ALUMINIUM PHOSPHIDE: TOXICITY MECHANISM AND CREDIBLE TREATMENTS

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ABSTRACT
Suicides and deaths by "accidental" ingestion or inhalation of Aluminium Phosphide poisoning are rising at an alarming rate year after year. Ascribing to the lack of an effective and safe antidote and with almost a 100% mortality rate, it becomes next to impossible to save the victim of this particular poisoning. In order to do the same, it is imperative to fully comprehend the mechanism and action of AlP on various organs, once it enters the body. Thus, this review explains the mode of action of phosphine gas produced by AlP inside the human body, with a special emphasis on the nucleophilic nature of phosphine and its role in inducing cytochrome c mediated oxidative stress, giving way to metabolic acidosis and multiple organ failure. The predicted treatments will include moieties capable of inhibiting the cytochrome c pathway and neutralizing the serum acid content along with already established agents combating various aspects of AlP poisoning.

KEYWORDS: Aluminium Phosphide, Phosphine, poisoning, fumigant.

INTRODUCTION
A highly toxic fumigant with the chemical formula of AlP, aluminium phosphide continues to kill millions around the globe, with an astonishing mortality rate of 40%-100% (Moghadamnia, 2002). The lack of a proper antidote is regarded as the underlying reason that accentuates the mortality rate associated with acute aluminium phosphide poisoning. The lethal dose (LD₅₀) is 11.5 mg/kg and the estimated time intervals beginning from the ingestion of its tablet to death has approximately been reported as 3 hours, or on an average,
between 1-48 hours, with the most common cause of death being cardiac arrhythmias. 95% of the patients die within 24 hours of ingestion of AlP (Chugh et al, 1993). Also, in a 25-year-long study reported by Singh et al (2003), a total of 5933 unnatural deaths by poisoning reported in north-west India, aluminium phosphide was found out to be a major cause.

The pesticidal activity of AlP is attributed to its property of releasing phosphine gas, also known as hydrogen phosphide (PH$_3$), first discovered by a German company named Degesch. Later, the Hollywood Termite Control Company, Inc in the United States of America registered it as a pesticide in 1958. The gas, if inhaled or if produced inside the human body after ingestion of AlP, affects a number of organs, like: kidneys, lungs, liver, gastrointestinal tract as well as the central nervous system (Chemistry learner).

Physically, it has a solid, colourless appearance and is sold in the market as yellow or grey crystals (3gm tablet) or as a grey-green powder (Kirk-Othmer Encyclopedia of Chemical Technology, 1982). The colour imparted is a result of residing impurities form hydrolysis or oxidation process. The smell usually resembles that of garlic or rotten fish (Ellenhorn et al, Medical Toxicology - Diagnosis and Treatment of Human Poisoning, 1988). The crystals or tablets, which are more commonly available in the markets have a zincblende crystal structure (Van Zeghbroeck, 1997) and are stable thermodynamically up to a 1000°C or 1830° F with the substance density of 2.85 gm/cm$^3$. The molar mass and the melting point of aluminium phosphide is 57.9552 g/mol and 2530° C or 4590° F respectively. Aluminium phosphide is readily soluble in water and reacts both, with water as well as moisture present in the air, to yield the highly toxic phosphine gas. The reaction takes place as follows, where the water molecule breaks down to produce H$^+$ and OH$^-$ ion (Holleman, 2001): $\text{AlP} + 3 \text{H}_2\text{O} \rightarrow \text{Al(OH)}_3 + \text{PH}_3$; $\text{AlP} + 3 \text{H}^+ \rightarrow \text{Al}^{3+} + \text{PH}_3$

Similarly, for the production of aluminium phosphide in laboratories, the mixture of red phosphorous (P) and powdered aluminium (Al) is made to react with each other and subjected to ignition in order to yield AlP (White et al, 1953). The reaction takes place as follows: $4\text{Al} + \text{P}_4 \rightarrow 4\text{AlP}$

AlP has a wide number of applications in agricultural industry, namely, as a fumigant, rodenticide, pesticide, insecticide as well as semiconductor material, as in aluminium gallium indium phosphide, when alloyed with different binary materials in order to be used in light-emitting diodes (Corbridge et al, 1995). As a fumigant, it is used to preserve a wide variety of
food products before they are sold in the market for human consumption. The products include various grains, like wheat, and many dry fruits and cereals (Chemistry learner).

Commonly known as the “wheat pill”, it is used to kill several varieties of verminous mammals, such as, rodents or moles. The phoshine gas, responsible for the killings is highly toxic and flammable, hence, in order to control its spontaneous and sudden ignition leading to explosion and development of toxic gas, aluminium phosphide preparations are commonly mixed with stabilizers such as ammonium carbamate (White et al., 1944). Commercially, it is supplied by the following companies worldwide: Pestcon (United States), Shanghai Kima Chemical Co. Ltd. (China), Sandhya Organic Chemicals P. Ltd. (India), Chemcolour (New Zealand), Excel Industries (Australia), Taiwan Chemicals (Taiwan), Globe Chemicals GmbH (Germany), Agrosynth (India), Penglai Chemical Inc. (China), Central & Western Chemicals (India).

The compound, AlP, is also available under the following most common brand names, like, Quick Phos, Phostoxin, Celphos, Talunex and Fumitoxin (White et al., 1944).

**EPIDEMIOLOGY**

An extremely toxic pesticide and a notably cheap fumigant since 1940, aluminium phosphide (Moghadamnia, 2012) causes approximately 68% of the total poisoning causalities reported in the Indian sub-continent. Most of the cases reported in India are, however, associated with the ingestion of phosphides, mainly among the agricultural workers (Mostafazadeh, 2012). This, in turn results from the improper storage facility for these fumigants. In India, AlP poisoning is most prevalent in the age group of 11-30 years, in rural areas (Moghadamnia, 2012). From 1979 to 2004, approximately, 895 patients have been admitted in PGIMER, Chandigarh, with acute AlP poisoning (Singh, unpublished data). Similarly, a year-round study conducted in Allahabad managed to record 301 suspicious cases of poisoning, out of which 11.7% were reported due to AlP. The affected male to female ratio in this study was 2:1 (Moghadamnia, 2012).

Other than in India, a few cases annually are reported from Iran and Jordan, mainly in an attempt to commit suicide from aluminium phosphide, commonly called as the “rice tablet” there. In Iran, a four-year study was conducted from 1997-2001, which was successful in recording about 1571 poisoning cases, of which, approximately, 2.1% or 33 cases had their underlying cause as aluminium phosphide (Moghadamnia, 2012).
Fatal dose in all the cases has been reported for a healthy adult of 70 kg as 150-500 mg (Chugh, 1988). Except for in India, Iran and Jordan, a few cases annually are reported from United Kingdom (Bogle, 2006), Australia (Nocera, 2000), Germany (Alter, 2001), Canada and the United States (Ragone, 2002), to name a few.

MECHANISM OF TOXICITY
The exact mechanism by which aluminum phosphide causes poisoning is still not known. Systemic complications and multi-organ failure are involved in acute aluminum phosphide poisoning (Abedini et al, 2014). Phosphine gas is generally released when aluminum phosphide is ingested (Moghadamnia, 2012). Phosphine molecule has three hydrogen atoms and a phosphorus atom i.e. PH₃. Phosphorus in turn, has 5 valence electrons, with 2 paired electrons in s-orbital and 3 unpaired electrons in its p-orbital. Three molecular bonds can easily be formed by these three unpaired electrons in the p-orbital (Kutzelnigg, 1984). Also, s-orbital electrons can participate in bond formation with oxygen. This happens in case of sufficient oxygen, where oxiderivatives of phosphine like H₃PO are formed with imbalances between blood phosphorous and oxygen.

Phosphine is cytotoxic and is mainly involved in free radical mediated injury. It is a nucleophile and a strong reducing agent and hence is capable enough of holding back many cellular enzymes in various metabolic processes (Mathai and Bhanu, 2010). PH₃ is fully reduced form of phosphorus in contrast to phosphate which is fully oxidized form and is thermodynamically favoured in biological tissues (Price and Sadler, 1988). It oxidizes slowly in weak acids and forms unstable H₃PO only if sufficient oxygen is available. This H₃PO is an intermediate and extremely unstable product and had not been observed either in vivo or experimental procedures (Robinson and Bond, 1970). In H₃PO, O₂ carries a partial negative charge and phosphorus carries a partial positive charge. Phosphorus acts as an electrophile due to polarity of the molecule which also contributes to the reactivity of the whole structure (Nath et al, 2011). But mechanism by which this transient H₃PO causes phosphine toxicity is yet to be fully discovered.

There are evidences that phosphine inhibits respiration in rat liver mitochondria (Nakakita et al, 1971) and insect mitochondria (Chefurka et al, 1976). This inhibition is significant when there is addition of precursors to ATP synthesis or any chemical uncoupler. It is also suggested that inner membrane of mitochondria, being highly impermeable, is a major hurdle in PH₃ uptake. But usually, it is overcome by activation of transport across mitochondrial
inner membrane (Nath et al., 2011). It is gradually absorbed by gastro-intestinal tract following a simple diffusion method wherein phosphine released inhibits cytochrome c oxidase in the mitochondria, which in turn inhibits cellular utilization. In an experimental procedure it was revealed that Complex IV, also known as cytochrome c oxidase, is a primary site for electron transport chain (ETC) and PH$_3$ interaction (Chefurka et al., 1976).

Kashi and Chefurka later suggested that oxidation state of cytochrome a was highly reduced on treatment with phosphine. Also, PH$_3$ can form complex with metal ion cofactors at active site of enzymes which is basis of cytochrome c oxidase inhibition (Chaudhry and Price, 1990). Due to this, around 70% of oxidative respiration which occurs in mitochondria is inhibited. Various harmful cellular radicals like superoxides and peroxides are generated as a result of lipid peroxidation which is a result of reduction in oxidative respiration (Moghadamnia, 2012). Furthermore, it promotes protein denaturation that results in breakdown of integrity of cell (Mehrpour et al, 2012). Cellular oxidative stress, hence, is a result of this suppression of oxidative respiration and ETC-PH$_3$ interaction (Nath et al, 2011).

**Fig. 1:** pictorial representation shows the interaction of PH$_3$ with various enzymes involved in metabolic processes in mitochondria and synapse.
Phosphine is shown in light blue, NO in orange, and ROS in red. The cross symbol behind enzymes indicate that they are inhibited. ROS generated at various sites in mitochondria leads to inhibition of various metabolic processes. The potassium and calcium currents are regulated by acetylcholine via NO. Ca\(^{2+}\) triggers the release of acetylcholine in cytoplasm into the neuronal synapse. The acetylcholinesterase degrades acetylcholine, reducing the strength of neurotransmission. [FAD/FADH\(_2\) (Flavin adenine dinucleotide oxidized/ reduced), NAD\(^+\)/NADH (Nicotinamide adenine dinucleotide oxidized/ reduced), ADP/ ATP (adenosine di/ tri nucleotide), NO (nitric oxide), ROS (reactive oxygen species) and TCA (tricarboxylic acid)].

A study conducted in 1996 by Chugh et al, stated that levels of serum superoxide dismutase (SOD) and malonyldialdehyde (MDA) were high and serum catalase levels were low which resulted in peroxide load in patients within first day of the poisoning. It confirmed the phosphine release. It was observed that indicators of oxidative stress reached their peak levels within 48 hours of exposure. Autopsy results in non survivors confirmed high levels of SOD and MDA indicating their direct relation with mortality and low catalase levels indicating the inverse relationship. However, patients who survived till fifth day of poisoning showed normal levels of SOD, MDA and catalase which suggested that phosphine was eliminated and there was a significant drop in levels of oxidative stress indicators.

Phosphine is mainly metabolized and excreted by kidneys, although, it has been studied that some amount of aluminum phosphide is slowly absorbed and later metabolized by liver. This results in release of phosphine at a very slow rate which is responsible for delayed onset of toxicity of aluminum phosphide (Wahab et al, 2008). In the same study it was revealed that, focal myocardial necrosis is also one of the signs observed in aluminum phosphide poisoning. This is due to alteration in the ionic permeability of ions such as sodium, magnesium and calcium. This is evident in a patient as cardiac arrhythmias and ECG anomalies. Also, adrenal gland damage, fluid loss (Mathai and Bhanu, 2010), hypoxemia with severe metabolic acidosis are some of the other abnormalities which are observed in aluminum phosphide poisoning (Anger et al, 2000).

Certain evidences of agitation followed by convulsions in humans and twitching after hyperactivity in non-human animals have been reported post ingestion of aluminium phosphide. Lethargy is also observed in a few individuals (Potter et al, 1993). Phosphine also contributes in increasing acetylcholine neurotransmission by suppressing acetylcholine
esterase (Mitra et al, 2001). This activation in acetylcholine signaling increases metabolic demand which can also cause hypersensitivity towards phosphine (Valmas et al, 2008).

Patients usually die within 24 hours due to cardiac toxicity. But if a person survives more than a day, acute respiratory distress syndrome (ARDS) is a major manifestation. There are also evidences of diffuse alveolar damage (DAD) which appear as alveolar edema and hemorrhages at times of autopsy, thereby confirming ARDS (Hugar et al, 2015). Also, it has been reported that ulcerations, gastro-intestinal disorders, liver failure and metabolic disorders were observed within 24 hours of poisoning.

Ischemic stroke can be considered as one of the delayed responses of aluminum phosphide poisoning as studied in case report of a 30 year old right-handed man in Iran (Abedini et al, 2014). It was revealed that the stroke was a result of sudden onset of left side hemiplegia (total or partial paralysis of one side of the body that results from disease of or injury to the motor centers of the brain) which occurred 11 days after the ingestion of aluminum phosphide. MRI (Magnetic Resonance Imaging) and MRA (Magnetic Resonance Angiogram) confirmed ischemic lesions and stenosis in the middle cerebral artery of brain respectively.
During inhalation, aluminum phosphide reacts with water whereas during ingestion, it reacts with HCl in stomach. Phosphine is formed via both processes. Phosphine follows same
pathway in both the cases and leads to mitochondrial damage by inhibiting Cytochrome c oxidase. Hydroxyl radicals, thus, produced cause lipid peroxidation and protein denaturation. This mitochondrial damage in gastro-intestinal tract cause ulcers and hemorrhages and eventually renal and hepatic failure whereas it causes diffused alveolar damage in lungs leading to alveolar edema, hemorrhages and in many cases Ischemic stroke.

SYMPTOMS AND DIAGNOSIS

Signs and Symptoms
The general signs and symptoms of aluminium phosphide poisoning (AlPP) are: metabolic acidosis, which may occur due to the accumulation of lactic acid caused by blockage of oxidative phosphorylation and poor tissue perfusion (Agarwal et al, 2014), gastrointestinal hemorrhage and ulcerations (Hugar et al, 2015), abdominal pain, vomiting, abnormality in Glasgow coma scale, systolic blood pressure, and central venous pressure (Louriz et al, 2009). Major complications observed in the course of severe aluminium poisoning are cardiac dysrhythmias, shock, respiratory distress, hypomagnesemia and lack of vomiting (leading to retention of AlP in body).

Some studies have reported that aluminium poisoning causes neurological toxicity which, in turn, can cause clinical effects like headache, stupor (a state of near-unconsciousness), restlessness, agitation, anxiety, ataxia (loss of full control on body), paresthesia (an abnormal sensation, typically tingling or pricking) and central nervous system depression leading to coma and seizures (Goel and Aggarwal, 2007).

Diagnosis
The diagnosis of AlPP ingestion can be confirmed by detecting phosphine in exhaled air or in GI aspirate. In stomach, phosphine gas can be detected by the silver nitrate test. To perform this test, gastric contents are diluted with of water in a flask and the flask is heated at 50°C for 15-20 minutes. Then, two round pieces of filter paper, one impregnated with 0.1 N silver nitrate and other with 0.1 N lead acetate are placed alternately on the mouth of the flask, if phosphine gas is present in the gastric contents, then due to conversion silver nitrate to metallic silver, the silver nitrate paper turns black while the lead acetate paper does not change color. If hydrogen sulphide is present, both the papers turn black. The reaction takes place as follows: $8\text{AgNO}_3 + \text{PH}_3 + 4\text{H}_2\text{O} \rightarrow 8\text{Ag} + \text{H}_3\text{PO}_4 + 8\text{HNO}_3$. 
A variant of silver nitrate test to detect phosphine gas is the breath test. The patient is asked to breathe through a filter paper impregnated with 0.1N silver nitrate for 15 minutes. Due to the presence of phosphine in the breath, the filter paper turns black. The test on gastric aspirate is much more sensitive than the breath test (Louriz et al, 2009).

The breath test is not reliable. A false negative result may occur in patients being given oxygen as phosphine may get converted to phosphorus pentoxide. A false positive result may also occur due to the presence of hydrogen sulfide in the air (Mehrpour et al, 2012). Gas chromatography is the most specific and sensitive method for detecting the presence of phosphine in blood/air and can detect even minute amounts of phosphine in the air (Anand et al, 2011).

LABORATORY ASSESSMENT AND PROGNOSIS

Laboratory assessment is generally done to obtain the prognosis. In case of AIP toxicity general prognostic factors are: elevated serum creatinine, low APACHE II (Acute Physiology and Chronic Health Evaluation II) score, low pH value (< 7.2), low serum bicarbonate value (<15mmol/L). Louriz et al have also reported that, the prognostic factors associated with mortality from acute AIP poisoning, includes a low APACHE II score, low Glasgow coma scale score, shock, electrocardiogram abnormalities, the presence of acute renal failure, low prothrombin rate, hyperleukocytosis (an unusual large increase in number and proportion of white blood cells in blood or tissues), use of vasoactive drugs and use of mechanical ventilation. Recently in 2008, Wahab, et al, reported that the development of refractory shock, ARDS, aspiration pneumonia, anaemia, metabolic acidosis, electrolyte imbalance, coma, severe hypoxia, gastrointestinal bleeding, and pericarditis are the factors associated with poor prognosis (Mathai and Bhanu, 2010; Louriz et al, 2009; Wahab et al, 2008). Simplified Acute Physiology Score II (SAPSII) was proposed for better estimating the outcome of patients with acute AIP poisoning requiring ICU admission. SAPSII calculated within the first 24 hours was recognized as a good prognostic indicator (Moghadamnia, 2012).

Leukopenia (decrease in the number of white blood cells in blood) indicates severe AIP toxicity. Increased amount of glutamic oxaloacetic transaminase (SGOT) or glutamic pyruvic transaminase (SGPT) in serum and induced metabolic acidosis signifies moderate to severe AIP toxicity. Analysis of body electrolytes show decreased magnesium level while level of potassium may be increased or decreased (Chugh et al, 1990). Analysis of plasma renin is
significant as its level in blood carries a direct relationship with mortality and is raised in
direct proportion with the dose of pesticide. In case of severe poisoning, the level of cortisol
in serum is usually found to be decreased. Chest X-ray may reveal hilar or perihilar
congestion if ARDS develops (Chugh et al., 1989).

Changes in cardiovascular and respiratory system can also result in death. In myocardial
tissue, AIP induces congestion, necrosis and leucocytes infiltration. ECG shows various
manifestations such as arrhythmias (Sinus tachycardia, bradycardia), supraventricular
ectopics, ventricular ectopics, atrial fibrillation, ventricular fibrillation conduction defects
(Wide QRS complex, A-V conduction defects), bundle branch block, complete heart block,
ST depression, ST elevation, T wave changes (Singh and Bhalla, 2015).

TREATMENT AND MANAGEMENT OF AIP

Table 1: Various treatment strategies for managing Aluminum phosphide poisoning

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Type of Study</th>
<th>Effects</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Digoxin (0.5 mg initially followed by 0.5 mg at 6 h intervals)</td>
<td>Case Report</td>
<td>Resolved cardiogenic shock due to left ventricle failure</td>
<td>Administration of digoxin as an adjustment therapy can improve the outcome</td>
<td>Mehrpour et al., 2011</td>
</tr>
<tr>
<td>Hyperbaric Oxygen</td>
<td>Experimental (Rats)</td>
<td>Increasing survival Time</td>
<td>Administration of hyperbaric oxygen may also be effective in humans</td>
<td>Saidi et al., 2011</td>
</tr>
<tr>
<td>25Mg 2 + carrying nanoparticle</td>
<td>Experimental (Rats)</td>
<td>Increased blood pressure and heart rate; increase in antioxidant power, Mg level in the plasma and the heart; reduction in lipid peroxidation and ADP/ATP ratio</td>
<td>25Mg PMC16 at 0.025 LD$_{50}$ + Nabicarbonate was the most effective combination</td>
<td>Baeeri et al., 2011</td>
</tr>
<tr>
<td>Intragastric irrigation with Sweet Almond oil</td>
<td>Experimental (Rats)</td>
<td>Protective role for plasma cholinesterase inhibition in AIP poisoning, decreased mortality rate</td>
<td>Significant reduction of mortality</td>
<td>Saidi and Shojai, 2011</td>
</tr>
<tr>
<td>Vitamin C (1 g at 6 h intervals, i.v.) + methylene blue (1 mg/kg of 1 % solution)</td>
<td>Case Report</td>
<td>Twelve hours after treatment with vitamin C, the methaemoglobin concentration decreased from 46 % to 33 %. high doses of methylene blue, the methaemoglobin concentration decreased to 23 %</td>
<td>Administration of vitamin C followed by methylene blue may have a role in successful treatment of methaemoglobinemia and haemolysis following phosphine poisoning</td>
<td>Soltaninejad et al., 2011</td>
</tr>
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</table>

Extensive gastric | Case Series | Survival rate 42 % | Recommendation to | Bajwa et al., 2011 |
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study Type</th>
<th>Description</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavage</td>
<td>Case Report</td>
<td>(33 patients)</td>
<td>Intensivists and physicians to use this particular regimen of gastric decontamination</td>
<td><em>al</em>, 2010</td>
</tr>
<tr>
<td>Intra-aortic Balloon Pump (IABP)</td>
<td>Case Report</td>
<td>IABP was used for cardiovascular support until the effects of AIP resolved</td>
<td>IABP used for treatment of cardiogenic shock due to AIP poisoning can improve the outcome</td>
<td>Siddaiah <em>et al.</em>, 2009</td>
</tr>
<tr>
<td>N-Acetylcysteine (NAC) (6.25 mg/kg/min, <em>i. v.</em> for 30 min)</td>
<td>Experimental (Rats)</td>
<td>Significantly increased survival time, stabilization of blood pressure and heart rate, decreased Malonyldialdehyde level and increased Glutathione peroxidase Levels</td>
<td>NAC increased the survival time by reducing myocardial oxidative injury</td>
<td>Azad <em>et al.</em>, 2011</td>
</tr>
<tr>
<td>N-omega-nitro-L-arginine methyl ester (L-NAME) (1 mg/kg/min., <em>i. v.</em> for 60 min)</td>
<td>Experimental (Rats)</td>
<td>Significant rise in blood pressure but precipitated ECG abnormalities. Pre and post-treatment of L-NAME with AIP neither improved the survival time nor the biochemical parameters despite significant rise in blood pressure</td>
<td>L-NAME showed no protective effects in rats exposed to AIP</td>
<td>Azad <em>et al.</em>, 2011</td>
</tr>
<tr>
<td>Atropine (1 mg kg-1, intraperitoneal) + Pralidoxime (5 mg/kg, intraperitoneal) administered five minutes after AIP exposure</td>
<td>Experimental (Rats)</td>
<td>Increased survival time. Plasma cholinesterase levels were inhibited in rats poisoned with AIP as compared to controls</td>
<td>Atropine and pralidoxime can increase survival time</td>
<td>Mitra <em>et al.</em>, 2001</td>
</tr>
<tr>
<td>Oral dose of 20 mg Trimetazidine twice daily</td>
<td>Case Report</td>
<td>Resolved dysrhythmia due to AIP poisoning after 48 h [ventricular premature complexes (&gt;600 per h) with periods of bigeminy]</td>
<td>Ventricular dysrhythmias were treated solely with oral trimetazidine resulting in rapid disappearance of all electrocardiographic abnormalities</td>
<td>Duenas <em>et al.</em>, 1999</td>
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</table>
OTHER POSSIBLE TREATMENTS

Patients suffering from AIP poisoning, toxicity occurs basically due to three reasons, i.e. inhibition of cytochrome c oxidase, increased pH of body and production of reactive oxygen species (ROS) so we need a treatment which could counter and restore all the three changes. Phosphine produced by AIP inhibits the cytochrome c oxidase. Phosphine is a reducing agent having potential of -1.18, it forms a complex with the metal ion cofactor at the active site of enzyme cytochrome c oxidase inside mitochondria. Inhibition of cytochrome c oxidase causes oxidative stress.

It is well known that metal phosphides having lower reduction potential are strong electron donors and therefore considered as strong poisons. Phosphine donates electron to cytochrome c oxidase \((E = +0.29)\) that leads to disruption of electron transport chain. Therefore, according to the electrochemical law, if a receiver with a reducing potential of more than +0.29 is given to the patient, then it will strongly interact with phosphine and in turn, cytochrome c oxidase will be left vacant and undisrupted.

**Table 2: metal ions having reduction potential more than cytochrome c oxidase**

<table>
<thead>
<tr>
<th>Metal ions</th>
<th>Reduction potential</th>
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<tbody>
<tr>
<td>Re(^{3+})</td>
<td>+0.30</td>
</tr>
<tr>
<td>Bi(^{3+})</td>
<td>+0.308</td>
</tr>
<tr>
<td>Cu(^{2+})</td>
<td>+0.337</td>
</tr>
<tr>
<td>Fe(^+)</td>
<td>+0.4</td>
</tr>
<tr>
<td>Cu(^{+})</td>
<td>+0.520</td>
</tr>
<tr>
<td>Fe(^{3+})</td>
<td>+0.77</td>
</tr>
<tr>
<td>Ag(^{+})</td>
<td>+0.7996</td>
</tr>
</tbody>
</table>

Depending upon the severity of these metals can be given to patients either as food supplements (in case of acute AIPP) or as recombinant biotech drug (in case of sever AIPP). Supportive treatments to reduce pH and degrade ROS should also be given. To maintain the pH of body as normal, various minerals can be used. Magnesium is an alkali forming mineral which can give best result when administered transdermally (via skin). Oral supplementation of magnesium alone is not enough since most of it is excreted without being processed in body. Antioxidants like polyphenols and ascorbic acid (vitamin C) can enhance the process of inhibition of oxidation and prevent the formation of ROS.

Another hope in the treatment for AIPP could come through the phosphine resistant gene found in *Rhyzopertha dominica* which requires further intensive studies and manipulations before it can be regarded as a plausible method to treat human patients.
CONCLUSION
Phosphine released from AIP has been identified as the primary culprit accentuating the morbidity and mortality associated with the acute poisoning cases. Owing to the rapidly increasing number of deaths and suicides due to ingestion or inhalation of aluminium phosphide, the need of the hour is the generation and development of a specific antidote capable of countering the action of PH₃ molecules, thus preventing the free radical mediated cellular and mitochondrial injury: the factors associated with the high mortality rate. We have suggested a number of possible treatments to combat the acute cases of poisoning, however, fumigants and compounds containing high levels of aluminium phosphide need to be phased out of the country as soon as possible or number of organic alternatives could also be employed to be used as fumigants for example, neem oil fumigation, chrysanthemum flower tea spray or using eucalyptus oil emulsion as fumigant, to name a few. In addition to this, public awareness and easy availability of AIP become the two most important issues. Strict measures, both at the administrative as well as the legislative levels are required to strategically modify and restrict the supply of AIP in India.

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