Review Article

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

Maryam Vasheghani Farahani, Davood Soroosh[1], Sayed Mahdi Marashi[2]

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

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.195712

Quick Response Code:

Introduction

For decades, aluminum phosphide (ALP) as a low cost and highly effective grain fumigant has been used in developing countries, and phosphine (PH3) gas is its active ingredient. Tablets are the most common forms, usually weighing 3 g.[1] Due to PH3 gas ignition properties, the main product is usually combined with ammonium carbonate. Acute poisoning can occur due to ingestion or indirectly through inhalation of PH3 gas

From:
Department of Forensic Medicine and Clinical Toxicology, AJA Medical School, AJA University of Medical Sciences, Tehran, [1]Department of Forensic Medicine, Sabzevar University of Medical Sciences, Sabzevar, [2]Department of Forensic Medicine and Clinical Toxicology, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Dr. Sayed Mahdi Marashi, Trauma Research Center, Emergency Room, Division of Medical Toxicology, Hazrat Ali-Asghar (p) Hospital, Meshkinfam Street, Shiraz 7143918796, Iran.
E-mail: marashi@sums.ac.ir

How to cite this article: Farahani MV, Soroosh D, Marashi SM. Thoughts on the current management of acute aluminum phosphide toxicity and proposals for therapy: An Evidence-based review. Indian J Crit Care Med 2016;20:724-30.

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

Proudfoot, in his review of the literature, reported a mortality rate of 40%–91% within the first 24 h.[2] After ingestion, PH3 is liberated in contact with gastric acidic fluids, which is absorbed through the gastric mucosa.[7] Therefore, PH3 content of the mother compound has an important role in the intensity of poisoning.[8]

Chugh *et al*. showed that blood PH3 concentrations are lower in patients poisoned with exposed tablets. Interestingly, they had indicated that patients with PH3 blood levels <1.067 ± 0.16 mg% could survive; thus, it was proposed that toxic levels should be above these limits.[9]

In vitro studies revealed that PH3 has an inhibitory effect on complex IV of cytochrome C oxidase.[10] Therefore, many authors have proposed that inhibition of cytochrome C oxidase is the leading cause of toxicity.[11] However, based on *in vivo* studies, it seems that this effect might be insignificant.[12] 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.[13]

Considering a similar decrease in cytochrome C oxidase activity in hemorrhagic and septic shock,[14,15] Marashi *et al*. proposed that cytochrome C oxidase inhibition might not be the primary mechanism of PH3 toxicity.[16] 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.[16-22]

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 PH3 through intraluminal mucous membrane.[23,24] 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.[25]

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.[26] It seems that the reaction of PH3 and oxyhemoglobin is responsible for denaturing its molecule and produce methemoglobinemia.[27] Some cases of intravascular hemolysis were reported in glucose-6-phosphate dehydrogenase (G6PD) deficient patients.[28,29] 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.[30] 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.[31,32]

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.[26]

Marashi *et al*. proposed that insufficiency in vascular wall integrity can explain everything that happens after adsorption of PH3. They claimed that the main problem is a massive intravascular fluid loss, causing refractory hypovolemic shock, which leads to multiorgan failure.[16] In this context, refractory metabolic acidosis may be a reflection of organ hypoperfusion.[33]

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

dissemination of PH3 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 PH3 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.[16,19,34-43] 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,[44,45] administration of sodium bicarbonate,[45,46] and activated charcoal (AC)[47] was routinely performed without any scientific background.

Recent studies accentuate that AC or potassium permanganate cannot interact with ALP or PH3 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 retinue their weak bonds with phosphors.[48]

However, Pajoumand *et al*. and Maitai *et al*. have claimed that gastric lavage with potassium permanganate can oxidize PH3 to nontoxic phosphate; Nasri Nasrabadi and Marashi had indicated that oxidation of PH3 as a hard nucleophile is chemically impossible.[49]

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.[31,32] In addition, Sanaei-Zadeh and Marashi believe that all the above-mentioned products are water-soluble compounds and can induce more PH3 gas liberation from the mother product.[50]

In contrast, *in vitro* studies support that liquid paraffin and vegetable oils can inhibit more PH3 fumigation,[51] which has successfully demonstrated to alleviate acute toxicity in a case report.[34] 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 PH3 liberation in contact to gastrointestinal moist as well as to accelerate gastrointestinal motility and flushing the toxic compound.[50]

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.[39]

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.[52,53] 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.[54] 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.[16] 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.[42]

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.[21,35,39]

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.[55]

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.[16]

Besides, Marashi and Nasri-Nasrabadi indicated that administration of $NaHCO_3$ cannot address severe metabolic acidosis existing in these patients. In fact, Na^+ and HCO_3^- will be produced after administration of intravenous sodium bicarbonate; even though HCO_3^- ion remains in the extracellular compartment and cannot influx through the cell membrane. Furthermore, in the acidic medium, reaction between HCO_3^- and H^+ ions produces carbonic acid which splits into H_2O and CO_2, and CO_2 can pass across the cell membrane. Therefore, we can expect some degrees of correction of circulatory pH along with intensifying intracellular acidosis.[33,56]

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.[33]

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

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.[57,58] 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.[59]

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.[35,60] Based on this background, intra-aortic balloon pump, digoxin, and trimetazidine are proposed to support heart function.[35,39,61]

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.[62] 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.[63]

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.[19,35,36,61,64]

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 myocardiocytes. They have reported that four out of five patients survived which were managed in this way.[65]

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*.[66] 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*.[67] 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.[68] There are two case reports regarding the efficacy of magnesium supplementation to terminate atrial and ventricular dysrhythmias.[69,70] There is only one case report that by correcting hypokalemia, resolved the related conduction disturbances, and saved a patient.[71]

Considering the risk of electrocardiogram abnormalities, we strongly recommend to correct hypokalemia and hypocalcemia along with administrating 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,[72] 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).[73] 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.[74] Hassanian-Moghaddam *et al*. reported a case of ALP poisoning that made a full recovery, which was supported by ECMO for 4 days.[75] In another study, Mohan *et al*.[76] 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.[76]

Antioxidant Therapy

Chugh *et al*. reported reduced plasma concentrations of glutathione after ALP toxicity.[77] 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.[6] However, Azad *et al*. reported that administration of N-acetylcysteine could significantly prolong survival time in a rat model.[41]

Marashi *et al*.[78] 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,[79-81] 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.

Acknowledgment

We would like to thank the Research Consultation Center of Shiraz University of Medical Sciences, for their valuable assistance in editing this review.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mehrpour O, Singh S. Rice tablet poisoning: A major concern in Iranian population. Hum Exp Toxicol 2010;29:701-2.
2. Proudfoot AT. Aluminium and zinc phosphide poisoning. Clin Toxicol (Phila) 2009;47:89-100.
3. Taghaddosi Nejad F, Banagozar Mohammadi A, Behnoush B, Kazemifar AM, Zaare Nahandi M, Dabiran S, *et al*. Predictors of poor prognosis in aluminum phosphide intoxication. Iran J Toxicol 2012;6:610-4.

4. Jain AK, Dubey BP, Garg SP, Nigam M. Trends of aluminium phosphide poisoning in Bhopal region – A retrospective study of 10 years. J Indian Acad Forensic Med 2009;31:971-3.
5. Lauterbach M, Solak E, Kaes J, Wiechelt J, Von Mach MA, Weilemann LS. Epidemiology of hydrogen phosphide exposures in humans reported to the poison center in Mainz, Germany, 1983-2003. Clin Toxicol (Phila) 2005;43:575-81.
6. Bogle RG, Theron P, Brooks P, Dargan PI, Redhead J. Aluminium phosphide poisoning. Emerg Med J 2006;23:e3.
7. Mehrpour O, Abdollahi M. Poison treatment centers in Iran. Hum Exp Toxicol 2012;31:303-4.
8. Sanaei-Zadeh H. Acute aluminium phosphide poisoning: Can we predict survival? Indian J Anaesth 2012;56:207-8.
9. Chugh SN, Pal R, Singh V, Seth S. Serial blood phosphine levels in acute aluminium phosphide poisoning. J Assoc Physicians India 1996;44:184-5.
10. Dua R, Gill KD. Effect of aluminium phosphide exposure on kinetic properties of cytochrome oxidase and mitochondrial energy metabolism in rat brain. Biochim Biophys Acta 2004;1674:4-11.
11. Shadnia S. Fumigants. In: Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR, editors. Goldfrank's Toxicologic Emergencies. 10th ed. New York: McGraw-Hill; 2015. p. 3213-30.
12. Jian F, Jayas DS, White ND. Toxic action of phosphine on the adults of the copra mite *Tyrophagus putrescentiae* [*Astigmata*: Acaricidae]. Phytoprotection 2000;81:23-8.
13. Singh S, Bhalla A, Verma SK, Kaur A, Gill K. Cytochrome-c oxidase inhibition in 26 aluminum phosphide poisoned patients. Clin Toxicol (Phila) 2006;44:155-8.
14. Kariman K, Jöbsis FF, Saltzman HA. Cytochrome a, a3 reoxidation. Early indicator of metabolic recovery from hemorrhagic shock in rats. J Clin Invest 1983;72:180-91.
15. Levy RJ, Vijayasarathy C, Raj NR, Avadhani NG, Deutschman CS. Competitive and noncompetitive inhibition of myocardial cytochrome C oxidase in sepsis. Shock 2004;21:110-4.
16. Marashi SM, Arefi M, Behnoush B, Nasrabad MG, Nasrabadi ZN. Could hydroxyethyl starch be a therapeutic option in management of acute aluminum phosphide toxicity? Med Hypotheses 2011;76:596-8.
17. Echtay KS, Roussel D, St-Pierre J, Jekabsons MB, Cadenas S, Stuart JA, *et al.* Superoxide activates mitochondrial uncoupling proteins. Nature 2002;415:96-9.
18. Hsu CH, Chi BC, Casida JE. Melatonin reduces phosphine-induced lipid and DNA oxidation *in vitro* and *in vivo* in rat brain. J Pineal Res 2002;32:53-8.
19. Sanaei-Zadeh H, Farajidana H. Is there a role for digoxin in the management of acute aluminum phosphide poisoning? Med Hypotheses 2011;76:765-6.
20. Mittra S, Peshin SS, Lall SB. Cholinesterase inhibition by aluminium phosphide poisoning in rats and effects of atropine and pralidoxime chloride. Acta Pharmacol Sin 2001;22:37-9.
21. Soltaninejad K, Nelson LS, Khodakarim N, Dadvar Z, Shadnia S. Unusual complication of aluminum phosphide poisoning: Development of hemolysis and methemoglobinemia and its successful treatment. Indian J Crit Care Med 2011;15:117-9.
22. Talukdar R, Singal DK, Tandon RK. Aluminium phosphide-induced esophageal stricture. Indian J Gastroenterol 2006;25:98-9.
23. Curry AS, Price DE, Tryhorn FG. Absorption of zinc phosphide particles. Nature 1960;184 Suppl 9:642-3.
24. Chan LT, Crowley RJ, Delliou D, Geyer R. Phosphine analysis in post mortem specimens following ingestion of aluminium phosphide. J Anal Toxicol 1983;7:165-7.
25. Mostafazadeh B. Aluminium phosphide poisoning. In: Aeree B, editor. Toxicity and Drug Testing. Rijeka: InTech; 2012. Available from: http://www.intechopen.com/books/toxicity-and-drugtesting/aluminium-phosphide-poisoning. [Last accessed on 2012 Feb 30].
26. Mostafazadeh B, Pajoumand A, Farzaneh E, Aghabiklooei A, Rasouli MR. Blood levels of methemoglobin in patients with aluminum phosphide poisoning and its correlation with patient's outcome. J Med Toxicol 2011;7:40-3.
27. Chin KL, Mai X, Meaklim J, Scollary GR, Leaver DD. The interaction of phosphine with haemoglobin and erythrocytes. Xenobiotica 1992;22:599-607.
28. Sood AK, Mahajan A, Dua A. Intravascular haemolysis after aluminium phosphide ingestion. J R Soc Med 1997;90:47-8.
29. Srinivas R, Agarwal R, Jairam A, Sakhuja V. Intravascular haemolysis due to glucose-6-phosphate dehydrogenase deficiency in a patient with aluminium phosphide poisoning. Emerg Med J 2007;24:67-8.
30. Zamani N, Mehrpour O. Protective role of G6PD deficiency in poisoning by aluminum phosphide; are there possible new treatments? Eur Rev Med Pharmacol Sci 2013;17:994-5.
31. Sanaei-Zadeh H. Response to "blood levels of methemoglobin in patients with aluminum phosphide poisoning and its correlation with patient's outcome". J Med Toxicol 2012;8:86-7.
32. Sanaei-Zadeh H. Aluminum phosphide poisoning and development of hemolysis and methemoglobinemia. Indian J Crit Care Med 2012;16:248-9.
33. Marashi SM, Nasri-Nasrabadi Z. Can sodium bicarbonate really help in treating metabolic acidosis caused by aluminium phosphide poisoning? Arh Hig Rada Toksikol 2015;66:83-4.
34. Shadnia S, Rahimi M, Pajoumand A, Rasouli MH, Abdollahi M. Successful treatment of acute aluminium phosphide poisoning: Possible benefit of coconut oil. Hum Exp Toxicol 2005;24:215-8.
35. Mehrpour O, Farzaneh E, Abdollahi M. Successful treatment of aluminum phosphide poisoning with digoxin: A case report and review of literature. Int J Pharmacol 2011;7:761-4.
36. Abbaspour A, Nasri-Nasrabadi Z, Ghorbani A, Marashi SM. Successful treatment of acute aluminum phosphide poisoning induced heart failure: A case report. Razi J Med Sci 2013;20:78-83.
37. Siddaiah L, Adhyapak S, Jaydev S, Shetty G, Varghese K, Patil C, *et al.* Intra-aortic balloon pump in toxic myocarditis due to aluminum phosphide poisoning. J Med Toxicol 2009;5:80-3.
38. Saidi H, Shokraneh F, Ghafouri HB, Shojaie S. Effects of hyperbaric oxygenation on survival time of aluminum phosphide intoxicated rats. J Res Med Sci 2011;16:1306-12.
39. Baeeri M, Shariatpanahi M, Baghaei A, Ghasemi-Niri SF, Mohammadi H, Mohammadirad A, *et al.* On the benefit of magnetic magnesium nanocarrier in cardiovascular toxicity of aluminum phosphide. Toxicol Ind Health 2013;29:126-35.
40. Saidi H, Shojaie S. Effect of sweet almond oil on survival rate and plasma cholinesterase activity of aluminum phosphide-intoxicated rats. Hum Exp Toxicol 2012;31:518-22.
41. Azad A, Lall SB, Mittra S. Effect of N-acetylcysteine and L-NAME on aluminium phosphide induced cardiovascular toxicity in rats. Acta Pharmacol Sin 2001;22:298-304.
42. Marashi SM, Nasri Nasrabadi Z, Jafarzadeh M, Mohammadi S. Hydroxyethyl starch could save a patient with acute aluminum phosphide poisoning. Acta Med Iran 2016;54:475-8.
43. Mehrpour O, Amouzeshi A, Dadpour B, Oghabian Z, Zamani N, Amini S, *et al.* Successful treatment of cardiogenic shock with an intraaortic balloon pump following aluminium phosphide poisoning. Arh Hig Rada Toksikol 2014;65:121-6.
44. Pajoumand A, Jalali N, Abdollahi M, Shadnia S. Survival following severe aluminium phosphide poisoning. J Pharm Pract Res 2002;32:297-9.
45. Maitai CK, Njoroge DK, Abuga KO, Mwaura AM, Munenge RW. Investigation of possible antidotal effects of activated charcoal, sodium bicarbonate, hydrogen peroxide and potassium permanganate in zinc phosphide poisoning. East Cent Afr J Pharm Sci 2002;5:38-41.
46. Gurjar M, Baronia AK, Azim A, Sharma K. Managing aluminum phosphide poisonings. J Emerg Trauma Shock 2011;4:378-84.
47. Moghadamnia AA. An update on toxicology of aluminum phosphide. Daru 2012;20:25.
48. Marashi SM, Majidi M, Raji Asadabadi H, Nasri-Nasrabadi Z. A common misconception in the management of aluminium phosphide poisoning. Arh Hig Rada Toksikol 2013;64:475-6.
49. Nasri Nasrabadi Z, Marashi SM. Comments on "A systematic review of aluminium phosphide poisoning". Arh Hig Rada Toksikol 2012;63:551.
50. Sanaei-Zadeh H, Marashi SM. Gastric decontamination in aluminium phosphide poisoning: A case against the use of water-based solutions. Arh Hig Rada Toksikol. 2016;67:339-40.

51. Goswami M, Bindal M, Sen P, Gupta SK, Avasthi R, Ram BK. Fat and oil inhibit phosphine release from aluminium phosphide – Its clinical implication. Indian J Exp Biol 1994;32:647-9.
52. Jain AK, Nigam M, Garg SD, Dubey BP, Arora A. Aluminium phosphide poisoning autopsy findings. J Indian Acad Forensic Med 2005;27:35-9.
53. Mehrpour O, Dolati M, Soltaninejad K, Shadnia S, Nazparvar B. Evaluation of histopathological changes in fatal aluminum phosphide poisoning. Indian J Forensic Med Toxicol 2008;2:34-6.
54. Siwach SB, Jagdish K, Katyal VK, Dhall A, Bhardwaj G. Prognostic indices in aluminium phosphide poisoning observations on acidosis & central venous pressure. J Assoc Physicians India. 1997;45:693-5.
55. Jaiswal S, Verma RK, Tewari N. Aluminum phosphide poisoning: Effect of correction of severe metabolic acidosis on patient outcome. Indian J Crit Care Med 2009;13:21-4.
56. Boyd JH, Walley KR. Is there a role for sodium bicarbonate in treating lactic acidosis from shock? Curr Opin Crit Care 2008;14:379-83.
57. Rumboldt Z. Hydroxyethyl starch should not be used to manage severe aluminium phosphide poisoning. Arh Hig Rada Toksikol 2015;66:219.
58. Hartog CS, Natanson C, Sun J, Klein HG, Reinhart K. Concerns over use of hydroxyethyl starch solutions. BMJ 2014;349:g5981.
59. Marashi SM, Nasri-Nasrabadi Z. Response to Professor Rumboldt's reaction to our letter on hydroxyethyl starch use in managing aluminium phosphide poisoning. Arh Hig Rada Toksikol 2015;66:221-3.
60. Mehrpour O, Jafarzadeh M, Abdollahi M. A systematic review of aluminium phosphide poisoning. Arh Hig Rada Toksikol 2012;63:61-73.
61. Dueñas A, Pérez-Castrillon JL, Cobos MA, Herreros V. Treatment of the cardiovascular manifestations of phosphine poisoning with trimetazidine, a new antiischemic drug. Am J Emerg Med 1999;17:219-20.
62. Marashi SM. A new concept against the priority of vasoactive agents in the management of severe hypotension associated with aluminum phosphide poisoning. Eur Rev Med Pharmacol Sci 2016;20:3517-8.
63. Lall SB, Sinha K, Mittra S, Seth SD. An experimental study on cardiotoxicity of aluminium phosphide. Indian J Exp Biol 1997;35:1060-4.
64. Marashi SM, Majidi M, Sadeghian M, Ahmadi S, Raji Asadabadi H, Nasri Nasrabadi Z. Is the use of cardioactive steroids appropriate in managing aluminium phosphide poisoning-induced heart failure? Arh Hig Rada Toksikol 2013;64:477-8.
65. Hassanian-Moghaddam H, Pajoumand A. Two years epidemiological survey of aluminium phosphide poison. Iran J Toxicol 2007;1:1-9.
66. Chugh SN, Kishore K, Aggarwal N, Attri S. Hypoglycaemia in acute aluminium phosphide poisoning. J Assoc Physicians India 2000;48:855-6.
67. Chugh SN, Kamar P, Sharma A, Chugh K, Mittal A, Arora B. Magnesium status and parenteral magnesium sulphate therapy in acute aluminum phosphide intoxication. Magnes Res 1994;7:289-94.
68. Siwach SB, Singh P, Ahlawat S, Dua A, Sharma D. Serum & tissue magnesium content in patients of aluminium phosphide poisoning and critical evaluation of high dose magnesium sulphate therapy in reducing mortality. J Assoc Physicians India 1994;42:107-10.
69. Chugh SN, Jaggal KL, Ram S, Singhal HR, Mahajan SK. Hypomagnesaemic atrial fibrillation in a case of aluminium phosphide poisoning. J Assoc Physicians India 1989;37:548-9.
70. Chugh SN, Malhotra S, Kumar P, Malhotra KC. Reversion of ventricular and supraventricular tachycardia by magnesium sulphate therapy in aluminium phosphide poisoning. Report of two cases. J Assoc Physicians India 1991;39:642-3.
71. Kochar DK, Shubhakaran, Jain N, Sharma BV, Meena CB. Successful management of hypokalaemia related conduction disturbances in acute aluminium phosphide poisoning. J Indian Med Assoc 2000;98:461-2.
72. Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. Ann Intern Med 1999;131:47-59.
73. Mohan B, Gupta V, Ralhan S, Gupta D, Puri S, Wander GS, *et al.* Role of extracorporeal membrane oxygenation in aluminum phosphide poisoning-induced reversible myocardial dysfunction: A novel therapeutic modality. J Emerg Med 2015;49:651-6.
74. Tariq S, Gass A. Use of extracorporeal membrane oxygenation in refractory cardiogenic shock. Cardiol Rev 2016;24:26-9.
75. Hassanian-Moghaddam H, Zamani N, Rahimi M, Hajesmaeili M, Taherkhani M, Sadeghi R. Successful treatment of aluminium phosphide poisoning by extracorporeal membrane oxygenation. Basic Clin Pharmacol Toxicol 2016;118:243-6.
76. Mohan B, Singh B, Gupta V, Ralhan S, Gupta D, Puri S, *et al.* Outcome of patients supported by extracorporeal membrane oxygenation for aluminum phosphide poisoning: An observational study. Indian Heart J 2016;68:295-301.
77. Chugh SN, Kolley T, Kakkar R, Chugh K, Sharma A. A critical evaluation of anti-peroxidant effect of intravenous magnesium in acute aluminium phosphide poisoning. Magnes Res 1997;10:225-30.
78. Marashi SM, Majidi M, Sadeghian M, Jafarzadeh M, Mohammadi S, Nasri Nasrabadi Z. Protective role of coenzyme Q10 as a means of alleviating the toxicity of aluminum phosphide: An evidence-based review. Tzu Chi Med J 2015;27:7-9.
79. Sander S, Coleman CI, Patel AA, Kluger J, White CM. The impact of coenzyme Q10 on systolic function in patients with chronic heart failure. J Card Fail 2006;12:464-72.
80. Keogh A, Fenton S, Leslie C, Aboyoun C, Macdonald P, Zhao YC, *et al.* Randomised double-blind, placebo-controlled trial of coenzyme Q, therapy in Class II and III systolic heart failure. Heart Lung Circ 2003;12:135-41.
81. Stafford RS, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. J Am Coll Cardiol 2003;41:56-61.