Toxin Excretion

Elevating phosphine excretion via urine and lungs is a classic concern in ALP intoxication. Traditionally, researchers have subscribed to the belief that phosphine excretion via urine can be occurred by proper intravenous hydration and also dopamine infusion in renal dose. Moreover, elevation of respiratory rate in patients supported by mechanical ventilation may be helpful in phosphine excretion via lungs [12].

Supportive Treatments Done for Each Organ

Generally, supportive treatment has a vital role in ALP-poisoning management and has been widely recognized as the most effective treatment in poisoning emergencies for decades. Thus, in this article the most common measures have been done recently to save the patient's life and also prevent the organ failure are listed in table 5. However, toxins and chemicals and medicines have harmful effects on human health (67-71) Medicinal

plants that can reduce the toxic effects of chemicals and side effects of drugs and chemicals can be used in the form of natural antioxidants (72-79).

Conclusion

Despite the absence of specific (100% effective) antidote, still there is a lack in preventative restricted rules to forbid the misuse of ALP tablets in general population. In this condition, it seems that the most effective measures are preventative ones including limitation of its selling to public, using non-fatal alternatives instead of ALP, training of general population and appropriate documentation as well. Beside these preventative measures, it is worth to mention that time plays a crucial role in management/treatment of the poisoned patients and their life saving. Because, early and correct diagnose can help with being able to select early, effective and improved clinical management strategies resulting in reduction in the case fatality rates. At the end, in order to decline the overall incidence of successful suicide or any unintended poisoning much needs to be done, especially in developing countries, by national governments.

Competing Interests

The authors have no conflict of interests.

Author Contributions

All authors contributed equally.

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