

Successful Treatment of Aluminum Phosphide; Is It Possible?

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Abstract

Background: The utilization of pesticides like AIP has expanded in the current years and enhanced the amount and nature of horticultural items in various developing nations. Considering that in addition research centers, many cases of suicide with rice tablet have been observed and various methods have been proposed for the treatment, it was decided to examine different methods and to finally compare the effectiveness of these methods with experiences and observations in the present study.

Methods: 30 articles were compiled from prestigious scientific databases such as PubMed, Scopus and Elsevier, from 2010 to 2017. The search was carried out in English, using “aluminum phosphide,” “treatment” and “rice tablet” as the keywords.

Results: Phosphine creates free oxygen radicals in body tissues, it has been demonstrated that organs with a higher requirement for oxygen (heart, lung, kidney, and liver) show higher sensitivity to the harm prompted by phosphine gas, which is consistent with the histopathological changes in these organs after death. In vitro experiences recommend that phosphides are retained as too tiny particles of unhydrolysed salt that for all time associate with free hemoglobin and hemoglobin in untouched erythrocytes (rat and human) to create a haemichrome.

Conclusion: Many articles refer to successful treatment of rice tablets. While some factors are not considered. Considering these issues and the importance of obtaining the patient's history and taking into account clinical affairs as well as mere research, the effectiveness of the treatment methods mentioned in the study requires further consideration and investigation of all factors.

Keywords: Aluminum Phosphide; Rice Tablet; Treatment

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INTRODUCTION

Pesticide poisoning is a global medical issue that can happen as a result of coincidental or work-related causes. In addition, self-intoxication represents 33% of suicides all through the world. Aluminum phosphide (AIP) is a solid fumigant utilized for the fumigation of agrarian compounds, in animal nourishing, and for pest control in horticultural fields. The utilization of pesticides like AIP has expanded in the current years and enhanced the amount and nature of horticultural items in various developing nations. Even though its savvy utilization may enhance the personal satisfaction and work efficacy for inhabitants of these countries, inappropriate utilization may cause extreme and intense intoxication. The drawback is that AIP causes serious health impacts that have reached significant extents in nations such as India, Iran, Bangladesh, and Jordan. About 300,000 individuals die because of pesticide intoxication on the planet annually (1).

AIP is a notable and exceptionally effective outdoor and indoor pesticide (2). It is promptly accessible in Asian markets such as India and Iran. In spite of the fact that its utilization has been prohibited in Iran, it is still used to preserve rice (locally also named “rice tablet”) and keep away rodents and other bugs and insects from grains (3). In the European nations, suicides by AIP ingestion are uncommon and have been accounted for in Denmark, Germany, France,

and the UK (4-8). This substance is a profoundly poisonous agent that hinders cytochrome oxidase c and causes oxidative stress. It is mainly the most ordinarily utilized deadly deliberate toxic in Iran and India, Sri Lanka, Oman, and Morocco, yet not in European and North American nations. In view of reports announced from developing nations, the greater part of AIP toxicities comes from self-destructive attempts (1, 4). Interestingly, a various example has been accounted for from developed nations, which demonstrates that most cases are inadvertent toxicities. Reports of mortality because of AIP intoxication are diverse over the world. In the vicinity of 1997 and 2003, UK issued just 93 cases of AIP poisoning, with every one of them being unintentional, and just one case refers to death (4). Through 1983 and 2003 in Germany, only 188 reports of AIP intoxication were accounted for, 65% of which incidental and for the most part inhalational. Mostly, they had caused transient disturbance of the gastrointestinal and respiratory system and none brought about a death. The rest of the deliberate poisonings included two deaths (9). In 2000 to 2007, AIP poisoning resulted in 146 deaths in Iran (1). Hosseinian et al. suggest that more than 90% of these poisonings bear self-destructive reasons. It is by all accounts the most well-known suicide factor in Tehran, particularly in individuals below 30 years old (10). The death rate runs between 18.6% and 24% and is higher in the rural regions (11).

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Metal phosphides make a substantial extent of the pesticides/fumigants that are now being utilized. The utilization of aluminum, magnesium, and calcium phosphides has turned out to be famous and favorable in developing nations for the most part since they are powerful, inexpensive, and have no unwanted impacts on horticultural items. However, the danger of mortality related to phosphide intoxication in humans goes between 30% and 100% (12). Being easily accessible in Asian nations, this fumigant insecticide creates an essential general health concern, particularly on the grounds that no particular treatment or cure is accessible. The survival rate is low, yet updating information of health practitioners and everybody else may help decrease the danger of intoxication (13).

The most widely recognized pesticides are specifically organophosphates, phosphides and AIP. AIP quickly turned into noticeably a standout amongst the most generally utilized grain fumigants on account of its properties which are thought to be almost perfect; it is lethal to all kinds of insects, exceptionally powerful, does not influence seed suitability, is free from harmful deposits and leaves little buildup on sustenance grains (8, 13).

AIP is known as a suicide factor that can undoubtedly be purchased and has no successful remedy. Its poisonous quality comes from the discharging of phosphine gas as moisture reaches the tablet. Phosphine gas principally influences the heart, lungs, gastrointestinal tract, and kidneys. Intoxication manifestations incorporate nausea, regurgitating, fretfulness, stomach torment, palpitation, persistent shock, heart arrhythmias, pulmonary oedema, dyspnoea, cyanosis, and tactile adjustments (13). AIP intoxication control appears to have seen a few changes over the current years (1). Once the rice tablet is exposed to air, phosphine gas which is colorless, emits a foul smell (like garlic or rotten fish) because of the presence of substituted phosphines and diphosphines (14,2). However, exposures to toxicologically pertinent concentrations of phosphine can happen without any clear smell. On account of oral insertion, the phosphine gas discharged is taken by the gastrointestinal tract with straightforward dissemination and is principally absorbed by the kidneys and lungs (15).

Two major courses of intense lethality because of AIP are ingestion of AIP tablets and inward breath of discharged PH_3 (12).

Considering that in addiction research centers, many cases of suicide with rice tablet have been observed and various methods have been proposed for the treatment, it was decided to examine different methods and to finally compare the effectiveness of these methods with experiences and observations in the present study.

METHODS

In the present review article, 30 articles were compiled from prestigious scientific databases such as PubMed, Scopus and Elsevier, from 2010 to 2017. The search was carried out in English, using "aluminum phosphide," "treatment" and "rice tablet" as the keywords. Based on the study goals, articles with different goals were then removed and the rest were used for the study. According to the above-mentioned

facts, 20 articles were eventually used in this study.

Results

AIP is in dark gray or yellow crystals and the tablets are accessible under an assortment of commercial names, including Phosfume, Synfum, Celphos, Phostoxin, Quickphos, Phostek, Chemfume, Degesch, Talunex, Alphosm, and Delicia (16). A three-gram tablet can discharge nearly one gram of phosphine gas when exposed to water. In Iran, the AIP tablet is available under the name of Phostoxin and consists of AIP, urea, and ammonium carbamate. Phosphine gas is combustible (16). To avert sudden ignition, the tablet ought to likewise contain ammonium carbamate at the 56:44 proportion of AIP and ammonium carbamate, individually (1).

The majority of the lethal impacts of metal phosphides are due to PH_3 , which is a protoplasmic harm that meddles with the capacity of the cell chemicals and proteins. As some authors remark, the function of its lethality is electron transfer blockage and non-aggressive blockage of cytochrome C oxidase, which restrains oxidative phosphorylation and, thus, cell breath and initiation of peroxide radicals. Phosphine can hinder catalase and drain glutathione, which may as well bring about cell wall and passage brokenness (1).

As indicated by Proudfoot, studies have demonstrated that phosphine disables cell breath (17). It hinders the insertion of amino acids into the cycle of myocardial protein synthesis and represses cytochrome C oxidase in cardiac cells. As Anand et al. state, these adjustments in the mitochondria and myocardial proteins disable cell porousness to sodium, potassium, magnesium, calcium, and other particles and change cardiac cell wall potential. Phosphine-initiated pathophysiological changes are more conspicuous in the myocardium, pulmonary cells, and little surrounding vessels (19).

AIP and phosphine alike restrain cholinesterase, yet this hindrance is probably not going to be clinically applicable. Another harmful activity of phosphine is that it changes the function of haeme. In vitro studies demonstrate that humans and rats can retain unhydrolysed AIP salt, which continues responding with free hemoglobin and hemoglobin in normal red blood cells (RBCs) to produce haemichrome, a subordinate of methaemoglobin (17, 20).

Levels of carbon monoxide, which can be built up by CO-oximetry, can help finding and anticipation of AIP poisoning. In particular, phosphine may influence oxyhaemoglobin that interfaces with CO and cause dyshaemoglobinemia, which can yield high CO discoveries (21).

Given that phosphine creates free oxygen radicals in body tissues, it has been demonstrated that organs with a higher requirement for oxygen (heart, lung, kidney, and liver) show higher sensitivity to the harm prompted by phosphine gas, which is consistent with the histopathological changes in these organs after death (1).

Methemoglobinemia and hemolysis are uncommon discoveries following phosphine intoxication.

The analysis of AIP ordinarily relies upon clinical doubt or history, yet can be made effectively by the basic silver nitrate test on gastric content or on breath. Early admission to

hospital, resuscitation and prediction diminish the presentation of toxic substance (by gastric lavage with KMnO_4 , coconut oil), and together with concentrated observing and strong treatment may bring about great result (22).

How AIP works

How AIP works is still an unknown fact. However, some underlying investigations on various animals demonstrated that phosphine principally ties cytochrome oxidase and changes the valences of the haem part of hemoglobin. In addition, it prompts oxidative stress and increases additional mitochondrial discharge of free oxygen radicals (15) that leads to lipid peroxidation and protein denaturation of the cellular wall in different organs. AIP poisoning influences the vast majority of the organs (3). Abdollahi et al. state that oxidative stress is one of the primary functions of AIP poisonous quality that is by one means or another like that of organophosphate (OP) compounds. Besides, AIP diminishes glutathione, which is one of the fundamental cell reinforcement barriers (23). Indeed, both AIP and OP induce a lethal stress that is joined by changes in glucose metabolism (3). Al-Azzawi et al. demonstrated that in vitro presence of phosphine prompts diminishment of human serum cholinesterase mechanism, contingent upon the span and phosphine level (24). Then again, a few investigations found no adjustment in erythrocyte cholinesterase mechanism in inadvertent phosphine inward breath cases (3).

Poisoning involves cell hypoxia because of the impact on mitochondria, hindrance of cytochrome C oxidase and development of exceedingly receptive hydroxyl radicals. The signs and indications are nonspecific and prompt (22).

Histopathological change like focal venous blockage, degeneration of hepatocytes, and mononuclear invasion are normally found in the liver of patients diagnosed with AIP poisoning. Moreover, Mehrpour et al. account for alveolar swelling and widened vessels in the lung, degeneration of Nissl granule in the brain cytoplasm, degenerated eccentric nucleus in the cortex, and clog inside glomerulus and intraparenchymal part of the kidney (3).

Some empirical tests propose that vitamin C, melatonin, glutathione and carotenes assume a critical part in lessening the impacts induced by oxidative phosphine (8).

Cardiovascular problems incorporate tachypnoea, tachycardia, thread pulse, acidosis, palpitation, noticeable hypotension and unresponsive shock to conventional treatment. Patients' brain functions properly until cerebral anoxia because of shock supervenes bringing about tiredness, hallucination and deep unconsciousness (8).

Pulmonary edema, dyspnoea, cyanosis, and adjusted sensorium might be found in AIP poisoning. Other uncommon impacts consist of hepatitis, dispersed intravascular coagulation, and intense tubular putrefaction. The problems mentioned are congestive cardiac disappointment, pericarditis, intense gastrointestinal haemorrhage and intense respiratory arrest (8, 27).

It has been shown that AIP can initiate hepatotoxicity. The principle discoveries were sinusoid blockage, greasy liver changes, focal vein clog, pulverization of neucleos of hepatocytes and centrilobular putrefaction. Indications of hepatotoxicity are for the most emerged 72 hours after AIP

inebriation. Death because of intense hepatocellular lethality and fulminant hepatic dysfunction has likewise been accounted for in intense inebriation (8).

Patients may show hyperglycemia and methemoglobinemia (28, 29). Advancement of refractory shock, frailty, aspiration pneumonitis, ARDS, metabolic acidosis, electrolyte unevenness, unconsciousness, gastro-intestinal bleeding, extreme hypoxia and pericarditis might be found following intense AIP intoxication; however, these signs and symptoms are pertinent to improper prognosis (8).

The danger of AIP especially influences the cardiovascular tissues, which represent significant and resistant hypotension, congestive heart stoppage and abnormal electrocardiographic (22).

Intense intoxication after intake

The primary manifestations of intoxication become apparent in 10-15 min, advance quickly, and influence the cardiovascular and respiratory functions. If the tablet is ingested, GI aggravation can likewise be distinguished (18). Early symptoms incorporate sickness and vomiting, epigastric and retrosternal torment, dyspnoea, nervousness, irritability, and garlic or ruined fish smell can be recognized from the patients' breath at the beginning periods of intoxication. This smell can be identified after inward breath as well (16). Early gastrointestinal manifestations incorporate haematemesis, retching, and epigastric agony. Dysphagia is a typical yet postponed inconvenience. Endoscopy for the most part demonstrates dangerous injuries of the throat and stomach, stomach sores, duodenal disintegrations, and oesophageal blockage or fistula (1).

Intoxication indications of the central sensory system by and large incorporate crabbiness, uneasiness, wooziness, ataxia, deadness, paraesthesia, and tremor. Notwithstanding, these manifestations are not conspicuous, unless essential side effects like hypoxia or hypotension happen. Deferred and serious neurological symptoms incorporate incoherence, seizure, and deep unconsciousness (30). Steady shock can cause laziness, restlessness, and deep unconsciousness. The most widely recognized hepatotoxicity discoveries in patients who ingested AIP tablets are increased aspartate transaminase and alanine transaminase (30-34). If jaundice becomes apparent, it might be an indication of liver dysfunction (31). Cytoplasmic vacuolation of the hepatocytes and sinusoidal clog are the most widely recognized histopathological discoveries in perished patients (1).

The most widely recognized respiratory manifestations are tachypnoea, dyspnoea, crepitation, and rhonchi. Respiratory distress syndrome and pulmonary oedema are prevalent in grown-up patients and go with the collection of bloody or full-protein fluids in the pleural space (18). Cardiac manifestations incorporate expanded size of the ventricles, left ventricular and septal hypokinesia, akinesia, decreased cardiac output, extreme hypotension, expanded systemic venous pressure, systemic venous pressure, and inappropriate systemic vasoconstriction (1). Electrocardiographic (ECG) changes are dependent on the time passed since AIP intake. After-death discoveries indicate heart failure, serious and constant hypotension, cardiac clog, subendocardial localized necrosis, pericarditis, cardiovascular fiber separation because

of oedema, fiber destruction, nonspecific vacuolation of the myocytes, local infarction, neutrophil invasion, and eosinophilia (31, 32).

Persistent intoxication

Patients exposed to persistent phosphine, ordinarily the individuals who work in storehouses, have signs and symptoms including cough, dyspnoea, chest torment, sluggishness, loss of hunger, and epigastric torment (35). Being exposed to small amounts of phosphine in a ceaseless manner may actuate toothache and mandibular swelling and destruction (phossy jaw). If the skin is exposed to 0.4 mg L⁻¹ (0.4 ppm) of phosphine gas perpetually, dermal blockage and affectability may be induced (35, 36). Bodily inspections of Indian laborers involved in fumigation of stockpiled grains were normal, and there were no remarkable irregularities in motor and tactile nerve conduction checks (26). Off the working environment, phosphide fumigants are much of the time involved in relationship with epidemiological reports of coincidental dismalness and mortality (8).

Intense intoxication therapy

The AIP intoxication treatment flowchart proposed is generally expected for Iran and can be utilized as a brought together strategy all through the nation (1).

Having made sure that a patient is associated with history of AIP intoxication, the initial step is to analyze if the patient has truly been in contact with AIP utilizing the previously mentioned demonstrative tests. The therapeutic staff checking the patient should put on a mask that fully covers the face together with elastic gloves. Remember that masks with very small holes are not capable of preventing PH₃ insertion (37). On the off chance that the patient's garments are infected, they ought to be removed. Infected skin and eyes ought to be completely washed (1). The regurgitation may have PH₃ and is perilous to others, therefore it ought to be cleaned and discarded. The hospital or clinic staff that do the cleaning ought to be cautioned about the perils. In the event that the gas is inserted through the mouth, the patient ought to quickly be taken away from the polluted place or room, their garments should be changed, and their skin should be washed, avoiding potential risks (1).

Given that AIP intoxication has no particular counteractant, the foundation of treatment is supportive care. Timing fundamentally influences the forecast. In case AIP intoxication is expected in view of the history and bodily checks, treatment must not be deferred until the point when test results are affirmed (38).

Some recommend to utilize coconut oil with routine treatment, as it contains immersed unsaturated fats and appears to decrease the discharge of PH₃ in gastric acid. Besides, coconut oil appears to cover the stomach mucosa and hinder PH₃ retention (39, 40).

Vegetable oils and liquid paraffin have likewise been accounted for to stop PH₃ discharge from AIP in vitro, however only case report confirms the fact (1). Saidi and Shojaie suggest sweet almond oil as a potential alternative, as it brought down deaths in rats caused by AIP, even though its activity has not been accounted for in humans (41). Hassanian-Moghaddam and Shahbazi suggested the utilization of gastric ventilation to clear PH₃ shortly after the

rice tablet has been consumed (42). More examinations and evidence are required to demonstrate the viability of this technique (1).

Some empirical tests indicate that glutathione, melatonin, vitamin C and carotenes assume a vital part in decreasing the impacts induced by oxidative phosphine (1).

No powerful remedy has ever been found for AIP intoxication and strong and basic care to adjust blood pH, electrolytes, and blood vessel pulse is the primary curative method (5). Most of the patients have low blood pressure resistant to inotropic support (6). PD was utilized as the principal management alongside conservative and routine medications of AIP intoxication in the treatment of extreme metabolic acidosis and pH and bicarbonate levels in these patients changed to a great deal (43).

The expanded penetrability of vessels, insufficient systemic vasoconstriction and diminishing the left ventricular ejection fraction amid AIP intoxication, are the main etiologies for cardiovascular failure. It is important to revive the patients with a lot of intravenous liquids and vasoactive substances as the initial phases in the treatment of AIP intoxication. Hydroxyethyl starch (HES) is the colloid that is mostly utilized and authorized to control hypotension (44).

Management incorporates early gastric lavage with potassium permanganate or a mix with coconut oil and sodium bicarbonate, injection of charcoal, and alleviative treatment. Particular treatment incorporates intravenous magnesium sulfate and oral coconut oil. Besides, acidosis can be treated with early intravenous injection of sodium bicarbonate, cardiogenic shock with liquid, vasopressor, and refractory cardiogenic shock with intra-aortic balloon pump or digoxin. Trimetazidine may as well have a valuable part in the therapy, since it can stop ventricular ectopic beats and bigeminy and protect oxidative metabolism (3).

Nearly 95% of the mortalities occur in the initial 24 hours because of heart failure and arrhythmias. On the other hand, it has been recommended that heart activity enhances up to 5 days after poisoning. This proposes that if the patient does not die after the initial hours of being affected, they may be able to overcome the intoxication. Aggressive cardiovascular support (ECMO) amid this stage may deny end-organ harm because of poor perfusion and let the fundamental organs of heart and lung recuperate from the intense poisoning (45).

ECMO can give the most elevated level of cardiopulmonary help as far as preserving oxygenation.

Be that as it may, some disagree with the utilization of sodium bicarbonate for metabolic acidosis treatment in ALP intoxication. Marashi and Nasri-Nasrabadi proposed the utilization of hydroxyethyl starch in ALP intoxication with the shock and arterial pH > 7 to determine the manifestations of shock and increment arterial pH without sodium bicarbonate being applied. Also, Cooper et al. detailed no advantageous hemodynamic impact of sodium bicarbonate in patients with serious lactic acidosis. Alternatives for therapy modalities depicted are intravenous methylene blue for methemoglobinemia, N-acetylcysteine, digoxin, hyperbaric oxygen, trimetazidine, and boric acid (46).

Some authors recommend that a blend of hyperinsulinaemia-euglycaemia and hyperventilation

oxygenation provides a broader assessment as a treatment for AIP intoxication (3).

Some reports indicate the positive clinical impacts of coconut oil regarding AIP intoxication in human beings. How it works is not clear, however it may generate a defensive layer around the gastric mucosa and hinder the retention of phosphine gas. Moreover, coconut oil may weaken HCl in the stomach and decrease the failure of phosphide (47).

Saidi and Shoajaie remarked that intragastric lavage with sweet almond oil extensively diminished the mortality of rats intoxicated with AIP. Also, it essentially brought down plasma cholinesterase levels. The authors proposed that sweet almond oil ought to be consumed orally instantly after AIP intake, however this has not been affirmed in humans yet (48).

It has been theorized that digoxin therapy (quick digitalisation) would increment myocardial contractility and blood pressure, countering hence the immediate impacts of AIP on cardiac myocytes which prompt persistent cardiogenic shock (49).

There would be a more chance to survive if the AIP taken is not much or the tablet's expiration date has passed or even that it has been out in the open. In addition, retching and early supportive care increment the survival rate (3).

patients poisoned by AIP and shocked by arterial pH >7.00 should receive 500 to 1000 mL of hydroxyethyl starch, which can successfully eliminate side effects of shock and increment arterial pH without extra injection of sodium bicarbonate (50).

IABP was effectively utilized and may enhance future forecasts for extremely intoxicated AIP patients with persistent cardiogenic shock (51).

In spite of numerous treatments suggested, patients with serious AIP intoxication keep on dying due to cardiogenic shock. This therapy is suggested to be utilized in different instances of persistent cardiogenic shock caused by AIP intoxication and urge clinical toxicology specialists to give an account of their observations (51).

Toxicokinetics

Retention: Having been taken, phosphine will be discharged because of contact amongst AIP and water/acid in the gastrointestinal (GI) tract. Some phosphide might be retained by the GI tract without hydrolysis and change into phosphine. Phosphine gas can quickly be retained by the lungs and GI tract. Ingestion through skin and eyes dose not typically happen however it sometimes might be the case (52).

Dissemination: Having been taken, phosphine level increments in the blood and liver. This little particle can simply be circulated in all tissues (18, 53).

How it works and can be eliminated: Metal phosphides convert into phosphine because of hydrolysis. The most imperative urine metabolite of phosphine is hypophosphite, however urine can have phosphate and phosphite as well. Phosphine itself is dispensed with by breathing out (19). AIP might be disposed of in the urine unaltered.

In light of the quick systemic intoxication, phosphine is immediately retained after ingested orally. Phosphine is

discharged when AIP or other phosphide salts are exposed to hydrochloric acid inside the stomach (25).

In vitro experiences recommend that phosphides are retained as too tiny particles of unhydrolysed salt that for all time associate with free hemoglobin and hemoglobin in untouched erythrocytes (rat and human) to create a haemichrome (a methaemoglobin subordinate coming from mutilated protein compliance) (3).

CONCLUSION

According to the findings of the research, many articles refer to successful treatment of rice tablets. While the following are not considered:

- Sometimes a person has not consumed rice tablets;
- Rice tablets have been expired;
- The tablet has been exposed to moisture and water and its phosphine gas has been released;
- The tablet is dissolved in water and its phosphine gas has been released;
- There is another tablet called "Banan," which is a derivative of garlic tablet, and is mistakenly called rice tablet in Iran;
- The rice tablet is completely crushed, resulting in a large extent release of its phosphine gas;
- Due to vomiting, the tablet and its contents have been removed immediately after ingestion.

Considering these issues and the importance of obtaining the patient's history and taking into account clinical affairs as well as mere research, the effectiveness of the treatment methods mentioned in the study requires further consideration and investigation of all factors.

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