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Aluminium Phosphide Poisoning

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1. Introduction

Acute aluminium phosphide poisoning is an extremely lethal poisoning. Ingestion is usually suicidal in intent, uncommonly accidental and rarely homicidal. Unfortunately the absence of a specific antidote results in very high mortality and the key to treatment lies in rapid decontamination and institution of resuscitative measures. Aluminium phosphide is a solid fumigant which has been in extensive use since the 1940s. It has rapidly become one of the most commonly used grain fumigants because of its properties which are considered to be near ideal; it is toxic to all stages of insects, highly potent, does not affect seed viability, is free from toxic residues and leaves little residue on food grains (Hackenberg, 1972).

They are formulated as compressed discs, tablets or pellets that commonly weigh 3 g and contain variable amounts of a single phosphide in combination with other substances such as ammonium carbonate. Tablets are dark brown or grayish in colour. It is freely available in the markets with the major virtues of being cheap and not leaving toxic residues. The specified fatal dose in human is 0.15–0.5 gm. Phosphides are used widely to protect grain held in stores, the holds of ships and in wagons transporting it by rail and are admixed with the grain at a predetermined rate as it is put into storage. Moisture in the air between the grains mixes with phosphide and release phosphine (hydrogen phosphide, phosphorus trihydride, PH3) which is the active pesticide. After contact with an acid, phosphine is released even more vigorous. Two kinds of acute poisoning with these substances are reported: indirect inhalation of the phosphine generated during their approved use or direct ingestion of the salts.

Pure phosphine is colorless and odorless up to toxic concentrations (200 ppm), a view accepted by the International Programme on Chemical Safety and others (Pepelko, et al., 2004; Chaudhry, 1997; IPCS, 1988; Dumas & Bond, 1974), it has an odor of garlicky or decaying fish due to the presence of substituted phosphines and diphosphines. If the former view is accepted the smell emanating from phosphide poisoned patients is probably due to contaminants in the pesticide formulations and not phosphine itself. It has been suggested that these volatile contaminants may be alkylphosphines (Fluck, 1976). For “phosphine” liberated from one pesticidal formulation of aluminium phosphide, the odor threshold was 0.01–0.02 ppm, ten times lower than that derived from the technical salt alone (Fluck, 1976). The usefulness of phosphide pesticides is now threatened by the development of resistance to them.

2. Methods

To complete this review, the terms aluminum and aluminum phosphide and phosphine were searched using the TUMS (Tehran University of Medical Science) digital library,
Medline, pubmed and Google Scholar databases. All applicable articles in English were attained. Many isolated case reports and small case series do not appear in the citation list. The ability to highlight important aspects is the only criterion for inclusion in this review.

The criteria used in the current review include below criteria: Articles were selected based on the impact of lifestyle, stress, and/or environmental factor/s predisposing aluminium phosphide poisoning exposure. Criteria for selection of the literature used included yes-no responses to the appropriateness of methodology; adequacy of subject numbers; specificity of sex and/or age of subjects, and statistically significant response rates to survey questionnaires. The time frame used was principally 1990-2011 inclusive, although articles of extreme importance from earlier decades were used where appropriate. A multifactorial overview of the factors eschewed concerning aluminium phosphide poisoning exposure was elucidated. It was supposed that collective articles detailing known factors of usage were not necessarily correlated with functionality and health. Collection of materials for the review started with the published literature or easily available academic research.

3. Epidemiology

Annually about 300,000 deaths are reported by pesticides poisoning worldwide (Eddleston & Phillips, 2004). The most reports of acute pesticide poisoning only based on hospital records admission and as a result absolutely reflect a small part of the real incidence. In Asian region about 25 million agricultural workers suffer from an episode of poisoning each year (Jeyaratnam, 1990). In “phosphine” poisonings reported from Germany, 28% were planned and mostly by eating, whereas the majority of the 65% accidental exposures were by inhalation (Lauterbach, et al, 2005). A report has also been published from the United Kingdom where the majority of 93 aluminium phosphide exposures were accidental and concerned inhalation of phosphine in agricultural locations (Bogle, 2006).

4. Ingestion of phosphides

5. Occupational and environmental phosphine exposure


Phosphine may be released during the illicit manufacture of methamphetamine (Burgess, 2001, Willers-Russo, 1999); deaths have resulted (Willers-Russo, 1999). In another incident, a packet of aluminium phosphide in a container from abroad burst open and the sweepings placed in water causing immediate fizzing and liberation of phosphine (Kamanyire & Murray, 2003). Close proximity to a source of phosphine is not required to be at risk of toxicity as phosphine gas can travel some distance as it is heavier than air (vapor density 1.2:1). Many years ago 12 individuals in a house adjacent to a warehouse used to store aluminium phosphide developed vomiting and one died. The illnesses were attributed to phosphine (Glass, 1959). More recently exposures have been alleged after use of metal phosphides to control pests in adjacent buildings (Popp, 2002).

6. Mechanism of action

The exact mechanism of action of aluminum phosphide poisoning is still unknown, however an initial survey on different animals showed non-competitive cytochrome oxidase binding by phosphine, changes valences of haeme component of haemoglobin.Other than later articles, distinguished significant inhibition of catalase goes to hydrogen peroxide agglomeration (Price, et al, 1982), Extra-mitochondrial release of hydrogen peroxide and oxygen free radicals (Bolter & Chertuka, 1989), leading to lipid peroxidation and protein denaturation of cell membrane are reported in more recent studies (Chug, et al, 1969). Also, aluminum and phosphine (Potter, et al, 1993; Al-Azzawi, et al, 1990), inhibit cholinesterases activity . Al-Azzawi showed in vitro exposure to phosphine lead to reducing human serum cholinesterase activity; in addition he showed the amount of the inhibition is related to the duration and concentration of phosphine (Al-Azzawi, et al, 1990). On the other hand, other studies declared there is no erythrocyte cholinesterase activity reduction in humans after accidental phosphine inhalation (Heyndrickx, et al, 1976; Wilson, et al, 1980).

7. Toxicokinetics

these reactions support the involvement of erythrocytes in the biotransformation of phosphine in vivo in humans (Stewart, et al, 2003).

8. Clinical features
Aluminium phosphate poisoning affects the most organs and a variety of signs and symptoms appear in patients. Early symptoms include nausea, vomiting, retrosternal and epigastric pain, dyspnea, anxious, agitation and smell of garlic (Popp, et al, 2002; Aggarwal, et al, 1999; Sood, et al, 1997). Moreover shock and peripheral circulatory failure are mainly imperative early signs of toxicity. Mortalities in past studies have ranged from 40–77% and in one survey 55% occurred within 12 h of ingestion and 91% within 24 h (Singh, et al, 1991).

8.1 Cardiac toxicity

8.2 Respiratory toxicity
Tachypnea, dyspnea, crepitations, and rhonchi were present on examination in 192 out of 418 cases (46%) of phosphide poisoning (Chugh, et al, 1991) and have been found by others (Gupta, et al, 2000). Pulmonary edema is common but it is not always clear whether it is cardiogenic or non-cardiogenic in etiology. It tends to develop 4–48 h after ingestion and the finding of a reduced arterial pressure of $O_2$ without an increase in pulmonary artery wedge pressure, suggested it was non-cardiogenic (Kalra, et al, 1991). Othetes have confidently diagnosed adult respiratory distress syndrome (Singh, et al, 1991, Bajaj, et al, 1988, Gupta, et al, 1995, Chugh, et al 1989) and non-specific pulmonary edema (Singh, et al, 1996, Chugh, et al, 1998). The edema fluid may be protein-rich and hemorrhagic (Singh, et al, 1996).

8.3 Gastrointestinal toxicity

8.4 Hepatic toxicity
Transient elevations of alanine aminotransferase and aspartate aminotransferase activities are not infrequent after ingestion of metal phosphides (Frangides & Pneumatikos, 2002;
Akkaoui, et al, 2007; Bayazit, et al, 2000; Memis, et al, 2007) but jaundice secondary to liver damage (Chugh, et al, 1998) is much less common. It was present in 12 out of 92 cases (Singh, et al, 1991) and was said to be common in another series of 15 patients (Singh, et al, 1985) but confirmatory laboratory data were not provided. Jaundice was alleged to be present in 16 (52%) members of the crew of a grain freighter who inhaled phosphine after an accidental release (Wilson, et al, 1980) but, in the six tested, serum bilirubin concentrations were normal and transaminase activities only minimally disturbed, casting doubt on the clinical observation. Acute hepatic failure and encephalopathy was considered to be the cause of death in one man (Chittora, et al, 1994), while a 12-yearold girl died from a combination of acute hepatic failure and encephalopathy with renal failure (Bayazit, et al, 2000). Portal edema, congestion of the portal tract and central veins, and vacuolization of hepatocytes are the most frequent findings at autopsy (Saleki, et al, 2007).

8.5 Electrolyte and metabolic abnormalities
Hypokalemia. metabolic acidosis, mixed metabolic acidosis and respiratory alkalosis, and acute renal failure are reported frequently. Also, Hypoglycemia and hypomagnesemia have been reported in several studies (Chugh, et al, 2000; Dueñas, et al, 1999). Hypokalemia is common soon after ingestion of metal phosphides and is probably secondary to vomiting, though catecholamine release could also contribute. It is thought to be the result of impaired gluconeogenesis and glycogenolysis (Frangides & Pneumatikos, 2002) possibly secondary to adrenal gland damage and low circulating cortisol concentrations (Chugh, et al, 2000). Hyperglycemia (Abder-Rahman, 1999) appears to be rare. The main controversy relates to the existence or otherwise of disturbances of magnesium homeostasis. In 1989, prompted by reports of the empirical use of magnesium sulphate to treat phosphide toxicity, this study (Singh, et al, 1989; Singh & Sharma, 1991) demonstrated that serum magnesium concentrations were increased, possibly secondary to release from damaged cardiac myocytes and hepatocytes, and confirmed the findings in subsequent studies (Singh, et al, 1991; Singh, et al, 1990). Unfortunately, other studies have found the converse, that is serum and erythrocyte concentrations were reduced rather than increased. Chugh, et al, (1991) compared serial serum and erythrocyte magnesium concentrations in four groups of people. One comprised patients poisoned with aluminium phosphide who had resulting shock and cardiotoxicity while the second included those poisoned but without shock or cardiac features. The remaining two groups acted as controls, the first being patients in shock secondary to trauma or hemorrhage but without other features of cardiac toxicity and the second, normal volunteers. The only significant finding in admission samples was that cell and serum concentrations were lower in shocked, cardiotoxic patients and hepatocytes, and confirmed the findings in subsequent studies (Singh, et al, 1991; Singh, et al, 1990). Unfortunately, other studies have found the converse, that is serum and erythrocyte concentrations were reduced rather than increased. Chugh, et al, (1991) compared serial serum and erythrocyte magnesium concentrations in four groups of people. One comprised patients poisoned with aluminium phosphide who had resulting shock and cardiotoxicity while the second included those poisoned but without shock or cardiac features. The remaining two groups acted as controls, the first being patients in shock secondary to trauma or hemorrhage but without other features of cardiac toxicity and the second, normal volunteers. The only significant finding in admission samples was that cell and serum concentrations were lower in shocked, cardiotoxic patients (mean serum and RBC concentrations 0.9 and 3.7 mEq/L respectively compared with 1.8 and 5.2 mEq/L in volunteers). Since, first, hypomagnesemia was found in toxic shocked patients but not in those with non-toxic shock and secondly, 75% of those in the toxic/shock group had ECG changes, it was concluded that the evidence supported a causal relationship between hypomagnesemia and phosphide induced shock. Without intervention both serum and cell values returned to normal by about 24 h. The authors confirmed their findings in a later study (Chugh, et al, 1994) and thought the hypomagnesemia secondary to consumption in combating free radical stress (Chugh, et al, 1997). Hypomagnesemia has also been found in a recent single case of phosphine inhalation from aluminium phosphide (Dueñas, et al, 1999). The situation became even more complicated when, in 1994, a study (Siwach, et al, 1994) found themselves unable to agree with either. They found pre-treatment mean serum and
red cell magnesium concentrations to be normal. Concentrations were increased in the brains, lungs, hearts, livers, kidneys, and stomachs of fatalities but later studies showed this to be the result of magnesium administration and not phosphide toxicity (Siwach, et al, 1995). Clearly, these studies cannot all be correct and the analytical method used to generate the results may be an important factor. The results of a study (Siwach, et al, 1994) carry particular weight because they used atomic absorption spectroscopy, a technique that is superior to the colorimetric method published in 1977 and used (Singh, et al, 1991) and the titan yellow method employed (Chugh, et al, 1991) despite it being claimed that results obtained using the former method correlated extremely well with those from atomic absorption spectroscopy (Khayam-Bashi, et al, 1977). If these studies (Siwach, et al, 1994) are considered the most reliable, there is no choice but to accept that neither hypomagnesemia nor hypermagnesemia is a feature of aluminium phosphate poisoning, though confirmation by another independent study would be welcome.

8.6 Hematological toxicity

Although phosphine causes Heinz body formation and hemoglobin oxidation in vitro (Chin, et al, 1992; Potter, et al, 1991), intravascular hemolysis and methemoglobinemia are unusual complications of phosphide poisoning in humans. Nine individuals with intravascular hemolysis after ingestion of aluminium phosphide have been identified from the literature. Three were glucose-6-phosphate dehydrogenase deficient (Srinivas, et al, 2007), including one young man who had previously developed haemolysis when given primaquine (Sood, et al, 1997). Two others had no history to suggest this possible predisposing disorder (Aggarwal, et al, 1999; Lakshmi, 2002) and in the remaining four the issue was not addressed (Chugh, et al, 1991). Intravascular hemolysis was associated with renal failure and severe metabolic acidosis to which 3 days of vomiting and diarrhea may have partly contributed (Memis, et al, 2007). In addition to hemolysis one man was found to have methemoglobinemia of 17% 32 h post-ingestion (Lakshmi, 2002) while another developed Heinz bodies (Srinivas, et al, 2007), a further indicator of damage to hemoglobin. Rats given aluminium phosphate had methemoglobin concentrations measured at 10 and 30 min intervals. They increased simultaneously with those of malonyldialdehyde suggesting that methemoglobinemia was secondary to increased oxygen free radical generation (Lall, et al, 2000). A study revealed that there is a significant association between blood level of methemoglobin and mortality in patients with aluminium phosphate intoxication (Mostafazadeh, et al, 2010). Disseminated intravascular coagulation was present in six out of 418 patients poisoned with aluminium phosphate (Chugh, et al, 1991).

8.7 Uncommon features

suffered an intracranial hemorrhage 5 days after the event. No explanation other than the poison was found (Dave, et al, 1994).

9. Diagnosis

A positive history of ingestion is the basis of diagnosis in most cases. The presence of typical clinical features, garlicky odour from the mouth and highly variable arrhythmias in a young patient with shock and no previous history of cardiac disease points towards aluminium phosphide poisoning. Aluminium phosphide poisoning risk is low down in the following instances, When taking patient's history should be special attention to these points:
- If the patient uses the expired one
- If aluminium phosphide is dissolved in water before use
- Confirmation can be done by the Silver Nitrate Test (Chugh, et al, 1989). In this test, 5 ml of gastric aspirate and 15 ml of water are put in a flask and the mouth of the flask is covered by filter paper impregnated with silver nitrate. The flask is heated at 50°C for 15 to 20 min. If phosphine is present the filter paper turns black. For performing the test on exhaled air, the silver nitrate impregnated filter paper is placed on the mouth of the patient and the patient is asked to breath through it for 15-20 minutes, blackening of the paper indicates the presence of phosphine in breath. The sensitivity of the test is 100%. However the most specific and sensitive method for detecting the presence of PH₃ in blood/air is gas chromatography (Vins Jansen A, Thrane, 1978). For spot sampling of phosphine in air, detector tubes and bulbs are available commercially (International Programme on Chemical Safety, 1998; Leesch, 1982).

10. Laboratory investigations

Laboratory evaluation is often performed to assess the prognosis. Leucopenia indicates severe toxicity. Increased aspartate aminotransferase or alanine aminotransferase and metabolic acidosis indicate moderate to severe ingestional poisoning. Electrolyte analysis shows decreased magnesium while potassium may be increased or decreased (Chugh, et al, 1990). Measurement of plasma renin is significant as its level in blood carries a direct relationship with mortality and is raised in direct proportion to the dose of pesticide. The serum level of cortisol is usually found to be decreased in severe poisoning (Chugh, et al, 1989). Chest X-ray may reveal hilar or perihilar congestion if ARDS develops. Electrocardiogram shows various manifestations of cardiac injury (ST depression or elevation, bundle branch block, ventricular tachycardia, ventricular fibrillation) (Jain, et al, 1985; Katira, et al, 1990; Siwach, et al, 1998; Singh, et al, 1989). Wall motion abnormalities, generalised hypokinesia of the left ventricle, decreased ejection fraction and pericardial effusion can be seen in echocardiography (Chugh, 1995).

11. Prognostic markers

Development of refractory shock, acute respiratory distress syndrom, aspiration, pneumonitis, anaemia, metabolic acidosis, electrolyte imbalance, coma, severe hypoxia, gastrointestinal bleeding, and pericarditis are associated with poor prognosis. The outcome correlates best with the number of vomiting the patient gets after ingestion and the severity of hypotension the patient develops (Singh, et al, 1998) 95% of the patients die within 24
hours and the commonest cause of death in this group is arrhythmia. Death after 24 hours is due to shock, acidosis, acute respiratory distress syndrome and arrhythmia. The mortality rate is highly variable, ranging from 37-100% and can reach more than 60% even in experienced and well equipped centres.

12. Management

12.1 Decontamination

Gastric lavage is probably best avoided after ingestion of phosphides as it might increase the rate of disintegration of the pesticide and increase toxicity (Maitai, et al, 2002). To reduce the absorption of phosgene, gastric lavage with potassium permanganate (1:10,000) is done. Permanganate is used as it oxidizes PH₃ to form non-toxic phosphate. This is followed by a slurry of activated charcoal (approximately 100 gm) given through a nasogastric tube. In vitro studies suggested that vegetable oil and liquid paraffin inhibit phosphine release from phosphides (Goswami, et al, 1994) but these oils have not been tested in clinical practice. However, vomiting may make the administration of charcoal difficult. Although the administration of sodium bicarbonate via a gastric tube to decrease gastric hydrochloric acid has been proposed in the belief that hydrochloric acid assists the conversion of phosphide to phosphine, there is no experimental support for its use. Moreover, based on an understanding of the mechanisms of toxicity of metal phosphides, this strategy is unlikely to reduce morbidity and mortality. Removal of victims of phosphine inhalation from the contaminated atmosphere will have been carried out by the emergency service first on scene. Supplemental oxygen may be given if necessary but further measures for airway control are unlikely to be required.

12.2 Supportive care

Many patients will die from metal phosphide poisoning despite intensive care. Supportive measures are all that can be offered and should be implemented as required by clinical developments. The most important factor for success is resuscitation of shock and institution of supportive measures as soon as possible. Intravenous access should be established and 2-3 litres of normal saline are administered within the first 8-12 hr guided by central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP). The aim is to keep the CVP at around 12-14 cm of water (Siwach, et al, 1997). Some workers have recommended rapid infusion of saline (3-6 litres) in the initial 3 hr (Kalra, et al, 1991). Low dose dopamine (4-6 μg/kg/min) is given to keep systolic blood pressure >90 mm Hg. The other vasopressures such as norepinephrine may be useful in critical patients. The use of high doses of glucagon may benefit in the treatment of aluminum phosphide poisoning; the likely mechanism of action is the increase of cAMP in the myocardium, effectively bypassing the β-adrenergic second messenger system. Oxygen is given for hypoxia. Acute respiratory distress syndrome requires intensive care monitoring and mechanical ventilation. The blood glucose concentration should be measured in every case and hypoglycemia corrected if found. Similarly, hypokalemia should be sought and, if clinically indicated, at least partially corrected; cardiac features have resolved in occasional patients on correction of potassium concentrations (Kochar, et al, 2000). It must be remembered, however, that the onset of acidosis, renal failure and cell damage may produce life-threatening hyperkalemia. Metabolic acidosis should be managed conventionally. Bicarbonate level less than 15 mEq/L requires bicarbonate in a dose of 50-100 mEq intravenously every 8 hour (Singh, et al, 1989).
All types of ventricular arrhythmias are seen in these patients and the management is the same as for arrhythmias in other situations (International Programme on Chemical Safety, 1998).

12.3 Magnesium supplementation
The problematic decision is whether or not supplemental magnesium should be given. If magnesium depletion does not occur such a course would appear illogical but single cases have been reported where magnesium administration appeared to terminate atrial fibrillation (Chugh, et al, 1989) and supraventricular tachycardia and ventricular tachycardia (Chugh, et al, 1991). On the other hand, magnesium sulphate 3 g given intravenously over 30 min did not abolish very frequent ventricular ectopic beats and bigeminy though it restored a normal magnesium concentration (Dueñas, et al, 1999). Only a few studies have attempted to assess the value of magnesium sulphate in large groups of patients and their results are conflicting. In a study, 50 patients after aluminium phosphide ingestion were given high doses of magnesium and the result compared with the control group that was not treated. The result showed (42%) of those given supplemental magnesium survived compared with (40%) not so treated. In addition, treatment did not considerably improve survival at any dose (number of tablets) consumed. As you see magnesium supplementation was of no value in this study (Siwach, et al, 1994). Chugh et al. (2004) obtained opposite results in a case control study. The authors showed survival remarkably improved after each dose ingested for those patients treated by magnesium (Chugh, et al, 2004). To illuminate the potential benefit of magnesium supplementation, additional studies are necessary.

12.4 N-acetylcysteine

12.5 Pralidoxime
There is experimental and clinical evidence that phosphine (Potter, et al, 1993) and aluminium (Marquis & Lerrick, 1982, 1983) inhibit acetylcholinesterase. A study (Mittra, et al, 2001) investigated the benefit of administering atropine 1 mg/kg and pralidoxime 5 mg/kg parenterally to rats dosed with aluminium phosphide 10 mg/kg (5.55 × LD50) 5 min previously. Treatment increased the survival time by 2.5-fold in nine out of 15 animals and resulted in the survival of the six remaining animals. There were no survivors in the two control groups. Further studies are required to confirm the benefit of oximes.

13. Conclusions
Acute poisoning with metal phosphides, particularly aluminium phosphide, is a worldwide problem most commonly encountered in the Indian Sub-Continent. The clinical features have been well described though it is only recently that the mechanisms of toxicity have been more clearly understood. Poisoning from phosphides is mediated by phosphine which has been shown to rapidly perturb mitochondrial morphology, inhibit oxidative respiration, and cause a severe drop in mitochondrial membrane potential. This failure of cellular
respiration is likely to be due to a mechanism other than inhibition of cytochrome C oxidase as phosphine inhibits cytochrome C oxidase activity less dramatically in vivo than in vitro and only partially inhibits cytochrome C oxidase activity in humans. Phosphine can also form the highly reactive hydroxyl radical and inhibit both catalase and peroxidase leading to lipid peroxidation. The gas or gases given of in addition to phosphine when phosphide formulations come into contact with water or acid need to be identified and their toxicity determined. The observation that both aluminium and phosphine may inhibit acetylcholinesterase activity needs to be investigated further as does the report that the administration of atropine and pralidoxime reduces morbidity and mortality in aluminium phosphide poisoning. There is conflicting evidence also on the occurrence and clinical importance of magnesium disturbances which some have described. The benefit of magnesium supplementation has still to be determined.

14. References


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Modern drug design and testing involves experimental in vivo and in vitro measurement of the drug candidate’s ADMET (adsorption, distribution, metabolism, elimination and toxicity) properties in the early stages of drug discovery. Only a small percentage of the proposed drug candidates receive government approval and reach the market place. Unfavorable pharmacokinetic properties, poor bioavailability and efficacy, low solubility, adverse side effects and toxicity concerns account for many of the drug failures encountered in the pharmaceutical industry. Authors from several countries have contributed chapters detailing regulatory policies, pharmaceutical concerns and clinical practices in their respective countries with the expectation that the open exchange of scientific results and ideas presented in this book will lead to improved pharmaceutical products.

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