

# Thoughts on the current management of acute aluminum phosphide toxicity and proposals for therapy: An Evidence-based review

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## Abstract

The majority of aluminum phosphide (ALP) toxicity cases are suicidal attempts. Despite advances in critical care medicine, the mortality rate of ALP remains very high. Unfortunately, knowledge on the toxicokinetics of ALP is very low. An obsolete idea was proposed that inhibition of complex IV of cytochrome C oxidase is responsible for multiorgan dysfunction. However, based on human studies, this effect might be insignificant. Thus, a novel idea proposes that the main mechanism might be vascular wall integrity disruption. The low frequency of acute toxicity and unanswered questions about the toxicokinetics and toxicodynamics has led to leaden advances of novel treatments. The aim of this review was to evaluate problems regarding current treatment protocols and propose new ideas based on updated information. For this purpose, we reviewed all available articles on the management of ALP poisoning published to date. Considering failure of conventional therapies on maintaining systolic blood pressure, correcting acid-base disturbances, and support cardiac function, the previous treatment protocols have been overruled. However, repudiate of conventional treatments in this deadly condition is not without penalties for the health-care provider. The introduction of new therapies including refuse of gastric lavage with water-soluble compounds, administration of a high molecular weight colloidal solution for fluid resuscitation and termination using sodium bicarbonate, and vasoactive agents has been prospected to improve patient survival. This protocol is in early clinical evaluation; nevertheless, it appears to improve patient's survival; hence, future randomized trials should be performed to support their effectiveness.

**Keywords:** Aluminum phosphide, new therapies, phosphine, toxicity

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## Introduction

For decades, aluminum phosphide (ALP) as a low cost and highly effective grain fumigant has been used in developing countries, and phosphine (PH<sub>3</sub>) gas is

its active ingredient. Tablets are the most common forms, usually weighing 3 g.<sup>[1]</sup> Due to PH<sub>3</sub> gas ignition properties, the main product is usually combined with ammonium carbonate. Acute poisoning can occur due to ingestion or indirectly through inhalation of PH<sub>3</sub> gas

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in an environment.<sup>[2]</sup> Based on studies reported from developing countries, the majority of ALP toxicities are as a result of suicidal attempt.<sup>[3,4]</sup> In contrast, a diverse pattern has been reported from industrial countries, which indicates that most cases are accidental toxicities.<sup>[5,6]</sup>

Proudfoot, in his review of the literature, reported a mortality rate of 40%–91% within the first 24 h.<sup>[2]</sup> After ingestion, PH<sub>3</sub> is liberated in contact with gastric acidic fluids, which is absorbed through the gastric mucosa.<sup>[7]</sup> Therefore, PH<sub>3</sub> content of the mother compound has an important role in the intensity of poisoning.<sup>[8]</sup>

Chugh *et al.* showed that blood PH<sub>3</sub> concentrations are lower in patients poisoned with exposed tablets. Interestingly, they had indicated that patients with PH<sub>3</sub> blood levels  $<1.067 \pm 0.16$  mg% could survive; thus, it was proposed that toxic levels should be above these limits.<sup>[9]</sup>

*In vitro* studies revealed that PH<sub>3</sub> has an inhibitory effect on complex IV of cytochrome C oxidase.<sup>[10]</sup> Therefore, many authors have proposed that inhibition of cytochrome C oxidase is the leading cause of toxicity.<sup>[11]</sup> However, based on *in vivo* studies, it seems that this effect might be insignificant.<sup>[12]</sup> In human studies, this poisoning only produced a 45% decrease in cytochrome C oxidase activity compared with controls, which showed no significant differences between those who died or survived.<sup>[13]</sup>

Considering a similar decrease in cytochrome C oxidase activity in hemorrhagic and septic shock,<sup>[14,15]</sup> Marashi *et al.* proposed that cytochrome C oxidase inhibition might not be the primary mechanism of PH<sub>3</sub> toxicity.<sup>[16]</sup> Other probable mechanisms were explained by some authors as reactive oxygen species overproduction, intracellular lipid peroxidation, heart failure, insufficiency in vascular wall integrity, inhibition of cholinesterase activity, hemolysis, methemoglobinemia, and corrosive effects on alimentary mucosa.<sup>[16-22]</sup>

Despite the interests of researchers in this field, knowledge on the toxicokinetics of ALP is very limited.

## Literature Review

We searched Google Scholar, Scopus, PubMed Central, and MEDLINE for all available articles on the management of ALP poisoning published to date. The keywords we used were “aluminum phosphide,” “toxicity,” “poisoning,” “management,” and “treatment.” We reviewed the articles, looking for the scientific basis of presented facts for ALP poisoning. Articles that did

not meet our criteria were excluded, and from those with similar data, the latest article was selected. Selected articles were discussed by all authors focusing on the mechanisms and novel treatment protocols.

## Clinical Manifestations

The rapid manifestation of systemic toxicity offers the rapid adsorption of PH<sub>3</sub> through intraluminal mucous membrane.<sup>[23,24]</sup> After ingestion, nausea, vomiting, and retrosternal and epigastric pain will appear within few minutes, followed by dyspnea, anxiousness, and agitation. The first signs after severe toxicity include refractory hypotension and metabolic acidosis, within the first few hours of admission.<sup>[25]</sup>

Mostafazadeh *et al.* reported that some degree of methemoglobin production is a usual finding in ALP toxicity. They also reported a significant link between methemoglobin blood levels and mortality.<sup>[26]</sup> It seems that the reaction of PH<sub>3</sub> and oxyhemoglobin is responsible for denaturing its molecule and produce methemoglobinemia.<sup>[27]</sup> Some cases of intravascular hemolysis were reported in glucose-6-phosphate dehydrogenase (G6PD) deficient patients.<sup>[28,29]</sup> Interestingly, Zamani and Mehrpour reported two ALP poisoning survivors with G6PD deficiency and extensive hemolysis. The authors proposed that the extensive hemolysis had prohibited the systemic toxicity.<sup>[30]</sup> However, Sanaei-Zadeh declared that these complications might be the consequence of gastrointestinal decontamination with potassium permanganate, which is a routine measure during conventional gastrointestinal decontamination.<sup>[31,32]</sup>

Pleural effusion, ascites, pericardial effusion, congestion of the heart, focal necrosis, separation of myocardial fibers by edema, protein-rich and hemorrhagic pulmonary edema, corrosive lesions of the esophagus and stomach, congestion of the portal tract, central veins, and vacuolization of hepatocytes, hemorrhage, and necrosis of the adrenal glands are the most frequent findings during autopsy.<sup>[26]</sup>

Marashi *et al.* proposed that insufficiency in vascular wall integrity can explain everything that happens after adsorption of PH<sub>3</sub>. They claimed that the main problem is a massive intravascular fluid loss, causing refractory hypovolemic shock, which leads to multiorgan failure.<sup>[16]</sup> In this context, refractory metabolic acidosis may be a reflection of organ hypoperfusion.<sup>[33]</sup>

Logically, this is not completely in contrast with previously proposed mechanism of toxicity. In fact,

dissemination of PH<sub>3</sub> through vascular system can cause depletion in cytochrome C oxidase activity of the vascular tissue cells which can explain the problem. However, this may need additional studies evaluating the direct effect of PH<sub>3</sub> on vascular tissue function, using electron microscopy.

### Aluminum Phosphide Poisoning Therapy

The low frequency of acute toxicity and unanswered questions about the toxicokinetics and toxicodynamics has led to leaden advances in novel treatments. Novel strategies are designed based on pharmacologic or chemical principles. Thus, repudiate of conventional treatments in this deadly condition is not without penalties for the health-care provider. However, the astute survey of potential misconceptions in the course of acute toxicity has led some scientists to introduce novel therapeutic approaches with reported success in alleviating severe toxicity.<sup>[16,19,34-43]</sup> Here, we have presented the mainstream opinion, as well as its possible detriments and have presented novel treatment protocols on the basic pharmacologic or chemical principles, and successful case reports.

### Gastric Decontamination

For many years, gastric lavage with potassium permanganate (1:10,000) solution,<sup>[44,45]</sup> administration of sodium bicarbonate,<sup>[45,46]</sup> and activated charcoal (AC)<sup>[47]</sup> was routinely performed without any scientific background.

Recent studies accentuate that AC or potassium permanganate cannot interact with ALP or PH<sub>3</sub> gas due to their chemical properties.

In fact, the molecular weight of ALP is only 58 Daltons, which is lesser than the adsorption properties of AC. Moreover, even if some of the ALP molecules were adsorbed by the AC, it does not guarantee that aluminum atoms retain their weak bonds with phosphors.<sup>[48]</sup>

However, Pajoumand *et al.* and Maitai *et al.* have claimed that gastric lavage with potassium permanganate can oxidize PH<sub>3</sub> to nontoxic phosphate; Nasri Nasrabadi and Marashi had indicated that oxidation of PH<sub>3</sub> as a hard nucleophile is chemically impossible.<sup>[49]</sup>

In addition, Sanaei-Zadeh has declared that potassium permanganate is a strong oxidizing agent and reported cases of hemolysis and methemoglobinemia after ALP poisoning which were initially managed by gastric lavage with potassium permanganate.<sup>[31,32]</sup> In addition, Sanaei-

Zadeh and Marashi believe that all the above-mentioned products are water-soluble compounds and can induce more PH<sub>3</sub> gas liberation from the mother product.<sup>[50]</sup>

In contrast, *in vitro* studies support that liquid paraffin and vegetable oils can inhibit more PH<sub>3</sub> fumigation,<sup>[51]</sup> which has successfully demonstrated to alleviate acute toxicity in a case report.<sup>[34]</sup> Consequently, we recommend that only vegetable oils or liquid paraffin to be used after acute ALP poisoning for a safe gastric decontamination. Even though gastric lavage with vegetable oils is technically possible, Sanaei-Zadeh and Marashi suggest that administration of castor oil is sufficient to inhibit more PH<sub>3</sub> liberation in contact to gastrointestinal moist as well as to accelerate gastrointestinal motility and flushing the toxic compound.<sup>[50]</sup>

### Management of Severe Hypotension

The most important problem facing a clinical toxicologist during management of acute ALP toxicity is refractory hypotension, which usually does not respond to massive crystalloid administration. Vasoactive agents such as norepinephrine, phenylephrine, or dopamine are the second step in the management of shock, with limited success.<sup>[39]</sup>

As mentioned earlier, autopsy studies have indicated that transudation of fluid into the serous cavities as well as congestion of vital organs are common findings in ALP mortalities.<sup>[52,53]</sup> However, these are general findings in cardiac insufficiency, it is indicated that despite high central venous pressure (CVP) and cardiac hypokinesia, administration of large amount of fluid does not associate with pulmonary edema.<sup>[54]</sup> In an earlier study, Marashi *et al.* proposed that insufficiency in the vascular wall integrity can explain congestion of vital organs, transudation of fluid into the serous cavities, and low response to vasoactive agents and massive crystalloid administration. Thus, they believed that these conditions were not associated with heart failure.<sup>[16]</sup> In fact, administration of excessive amount of fluid will rapidly make transudation into the serous cavities, without any success to maintain systolic blood pressure. Considering this novel idea about vascular integrity insufficiency as the main problem, they proposed to use hydroxyethyl starch (a high molecular weight colloidal solution volume expander) for fluid resuscitation, which successfully saved a patient from acute toxicity in a case report.<sup>[42]</sup>

### Management of Severe Metabolic Acidosis

The second fatal complication of acute ALP toxicity is severe metabolic acidosis. However, there is no certain

comment in the literature, but most authors assume that inhibition of cytochrome C oxidase is the main reason. Hence, many authors have proposed to correct this complication by administration of intravenous sodium bicarbonate.<sup>[21,35,39]</sup>

Based on this background, Jaiswal *et al.* launched a full correction of severe metabolic acidosis by intravenous sodium bicarbonate guided by base excess. Despite a survival rate of 55%, no significant difference in base excess or pH among survivors and nonsurvivors was reported. Thus, the authors concluded that even with aggressive correction of acidosis, the prognosis is still very poor. Moreover, they reported that 35% of patients had refractory shock, which only two patients survived after the proposed management.<sup>[55]</sup>

Consequently, one can infer that refractory shock and severe metabolic acidosis are associated problems in these patients. Accordingly, Marashi *et al.* stated that the main cause of severe metabolic acidosis might be the generalized tissue hypoperfusion.<sup>[16]</sup>

Besides, Marashi and Nasri-Nasrabadi indicated that administration of  $\text{NaHCO}_3$  cannot address severe metabolic acidosis existing in these patients. In fact,  $\text{Na}^+$  and  $\text{HCO}_3^-$  will be produced after administration of intravenous sodium bicarbonate; even though  $\text{HCO}_3^-$  ion remains in the extracellular compartment and cannot influx through the cell membrane. Furthermore, in the acidic medium, reaction between  $\text{HCO}_3^-$  and  $\text{H}^+$  ions produces carbonic acid which splits into  $\text{H}_2\text{O}$  and  $\text{CO}_2$ , and  $\text{CO}_2$  can pass across the cell membrane. Therefore, we can expect some degrees of correction of circulatory pH along with intensifying intracellular acidosis.<sup>[33,56]</sup>

Accordingly, Marashi and Nasri-Nasrabadi strongly have recommended focusing all efforts on correction of severe hypotension and limiting intravenous sodium bicarbonate at arterial pH <7. They believe that administration of hydroxyethyl starch solution in addition to crystalloid ones can overcome symptoms of shock and amendment of tissue perfusion, which consequently alleviates metabolic acidosis.<sup>[33]</sup>

In fact, this opinion was supported successfully in a case who received hydroxyethyl starch solution for fluid resuscitation.<sup>[42]</sup>

On the other hand, because of its adverse effects such as acute renal failure and coagulopathy, some doubt exists in using hydroxyethyl starch as a routine strategy in the management of ALP toxicity.<sup>[57,58]</sup> Nonetheless,

Marashi and Nasri-Nasrabadi believe that due to its high mortality rate, these adverse effects may be acceptable if hydroxyethyl starch could overcome mortal complications.<sup>[59]</sup>

## Management of Cardiac Dysfunction

Authors generally believe that myocardial injury is the most probable mechanism of cardiovascular toxicity and have recommended controlling the CVP or pulmonary artery wedge pressure during fluid therapy.<sup>[35,60]</sup> Based on this background, intra-aortic balloon pump, digoxin, and trimetazidine are proposed to support heart function.<sup>[35,39,61]</sup>

As mentioned earlier, being uncertain about myocardial injury to be the probable mechanism of cardiovascular toxicity is formed. In fact, tissue hypoperfusion and intracellular acidosis could cause a reduction in cardiac function.<sup>[62]</sup> In addition, Lall *et al.* have considered that oxidative stress, inhibition of cellular metabolism, and necrosis of the cardiac tissue can be responsible for deleterious effect of ALP on heart.<sup>[63]</sup>

It is clear that in the presence of “cellular arrest,” administration of digoxin or trimetazidine could not address the problem. On the contrary, some prospering case reports have developed a new concept of their probable effect on the improvement of the neurohormonal profile.<sup>[19,35,36,61,64]</sup>

Hassanian-Moghaddam and Pajoumand proposed that administration of large doses of insulin can improve myocardial contractility by stimulating the energy generated from carbohydrates and restoring calcium fluxes in myocytes. They have reported that four out of five patients survived which were managed in this way.<sup>[65]</sup>

Another important subject during ALP toxicity management is electrolyte abnormalities. In fact, some cardiac dysfunction may be attributed to electrolyte imbalance. A wide variety of changes in potassium, magnesium, and calcium plasma levels can be expected. Chugh *et al.*<sup>[66]</sup> believe that low circulating cortisol concentrations due to adrenal gland damage might be responsible. It seems that all these changes could be attributed to administration of large amounts of sodium bicarbonate during conventional management of ALP toxicity.

Despite the importance of this subject, only a few studies have attempted to evaluate the value

of magnesium sulfate supplementation. Chugh *et al.*<sup>[67]</sup> indicated that administration of a large amount of magnesium supplementation can significantly increase the survival rate in ALP toxicity which is in contrast with Siwach *et al.* findings.<sup>[68]</sup> There are two case reports regarding the efficacy of magnesium supplementation to terminate atrial and ventricular dysrhythmias.<sup>[69,70]</sup> There is only one case report that by correcting hypokalemia, resolved the related conduction disturbances, and saved a patient.<sup>[71]</sup>

Considering the risk of electrocardiogram abnormalities, we strongly recommend to correct hypokalemia and hypocalcemia along with administering sodium bicarbonate if pH is <7.

As addressed earlier, conventional therapy with large amounts of crystalloid solutions is not successful in overcoming severe shock. Thus, administering vasoactive agents as the second line of treatment is proposed by other authors. Nevertheless, if one would accept the opinion that vascular wall integrity disruption occurs during acute phase of ALP toxicity, it is clear that administration of vasoactive agents may not be helpful, and it only imposes major stress on a hypoperfused myocardium, which is usually associated with terminal cardiac dysrhythmias and actuate the patient to gravel outcome,<sup>[72]</sup> which is the general scenario of ALP toxicity.

### Role of Extracorporeal Membrane Oxygenation in Patients Suffering from Myocardial Dysfunction

Mohan *et al.* reported the first series of successful ALP poisoning management with refractory cardiogenic shock, using extracorporeal membrane oxygenation (ECMO).<sup>[73]</sup> In this technique, patient suffering from refractory cardiogenic shock is supported by a machine, providing mechanical circulatory for a few days, until acceptable levels of myocardial function are achieved.<sup>[74]</sup> Hassanian-Moghaddam *et al.* reported a case of ALP poisoning that made a full recovery, which was supported by ECMO for 4 days.<sup>[75]</sup> In another study, Mohan *et al.*<sup>[76]</sup> indicated that veno-arterial ECMO had a significant role in amelioration of toxicity and improvement of patient survival, principally for high-risk patients. It seems that a swift decision on using ECMO, before considerable reduction in ventricular ejection fraction, is pivotal for a reasonable response.<sup>[76]</sup>

### Antioxidant Therapy

Chugh *et al.* reported reduced plasma concentrations of glutathione after ALP toxicity.<sup>[77]</sup> Thus, administration

of N-acetylcysteine can be considered as a therapeutic agent along with multitherapy approach. Unfortunately, there is only one case report that showed administration of N-acetylcysteine as one component of a complex treatment could not save a patient.<sup>[6]</sup> However, Azad *et al.* reported that administration of N-acetylcysteine could significantly prolong survival time in a rat model.<sup>[41]</sup>

Marashi *et al.*<sup>[78]</sup> proposed that administration of coenzyme Q10 as an antioxidant could be considered as another means of therapy. However, this opinion has not been evaluated yet, but they claim that based on previous studies in heart failure patients,<sup>[79-81]</sup> it could enhance cardiac systolic function as well.

### Conclusion

Considering the high mortality rates, the conventional treatment strategies for ALP toxicity have largely disappointed scientists. The goal is to overcome acute hypotension, severe metabolic acidosis, and organ dysfunction. The main attention of toxicologists must be directed toward alleviation of toxic gas liberation and correction of mortal complications.

The current opinion of ALP toxicity does not help us to treat and save the patients despite progress in intensive care. Consequently, some novel ideas of its toxicokinetics including disruption of vascular wall integrity were formed and helped the statement of clinical presentations as well as changes in treatment strategies. Successful case reports beyond the conventional treatment protocols have highlighted the need to reconsider and revise our knowledge of ALP toxicity.

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### Conflicts of interest

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