

Research Paper: Cardiovascular Conditions in Patients With Aluminum Phosphide Poisoning



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ABSTRACT

Background: Aluminum Phosphide (AIP) is a well-known rodenticide and insecticide, used as a fumigant to control pests and rodents in grain-storage facilities. Its intoxication presents a medical emergency that requires early rigorous management. This study aimed to investigate cardiac function by Electrocardiogram (ECG) changes in patients with AIP intoxication. We also explored the potential relationship between low bicarbonate and cardiac function.

Methods: This cross-sectional study investigated 42 patients in the age range of 17-47 years, with a history of orally-administered AIP poisoning, known as “rice tablet”, admitted to the toxicology ward of Imam Reza Hospital from March 2019 to March 2021. The study patients’ demographic data were collected by trained interviewers, using pretested questionnaires. Systolic and diastolic blood pressure, as well as blood samples, were measured 12 hours from admission. Echocardiography was performed during the first 12 hours and on the fifth-day post-admission. All statistical analysis was performed using R 3.6.1. The significance level was set at 0.05 for all statistical tests.

Results: In total, 48.78% of patients presented normal bicarbonate levels, and 24.39% and 26.83% had moderate and severe acidity, respectively. Moderately and severely decreased Left Ventricular Ejection Fraction (LVEF) was observed among 21 (51.2%) and 10 (24.4%) patients, respectively. Furthermore, mild Right Ventricular (RV) function was observed among 11 (26.8%) patients. A statistically significant association was observed between bicarbonate level and RV function ($P<0.001$) and LVEF ($P<0.001$). Besides, 19.5% of the explored patients expired. The proportion of expired patients was significantly higher in patients with mild RV function, compared to the other patients ($P<0.001$).

Conclusion: Acute AIP intoxication is a worldwide serious problem. Severe metabolic acidosis and ECG abnormalities are associated with poor outcomes in this respect. Thus, conducting early ECG and echocardiography could be desirable instruments to predict prognosis. There is no antidote for AIP poisoning; thus, the replacement of a safer agent for in-store grain protection is strongly suggested.

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1. Introduction

Aluminum Phosphide (AIP) is a well-known rodenticide and insecticide, used as a fumigant to control pests and rodents in grain-storage facilities [1]. AIP is an easily accessible and low-cost toxin and a major cause of poisoning in developing countries [2]. It is available in different forms, such as tablets, pellets, and compressed disks, containing 56% AIP and 44% ammonium carbonate. The combination of the moisture in the air and phosphide grains sets off phosphine, i.e. an active form of the pesticide. Following ingestion, AIP also reacts with hydrochloric acid and water in the stomach which leads to the immediate release of the Phosphine gas (PH_3) [3]. Phosphine is a mitochondrial poison that interferes in protein synthesis and enzymes; it may lead to multi-organ dysfunction, particularly affecting cardiovascular and respiratory systems [4]. Evidence suggested that AIP intoxication causes severe metabolic acidosis, the rapid onset of shock, and cardiac arrhythmias. The heart rate often decreases per the degree of shock [5]; thus, Electrocardiography (ECG) may indicate sinus tachycardia or tachyarrhythmia. ST-elevation, ST-depression, T-wave changes, and the widening of the QRS complex can also appear in AIP poisoning [6-8]. Furthermore, if a patient survives from cardiac arrhythmias and sinus arrest, ECG changes may last for three weeks to normalize [5, 8]. Accordingly, the variation in ECG can help identify the stage of the poisoning.

Overall, AIP intoxication is a medical emergency that requires early rigorous management. It consists of a spectrum of clinical and laboratory findings that should be applied for therapeutic procedures. Despite the importance of the subject, comprehensive reviews evaluating cardiac function in patients with AIP poisoning in the middle-east countries are scarce. Therefore, the current study aimed to investigate cardiac function by ECG changes in patients with AIP intoxication. We also explored the potential relationship between low bicarbonate and cardiac function in this population.

2. Materials and Methods

This cross-sectional study was conducted in Mashhad City, Iran. The study participants were Iranian urban residents who were admitted to the toxicology ward of Imam Reza Hospital from March 2019 to March 2021 with orally-administered AIP poisoning, known as “rice tablet”. Initially, all study participants provided written informed consent. Subjects with a history of Ischemic Heart Disease (IHD), Hypertension (HTN), valvular

heart disease, or congenital heart disease, a history of taking anti-cancer drugs, like cytostatic or chest X-ray were excluded from this study. Due to the strong association between age and Cardiovascular Diseases (CVDs), subjects aged ≥ 45 years (whether having a history of CVDs or not) were also excluded from our study. Additionally, patients whose results confirmed the concurrent oral ingestion of AIP and other drugs or toxins were also excluded from this research.

on the study participants' demographic data, including age and gender were collected by trained interviewers, using pretested questionnaires. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured in a sitting position on the right arm 12 hours after admission. Blood samples were collected and blood PH was measured 12 hours from admission. Moreover, echocardiography was performed during the first 12 hours and on the fifth-day post-admission.

According to Gupta et al. [9], trans-thoracic echocardiography was performed on the first and fifth days post-admission for subjects who survived. Left Ventricular (LV) dimensions and Left Ventricular Ejection Fraction (LVEF) were examined in the parasternal long-axis view. Permission to undertake the study was obtained from the Ethics Committee of Mashhad University of Medical Sciences, (No.: MUMS.MEDICAL.REC.1398.828), Mashhad, Iran.

The obtained data are represented as mean and standard deviation [10] as well as frequency and percentage. Chi-squared test and Kendal's tau-b coefficient of association were calculated. All statistical analyses were conducted using R 3.6.1 at the significance level of 0.05.

3. Results

In this study, 41 patients poisoned with AIP were included. In total, 56.1% of the study subjects were male and 43.9% were female. The Mean \pm SD age of the study patients was 27.56 \pm 7.09 years (age range: 17-47 years). The Mean \pm SD bicarbonate level of the study subjects was 18.23 \pm 5.19. Twenty patients presented normal bicarbonate levels, 10 patients had moderate acidity, and 11 patients had severe acidity. The baseline characteristics of the study patients are listed in Table 1.

LVEF was normal among 10 (24.4%) patients, moderately and severely decreased LVEF were observed among 21 (51.2%) and 10 (24.4%) patients, respectively. Mild Right Ventricular (RV) function was observed among 11 (26.8%) patients; also 12 (29.3%) and

Table 1. Baseline characteristics of admitted patients

Variables		No. (%)
Gender	Male	23 (56.1)
	Female	18 (43.9)
Bicarbonate level	Normal	20 (48.8)
	Moderate acidity	10 (24.4)
	Sever acidity	11 (26.8)
Age (Mean±SD)		27.56±7.09

International Journal of
Medical Toxicology & Forensic Medicine

18 (43.9%) patients presented moderate and good RV function, respectively. Most of the patients with normal bicarbonate levels presented good RV function (90%); however, 40% of patients with moderate acidity and 63.6% of those with severe acidity indicated mild RV function. A significant association was observed between RV function and bicarbonate level (Kendal's tau-b coefficient=-0.792; P<0.001). Severely decreased LVEF was observed among 63.6% of patients with severe acidity and 30% of those with moderate acidity bicarbonate level; the same was not observed among the patients with normal LVEF. LVEF significantly increased with bicarbonate level (Kendal's tau-b coefficient=-0.661; P<0.001) (Table 2).

In total, 8 (19.5%) study participants expired. Among the group with mild RV function, 7 (63.6%) patients died; 1 (8.3%) patient with moderate RV function also died (Figure 1). The proportion of expired patients was significantly higher among the mild RV function group, compared to the other patients (P<0.001). Furthermore, a significantly higher proportion of patients with severely decreased LVEF (70%) died, compared to those with

moderately decreased LVEF (12.5%) and normal LVEF (0%) (P<0.001) (Figure 2).

4. Discussion

The present study results provided clear support for the association between AIP intoxication and cardiac function. Accordingly, as the severity of AILP poisoning increases, RV and LV function decreased, leading to a higher mortality rate. In this regard, echocardiography might be a good tool to predict the therapeutic outcomes.

Previous studies investigated the relationship between ECG abnormalities and severe AIP poisoning. In this regard, Kalawat et al. [11] conducted an observational study in 2016 and examined cardiovascular function and its clinical features in 50 patients with AIP poisoning who were admitted to the poisoning intensive care unit. They concluded that ECG was abnormal in 30 subjects out of 50. The most common abnormal ECG finding was sinus tachycardia (24%), while the heart block was only detected in 2 out of 50 patients (4%). Negative EEG findings included hypokinesia and decreased cardiac output.

Table 2. Association between bicarbonate level and RV function and LVEF

Bicarbonate Level	No. (%)			P	Kendal's Tau-b	
	Normal	Moderate Acidity	Sever Acidity			
RV function*	Good	18 (90)	0 (0)	0 (0)	<0.001	0.792
	Moderate	2 (10)	6 (60)	4 (36.4)		
	Mild	0 (0)	4 (40)	7 (63.6)		
LVEF**	Normal	10 (50)	0 (0)	0 (0)	<0.001	0.661
	Moderately decreased	10 (50)	7 (70)	4 (36.4)		
	Severely decreased	0 (0)	3 (30)	7 (63.6)		

* Right ventricular function; ** Left ventricular ejection fraction.

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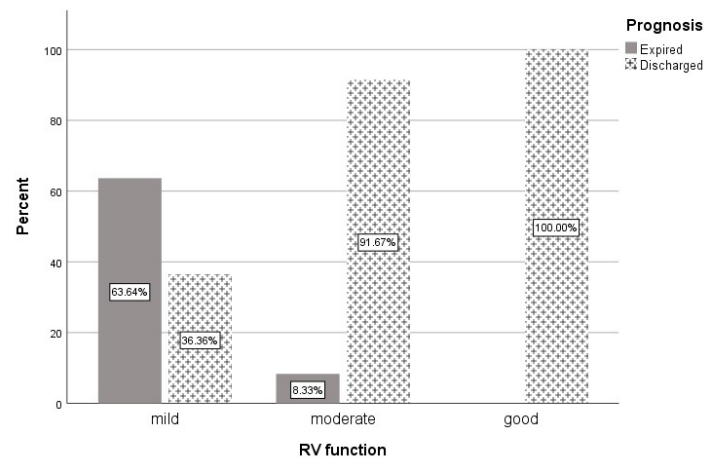


Figure 1. The prognosis of aluminum phosphide poisoned patients according to RV function

International Journal of
Medical Toxicology & Forensic Medicine

They argued that besides ECG, echocardiography is a useful tool to evaluate cardiac function in patients with AIP poisoning.

Agrawal et al. [12] also examined 7 cases of AIP poisoning with severe hemodynamic impairment. Two-dimensional echocardiography demonstrated a reduction in LV ejection fraction (27.85%) in all patients. Moreover, 4 patients with a primary normal ECG survived; however, cardiac arrhythmias (VF & AF) were noted in all 3 patients with mortality.

AIP is regionally known as “rice tablet”. Iranians usually store large amounts of rice at home; to protect the rice from pests and rodents, they commonly use rice tablets. Therefore, it is highly accessible in Iran. AIP poisoning may cause multi-organ dysfunction. The majority of re-

lated deaths occur because of cardiovascular dysfunction within the first 12-24 hours [13]. ECG findings include changes in ST-T (depression/elevation), reverse T-wave, and the broadening of the QRS complex [5, 7, 8, 14]. Arrhythmias and conduction disturbances consist of sinus tachycardia, myocardial infarction, atrial fibrillation, complete heart block, A-V Right Bundle Branch Block (RBBB) dissociation, and Left Bundle Branch Block (LBBB) [7, 14]. Nevertheless, ECG changes should return to normal up to three weeks, indicating a reversible myocardial injury [15]. However, studies reported that vasoactive drugs, i.e. commonly used to stabilize blood pressure, may cause cardiac dysrhythmias in patients [16, 17].

Other evidence indicated that myocardial injury included elevated serum levels of cardiac enzymes (i.e.

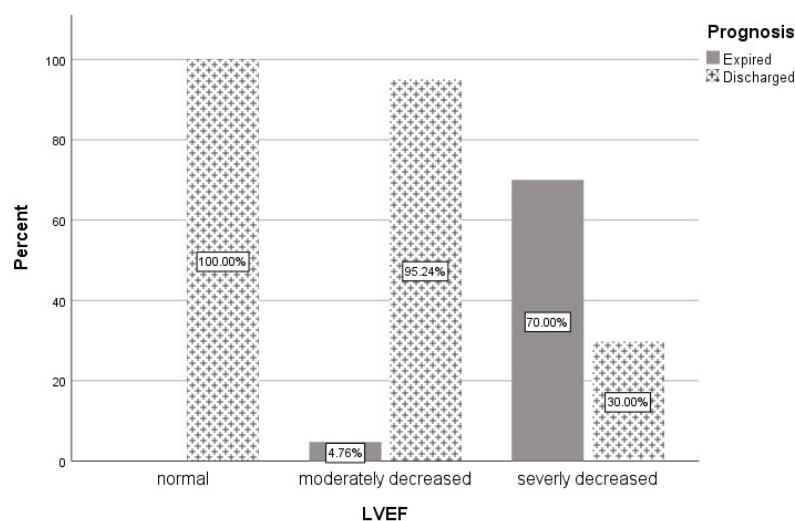


Figure 2. The prognosis of aluminum phosphide poisoned patients according to LVEF

International Journal of
Medical Toxicology & Forensic Medicine

CPK-MB & LDH) [18]. During the first 1 to 4 days, in up to 50% of subjects, decreased ejection fraction was observed on echocardiography due to hypokinesia of LV and intraventricular septum [18, 19].

The congestion of the heart and the separation and segmentation of myocardial fibers, non-specific myocytes vacuolation, neutrophil and eosinophil infiltration, and focal necrosis are repeated findings, i.e. detected in autopsy [20]. The exact mechanism underlying phosphine toxicity remains unexplained; however, we believe that the cause of cardiac dysfunction might be PH₃-induced myocardial damage. In line with this theory, the present study revealed that in patients with severe acidity (low bicarbonate), RV and LV function decrease. Focal myocardial damage could lead to improper conduction pathways and arrhythmias; concurrent extensive myocardial damage could cause contractile dysfunction and hypotension [21].

Most of the patients who eventually died presented severely decreased LV and RV function. This condition was related to severe acidity in our study. In previous studies, cardiovascular shock, ECG abnormalities, and different types of cardiac arrhythmia were reported as predictors of poor prognosis [10, 22, 23]. There exists no specific antidote or comprehensive management for AIP poisoning. However, early diagnosis and constant intensive supportive care are critical in AIP poisoning management.

5. Conclusion

Acute AIP intoxication is a worldwide serious problem. Severe metabolic acidosis and ECG abnormalities are associated with poor treatment outcomes. Thus, early ECG and echocardiography could be good instruments to predict prognosis in these patients. There exists no antidote for AIP poisoning; thus, the replacement of a safer agent for in-store grain protection is strongly suggested.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad (No.: MUMS.MEDICAL.REC.1398.828).

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Author's contributions

Conceptualization and supervision: Zahra Sheikhveisi, Bita Dadpour; Writing – original draft, data analysis: Zahra Sheikhveisi, Alireza Banaye Yazdipour; Participation in its sequence alignment: Seyed Reza Mousavi, Zahra Ataei, Mohammad Moshiri; Final approval: All authors.

Conflict of interest

The authors declare that there is no conflict of interests.

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