An Overview about Acute Aluminum Phosphide Poisoning (Wheat Pill)

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Abstract

Background: Acute Aluminum phosphide poisoning is a case of emergency with dangerous clinical findings up to shock and death within several hours. Therefore, aggressive intervention and careful life support are immediately essential based on history and clinical evidence to maintain patient life. The mode of acute Aluminum phosphide poisoning (AlP) can be accidental, suicidal, or homicidal. The lethal dose of AlP in humans after oral poisoning is reported to be 150-500 mg/70kg approximately.After oral administration of AlP phosphine gas (PH3) is released in the stomach and absorbed through the respiratory tract causing severe toxicity.Early symptoms of poisoning start in 10-15 minutes including GIT irritation (Nausea, vomiting, epigastric pain), shortness of breath, irritability, and anxiety. Garlic or spoiled fish odor from the patient's breath is also detected. Delayed symptoms include dysphagia, delirium, seizure, coma, and shock. Common complications in adult patients include respiratory distress syndrome and pulmonary edema in addition to the accumulation of bloody or full-protein effusion in the pleural space.Aluminum phosphide poisoning is diagnosed by clinical suspicion and history. Treatment should be started immediately on suspecting AlP without waiting for confirmatory test results. The investigations are done to follow up the case, manage the outcome adequately and predict the fate. As there is no specific antidote for AlP poisoning, therefore the cornerstone of therapy is supportive care. AlP poisoning is suspected based on the history and physical examination. Treatment must not be delayed until test results are confirmed. All symptomatic patients should be monitored in the intensive care unit (ICU) for at least 72 hours. There are new trials of treatment introduced to improve the outcome as antioxidants, corticosteroids, and cardiac supportive drugs.

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Introduction

Acute Aluminum phosphide poisoning (wheat pill) is a case of emergency with dangerous clinical findings up to shock and death within several hours. Therefore, aggressive intervention and careful life support are immediately essential based on history and clinical evidence to maintain patient life **(1).**

A. Mode of toxicity and toxic dose

The mode of acute Aluminum phosphide poisoning (AlP) can be accidental, suicidal, or homicidal**.** The lethal dose of AlP in humans after oral poisoning is reported to be 150-500 mg/70kg approximately **(2).**

B. Clinical Scenarios according to the route of exposure

1. Acute AlP poisoning due to ingestion:

After oral administration of AlP phosphine gas (PH_3) is released in the stomach and absorbed through the respiratory tract causing severe toxicity. Early symptoms of poisoning start in 10-15 minutes including GIT irritation (Nausea, vomiting, epigastric pain), shortness of breath, irritability, and anxiety. Garlic or spoiled fish odor from the patient's breath is also detected. Delayed symptoms include dysphagia, delirium, seizure, coma, and shock. Common complications in adult patients include respiratory distress syndrome and pulmonary edema in addition to the accumulation of bloody or full-protein effusion in the pleural space **(3)**

The toxic effect of AlP on various body organs. The case of severe AlP poisoning is mainly manifested by metabolic acidosis, tachypnea, tachycardia, refractory hypotension, and shock which does not respond to fluids. Patients remain conscious until shock causes cerebral hypoxia resulting in drowsiness, delirium, and coma**.** Electrocardiographic (ECG) changes include Sinus tachycardia within the first three to six hours of intake, followed by ST-T changes and different types of dysrhythmias **(4)**.

2. Acute poisoning due to inhalation

The inhalational exposure results from contact of aluminum phosphide with water or humidity releasing PH3 into the atmosphere with subsequent nonspecific symptoms such as headache chest tightness, cough, and GIT manifestations almost immediately which may progress to collapse and death as phosphine gas is lethal within 30 minutes at air level of 400–600 ppm (Part per million) **(4).**

C. Diagnostic workup in acute AlP poisoning

Aluminum phosphide poisoning is diagnosed by clinical suspicion and history. Treatment should be started immediately on suspecting AlP without waiting for confirmatory test results. The investigations are done to follow up the case, manage the outcome adequately and predict the fate **(5).**

1. Laboratory investigations

a) Nonspecific laboratory investigations (performed as a routine for all poisoned patients):

i. Arterial blood gas (ABG)

The analysis and monitoring of arterial blood gas (ABG) is an important process in the follow-up of acid-base balance and oxygenation in high-risk and critically ill patients. In the case of AlP toxicity, severe metabolic acidosis has been always witnessed **(3). Saleh and Makhlof (6)** reported that metabolic acidosis correlates with a high incidence of mortality and can be used as a prognostic tool to predict the outcome of AlP acute poisoning cases.

ii. Complete blood count (CBC)

A complete blood count (CBC) is a group of medical laboratory tests which provide information about the blood cells in a person.

In the case of AlP poisoning, hemoglobin content is usually normal but some cases may have leucopenia; WBC changes like neutrophils, eosinophils, and lymphocyte degeneration or deformed morphology, also monocytes may show nuclear disintegration, fragmentation, and cytoplasmic vacuolation **(7).**

However, **Hosseinian et al. (8)** declared leukocytosis among intoxicated cases as one of the most common biochemical findings during their hospital stay**.**

iii. Liver function tests:

Liver function tests are a group of tests that provide information about the state of the liver by measuring specific enzymes and proteins in the blood. Aspartate aminotransferase (AST or SGOT) is an enzyme found in the liver, heart, skeletal muscle, kidneys, brain, and red blood cells and plays an important role in amino acid metabolism. Alanine aminotransferase (ALT or SGPT) is found in plasma and various body tissues but is most common in the liver **(9).**

In the case of AlP poisoning, AST, ALT, and bilirubin may show some changes upon exposure. **El-Sarnagawy (10)** reported an elevation in AST and ALT among the AlP deceased cases. However, **Taramsari et al. (11)** found that there was no statistical correlation between AST and ALT and the outcome.

iv. Kidney function tests:

This group of tests determines the state of kidneys and their ability to maintain their functions. Aluminum phosphide causes multiple organ damage and induces acute renal failure which can be presented in form of oliguria and anuria **(3)**

In the case of AlP poisoning, serum creatinine and blood urea nitrogen can be used to predict the outcome of cases as they are commonly elevated in the non-survivors **(12).**

b) Specific investigations: (to assess AlP-specific toxic mechanism and effects):

i. Oxidative stress markers (SOD, Catalase activity, MDA)

Super oxide dismutase (SODs):

Superoxide dismutase is a group of important metalloenzymes that act as a defense mechanism against oxidative stress, it catalyzes the superoxide (O_2^-) radical into ordinary molecular oxygen (O_2) and hydrogen peroxide. Superoxide is a product of oxygen metabolism and, if not regulated, causes many types of cell damage. AlP-induced oxidative stress decreases superoxide dismutase **(13)**.

Catalase activity

Catalase is one of the necessary antioxidant enzymes that minimize oxidative stress and restore tissue viability by acting on ROS such as cellular hydrogen peroxide (H2O2) and changing it into water (H2O) and oxygen (O2). In the case of aluminum phosphide toxicity, there is a significant reduction in catalase activity in intoxicated cases **(14).**

Malondialdehyde (MDA)

Malondialdehyde is one of the end products of the lipid peroxidation process due to the reaction of oxygen with unsaturated lipids in lower PH which is expected in the case of oxidative stress. The qualification of the process of lipid peroxidation is mainly done by measuring aldehydes, such as MDA. In the case of AlP poisoning, the phosphine-induced lipid peroxidation results in elevation in MDA level **(15).**

ii. Renin level:

Renin is an enzyme secreted by the kidneys in an active form in response to hypotension, decreased blood volume, or sodium loss to

regulate blood pressure, urine output, and water intake. Renin is responsible for the conversion of angiotensinogen into angiotensin I followed by starting the renin-angiotensin-aldosterone cycle, Angiotensin I, in turn, is converted to angiotensin II in the lung. Angiotensin II is a powerful blood vessel constrictor **(16).**

i. Cortisol level:

Cortisol is widely known to be the stress hormone of the body. It is produced from the fasciculate layer of the adrenal cortex gland. It is regulated by adrenocorticotropic the pituitary gland and hypothalamus by the hypothalamic-pituitary-adrenal (HPA) axis so its measurement can assess adrenal or pituitary diseases **(17)**.

i. Troponin I

Cardiac troponins are the most appropriate biomarkers for diagnosis of cardiac injury as acute toxic myocarditis; as they are normally found in the blood in small undetectable concentrations but in the case of heart muscle injury, troponins are released in high concentrations and the higher its concentration the more damage there is, for this reason, cardiac troponins are considered specific and highly sensitive markers of myocardial injury and cardiac toxicity. **(17)**.

a) Phosphine (PH3) detecting tests:

If there is any doubt about the AlP toxicity, a simple bedside breath test can be done by using silver nitrate (0.1 N AgNO3) impregnated paper, it also can be performed on gastric aspirate. The presence of phosphine in breath or gastric content turns silver nitrate paper black due to the formation of silver phosphate **(18).**

1. E.C.G evaluation and monitoring

ECG changes in cases of AlP poisoning include sinus tachycardia, sinus bradycardia, ventricular tachycardia, and ventricular fibrillation. There is a direct relationship between ECG abnormalities and poor outcomes after AlP toxicity**(18).**

D. Management of acute aluminum phosphide poisoning and newly introduced modalities

As there is no specific antidote for AlP poisoning, therefore the cornerstone of therapy is supportive care. AlP poisoning is suspected based on the history and physical examination. Treatment must not be delayed until test results are confirmed. All symptomatic patients should be monitored in the intensive care unit (ICU) for at least 72 hours. There are new trials of treatment introduced to improve the outcome as antioxidants, corticosteroids, and cardiac supportive drugs **(19).**

1. Emergency stabilization

Urgent stabilization steps for airway, breathing and circulation (ABC**)** are taken in the emergency room as soon as possible. Firstly by securing a patent airway to avoid suffocation, maintaining breathing by providing 100% oxygen inhalation through facemask at 5-10 l/min to reach a PaO2 of 60-70% with low FiO2 to treat hypoxia. Endotracheal intubation for unconscious patients is a must. Protecting circulation by insertion of two i.v. lines with wide bore cannula to give IV fluids and drugs is mandatory **(20)**.

In more severe cases special procedures should be performed to save a patient's life, for example:

a) Mechanical ventilation:

Intubation and mechanical ventilation can be used in the treatment of pulmonary complications which are common in AlP

poisoning as acute respiratory distress syndrome (ARDS) which may develop later and pulmonary edema which resulted from circulatory impairment and heart failure **(20)**.

b) Cardiovascular support:

Cardiovascular support is recommended in all patients because of the cardiovascular effects of the toxin. So, cardiac monitoring by ECG, checking central vein pressure (CVP) and pulmonary artery wedge pressure (PAWP) are essential **(21)**.

i. Severe hypotension:

As the main cause of death in cases of AlP is severe hypotension which does not respond to fluids, the usage of vasoactive agents and inotropes are recommended; norepinephrine, phenylephrine, dopamine, or dobutamine can be used to treat hypotension and persistent shock but unfortunately, limited success for using inotropes was reported, as the main cause of the refractory hypotension is the vascular wall weakness which causes organs congestion and transudation of fluids without improvement of blood pressure and eventually cause heart failure **(22).**

ii. Arrhythmia:

Cardiac arrhythmia is a common complication among cases of AlP toxicity which may lead to death. Cardiac dysrhythmia is most probably caused by cardiac insufficiency (heart failure). It is mainly managed by anti-arrhythmic drugs, defibrillation, or temporary pacemaker some studies showed that using digoxin could improve cardiovascular symptoms **(22).**

iii. Intra-aortic balloon pump:

The usage of an intra-aortic balloon pump (IABP) was reported for mechanical support of the heart in patients with toxic myocarditis, persistent shock, or persistent cardiac complications of the poisoning **(22).**

iv. Extracorporeal membrane oxygenation (ECMO)

The idea behind this maneuver is the treatment of intractable cardiogenic shock by providing the patient with mechanical circulation for a few days until restoring the normal myocardial function levels **(23)**.

2. Decontamination:

Gastric decontamination in cases of AlP toxicity by vegetable oil or paraffin oil is the most beneficial method of decontamination within the first hour after ingestion as they contain saturated fatty acids which seem to reduce the release of PH3 in contact with gastric fluids, also coconut oil covers the stomach and decreases AlP absorption rate and may be used as a potent protective agent against AlP toxicity**. Darwish et al. (24)** have evaluated the benefits of using 250-500 ml paraffin oil along with CoQ10 in improving the outcome of cases of AlP acute ingestion toxicity and found that rapid use of any available oil as a first aid improves the outcome and adding CoQ10 to the oil gives better outcome results.

In the past, gastric lavage was done by potassium permanganate (1:10,000) solution, sodium bicarbonate, or activated charcoal routinely but neither activated charcoal nor potassium permanganate can eliminate aluminum phosphide or phosphine gas due to the low molecular weight of AlP, in addition to the fact that these products are water-soluble and cause

more release of phosphine gas and more toxicity. Some studies tried to prove the efficacy of gastric lavage with potassium permanganate in the management as it can oxidize PH3 into nontoxic phosphate but further studies showed that the oxidation of phosphine gas is impossible. Also since potassium permanganate is a strong oxidant, therefore it could cause hemolysis and induce methemoglobinemia **(25).**

3. Supportive and symptomatic treatment

a) Management of metabolic acidosis

As most cases of acute AlP suffer from severe metabolic acidosis so, using intravenous sodium bicarbonate in order to correct metabolic acidosis is a common maneuver**.** Some studies have limited the usage of sodium bicarbonate only when PH is < 7 and focused on the correction of severe hypotension. This is based on the fact that $NaHCO_3$ infusion cannot correct metabolic acidosis in AlP cases as the main cause of metabolic acidosis is generalized tissue hypoperfusion. Na^+ and HCO_3^- will be produced after sodium bicarbonate infusion and HCO_3^- ion will not be able to pass through the cell membrane and remains in the extracellular compartment. It is worth knowing that in the acidic medium, HCO_3^- will react with H^+ ions and produces carbonic acid which splits into H_2O and CO_2, producing CO_2 which can pass across the cell membrane causing correction of circulatory pH but increasing the intracellular acidosis **(22).**

b) Hemodialysis (HD):

It can be performed as a treatment for renal failure, volume overload or severe metabolic acidosis, although it cannot expel PH3 from the blood so, it is not a specific treatment for toxicity **(26).**

c) Newly Proposed modalities in the treatment of acute AlP poisoning:

i. Hydroxyethyl starch solution: Depending on the fact that the lack of vascular wall integrity in AlP poisoning is the main cause of refractory hypotension, hydroxyethyl starch solution along with crystalloid solutions can overcome symptoms of shock and improve tissue perfusion **(22).**

ii. Glucagon could be used as a treatment for AlP poisoning; as glucagon activates adenylate cyclase at a different site to β-adrenergic agents causes increasing in cyclic adenosine monophosphate; this increases the calcium pool available for release during cardiac depolarization and contraction. Glucagon can also increase heart rate with no effect on arterial pressure. So, treating cardiogenic shock with glucagon may enhance tissue perfusion. **(27)**

iii. N-acetylcysteine (NAC) can act as an antioxidant, also its effects as a supportive treatment of AlP poisoning have been investigated in rats and humans. The recommended intravenous (I.V.) injection dose for routine treatment is 50-100 mg\ kg three times a day**. (28,29)**

iv. Administration of vitamin E can act as an antioxidant and protect the cells by lowering reactive oxygen species and lipid peroxidation; **Halvaei et al. (30)** found that the intramuscular administration of vitamin E in acute AlP poisoning cases improves the systolic blood pressure and decrease the mortality rate if given with the supportive protocol.

v. Calcium gluconate is generally recommended to stabilize cell membranes.

Administration of calcium gluconate or chloride is also recommended in case of hypocalcemia-induced tetany **(31).**

vi. Magnesium sulphate (MgSO4) is another cell membrane stabilizer with anti-oxidant properties used in cases of AlP poisoning since AlP induces oxidative stress in the early phase of poisoning causing an increase in lipid peroxidation and transient fall in magnesium and magnesium-dependent glutathione (GSH) **(32).**

vii. Several studies reported that Early administration of L-carnitine IV infusion along with the supportive therapy was safe and improve the outcome **(33)**.

viii. Steroids can be used as a treatment of inflammation but their efficacy in the treatment of AlP poisoning is not proven yet, also diuretics can be used in the treatment of cardiogenic and non-cardiogenic pulmonary edema **(31).**

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