Chapter

1

Aluminum Phosphide Poisoning

ABSTRACT

Aluminum phosphide (AlPhos) is a solid fumigant used extensively in agricultural practices in India. It is cheap, easily available and lethal. It is a potent pesticide and does not affect or leave residue in grains. AlPhos poisoning is mostly suicidal with very high mortality. Phosphine gas (PH_3) produced after ingestion seems to be the main culprit for all the toxic effects of AlPhos. Phosphine released in ALP affected patients seems to be inordinately high and has not been measured in any study as per our literature review. High anion gap, severe metabolic acidosis because of lactic acid accumulation is the major metabolic dysfunction observed in these patients. This leads to profound myocardial depression leading to intractable cardiogenic shock. There is no specific antidote, and management concentrates on early diagnosis, aggressive resuscitation and supportive care. Various experimental therapies have been advocated to improve survival rates. This includes sodium bicarbonate, magnesium sulfate, vitamin C, glutathione, intralipids, N-acetyl cysteine (NAC) and many other therapies. Intra-aortic balloon pump (IABP), renal replacement therapy (RRT), and extracorporeal membrane oxygenation (ECMO) Life support systems have added value in the management of these cases. This article aims to highlight the magnitude of the problem, review of literature, clinical presentation, management options, and scope for future research in relation to this lethal toxin.

Key words: Pesticide poisoning; Aluminum phosphide; Phosphine gas; High-anion gap metabolic acidosis; Myocardial dysfunction; Shock; RRT; ECMO.

INTRODUCTION

Aluminum phosphide (AlPhos) and organophosphate (OP) remain the most common poisons being used in Indian subcontinent for suicidal purposes.[1] They constitute >50% of all poisoning cases reported in emergency room. Organophosphate poisoning (OPP) has a specific and effective antidote, whereas AlPhos does not have any. Therefore, management of AlPhos largely remains supportive and carries high mortality. Poor understanding of mechanism of action of AlPhos toxicity[2] in human body is probably major factor related to nonavailability of effective antidote. In many parts of India, it is household pesticide used to protect grains, therefore, easily accessible to the family members. It is a solid fumigant available as tablets, pellets, and powder. It continues to be at the top of the lists of toxic agents where there is tremendous scope of research. The different names[3] in which aluminum

phosphide is available commercially include Celphos, Rice tablets, Alphos, Quickphos, Phosfume, Phostoxin, Talunex, Degesch, Synfume, Chemfume, Phostek, Delicia, etc.

Usual poisoning is caused by ingestion, but inhalational poisoning[4] can also occur. Maximum permissible exposure limit of phosphine gas is 0.3 ppm (parts per million) over an eight-hour work-shift, which is the occupational safety and heath administration's (OSHAs) permissible exposure limit. Levels greater than 50 ppm are dangerous to life, with levels >400 ppm being lethal within half an hour. Those working in manufacturing units of AlPhos or methamphetamine industry (where phosphine is a by-product) and those working to place AlPhos tablets in granaries are at risk of unintentional phosphine gas exposure or accidental AlPhos poisoning. Olfactory fatigue may be contributory to occupational hazard.

EPIDEMIOLOGY

AlPhos poisoning is a problem mainly in the developing world and so in the Indian subcontinent. There were few reports until 1980s, but now it is a common mode of suicide in the middle socioeconomic group, particularly in northern India[5], where there is tradition of storing grains for long periods after new harvests. It usually involves young adult population from rural or semiurban areas. However, it is also reported from big towns and cities because of easy availability. It is more common in males as compared to females. However, in a recent study reported from Ethiopia[6], females outnumbered the males in AlPhos poisoning. Apart from the 93 cases reported to National Poisons Information Service (London) between 1993 and 2003, very few cases have been reported from Europe or other Western countries. It is also reported from Iran, Jordan, Morocco and Saudi Arabia.[7]

MECHANISM OF ACTION/ PATHOPHYSIOLOGY

The exact pathophysiology and mechanism of AlPhos is ill understood. However, there appears to be a general consensus that AlPhos releases phosphine gas as it comes in contact with moisture or air.[8] It is understood that it is rapid absorbed rapidly from gut. It is also released into atmosphere by the patient, who emits a foul odor of decaying fish or garlic. It is also purported that it may be absorbed through lung mucosa.[9]

The following is the chemical reaction which ensues:

- $AlP + 3H_2O = Al(OH)_3 + PH_3$
- $AlP + 3HCl = AlCl_3 + PH_3$

One of the major mechanisms which looks more credible than others is that the phosphine gas after absorption acts at the cellular level on the mitochondria through a poorly understood chain of events. The major event that is observed is the accumulation of lactic acid to very high levels.[10] This seems to be caused by non-entry of pyruvate into mitochondria and its diversion to produce large quantities of lactate. This overwhelms all the alkali reserves and the bicarbonate generating capacity by the renal system. Thus, all these patients present with high-anion gap metabolic acidosis with very high lactates and very low bicarbonates, with a very low pH (from 6.8 to 7.2). These patients have all the clinical manifestations of severe metabolic acidosis[11] like acidotic breathing, cardiac dysfunction leading to decreased myocardial contractility with low ejection fraction, and conduction disturbances, producing a variety of cardiac arrhythmias. Studies suggest that "bundle of His" in the myocardium is the worst affected.[12] The ultimate challenge is cardiogenic shock which develops rapidly and is profound. It appears that the toxic gas does not cross the blood–brain barrier, since

all patients are conscious till the end. There are many proposed theories, however none of these explain the complete mechanism. These mechanisms are mentioned below:[13]

1. It will block the oxygen uptake due to inhibition of adenosine diphosphate uncoupler, as observed in the isolated rat liver mitochondria.
2. It causes direct inhibition of electron transport chain that could not be reversed by the uncoupler due to blocking of mitochondrial respiration in active state (state 3) than in resting state (state 4) as observed in mouse liver, housefly flight muscles, granary weevils and beef heart. It was found to inhibit ion pumping state affecting pyruvate, malate, succinate, glycerophosphate and ascorbate cytochrome substrates of the Krebs' cycle.
3. It acts as a mitochondrial poison that leads to the generation of reactive oxygen species. Accelerated free radical damage and lipid peroxidation causes cellular damage, disruption of ionic barrier, and nucleic acid disintegration leading to myocardial necrosis and changes in cell electrophysiology.
4. Higher levels of superoxide dismutase, glutathione, malonyl dialdehyde and catalase were found in postmortem studies and reduction in their serum levels in survivors suggests their possible role in mechanism of poisoning.
5. Another purported mechanism is disruption of vascular wall integrity. Direct toxic effects on cardiac myocytes and adrenals leading to circulatory shock.

CLINICAL PRESENTATION

The clinical features of AlPhos poisoning depend on the route, the dose, and the interval between ingestion and presentation.[14, 15] Inhalation of phosphine is a difficult clinical diagnosis, although the smell of rotten eggs or a garlic-like odor may be an important clue.[16]

The most common clinical features include the following:

Restlessness, foul garlicky-rotten fish odor, nausea, vomiting, pain abdomen, deep acidotic breathing, tachyarrhythmias and hypotension with maintained consciousness level.[17]

The first signs after severe toxicity include refractory hypotension and metabolic acidosis, within the first few hours of admission.[18]

The major clinical and laboratory features as per various studies, case reports and unpublished case series include the following:[19, 75]

- Hypotension (SBP <90 mm Hg)
- Tachycardia (HR >120/min)
- Consciousness is not affected.
- Metabolic acidosis (pH 6.8–7.1)
- High lactate levels (>10 mmol/L)
- Hypoglycemia (blood sugar level <80 mg/dL)
- Low ejection fraction (LVEF = 20–35%)
- Arrhythmias (other than sinus tachycardia)
- Hypokalemia (K^+ <3 mmol/L)
- Hypomagnesemia (Mg^{2+} <1.4 mg/dL)
- Significantly raised transaminases (>200 U/L)

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.[20] It seems that the reaction of PH_3 and oxyhemoglobin is responsible for denaturing its molecule and produce methemoglobinemia[21] (Table 1.1).

Table 1.1: Organ specific clinical features of AlPhos[10, 14, 22–31]	
System affected	***Clinical features***
Cardiovascular system	• Reduced left ventricular ejection fraction to as low as <20%, suggestive of cardiogenic shock. • Arrhythmias: Supraventricular and ventricular tachycardia, atrial fibrillation/flutter, ventricular tachycardia/fibrillation (VT/VF), sometimes bradyarrthmias requiring pacing, QT dispersion
Respiratory system	Airway irritation, deep rapid acidotic breathing, cough, chest tightness, SPO_2 is maintained, unless there are secondary complications like aspiration, ARDS
Renal	Oliguria and AKI (acute kidney injury)
Acid base, electrolyte and metabolic disturbances	High-anion gap metabolic acidosis: Degree of acidosis depends on severity of toxiceffects. Most admitted cases show a pH of 6.8– 7.15. • Hyperlactemia • Dyselectrolytemia—all types of electrolyte disturbances are reported and nonspecific • Hypoglycemia has been reported and attributed to sustained vomiting and other unknown metabolic disturbances
Central nervous system	• All patients are conscious and are able to tell the complete history. The sensorium is initially normal in most patients, until hypoxia supervenes resulting in altered mentation and delirium • They may have ataxia, numbness, paresthesia, tremors, muscle weakness and diplopia
Gastrointestinal system	Nausea, vomiting, diarrhea, pain in abdomen, mild derangement of transaminases.

DIAGNOSIS

The following can aid in diagnosis of ALP poisoning:

1. History
2. Clinical features at presentation
3. Odor analysis: Garlicky or decaying fish odor from the patient.
4. Silver nitrate test:[32] Detection of phosphine (PH_3) gas in exhaled air or in gastric contents. In this test, diluted gastric content is heated in a flask up to 50°C for 15–20 minutes, keeping silver nitrate paper on the mouth of the flask. If phosphine is present, then the paper will turn black due to silver phosphate.
5. Chemical analysis of PH_3 in blood is not recommended because it is rapidly oxidized to phosphite and hypophosphite. However, specialized phosphine detector tubes have been reported to detect PH_3 in the breath.
6. Gas chromatography:[33] Most sensitive and specific test to detect even minute amounts of PH_3 in viscera and gastric contents collected during autopsy (mainly used in post-mortem).

MANAGEMENT

- In view of nonavailability of antidote, management is largely supportive.
- It should be aggressive and initiated without any delay. Time is key to management of these patients.
- These patients should preferably be managed in an intensive care unit for better monitoring and management.
- Sodium bicarbonate has been used extensively to correct severe metabolic acidosis. Until further research, it may be looked upon as a "surrogate antidote". High dose and continuous infusion of sodium bicarbonate has been reported to be effective in AlPhospoisoning.[34, 35]

A. Initial Assessment and Resuscitation

CAB (Circulation–Airway–Breathing)[36] may be the right approach in these patients, because circulatory collapse requires immediate attention.

1. Circulation: The patients' circulation can be supported by using intravenous fluids and sodium bicarbonate, vasopressors and inotropes, IABP and ECMO.

a. **Intravenous fluids and sodium bicarbonate:** Intravenous fluids are indicated as leakage of fluids from the intravascular to the extravascular space occurs as a result of capillary dysfunction.[37] Fluid resuscitation with crystalloids should be started immediately as per standard prevalent practices.[38–40] It should be administered judiciously only after measuring central venous pressure or inferior vena cava (IVC) diameter. As most of these patients present with severe metabolic acidosis, therefore the parallel use of 7.5 % or 8.4% sodium bicarbonate solution in high doses is also recommended.[34, 35] Intensivists have used as much as more than two litres of sodium bicarbonate solution in the first 2–3 hours of resuscitation. ABG samples are recommended to be done frequently to assess the pH and lactate levels of the patient.[28] This point of care investigation will be helpful to monitor the requisite trend towards declining lactate and rise in pH levels.[41] It is imperative to maintain a pH above 7, which is a challenging task indeed.[41–42] Hypernatremia should be monitored in the patient and sodium levels should not be allowed to go beyond 150 mEq/L.

   Correction of hypoglycemia is important and a blood sugar level of 150–180 mg/dL should be maintained with continuous infusion of hypertonic dextrose solution.[30, 31]

b. **Vasopressors and inotropes:** Invasive arterial blood pressure monitoring will be required, since noninvasive monitoring may not be rewarding in view of very poor peripheral pulses. Frequent bedside echocardiography is always recommended to monitor cardiac functioning and assess ejection fraction. Vasopressors should be started early and Noradrenaline is the vasopressor of choice, followed by vasopressin as the next choice.[43,44] A target should be set to maintain the systolic BP at >90 mm Hg, so that inotropes like dobutamine can be introduced which can enhance the myocardial contractility. Vasoactive agents with more β-receptor agonist action like dopamine and dobutamine should be used cautiously as they are prone to inducing arrhythmias.[17] Tachyarrhythmia can be addressed if the patient develops arrhythmias with synchronized cardioversion and antiarrhythmic medications such amiodarone. Bradyarrhythmias may necessitate the temporary use of a pacemaker.

c. **IABP (intra-aortic balloon pump):**[45–47] It has also been advocated for treating cardiogenic shock and toxic myocarditis in several case reports. Therefore, early use of IABP looks logical in AlPhos poisoning patients who survive more than 12 hours and have refractory hypotension, despite maximal supportive therapy. But, the cost and availability are the limiting factors.

d. **Use of ECMO:**[48–51, 76] Several case series and reports of the successful use of extra-corporeal membrane oxygenation therapy (ECMO) for salvage of patients with severe aluminium phosphide poisoning with promising results are available in literature.VA-ECMO (Veno-Arterial ECMO) has been used with improved outcomes in these patients. It has been shown to increase the survival outcome of the AlPhos poisoned patients having severe left ventricular dysfunction by supporting the hemodynamics until the effect of the poison wears off. A longer delay in hospital presentation was associated with higher mortality even after ECMO use. Therefore, it has been suggested to initiate ECMO as soon as possible if patient has severe metabolic acidosis (pH <7.1), marked LV dysfunction (LVEF <30%), refractory hypotension (Systolic BP <90 mm Hg despite inotropic/vasopressors support), severe lactic acidosis (lactate levels >10 mmol/L), life-threatening arrhythmias and multi-organ failure. As the ultimate outcome of these patients is decided by the course taken in the first 72 hours of management, the decision to initiate ECMO has to be made very fast. Therefore, time and affordability are vital elements in the final decision making to initiate ECMO. Since the use of ECMO is in its nascent stage in India; therefore, indications and contraindications have to be considered in these cases more carefully. Ethical considerations will also come into play. More randomized controlled trials are required.

2. Airway and breathing: High-flow supplemental oxygen may be initiated to support the patient and to reduce the work of breathing. Ventilatory support is seldom needed in these patients, and it is an ominous sign if required. Such patients have severe myocardial dysfunction with very low LVEF. Therefore, positive pressure ventilation will further compromise the critical hemodynamics of these patients. Some reports in literature about removing phosphine gas through lungs by mechanical ventilation require corroboration and research before it can be recommended for use.

B. Reduce Toxin Exposure

a. Decontamination of skin, eye and other body surfaces as soon as possible: This helps to limit phosphine absorption through the mucocutaneous route.

b. Gastric lavage: There is an ongoing debate concerning whether gastric lavage must be administered or not and regarding which agents to be used. It will be useful only if performed early (within 1–2 hours of ingestion). Forced emesis is not recommended. The personnel performing the gastric lavage should protect themselves with appropriate PPE (personal protective equipment).

After acute AlPhos poisoning, solutions made of water should not be utilized for gut decontamination.[52] There will be a greater release of PH_3 from aluminium phosphide when it comes into touch with water. Due to the oxidizing qualities of potassium permanganate, there will also be exothermic reaction, induction of hemolysis, and methemoglobinemia.[20–21,53] Due to this, it may be practical to use castor oil or vegetable oil for gastric lavage instead of water.

The following gastric lavage agents have been used in literature (Table 1.2).

c. Phosphine excretion can be enhanced by maintaining adequate renal perfusion and urine output.

Table 1.2: Agents to be used for gut decontamination[54–56, 57–60]		
Agent	***Dose/concentration***	***Suggested mechanism of action***
Potassium permanganate (water used in the solution may be harmful due to greater PH_3 production)	1:10,000	It oxidises PH_3 to the nontoxic phosphate
Activated charcoal (cautious use in selected cases); use of water is not recommended	1 g/kg (maximum 100 g)	Adsorbs the PH_3 and limits its absorption into the body
Vegetable oil (least viscous)	Aliquots 150 mL vegetable oil (12 g) + followed by aspiration: maneuver repeated 10–15 times in the first hours. However, it is easier said than done	Protective layer on gastric mucosa by coconut oil, thereby preventing absorption of phosphine gas.

C. Treating Metabolic Acidosis[34,35, 41, 42]

There are three possible methods of treating metabolic acidosis:

1. Required doses of sodium bicarbonate will be helpful to treat lactate-induced severe metabolic acidosis.
2. Successful renal replacement therapy (RRT), HD/SLED results in improvement in pH, LVEF and BP of the patients. Therefore, early use of RRT is needed during the first 24–48 hours to generate more endogenous bicarbonates. These patients require rapid correction of metabolic acidosis. Therefore, continuous RRT is not advisable because of its slow mode of action. It must be understood that lactate is not a dialyzable molecule.
3. Last but not the least, is treating the cause and prevent further production of lactic acid, which remains a matter of research.

D. Other Supportive Measures

1. Use of mild sedatives like haloperidol which do not depress the cardiorespiratory system may be considered. These patients are very irritable, combative and noncooperative. Therefore, for implementation of management protocols such sedation may be required.
2. Use of prokinetics like metoclopramide to stop vomiting and promote emptying of stomach is suggested. Active nutrition may be withheld for a day or two to prevent aspiration. However, hypoglycemia should be prevented under all circumstances.
3. Treatment of dyselectrolytemia is done by standard protocols.
4. Psychiatric and medical jurisprudence help should be taken in all cases. Early involvement of regional poison control cells is advisable.

E. Experimental/Historical Therapies Used without Much Supportive Evidence

Other supportive measures include intravenous magnesium sulfate, GIK (glucose-insulin-potassium) infusion, steroids, N-acetylcysteine (NAC), glutathione, melatonin, vitamin C, beta-carotene and trimetazidine.

The agents listed in Table 1.3 have shown promising results in ALP poisoning and can be used as supportive therapies to enhance patient survival:

Table 1.3: Experimental/historical agents

Agent	*Dose (Note: Exact dose mentioning may not be of great use)*	*Mechanism*
N-Acetylcysteine[61–63]	NAC at a dose of 150 mg/kg iv over I hour in 200 mL 5% dextrose, followed by 50 mg/kg in 500 mL over 4 hours, followed by 100 mg/kg in 500 mL over 16 hours[52]	Antioxidant and free-radical scavenger
Magnesium sulphate[64–67] (The dosages for magnesium sulphate were different in different studies)	(a) 3 g as infusion over 3 hours, followed by 6 g per 24 hours for 3–5 days, (b) 1g stat, then 1 g every hour for the next 2 hours and then 1–1.5 g every 6 hours for 5–7 days, (c) 4 g stat, 2 g after one hour and then 1 g every three-hourly and (d) 3 g bolus followed by 6 g infusion over the next 12 hours for 5–7 days.	Membrane stabilizing agent; Free-radical scavenger; antiarrhythmic
Vitamin E	400 units IM	Antioxidant
Liothyronine	50 µg oral	Limits cardiac complications and oxidative stress
Trimetazidine dihydrochloride[68]	20 mg TDS daily	Cardioprotective agent reducing myocardial O_2 consumption

A few other studies have shown beneficial effects of several agents like melatonin, vitamin C, sodium selenite, tri-iodothyronine, milrinone, boric acid, laurusnobilis, vasopressin, 6-amino nicotinamide, glucose-insulin-potassium (GIK) infusion, acetyl L-carnitine and dihydroxy-acetone. Further human studies would be required to recommend and standardize their use in AlPhos poisoning.

PROGNOSIS[69–75]

A very low pH <7.0, LVEF <25%, and serum phosphine levels >1.6 mg/dL correlates with high mortality. Arterial pH was cited to be an important prognostic indicator, with very high mortality in those with pH <7.0, along with hyperglycemia, hyperleukocytosis, refractory shock and renal failure.

Future Research[76]

AlPhos poisoning still remains an enigma for all intensivists and toxicologists. The scientific quest for its antidote still continues. Various experimental therapies have evolved for supportive care of these patients and future research must focus on them for improving survival rates. There has been a boom in the use of ECMO as a lifesaving measure in severe ALP poisoning. Further randomized controlled trials are needed to standardize the management, especially in resource-limited countries.

CONCLUSION

Aluminum phosphide poisoning is a common, cheap and easily available suicidal poisoning agent, especially in agricultural communities, and it still has a high mortalityrate (30–100%)

in the best of centres. In the absence of a specific antidote, therapy is mostly supportive, which focuses on early and aggressive resuscitation and prevention of organ failure. Most important cause of death is cardiac arrhythmias. Severity of metabolic acidosis and shock are prognostic determinants. The adult lethal dose is 150–500 mg, nevertheless survival has been reported after ingestion of greater amounts, explained partially by the possibility of vomiting, tablet exposure prior to ingestion and early availability of resuscitative care. Strict pesticide regulation laws, nation-wide poison centers and improved critical care of patients has resulted in improvements in mortality rates.

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