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Comprehensive Review of the Mechanistic Approach and Related Therapies to Cardiovascular Effects of Aluminum Phosphide

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Abstract: Aluminum Phosphide (AIP) is an active ingredient of fumigant pesticide which is commonly used in developing countries in order to control pests in stored grain. Acute poisoning with AIP usually occurs in committed suicide through ingestion of its tablets. AIP releases fatal phosphine gas in contact with hydrochloric acid of the stomach. Its detrimental clinical features may range from nausea and headache to vital organ failure and death. However, cardiovascular complications and refractory hypotension are the main cause of death. The exact mechanism of phosphine has not been proved in humans. However, it seems to work as a mitochondrial toxin with inhibition of cytochrome oxidase and cellular oxygen utilization. Since there is no specific antidote for acute AIP poisoning, management of cardiovascular disorders can be an appropriate approach to save poisoned patients. This article reviews cardiovascular toxicities associated with AIP and current therapeutic approaches and tries to clarify possible ways to treat this complication.

Key words: Aluminum phosphide, cardiovascular toxicity, heart failure, phosphine, systematic review

INTRODUCTION

Aluminum Phosphide (AIP) is used as a fumigant insecticide and rodenticide in protection of grains during the storage and transportation process (Mehrpour and Singh, 2010). This agent is widely used in developing countries for several reasons such as being highly potent and cost benefit, having no effect on seed viability and leaving little residue on food grains (Bumbrach *et al.*, 2012; Mostafalou *et al.*, 2013; Birnbaum *et al.*, 1997). Poisoning with this compound can occur through ingestion of salts or inhalation of phosphine gas. Phosphine is generated from AIP after exposure to the water or an acidic media such as the acidic contents of the stomach (Proudfoot, 2009). Due to lack of a specific antidote, the mortality rate is more than 70% of the intoxicated cases (Anand *et al.*, 2011; Singh *et al.*, 1989; Singh *et al.*, 1991). Typical features of AIP poisoning are gastrointestinal disorders, refractory hypotension and cardiogenic shock (Mehrpour *et al.*, 2012). Left ventricle and septum hypokinesia, ejection fractions reduction

(Bhasin *et al.*, 1991), raised systemic venous pressure, normal pulmonary artery wedge pressure, inadequate systemic vasoconstriction and electrocardiographic (ECG) abnormalities (Kalra *et al.*, 1991; Hosseinian *et al.*, 2011) are cardiovascular features of phosphine poisoning. This agent can cause a multi organ failure such as heart failure that is the main cause of death within 12-24 h after acute exposure (Chugh *et al.*, 1991; Bogle *et al.*, 2006; Mostafazadeh and Farzaneh, 2012; Moghadamnia, 2012; Singh *et al.*, 1991). Thus, it is essential to focus on cardiovascular complications of phosphine poisoning to find an effective and appropriate therapeutic strategy because if cardiac dysfunction and arrhythmias improve, most likely the patients will survive from acute phosphine poisoning through supportive cares. In this study we reviewed all the studies related to cardiovascular toxicity of AIP. Since the exact underlying mechanism of cardiotoxicity and peripheral circulatory failure caused by phosphine is still unknown, this study can reveal the direction of future studies.

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METHOD

The keywords “aluminum phosphide”, “phosphine”, “heart failure”, “cardiovascular toxicity”, “cardiac dysfunction”, arrhythmias” and “hypotension” were searched in bibliographic databases including PubMed, Web of Science, Google Scholar and Scopus between years 1980 and 2014. The title and abstracts of all paper were scrutinized and read initially and those that obviously did not meet inclusion criteria were excluded.

RESULTS AND DISCUSSION

Electrocardiography findings and refractory hypotension: AIP poisoning is known to be associated with various ECG abnormalities, ranging from acute myocardial infarction, to atrial fibrillation, premature supraventricular or ventricular contractions, ST segment elevation/depression, bundle branch blocks, PR and QRS interval prolongation and sinoatrial block (Udriste *et al.*, 2013; Khosla *et al.*, 1988; Gurjar *et al.*, 2011; Moghadamnia, 2012). The incidence of ECG and ECG abnormalities reported in various studies are 45% (Shadnia *et al.*, 2010; Soltaninejad *et al.*, 2012), 65% (Shadnia *et al.*, 2009), 80% (Gupta *et al.*, 1995) and 50% (Chugh *et al.*, 1991) in phosphine poisoned patients that summarized in the Table 1. ECG changes are mostly non-specific indicator for phosphide poisoning (Chugh *et al.*, 1991; Anand *et al.*, 2011) but evaluations of ECG parameters can predict the severity and usefulness of therapeutic strategies in the poisoned patients. Soltaninejad *et al.* (2012) found that there was a significant correlation between ECG abnormalities and mortality and subsequently, anti-arrhythmic agents can be used as prophylactic treatment in acute AIP intoxication.

In the survey by Shadnia *et al.* (2009, 2010) the ECG abnormalities were observed in 65.6% of cases who did not survive and most of them had ST segment depression and sinus tachycardia and there was a significant difference between survival and non-survival cases according to ECG abnormality. On the other hand, Chugh *et al.* (1991) reported no relationship between the ECG abnormalities and mortality. In another study, the ECG abnormalities were noted in 28 cases (58.7%) at the time of admission and was considered as prognostic factor along with other factors such as shock, low Glasgow coma scale for AIP poisoning (Louriz *et al.*, 2009). In Kaushik’s case report, ECG abnormalities along with T-wave abnormalities were observed which is attributed to subendocardial infarction rather than toxic myocarditis alone, because subendocardium which is the well-perfused zone of myocardium, is most vulnerable to any reduction in coronary flow and cellular hypoxia (Kaushik *et al.*, 2007). In another case report, broad QRS complex, ST-T changes along with raised CK-mb were observed which indicates severe myocardial injury (Shah *et al.*, 2009). In three other cases, Brugada type pattern in combination with various ECG abnormalities were observed in AIP poisoning (Mahajan *et al.*, 2012; Udriste *et al.*, 2013; Nayyar and Nair, 2009). Brugada syndrome is a disorder presenting with ST segment elevation, right bundle branch block, susceptibility to ventricular tachycardia and structurally normal heart (Mahajan *et al.*, 2012). It is most probably due to hypomagnesaemia caused by direct toxic effect of phosphine on cardiac tissue (Mahajan *et al.*, 2012). Khosla *et al.* (1988) reported that ECG abnormalities were detected in 6 of their 11 patients and there was metabolic acidosis in all 6. ECG changes completely associate with acid-base disturbances. Metabolic acidosis which is

Table 1: Cardiac electrophysiology disorders and evidences of hypotension in associated with AIP poisoning

Study	Study on:	BP	SBP	DBP	Electrocardiography findings					
					Pulse rate (beats/min)	QRS complex	ST segment	QTc intervals	BBB	LVEF
Soltaninejad <i>et al.</i> (2012)	Human (n:20)	-	60-130	40-70	-	-	!In 45% of patient	!In 35% of patient	!In 20% of patient	-
Shah <i>et al.</i> (2009)	Human (n:1)	70/30	-	-	110	Wide		-	-	-
Kaushik <i>et al.</i> (2007)	Human (n:1)	70/40	-	-	128	-			-	<20%
Akkaoui <i>et al.</i> (2007)	Human (n:2)	70/40	-	-	110	-		-	-	<20%
		90/50	-	-	108	-		-	-	30%
Siwach <i>et al.</i> (1994)	Human (n:30)	-	-	-	-	-	!in 10% and !In 90%	-	-	-
Gupta <i>et al.</i> (1995)	Human (n:25)	-	-	-	-	-	-	-	-	43.5±10.2%
Bogle <i>et al.</i> (2006)	Human (n:1)	70/58	-	-	100	Wide	-	-	-	-
Udriste <i>et al.</i> (2013)	Human (n:1)	-	60	-	-	-		-		-
Shadnia <i>et al.</i> (2010)	Human (n:39)	-	<100	-	60-100	-	-	-	-	-
Duenas <i>et al.</i> (1999)	Human (n:1)	80/40	-	-	100	-		-	-	-

BP: Blood pressure, SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg), BBB: Bundle branch block, LVEF: Left ventricle ejection fraction

probably caused by blockage of oxidative phosphorylation and cellular hypoxia (Mehrpour *et al.*, 2008), should be treated by administering sodium bicarbonate (Bumrah *et al.*, 2012; Gurjar *et al.*, 2011; Mehrpour *et al.*, 2008).

Refractory hypotension and shock which have been increasingly seen, are other fatal cardiovascular complications following acute AIP poisoning (Khosla *et al.*, 1988). Death after 24 h occurs usually owing to shock, cardiac dysrhythmia, metabolic acidosis and acute respiratory distress syndrome (Moghadamnia, 2012). Non-survivors have more refractory hypotension and acidosis than the survivors (Moghadamnia, 2012). The exact mechanism of refractory hypotension and intractable shock is not clear; however, they possibly occur due to arrhythmia, conduction disturbance and myocardial damage and myocardial depression. Moreover, the peripheral circulatory failure owing to capillary dysfunction or widespread small vessel damage can lead to peripheral vasodilatation, resulting in refractory hypotension and shock (Anand *et al.*, 2011). Refractory hypotension and shock are usually unresponsive to conventional treatment; however, managing AIP poisoning, especially resuscitation of shock and institution of supportive measures should be started as soon as the patient's arrival. All acute AIP poisoned patients require continuous invasive hemodynamic monitoring and early resuscitation with fluid and vasoactive agents. Norepinephrine or phenylephrine, dopamine, dobutamine and anti-arrhythmic agents can be used to treat refractory hypotension and shock.

Several studies which have been published about the beneficial effect of magnesium, show that treatment of hypomagnesaemia by magnesium sulphate can decrease AIP cardiac toxicity (Katira *et al.*, 1990; Gupta and Ahlawat, 1995; Chugh *et al.*, 1994b) and reduce the mortality rate from 90-50% of poisoned patients (Jadhav *et al.*, 2012; Anand *et al.*, 2011; Chugh *et al.*, 1994a; Chugh *et al.*, 1997; Singh *et al.*, 1990; Siwach *et al.*, 1994). Baeri *et al.* (2013) reported that $^{25}\text{Mg}^{2+}$ -carrying nanoparticle significantly elevates blood pressure and heart rate of rats poisoned with AIP (Baeri *et al.*, 2013). There is only one study in 1994 that claimed supplemental magnesium cannot improve the survival rate of AIP poisoned patients (Siwach *et al.*, 1994). Also, Jadhav *et al.* (2012) reported that in addition to magnesium sulfate and electrocardioversion, amiodarone has beneficial role in treatment of ventricular tachycardia caused by AIP poisoning (Jadhav *et al.*, 2012). In another study, Mehrpour *et al.* reported that digoxin by elevation of myocardial contractility and blood pressure is useful in

management of cardiogenic shock (Mehrpour *et al.*, 2011, 2012). Although the use of digoxin does not seem to be logical, it can be considered as an alternative treatment of the cardiogenic shock induced by AIP poisoning. Another approach in management of acute AIP poisoning is administration of high doses of glucagon (Arefi and Tabrizchi, 2012; Torabi, 2013). Glucagon is usually used as cardiac inotropic agent in the treatment of shock caused by beta-blockers and calcium channel blockers poisoning (Arefi and Tabrizchi, 2012). Inotropic action of glucagon is mediated by elevation of intracellular cAMP and calcium (Arefi and Tabrizchi, 2012). At the end, there is an interesting study about the beneficial effect of Intra-aortic Balloon Pump (IABP) as a cardiocirculatory assist device for treatment of cardiogenic shock following AIP poisoning (Siddaiah *et al.*, 2009). IABP can mechanically support the heart, decrease the afterload and improve perfusion to the vital organs and coronary arteries (Siddaiah *et al.*, 2009; Elabbassi *et al.*, 2013; David *et al.*, 2000). Intravascular hydroxyethyl starch solution (a colloid volume expander) is another route for treatment of severe hypotension that decrease the extravascular leakage of albumin and fluids (Marashi *et al.*, 2011).

Possible mechanisms of cardiotoxicity: The exact mechanism of toxicity of phosphine remains still unclear. It seems that main part of its toxicity is done through non-specific mechanisms due to the small size of the phosphine molecule (Nath *et al.*, 2011). However, several mechanisms have been proposed for phosphine toxicity which is discussed in below.

Mitochondrial disorders and energy depletion: As previously mentioned, one of the main target organs of phosphine is heart. The heart needs large amounts of energy to maintain its contractile performance. Adenosine Triphosphate (ATP) works as immediate source of energy, however intracellular ATP is limited. Phosphine has been reported to decrease cardiac energy reserves such as ATP (Anand *et al.*, 2011; Baeri *et al.*, 2013). Phosphine can cause myocardial energy depletion due to changes in mitochondrial morphology (Proudfoot, 2009; Bumrah *et al.*, 2012). Ultrastructural changes which were observed in the heart and other tissues, showed mitochondrial injury (Anand *et al.*, 2011), including dysmorphic and swollen mitochondria with enlarged and disrupted cristae (Anand *et al.*, 2011; Bumrah *et al.*, 2012; Proudfoot, 2009). In view of the fact that oxidative phosphorylation is strictly dependent on the structure and integrity of the inner mitochondrial membrane, even if the activity of mitochondrial complexes is not inhibited

directly following phosphine exposure, it can be affected by changes in mitochondrial morphology (Proudfoot, 2009). Numerous studies demonstrated that phosphine can cause myocardial energy depletion due to inhibition of activity of cytochrome c oxidase as an enzyme of the Electron Transport Chain (ETC) (Singh *et al.*, 2006; Bumbrah *et al.*, 2012; Gurjar *et al.*, 2011). Phosphine disturbs the mitochondrial morphology, inhibits complexes I, II, IV of the mitochondrial ETC and reduces the oxidative respiration by 70% leading to severe drop in the mitochondrial membrane potential (Proudfoot, 2009; Bumbrah *et al.*, 2012). Some other agents which are known to protect mitochondrial oxidative phosphorylation such as hydroxycobalamine (Jones, 2008), mitoQ (Tauskela, 2007; Smith and Murphy, 2010) and vitamin C should also be tried (Singh, 1989).

Oxidative stress: Like other kinds of pesticides (Mostafalou *et al.*, 2013; Mostafazadeh and Farzaneh, 2012), there is strong evidence that oxidative stress can be induced by phosphine and the heart is not secure from damaging effects of these reactive radicals that increased through reduction of glutathione level (Chugh *et al.*, 1995; Mehrpour *et al.*, 2012; Kariman *et al.*, 2012). Phosphine induces the production of free radicals not only through inhibition of the antioxidant enzymes (catalase and peroxidase) and reduction of glutathione level, but also via disruption of oxidative phosphorylation (Nath *et al.*, 2011; Anand *et al.*, 2011; Mehrpour *et al.*, 2012). Oxidative stress and especially mitochondrial cytochrome C oxidase inhibition can lead to morphological and functional disorder of heart. The membrane action potential damage caused by AIP is due to lipid peroxidation of cell membrane (Mehrpour *et al.*, 2012) and it seems that probable mechanism of magnesium in improvement of arrhythmias is to stabilize the membrane action potential (Katira *et al.*, 1990; Chugh *et al.*, 1997). Based on these studies, oxidative stress and lipid peroxidation can be considered as a main cause of myocardial injury due to AIP poisoning. There are several studies focused on these pathways for planning new therapeutic strategies; N-acetyl cysteine as an antioxidant and cytoprotective agent (Azad *et al.*, 2001; Hsu *et al.*, 2002) can reduce myocardial oxidative injury and increase survival time (Bogle *et al.*, 2006). Other options for the management of cardiac complication of AIP are antiischemic drugs such as trimetazidine. These agents have protective effects on myocardium through decreasing the production of oxygen-derived free radicals and stimulating the oxidative metabolism of glucose (Moghadamnia, 2012; Duenas *et al.*, 1999). Magnesium nanoparticle in addition

to treatment of hypotension and cardiac shock can elevate the intracardiac magnesium levels, reduce lipid peroxidation and improve mitochondrial function (Baeeri *et al.*, 2013).

Histopathological and biochemical changes: Mild to severe myocyte vacuolation, areas of myocytolysis and degeneration were specially revealed in the left ventricle and interventricular septum following AIP poisoning which are all indicative of myocardial injury (Shah *et al.*, 2009). Other histopathological findings showed varying degrees of congestion in the heart and other organs, similar to those produced by hypoxic injury (Louriz *et al.*, 2009; Bumbrah *et al.*, 2012) and myocardial necrosis (Khosla *et al.*, 1988; Abder-Rahman, 2009). There were some reports regarding inhalation of phosphine gas and cardiovascular findings varying from congestion, focal myocardial infiltration, to small-vessel injury (Chugh *et al.*, 1991; Wilson *et al.*, 1980; Abder-Rahman, 2009). In a study by Abder-Rahman (2009) autopsy findings revealed subendocardial flame hemorrhages in the heart of two sisters and minimal neutrophil inflammatory in the cardiac muscle of the 6-year-old child. Anand *et al.* (2012) reported myocyte swelling, disarray and interstitial edema in cardiac tissue using electron microscopy and they thought tissue histology findings are non-specific. In Rahbar Taromsari's study, histopathological findings in myocardium showed congestion (86%), necrosis (7%) and leukocyte infiltration (7%) (Taromsari *et al.*, 2011). Jadhav *et al.* (2012) disclosed contraction band necrosis, edema, hemorrhage and pyknosis of cardiac myocyte nuclei in the postmortem histological examination of myocardium. It seems there is a direct correlation between heart tissue injury and cellular hypoxia-induced mitochondrial dysfunction. Biochemical findings also confirm myocardial injury following AIP poisoning. Creatine phosphokinase (CPK), CPK-myocardial band (CPK-mb) and troponin-T (TnT) are considered as biochemical markers of cardiac muscle injury (Soltaninejad *et al.*, 2012). Elevation of serum levels of CPK-mb and LDH by many folds has been seen in AIP poisoning and indicates myocardial damage (Anand *et al.*, 2012; Shah *et al.*, 2009; Wilson *et al.*, 1980). However, Duenas *et al.* (1999) reported that CPK levels were elevated without any changes in CPK-mb fraction. Soltaninejad *et al.* (2012) revealed that the serum cardiac TnT has a positive relationship to the mortality but increase in CPK or the CPK to CPK-mb ratio does not have such relationship (Soltaninejad *et al.*, 2012). In another case reported by Nayyar and Nair (2009) TnT and CPK levels were normal at admission. Changing in CPK, CPK-mb, TnT levels as a clinical and laboratory indicator

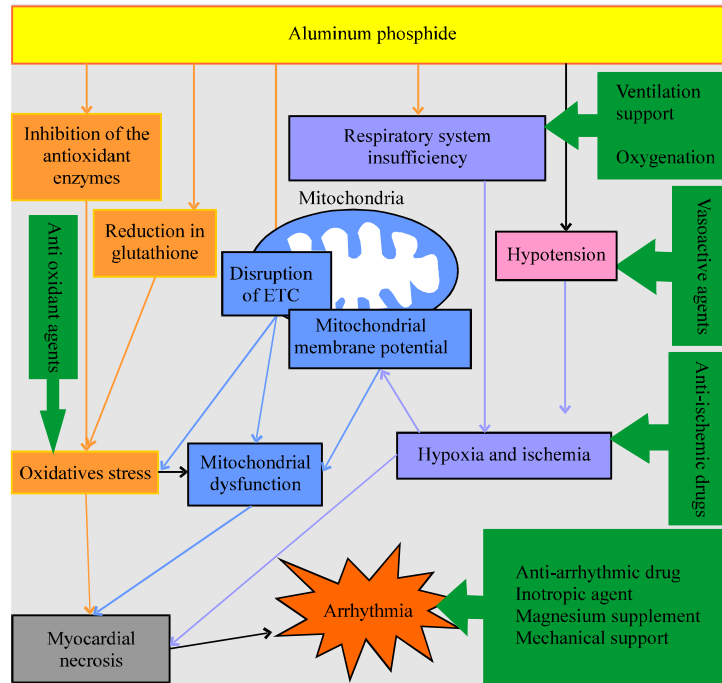


Fig. 1: Cardiotoxicity mechanisms involved in phosphine poisoning and its possible treatment strategies

of cardiac muscle injury is sometimes observed, but reports are controversial. Because in some case reports which were reported by Nayyar and Nair (2009) Bogle *et al.* (2006) serum levels of these markers were in normal range following acute ALP poisoning (Bogle *et al.*, 2006; Nayyar and Nair, 2009) but in other reports, their levels were elevated, indicating myocardial damage (Kaushik *et al.*, 2007; Shah *et al.*, 2009; Akkaoui *et al.*, 2007; Singh *et al.*, 2011). On the other hand, some researchers did not discover any evidence about myocardial damage on autopsy in any of their patients (Khosla *et al.*, 1988; Singh, 1989). Thus, it is concluded that elevated levels of these enzymes confirm myocardial injury but their normal levels cannot disprove phosphine cardiotoxicity.

CONCLUSION

Taking collectively, AIP is used as insecticide and rodenticide and is very common in suicide attempts. The heart is the predominantly affected organ and the most of the poisoned patients die due to cardiovascular complications (Bumrah *et al.*, 2012). Clinical manifestation of cardiac failure varies depending on the dosage and duration of consumption and include peripheral circulatory failure and hypotension (Alter *et al.*, 2001; Bayazit *et al.*, 2000; Ragone *et al.*, 2002),

congestion of the heart, separation of myocardial fibres by edema, fragmentation of fibres, non-specific vacuolation of myocytes, focal necrosis, neutrophil and eosinophil infiltration (Katira *et al.*, 1990; Sinha *et al.*, 2005). The ECG changes have been studied in several studies and include atrial fibrillation, tachycardia, QRS complex and ST-T changes and bundle branch blocks. Although the exact underlying mechanism of cardiotoxicity and peripheral circulatory failure caused by phosphine is still unknown, the possible mechanisms are discussed in this article and summarized in Fig. 1. It seems that the main effect of this poison is disruption of cellular oxygen utilization and hypoxia through refractory hypotension and respiratory system insufficiency. This hypoxia can cause irreparable damages on mitochondria as the main site of oxygen consumption. Therefore, the first priority in treatment of phosphine poisoning is correction of hypotension and improvement of tissue oxygen levels through ventilation support and oxygenation. Extracorporeal Membrane Oxygenation (ECMO) is a novel technique for supplying oxygen and it may have a beneficial role in management of ALP poisoning (Elabbassi *et al.*, 2013). On the other hand, direct effects of phosphine on cardiac tissue mediated through inhibition of mitochondrial toxins, induction of oxidative damage and reduction of energy production should be discussed further in the future studies. Focus

on the inhibition of oxidative stress and mitochondrial injuries along with the remediation of refractory hypotension can be a useful therapeutic strategy in treatment of AIP poisoned patient.

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