Supportive Measures in the Treatment of Aluminum Phosphide Poisoning as a Trial to Reduce Mortality at Assiut University Hospital, Egypt

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Abstract

Aluminum phosphide (AlP) poisoning is a major problem, accounting for many Emergency Unit visits and hospitalization with increasing incidence of AlP toxicity in the last few years. In spite of the progress achieved in the field of toxicology and associated therapies, AlP is still responsible for a high rate of mortality due to the rapid onset of life-threatening symptoms, ineffective treatment and inadequate data on the efficacy of therapeutic interventions. AlP poisoning is a serious medical emergency demanding early and adequate management.

In this prospective study of AlP toxicity, 44 patients admitted to emergency unit of Assiut university hospital in the period from 1st January to 30th June 2016 were included.

There were 28 males (68.2%) and 16 females (31.8%). The majority of the cases were in the age group from 21 to 30 years (n=28, 54.6%). Thirty-six (81.8%) of admitted patients were from rural areas. Suicidal intake was the main mode of toxicity in 81.8% of cases. About 41% of the cases were shocked at their presentation and had metabolic acidosis. The mortality rate was 45.5%. The incidence of death in patients treated with N-acetyl cysteine to the incidence of death in non-treated patients was 1:12.

AIP poisoning needs more attention due to associated fatality, the absence of an antidote, and a high number of youth victims. Supportive measures are vital in these patients. N-acetyl cysteine has a protective effect.

Keywords: Forensic Science, Aluminum Phosphide Poisoning, Cardiotoxicity, Pesticides, Emergency, N-acetyl cysteine.

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1. Introduction

Aluminum phosphide (AlP) poisoning is a real medical emergency demanding early and adequate management. In spite of the progress achieved in the field of toxicology and associated therapies, AlP poisoning is still responsible for a high rate of mortality [1]. AlP has been used in pesticides for many years to protect grains in stores and during their transportation. The easy availability and low cost of AlP make it the most common means of suicide in Egypt with the increasing incidence of social and financial problems that face the youth. It is also known as “wheat pills” or “pest pills”[2]. It is available as dark brown or greyish 3 g tablets, under trade names such as Phostoxin, Bhostoxin, Quickphos, Phosphume and Phostek, releasing 1 g PH3 (Phosphin Gas) or as pellets 0.6 g, (Quickphos, Alphos and Cellphos) releasing 0.2 g of PH₃ [3].

AlP has the potential to induce multi-organ failure, the major one being circulatory failure resulting in congestion and edema of most organs including, critically, the lungs [4]. In most cases, the diagnosis is based mainly on positive history of exposure, the presence of clinical features, and highly variable arrhythmias with shock and no previous history of cardiac disease [5].

In management, the main objective is to provide effective oxygenation, ventilation and circulation till phosphine is excreted. All patients with severe AlP poisoning require continuous invasive hemodynamic monitoring and early resuscitation with fluid and vasoactive agents [6].

N-acetyl cysteine (NAC), as an antioxidant and cytoprotective agent, reduces myocardial oxidative injury and increases survival time [7,8]. Depletion of glutathione and evidence of free radical induced damage in AlP poisoned patients have prompted the use of NAC as a therapeutic measure to replenish the glutathione. NAC also improved the hepatic manifestations and prevented hepatic necrosis. The NAC also delayed the mortality latency time [9].

This study was conducted to evaluate AlP toxicity among cases admitted to emergency unit of Assiut University Hospital and to prove the role of N-acetyl cysteine and adequate supportive measures in AlP management.

2. Methodology

A descriptive cross-sectional (prospective) study was conducted on cases of AlP toxicity admitted to Assiut University Hospital emergency unit during the period from 1st January 2016 to 30th June 2016 with a total coverage of 44 patients. The study was conducted at Assiut University Hospital Emergency Unit, General Intensive Care Unit, Assiut University Hospital and Clinical Pathology Emergency Lab in the Department of Clinical Pathology at Assiut University Hospital, Egypt.

Exclusion criteria
1- Patients aged less than 18 years old.
2- Patients with a history of AlP poisoning with a delay time of more than 48 hours.
3- Patients with a history of cardiac, hepatic and renal disease.

Statistical Analysis
Statistical analysis was performed by SPSS, version 16. Statistical methods which were applied included descriptive statistics and chi-square test. A p-value less than 0.05 was considered significant.
3. Results

In the period from 1st January to 30th June 2016, 44 patients diagnosed as AlP poisoning cases were admitted to the emergency unit of Assiut University Hospital. The number of cases that are reported at a tertiary care hospital is far less than the actual number of cases, especially in suicidal ingestions. This indicates a lack of awareness of hazards associated with this drug.

Personal Data Analysis

Table-1 demonstrates the distribution of age and sex in AlP poisoning cases. Males were predominant in all age groups. Thirty-six (81.8%) of the admitted patients were from rural areas with a low socioeconomic level. Figure-1 shows that the survival rate increased with early presentation of patients to the hospital. Table-2 shows the number and condition of AlP tablets taken by the patients. It was found that 28 patients ingested one tablet only. Eight patients ingested half a tablet, 6 persons ingested 2 tablets and 2 ingested 1/4 tablet. Forty patients were exposed to fresh tablets and only four exposed to old ones. The highest incidence (n=36; 81.8%) of the cases was suicidal and only 8 (18.2 %) were caused by accidental exposure. No homicidal cases were present in the studied group.

Vital Data Analysis

Table-3 shows vital data including level of consciousness, pulse and blood pressure. Thirty patients were above grade 13 in the Glasgow Coma Scale (GCS), 8 were between grade 12 to 8, and 6 were less than grade 8. Tachycardia (pulse ≥100 beats/minute) at presentation was recorded in 14 patients and normal pulse at presentation was recorded in 14 patients and normal pulse at presentation in 12 cases. No palpable peripheral pulse due to shock was recorded in 10 cases and did not improve with treatment.

Table 1- Demographic data of AlP intoxicated patients.

| Age Groups (Years) | Male (n=28) | Female (n=16) |
|--------------------|-------------|---------------|
|                    | n | % | n | % | n | % |
| 18 to 20           | 10 | 22.7 | 6 | 60 | 4 | 40 |
| 21 to 30           | 24 | 54.6 | 14 | 58.3 | 10 | 41.7 |
| 31 to 40           | 4 | 9.1 | 4 | 100 | 0 | 0.0 |
| 41 to 50           | 6 | 13.6 | 4 | 66.7 | 2 | 33.3 |

Table 2- Number and condition of AlP tablets taken by intoxicated patients.

| Number of Tablets | n | % |
|-------------------|---|---|
| 1/4 tablet        | 2 | 4.5 |
| 1/2 tablet        | 8 | 18.2 |
| One tablet        | 28 | 63.6 |
| Two tablet        | 6 | 13.6 |
| Total             | 44 | 100 |

| Condition of Tablet | n | % |
|---------------------|---|---|
| Fresh               | 40 | 90.9 |
| Old                 | 4 | 9.1 |
| Total               | 44 | 100 |
Two patients shocked at presentation improved with treatment. Six patients had a normal pulse at the time of presentation then suffered shock despite treatment. Patients’ blood pressure at the time of presentation was normal in 20 cases, hypotensive without improvement during therapy in 14 cases, or hypotensive with improvement with management in 6 (13.6%) cases.

**Laboratory Findings**

Figure-2 shows the assessment of the arterial blood gases (ABG) findings in the AIP cases. Acidosis with pH less than 7.35 was present in 18 (40.9%) patients, 10 (22.7%) of the patients had pH above 7.45 (alkalosis), and the rest of patients had pH from 7.35 to 7.45 (normal). The $O_2$ saturation ($SaO_2$) range was from 21% to 99% and the mean was 91.4±17.22%. The range of partial pressure of $O_2$ ($PaO_2$) was from 17-127 mmHg and the mean was 91.1±31.13 mmHg.

The partial pressure of carbon dioxide ($PaCO_2$) ranged from 16 to 41 mmHg and the mean was 28±7.66 mmHg. Bicarbonate level ($HCO_3$) ranged from 3 to 24.8 (mean 15.89±6.29).

ALT and AST activity was elevated in 20.5% of the cases, and elevated urea and creatinine was found in 31.8% of the cases.

**Electrocardiographic (ECG) Findings**

ECG was done in patients on admission and repeated every 4 hours. Positive findings included sinus tachycardia in 12 (27.3%) cases and S-T segment elevation and AF in four cases and ectopics in only two cases.

Table-4 shows the management or the treatment plan for AIP intoxicated patients.

### Table 3- Vital data assessment in AIP intoxicated patients.

| Conscious level (GCS)          | n  | %    |
|-------------------------------|----|------|
| Less than 8                   | 6  | 13.6 |
| From 12 to 8                  | 8  | 18.2 |
| Above 13                      | 30 | 68.2 |
| Total                         | 44 | 100  |

| Pulse                          | n  | %    |
|--------------------------------|----|------|
| Shocked patients at presentation (no peripheral pulsation) and not improved | 10 | 22.7 |
| Shocked patients at presentation and then improved | 2  | 4.5  |
| Normal at presentation then shocked | 6  | 13.6 |
| Normal (from 60 to 100 beats/minute) | 12 | 27.3 |
| Tachycardia (more than 100 beats/minute) | 14 | 31.8 |
| Total                          | 44 | 100  |

| Blood pressure                 | n  | %    |
|--------------------------------|----|------|
| Normal                        | 20 | 45.4 |
| Hypotensive then improved      | 6  | 13.6 |
| Shocked from the start         | 14 | 31.8 |
| Normal at presentation then shocked | 4  | 9.1  |
| Total                          | 44 | 100  |
Table 4 - Management plan for aluminum phosphide intoxicated patients.

|                                         | n   | %     |
|----------------------------------------|-----|-------|
| **I.V. fluids and oxygen**             |     |       |
| Yes                                    | 40  | 90.9  |
| No                                     | 4   | 9.1   |
| **CVP**                                |     |       |
| Yes                                    | 6   | 13.6  |
| No                                     | 38  | 86.4  |
| **Vasopressor drugs**                  |     |       |
| Yes                                    | 8   | 18.2  |
| No                                     | 36  | 81.8  |
| **Gastric Lavage by diluted Potassium permanganate and Sodium bicarbonate** |     |       |
| Done                                   | 40  | 90.9  |
| Not done                               | 4 (arrested case at presentation) | 9.1   |
| **Activated charcoal**                 |     |       |
| Used                                   | 24  | 54.5  |
| Not used                               | 20  | 45.5  |
| **Inotropic drug e.g. dopamine**       |     |       |
| Given                                  | 20  | 45.5  |
| Not given                              | 24  | 54.5  |
| **Antiarrhythmic Drugs**               |     |       |
| Given                                  | 6   | 13.6  |
| Not given                              | 38  | 86.4  |
| **Endotracheal intubation**            |     |       |
| Yes                                    | 12  | 27.3  |
| No                                     | 32  | 72.7  |
| **Mechanical ventilation**             |     |       |
| Yes                                    | 8   | 18.2  |
| No                                     | 36  | 81.8  |
| **NaHCO₃ for acidosis**                |     |       |
| Yes                                    | 18  | 40.9  |
| No                                     | 26  | 59.1  |
| **N- acetyl cysteine**                 |     |       |
| Yes                                    | 28  | 63.6  |
| No                                     | 16  | 36.4  |
epinephrine were given in 18.2% of the cases.

b- Decreasing the Absorption of AIP

Gastric lavage was done in 90.9% (40 patients) of the presented cases even with a long delay. Diluted potassium permanganate (1:10000) and 8.4% sodium bicarbonate were used. Activated charcoal was used in 54.5% of the cases after the lavage.

c- Organs support

Twenty (45.5 %) of the cases needed the infusion of an inotropic drug like dopamine to combat the refractory hypotension and cardiogenic shock. Antiarrhythmic drugs like amiodarone were used in only 6 (13.6%) cases. Twelve (27.3%) patients needed endotracheal intubation at presentation, and 18 (40.9 %) patients needed bicarbonate infusion intravenously for correction of metabolic acidosis associated with AIP poisoning.

d- Other supportive therapy

N-acetyl cysteine was given orally to 28 (63.6%) of the admitted cases in conscious patients or through a nasogastric tube (120mg/kg).

Outcome of the Treatment

Mortality rate was 45.5%. The cause of death in aluminum phosphide poisoning was cardiac in all fatal cases in the form of cardiac arrhythmia and arrest not responding to CPR.

Relation between different risk factors and death

Table-5 illustrates that NAC has a protective effect in AlP poisoning. It was found that the ratio of incidence of death in patients treated with NAC to the incidence of death in those patients not treated with NAC was 1:12. This difference was significant at \( p < 0.05 \). The frequency of death among those who ingested fresh AIP was nine times higher than it the case of old tablets. This difference was significant at \( p < 0.05 \). There was a significant difference in rate of death between patients with normal ECG and different forms of arrhythmia at \( p < 0.05 \). There was a statistically significant difference in the rate of death between patients with low pH at presentation and patients with normal pH at \( p < 0.01 \). The patients admitted to the hospital after a longer delay had a higher rate of fatal outcome than those with a shorter delay (\( p < 0.01 \)) (Figure-1).

Table-6 shows that there was a significant difference in the rate of death between patients with impaired liver or renal functions and patients with normal function at \( p < 0.05 \). Impaired liver or renal functions appeared to be bad
ment with Hassanian-Moghaddam and Pajoumand, 2007 [11], and Raizada et al. 2012 [12].

Also, similar results were reported by Louriz et al. 2009 [13] in Morocco and Taghaddosi Nejad et al. 2012 [14] in Iran. Sulaj et al. 2015 [15] also reported, that the victims of AlP poisoning mainly belong to the third and fourth decades of life.

In the current study males represented 63.6% of cases. Male predominance was also observed in other studies as performed by Soltaninejad et al. 2012a, Taramsari et al.

Table 5- Protective and risk factors in relation to mortality in aluminum phosphide intoxicated patients.

|                        | Survived | Died  | p value | Odds (95% CI) |
|------------------------|----------|-------|---------|---------------|
| Conscious level (GCS)  |          |       |         |               |
| Yes                    | 20       | 83.3  | 8       | 0.035*        |
| No                     | 4        | 16.7  | 12      | 7.5(1.9-30.3)#|
| Type of Tablet         |          |       |         |               |
| Old                    | 4        | 16.7  | 0       | 0.050*        |
| Fresh                  | 20       | 83.3  | 20      | 9(0.5-178.1)  |
| ECG finding            |          |       |         |               |
| Normal                 | 10       | 41.7  | 16      | 1             |
| At presentation normal | 2        | 8.3   | 0       | 0.13(0.006-2.92) |
| Ectopics               | 0        | 0.0   | 2       | 3.18(0.14-73.03) |
| Sinus tachy car-dia    | 12       | 50.0  | 0       | 0.03(0-0.047)#|
| S-t segment ele-vation | 0        | 0.0   | 2       | 3.18(0.14-73.03) |

* Statistically significant difference (p<0.05)  Chi-square test used

Table 6- Role of renal and liver functions in predicting mortality in aluminum phosphide intoxicated patients.

|                | Died | Survived | p value |
|----------------|------|----------|---------|
| ALT&AST        |      |          |         |
| Elevated       | 9    | 45.0     | 0       |
| Normal         | 11   | 55.0     | 24      |
| Urea & Creatinine |    |          |         |
| Increase       | 12   | 60.0     | 2       |
| Normal         | 8    | 40.0     | 22      |

Chi-square test used.

prognostic factors.

4. Discussion

AlP poisoning is a major problem, accounting for many Emergency Unit visits and hospitalization. AlP is being used as a common outdoor and indoor pesticide in developing countries due to its various advantages as it is cheap, availability, effective, free from toxic residue and does not affect seed viability [10].

In the present study, 80% of the patients were in the age group from 18-30 years. The current results are in agree-
This is in agreement with the results reported by other authors [24,25,26] who considered that fresh tablets are more dangerous, as it has been showed that blood phosphine gas concentration is higher in shocked patients who took fresh tablets compared with those who ingested the powder form or old tablets.

In this study, the conscious level of more than 50% of poisoned cases at the time of presentation according to Glasgow Coma Scale (GCS) was more than 13. This may have been due to early presentation at the hospital. Also, Louriz et al. 2009 [13] reported the same findings. The depth of coma at presentation is considered one of the risk factors, as mentioned in the study of Sulaj et al. 2015 [15]. Assessment of pulse showed that 27% of the cases had shock at presentation (no peripheral pulsation was palpable), and only in 4.5% of them the shock was corrected by treatment. On the other hand, 13.6% of the cases were normal at presentation but then became shocked. Tachycardia was observed in 31.8% of the cases. This was also reported by Siwach et al. 1998 [27], who concluded that in the initial 3-6 hours tachycardia is predominant. Mean pulse at presentation was 92.94±11.6 beats/minute and mean blood pressure was 105.29±18.07/65.88±13.72 mmHg. These vital data values are matched with the study of Farnaghi et al. 2013 [28]. At this time, their pulse rate was 94±1.5 as 54.5% of the patients showed normal blood pressure at their presentation; 9.1% of them showed hypotension later on and 45.4% showed hypotension. Only 13.6% improved with treatment. The mean respiratory rate was 19.18±1.63 cycle/minute.

Arterial blood gas (ABG) is one of the very important indicators of the prognosis of the case and assessment of improvement. In a retrospective analysis of one of the largest series of AlP poisoning in India, arterial pH, serum bicarbonate level and ECG abnormalities were significantly poor prognostic factors [29]. In the current study,
ABG was done for every case at presentation and every 4 hours for follow up. It was found that 40.9% of the cases showed metabolic acidosis at presentation, and it was the most common change in the pH which was associated with more morbidity with statistical significant difference at \( p < 0.01 \). Mean arterial pH was 7.3±0.24 and mean bicarbonate level was 15.89±6.29 mEq/L at time of presentation. These values are similar to that reported by Farnaghi et al. 2013 [28]. This in accordance with the present results, as there is a statistical significant difference in rate of death between patients with low pH at presentation (acidosis) and patients with normal PH at \( p < 0.01 \). This is also found in the studies of Shadnia et al. 2009 and Taghaddosi Nejad et al. 2012 [29,14], who considered acidosis as one of the risk factors.

The present study results present a detailed assessment of liver functions and renal functions in AlP poisoned cases and concludes that those paly an important role in evaluating the case, the treatment, and the prognosis. In this study, 20.5% of the cases showed elevated ALT and AST (liver enzymes) which became evident in the second day of the poisoning. This finding is in agreement with Taramsari et al. 2013 [17]. In another study in India by Louriz et al. 2009 [13], elevated enzymes were more than three times higher than our findings. 31.8% of cases showed elevation in urea and creatinine level in the present study, which is considered as a bad prognostic factor as there were significant differences in rate of death between patients with impaired renal functions and patients with normal renal function at \( p < 0.05 \). This is in agreement with the findings of Louriz et al. 2009 [13], who reported that renal failure is considered a bad prognostic factor.

ECG done at presentation was normal in 63.6% of the cases; 27.3% showed sinus tachycardia, 4.5% showed S-T segment elevation and atrial fibrillation (AF), and 4.5% showed ventricular ectopics. The incidence of ECG abnormalities reported in various studies are 45% [29,16], 65% [30], 80% [31] and 50% [32] in phosphine gas poisoned patients. In the present study, there was a significant difference in rate of death between patients with normal ECG and different forms of arrhythmia at \( p<0.05 \). This finding is in concordance with previous studies such as [33,34,16]. However, other studies such as Chugh et al. 1991a [32] reported no relationship between the ECG abnormalities and mortality in cases of AlP toxicity.

The study of Agrawal et al. 2015 [6] showed that all survivors had initial electrocardiogram (ECG) readings showing normal sinus rhythm or sinus tachycardia. All non-survivors had cardiac arrhythmias on presentation including ventricular fibrillation and atrial fibrillation. In the survey by Shadnia et al. (2009, 2010)[29,30], the ECG abnormalities were observed in the majority of cases who did not survive, and there was a significant difference between survival and non-survival cases according to ECG abnormality. In addition, Soltaninejad et al. (2012a) reported the same [16]. Therefore, anti-arrhythmic agents can be used as prophylactic treatment in acute AlP intoxication.

In the present study, management of the intoxicated patients was done in the form of initial evaluation and resuscitation, which were done in 90.9% of the admitted patients who received intravenous fluids (saline and glucose 5%) and oxygen at the emergency unit. Central venous pressure was measured in 13.6% of the cases done in ICU. Vasopressor drugs like epinephrine and nor-epinephrine were given in 18.2% of the cases. To decrease exposure to the poison, gastric lavage was done for 90.9% (40 patients) of the presented cases even with a longer delay. This was done using diluted potassium permanganate (1:10000) and sodium bicarbonate concentration 8.4 %. Activated charcoal was used in 54.5% of the cases after the lavage. Cardiac support was needed in 45.5% of the cases by infusion of inotropic drugs like dopamine to combat the refractory hypotension and cardiogenic shock. Antiarrhythmic drugs
like amiodarone were used in 13.6% of the cases only. To prevent different types of organ failure, 27.3% of the cases needed endotracheal intubation and mechanical ventilation at presentation. 40.9% of the cases needed bicarbonate infusion intravenously for correction of metabolic acidosis. In the present study, NAC was given to 63.6% of the admitted cases orally in conscious patients or through a nasogastric tube (120mg/kg). There was a significant difference in the rate of death between patients treated with NAC and non-treated patients. NAC showed a protective effect which is in agreement with other studies [35,36]. Also, in an experimental study on AIP poisoned rats by [7], NAC reduced myocardial oxidative injury resulting in improved hemodynamics and prolonged survival time. In the study of Bhat and Kenchetty [36], patients who received NAC had a lower mortality rate compared to those patients who did not receive NAC. Therefore, treatment with NAC, which is inexpensive and relatively safe, would be a viable treatment option for patients admitted with AIP tablets consumption.

The current study showed that a mortality rate of 45.5%. The survival rate of the remaining 54.5% may have been due to ingestion of small doses, early presentation at hospital, and ingestion of old tablets. The cause of death in AIP poisoning was cardiac in all cases, in agreement with Taramsari et al. [16]. This can be explained based on the effect of pH3 on the heart, which is multifactorial. Phosphine gas inhibits mitochondrial respiration results in myocardial energy depletion, similar to that which occurs with ischaemia. It also results in the generation of reactive oxygen species causing lipid peroxidation [2]. These effects can cause alterations in cardiac transmembrane action potentials leading to dysrhythmia, an ischaemia-like effect on metabolism and on the ECG, inducing focal areas of necrosis and cardiac failure [27].

This mortality rate is similar to that reported by Louriz et al. 2009 and Soltaninejad et al. 2012b [13,26]. Other studies by Moghadamnia and Abdollahi 2002, Hajouji et al. 2006 and Siddaiah et al. 2009[37,1,38] reported a higher mortality rate ranging from 60% up to 100%. In a 25-year-long study in north-west India, AIP poisoning was found to be the major cause of death among all cases of poisonings [39].

The present study has covered only a six-month period, and it was performed in a single center, which is Assiut University Hospital. It did not cover all the cases of AIP poisoning in Assiut, with such a fact limiting the overall validity of our data. Another limitation is the retrospective collection of the clinical data from medical files, where errors can occur, especially when relatives try to conceal or mask the suicidal intents of the patient, as they might do this for a variety of reasons. The inaccessibility of forensic findings (autopsy data included) might be another limitation of this study.

5. Conclusion

AIP poisoning needs more attention, as it is a potentially fatal toxin and till now there is no antidote. The last few years have witnessed an increased number of victims among the youth with AIP being used as a suicidal agent. Supportive measures are vital in these patients and N-acetylcysteine has a protective effect. Preventive action, including awareness raising campaigns about the hazards of AIP in society, is recommended.

Ethical Consideration

This study was reviewed and approved by the Ethics Review Committee of Assiut Faculty of Medicine, prior to the data collection.

Conflict of Interest

None.
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