Editorial

N-acetyl cysteine in aluminum phosphide poisoning: Myth or hope

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Pesticide poisoning, a global public health problem, is an important cause of morbidity and mortality in India. The organophosphate, organochlorines and aluminum phosphide (AlP) compounds are commonly used pesticides. Aluminum phosphide is cheap, effective, and free from toxic residue and does not affect seed viability. Hence, its use as a pesticide is widespread. Unheard until 1980, it is now a common mode of suicide in the agricultural community in northern India, usually involving young adult population from rural areas.[1]

The mortality rates published in the literature for AlP poisoning vary from 40% to 80%. In a study conducted at a tertiary center in Haryana-Rohtak in 1995, of the 559 cases of acute poisonings, AlP was found to be the most commonly abused substance (67.8%) with a mortality of 67.6%,[2] with no change even a decade later (personal communication).

The toxic effects of the AlP are due to phosphine gas (PH 3) released when it comes in contact with moisture or hydrochloric acid. Phosphine is rapidly absorbed by inhalation, ingestion, and skin or mucosal contacts. It is available as a tablet of 3 g that contains 56% AlP and 44% ammonium carbonate.

Various mechanisms have been described for AlP toxicity. Oxidative stress, caused by an imbalance between the production of free radicals and their elimination by antioxidants, has been recognized as a central contributor to cellular injury and death. Phosphine, a nucleophile, acts as a strong reducing agent and noncompetitively inhibits mitochondrial respiratory chain enzyme cytochrome c oxidase leading to the generation of reactive oxygen species and cellular peroxides. Oxidative degradation of lipids known as lipid peroxidation, and other oxidant mechanisms damage biological macromolecules specially the cell membrane ultimately leading to cell death.[3] Additionally, the direct toxic effects of phosphine on myocardial cells can cause circulatory collapse. A direct relation to mortality has been suggested on the basis of superoxide dismutase (SOD), catalase and malonyldialdehyde levels on post mortem studies of these patients.[4] The defense system to counteract free radicals is antioxidant agents, which scavenge free radicals and other toxic oxidizing species. The enzymes superoxide dismutase, catalase and glutathione reductase (GR) are important antioxidants.

The signs and symptoms are nonspecific and depend on the dose, route of entry and time since exposure to poison. After ingestion, toxic features such as nausea, vomiting, retrosternal burning, diarrhea, headache, abdominal discomfort develop within few minutes, followed by involvement of the gastrointestinal, cardiovascular, respiratory and nervous systems. Later on, renal and hepatic failure and disseminated intravascular coagulation may also occur. The cardiovascular toxicity of AlP manifests as profound and refractory hypotension, myocarditis, congestive heart failure, subendocardial infarction or pericarditis. Electrocardiogram abnormalities include rhythm disturbances, ST-T changes and conduction defects. Respiratory complications include pulmonary edema, respiratory failure and acute respiratory distress syndrome. Blockage of oxidative phosphorylation and

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poor tissue perfusion lead to accumulation of lactic acid causing metabolic acidosis. Patients generally remain conscious till cerebral anoxia due to shock supervenes, resulting in drowsiness, delirium, and coma.

Diagnosis is confirmed by detecting phosphine in exhaled air or stomach contents. There is no specific antidote for this poisoning. Therefore supportive therapy is extremely important. Gastric lavage with potassium permanganate, which oxidizes phosphine to nontoxic phosphate, is useful if done within 1 h of ingestion.

Myocardial toxicity and cardiovascular failure should be managed aggressively. Adequate tissue perfusion and oxygenation needs to be maintained until the tissue poison levels are reduced, and spontaneous circulation is restored. Patients of severe AlP poisoning preferably need continuous invasive hemodynamic monitoring. Intravenously fluids should be used judiciously. For refractory hypotension, norepinephrine should be preferred over dopamine and dobutamine because of their higher propensity to cause arrhythmias. The role of intra-aortic balloon pump and extracorporeal life support as a supportive measure for intractable circulatory collapse is anecdotal.[5] Magnesium sulfate reduces the incidence of arrhythmias by stabilizing the cell membrane, but routine use of intravenous magnesium sulfate has failed to elicit mortality benefit.[6] Aggressive correction of acidosis with intravenous sodium bicarbonate may result in significant improvement in outcome.[7] Hemodialysis is not very effective in removing phosphine, but is indicated for severe metabolic acidosis, fluid overload or renal failure.

Considering the role of oxidative stress in AlP poisoning, many agents with antioxidant properties have been tried in experimental studies, like glutathione, melatonin, Vitamin C and beta carotene, but the only antioxidant that has shown some promise is N-acetylcysteine (NAC). It stimulates glutathione synthesis and counteracts damaging effects of free radicals by either repairing the oxidative damage or directly scavenging the free radicals.

In an experimental study on Aluminum phosphide poisoned rats by Azad *et al*., NAC reduced myocardial oxidative injury resulting in improved hemodynamics and prolonged survival time.[8]

A study published in the current issue shows improved survival in patients receiving NAC along with supportive therapy.[9] Levels of antioxidant enzymes catalase and SOD were reduced at presentation, with significantly lower values in patients who expired. GR was reduced by day 1, suggesting that AlP toxicity affects GR activities maximally by the day 1 which is consistent with findings by Chugh *et al*. showing that indicators of oxidative stress peak within 48 h of exposure of poisoning.[4] Bicarbonate and lactate levels at presentation correlated with the outcome. Lactate levels >6.9 mmol/l showed 100% sensitivity in prediction of mortality. The limitations of this study were the small number of cases, lack of blinding and not able to demonstrate a reduction in levels of free radicals with antioxidants.

In a prospective, randomized, controlled open-label trial conducted by Tehrani *et al*. in Iran, NAC infusion significantly decreased the duration of hospitalization, rate of intubation and mechanical ventilation, as well as mortality rate in acute AlP poisoning.[10]

Though the well-established role of oxidative stress in AlP toxicity confers biological plausibility to use of antioxidants, there is a paucity of human studies showing a significant mortality benefit. Thus, it may be too early to recommend the use of NAC in AlP poisoning. Nevertheless, it opens the door of opportunity for larger clinical trials to evaluate whether the early enthusiasm with NAC translates into a therapeutic option with improved outcomes in this highly fatal poisoning.

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