

Aluminum Phosphide Poisoning

Professor Surjit Singh

Department of Internal Medicine, Postgraduate Institute of Medical Education and Research
Chandigarh-160012 (INDIA)

Introduction: Pesticide poisoning is an important cause of morbidity and mortality in India (1). Till 1980, aluminium phosphide (ALP) had not appeared on scene. We recorded our first case of ALP ingestion in late 1979 and after publication of our first largest series in literature in 1985 (2), there has been an explosion of reports from parts of India predominantly being northwest and central India (3-13). Since our first case, 895 patients have been admitted with us till 2004 (unpublished). It is uncommon in other parts of India as well as in rest of the world except Iran and Jordan from where a few case series have been reported (14-16)). Since late 90's, ALP is being marketed in India mainly as granulated powder in plastic pouches [10 gm] as Celphos [Excel industries]. However 3 gm tablets are still available either as imported from China or manufactured by some small producers with different brand names. It liberates phosphine in presence of moisture which is the cause of toxicity (2).

Clinical Features: The initial symptoms after ingestion are retrosternal burning, epigastric pain and vomiting which are soon followed by development of hypotension which is the cardinal feature. Other common features are restlessness, tachypnoea, oliguria or anuria, jaundice, impaired sensorium and cardiac arrhythmias (2-12,17). Several EKG abnormalities have been described (2,9,12-17). These have been attributed to focal myocardial necrosis and changes in action membrane potential as result of alteration in permeability of Na⁺, Mg⁺⁺ and Ca⁺ ions (18). Both hypo and hypermagnesemia (18) have been reported. The outcome correlates best with number of vomits patient gets after ingestion and severity of hypotension and acidosis (18).

Patho -physiology: The exact mechanism by which it acts is not clear. Nakakita et al (19) found that oxygen uptake in isolated rat liver mitochondria was inhibited by it. It inhibited ADP uncoupler and ion stimulated respiration but exact target site was not identified. In a later detailed study (20) it was found to be strong inhibitor of mitochondrial respiration in active state (state-3) then in resting state (state-4) in mouse liver, housefly flight muscles, granary weevils and beef heart. It was found to inhibit uncoupled site and ion pumping state affecting pyruvate, malate, succinate, glycerophosphate and ascorbate cytochrome substrates. The effect was maximum on liver mitochondria while that on beef heart was of intermediate nature. This inhibition could not be reversed by uncouplers suggesting that it is due to direct effect on electron transport which is an important electrochemical link between respiration and phosphorylation in mitochondria. The spectral and dichroism studies revealed an interaction with heme moiety of cytochrome oxidase (cytochrome-C) but is yet to be determined whether it interacts with either cytochrome a or a₃ or both. In a study (21) involving three species of stored beetles, insect catalase and not cytochrome-c-oxidase system was found to be inhibited. In a recent experimental study where parameters of energy metabolism and oxidative stress were measured in rat brain and liver, following administration of ALP in LD50 dose i.e. 10 mg/kg body weight, it was found that cytochrome-c oxidase activity in platelets was inhibited with decrease being in a concentration dependant manner. The ATP synthesis was found to be decreased with marked decrease in ATP levels in both liver and brain. The activity of succinic dehydrogenase and NADH dehydrogenase was

markedly lower along with depletion of glycogen content in liver and activity of glycolytic enzyme was found to be increased in it. The activity of G-6PD was decreased in both organs. The results suggest that inhibition of cytochrome oxidase disturbs electron transport, leading to impaired energy metabolism (22,23). In a recent study, cytochrome-c- oxidase activity in platelets of 26 patients with severe ALP poisoning was found to be inhibited by more than 50 % ($p < .001$) as compared to healthy controls as well as those in shock due to other causes like sepsis, massive bleed and myocardial infarction (24). The exact mechanism by which phosphine acts as cellular toxin, however is still not clear and more studies are required.

Laboratory Diagnosis: The diagnosis of ALP ingestion can be confirmed by detecting phosphine in exhaled air or in stomach aspirate . Chugh et al (25) using silver nitrate impregnated strips could get good results. For spot sampling of phosphine in air, detector tubes and bulbs are available commercially (26-28). However, the most specific and sensitive is gas chromatography which can detect minute amounts of phosphine in air (29).

Management: The management continues to be unsatisfactory as there is no specific antidote and remains supportive only. The factors which have been found to correlate best with outcome are numbers of vomits patient has after ingestion and severity of shock and acidosis. The main factor which guides the management is treatment of shock / hypo tension with appropriate measures. Intravenous fluids should be administered as leakage of fluids from intravascular to extravascular space occurs as a result of capillary dysfunction (9). However CVP is generally high in them. In eleven intensively monitored patients, global hypokinesia of left ventricle with decreased ejection fraction was observed but administration of large quantities of fluids administered to combat this did not make any significant difference in the outcome (9) The administration of fluids can be combined with dopamine / dobutamin infusion to maintain systolic BP above 80 mmHg.

Magnesium sulfate, a membrane stabilizer and can reverse arrhythmias has been used. Though arrhythmia's improve, mortality does not decline. In severe cases compromised adrenal function has been reported (30). Though corticosteroids has been administered, outcome remains poor.

Future options: The mechanism of action of phosphine is not clearly known. More basic research is required to find exact mechanism of action of phosphine so that a specific antidote can be developed. There is need to develop better confirmatory tests to confirm poisoning with ALP either by detecting phosphine in breath by phosphine detector tubes or gas chromatography. As there is some experimental evidence to suggest that N- acetylcysteine may help in improving outcome (31), it may be worthwhile conducting an RCT's using it. Some other drugs which are known to protect mitochondrial oxidative phosphorylation such as hydroxycobalamine and vitamin c may also be tried.

Prevention: An important preventive measures lies in better regulated supply of ALP which otherwise is an excellent and safe fumigant as it leaves little residue on grain (32). Legislative and administrative measures have been suggested to restrict and modify its supply in India (33). Unfortunately there has been a failure in their application except largest producer of it in India has started marketing it as granulated powder in 10 gm plastic sachets. However, patients continue to come with severe poisoning. In our retrospective analysis , we have observed that though, number of cases due to ALP have continued to increase, a consistent decline in mortality was

observed from year 2000 onwards since bulk of ALP available in market has been in form of granulated powder in plastic sachets. These sachets could have led to an decreased severity of poisoning as ALP gets exposed to atmospheric moisture leading to escape of phosphine during opening of these sachets to swallow ALP granules (unpublished).

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