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The effects of amiodarone prophylaxis on cardiac dysrhythmia in acute aluminium phosphide poisoning

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Cardiovascular toxicity is the most common cause of fatality in the first 24 hours of poisoning with aluminium phosphide (AlP). Most often manifesting itself in cardiac dysrhythmias. The aim of this study was to evaluate the benefits of amiodarone prophylaxis against cardiac dysrhythmia in 46 patients with acute AlP poisoning. They were divided in two groups of 23: one receiving amiodarone and the other not (control). The treatment group received amiodarone prophylaxis in the initial intravenous bolus dose of 150 mg, followed by a drip of 1 mg/min for six hours and then of 0.5 mg/min for eighteen hours. Both groups were Holter-monitored for 24 hours since admission. Save for amiodarone, both groups received the same standard treatment. Amiodarone had a significant beneficial effect in reducing the frequency of ST-segment elevation and ventricular fibrillation plus atrial fibrillation (P=0.02 and P=0.01, respectively), but the groups did not differ significantly in mortality (9 vs 11 patients, respectively). The mean time between ICU admission and death (survival time) was significantly longer in the treatment group (22 vs 10 h, respectively; P=0.03). Regardless its obvious limitations, our study suggests that even though amiodarone alone did not reduce mortality, it may provide enough time for antioxidant therapy to tip the balance in favour of survival and we therefore advocate its prophylactic use within the first 24 h of AlP poisoning.

KEY WORDS: AlP; antidysrhythmics; atrial fibrillation; ECG; Holter; rice tablet; ST-segment; toxicity; ventricular fibrilation

Aluminium phosphide (AlP) is used in agriculture due to low cost and high efficacy as a fumigant pesticide. Acute AlP poisoning is mainly reported in Asian countries like India and Iran (1-3) and is the most common cause of death among pesticides, with a mortality rate of 31% to 77% (2-6).

Signs and symptoms of acute AlP poisoning include gastrointestinal, cardiovascular, hepatic, renal, and neurologic (1). Most of the deaths occur within the first 24 hours after ingestion due to cardiovascular involvement, dysrhythmias such as ventricular tachycardia (VT), ventricular fibrillation (VF), supra-ventricular tachycardia (SVT), and atrial flutter and fibrillation (AF) in particular (7-10).

Amiodarone is an antidysrhythmic used to treat SVT and ventricular tachydysrhythmia, by blocking repolarisation and prolonging the refractory period of the myocardium, which prevents tachydysrhythmia. It is associated with improved survival in non-ischaemic cardiomyopathy but not in post-myocardial infarction, yet its use in post-myocardial infarction and congestive heart failure patients is safe (11, 12). Amiodarone also improves survival in patients with AF by effectively converting AF to sinus rhythm and maintaining it after conversion (12).

For all these reasons, the aim of this study was to evaluate its potential as prophylaxis against AlP-induced dysrhythmia.

SUBJECTS AND METHODS

Study population

This was a prospective, randomised, controlled, open label clinical trial in patients with acute AlP poisoning. The study included 46 patients older than 12 years admitted to the Medical Toxicology Intensive Care Unit (MT ICU) of the Loghman Hakim Hospital Poison Center, Tehran, Iran

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over six months. Patients with the history of diabetes mellitus, cardiovascular, respiratory, renal, and hepatic failure, substance abuse, co-ingestion, advanced medical management for poisoning, and antidysrhythmic therapy started elsewhere before admission were excluded from the study.

The diagnosis was based on the history of exposure, clinical manifestations, and positive silver nitrate test on exhaled breath or stomach content samples. The study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences in Tehran and observed the Declaration of Helsinki.

Treatment protocol

The treatment started with gastric decontamination in the Emergency Department, followed by immediate admission to the ICU and management based on the same standard protocol for all patients (4–6 g of magnesium sulphate and 4 g of calcium gluconate by intravenous (IV) infusion daily and adequate hydration), except for amiodarone treatment. IV infusion of 10 µg/min norepinephrine was administered as required. All the patients were treated under the supervision of the same physicians and nurses.

The patients were randomised in two groups: those with even file number were assigned to the treatment group receiving amiodarone prophylaxis (n=23) and those with the odd file number were assigned to control (not receiving amiodarone) (n=23).

The initial loading dose of 150 mg was given as IV bolus, followed by IV infusions of 1 mg/min for six hours and then of 0.5 mg/min for another 18 hours, as described elsewhere (13). Both groups were monitored with a 24-hour Holter from admission to the ICU or until the time of death if it occurred within the first 24 h. Holter records were then given to a cardiologist blind to the treatment and control groups for interpretation. All the patients were followed up until discharge from the hospital or death.

Patient information about sex, age, cause of poisoning, ingested AlP dose, time between ingestion and ICU admission, clinical manifestations and paraclinical findings on admission time, duration of hospitalisation, and outcome were taken from the patients' medical files. All information was kept confidential during the study.

Statistical analysis

The data were expressed as mean ± standard deviation (SD), frequency, and ratio and analysed with SPSS version 16 (SPSS Inc., Chicago, IL, USA). Qualitative variables were compared with the chi-square test, and quantitative variables were tested for normality of distribution with the Kolmogorov-Smirnov test. Variables with normal distribution were further tested with Student's *t*-test and others with the Mann-Whitney U-test. P values of 0.05 or less were considered statistically significant.

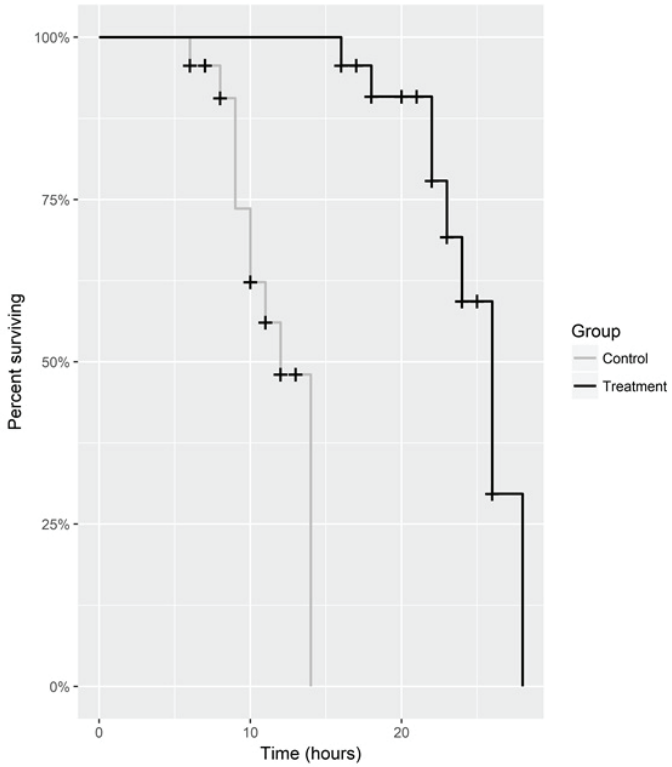

Figure 1 Comparison of survival time between the treatment and control group; + – censored observations (patients discharged from the ICU, with unknown survival time)

Table 1 Demographic, clinical, and laboratory data of patients with acute AlP poisoning admitted to ICU

Parameter (normal range)		Treatment group (n=23)		Control group (n=23)		*P* value
		Number (Ratio)	Mean ± SD (range)	Number (Ratio)	Mean ± SD (range)	
Sex	Women	14 (0.609)		13 (0.565)		0.8
	Men	9 (0.391)		10 (0.435)		
Age (year)		22.7±6.1 (15–36)		25.7±10.6 (13–52)		0.5
Number of ingested AlP tablets		2±2 (0.25–8)		1.2±0.7 (0.25–3)		0.08
Time between AlP ingestion and ICU admission (hours)		5.6±5.4 (1.2–20)		5.3±5.8 (0.45–18.1)		0.2
Abdominal pain	No	8 (0.348)		7 (0.304)		0.8
	Yes	15 (0.652)		16 (0.696)		
Vomiting	No	2 (0.87)		3 (0.13)		0.6
	Yes	21 (0.913)		20 (0.87)		
Chest Pain	No	12 (0.522)		11 (0.478)		0.8
	Yes	11 (0.478)		12 (0.522)		
Dyspnoea	No	15 (0.652)		16 (0.696)		0.8
	Yes	8 (0.378)		7 (0.304)		
Loss of consciousness	No	22 (0.957)		21 (0.914)		1
	Yes	1 (0.43)		2 (0.86)		
Systolic blood pressure (120–140 mmHg)		103±18.9 (72–150)		94.5±19.5 (63–139)		0.3
Diastolic blood pressure (70–90 mmHg)		60.7±13 (40–86)		55.5±13.9 (35–88)		0.2
Pulse rate (60–100/min)		108±17.9 (70–133)		97.1±18.6 (61–135)		0.05
Respiratory rate (12–20/min)		15.8±10.3 (0–30)		19.3±6 (0–31)		0.4
Need for intubation and mechanical ventilation	No	19 (0.826)		21 (0.913)		0.7
	Yes	4 (0.174)		2 (0.087)		
Blood chemistry						
pH (7.35–7.45)		7.34±0.15 (6.90–7.35)		7.37±0.12 (7.08–7.57)		0.7
PCO_2 (35–45 mmHg)		35 ±14.3 (19–87)		30.6±7.2 (19.6–45.9)		0.6
Serum HCO_3 (22–26 mEq/L)		17.6±5.4 (9.4–29)		18.5±5.9 (10.6–32.8)		0.6
O_2 saturation (%)		90.3±5.7 (77–98)		92.3±4.2 (85–98)		0.3
Sodium (135–145 mEq/L)		141.5±4.5 (131–148)		142.1±3.9 (136–150)		0.6
Potassium (3.5–5 mEq/L)		3.8±0.4 (3–5)		3.9±0.3 (3.5–4.4)		0.4
Calcium (8.4–10.2 mg/dL)		8.9±0.7 (8–10.1)		9.1±0.8 (8–10.5)		0.4
Magnesium (1.9–2.5 mg/dL)		2.3±0.5 (1.6–3)		2.1±0.4 (1.4–2.6)		0.5
Blood glucose (70–110 mg/dL)		103±18.9 (72–150)		94.5±19.5 (63–139)		0.1

SD=standard deviation

RESULTS

In 45 of the 46 cases poisoning was intentional, and 20 patients died (ratio 0.435). Table 1 shows the demographic, clinical and laboratory data for both groups on admission to the ICU.

Table 2 compares the frequencies of dysrhythmias registered by the Holter between the groups. Amiodarone significantly lowered the occurrence of ST-segment elevation and VF+AF.

The need for the administration of vasopressor norepinephrine and mortality did not significantly differ between the treatment and control group [12 vs 13 patients (P=1) for norepinephrine and 9 vs 11 patients for mortality (P=0.8), respectively].

Median time elapsed between ICU admission and death (survival time) was 23 h (range: 16–28) in the treatment group and 10 h (range: 6-14) in the control group (P<0.001) (Figure 1).

DISCUSSION

To the best of our knowledge there are only two studies on IV administration of amiodarone in acute AlP poisoning,

Table 2 The frequencies of dysrhythmias monitored by 24-hour Holter in patients with acute AlP poisoning

Type of dysrhythmia	Treatment group (n=23)	Control group (n=23)	P value
Sinus bradycardia	1	1	1
First-degree atrioventricular block	0	1	0.3
Second-degree atrioventricular block (Mobitz type II)	1	0	0.3
Atrial premature contraction (APC)	13	9	0.2
Sinus tachycardia	9	7	0.5
Atrial fibrillation (AF)	3	8	0.08
Junctional rhythm	2	1	0.5
Idioventricular rhythm	4	3	0.6
Ventricular premature contraction (VPC)	10	13	0.3
Ventricular tachycardia (VT)	9	6	0.5
Ventricular fibrillation (VF)	1	5	0.3
Left bundle branch block (LBBB)	3	1	0.3
Right Bundle Branch Block (RBBB)	7	3	0.2
ST-segment elevation	1	7	0.02*
ST-segment depression	2	3	0.6
VF+AF	3	11	0.01*
VT and VF and AF	8	13	0.1
Asystole following AF	2	7	0.06

*Statistically significant difference between the two groups (P<0.05)

and one reported no VT response to treatment (14) and the other reported very limited beneficial effects (15). Even though amiodarone prophylaxis in our study significantly decreased the occurrence of AF+VF and ST-segment elevation and significantly increased survival time, it did not reduce mortality. However, interpretation of our results is quite limited by the small sample.

Another limitation of our study is that we did not observe or treat myocardial oxidative damage, whereas other studies showed significant beneficial effects of antioxidants against cardiovascular toxicity (16–18). Future studies should therefore combine amiodarone and antioxidant treatment.

Even though amiodarone alone did not reduce mortality, it may provide enough time for antioxidant therapy to tip the balance in favour of survival and we therefore advocate its prophylactic use within the first 24 h of AlP poisoning.

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Conflicts of interest

None to declare.

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Djelotvornost amiodarona u profilaksi srčane disritmije uzrokovane akutnim otrovanjem aluminijevim fosfidom

Najčešći uzrok smrti u prva 24 sata od otrovanja aluminijevim fosfidom (AlP) jesu njegovi toksični učinci na srce i krvožilje. Oni se obično manifestiraju srčanim disritmijama. Cilj je ovoga ispitivanja bio procijeniti blagotvorne učinke amiodarona u profilaksi srčane disritmije u 46 bolesnika primljenih na intenzivnu njegu s otrovanjem AlP-om. Bolesnici su podijeljeni u dvije skupine od 23 ispitanika. Jedna je primala amiodaron, a druga (kontrolna) nije. Ostalo liječenje bilo je standardno i identično u objema skupinama. Amiodaronska se je profilaksa sastojala od udarne intravenske bolusne doze od 150 mg, nakon čega je uslijedila infuzija u dozi od 1 mg/min prvih šest sati, a zatim od 0,5 mg/min sljedećih osamnaest sati. Obje su skupine od prijama na intenzivnu njegu bile nadzirane 24-satnim holterom. Amiodaron je iskazao značajnu djelotvornost u smanjenju učestalosti povišenoga ST-segmenta odnosno ventrikulske i atrijske fibrilacije (P=0,02 odnosno P=0,01), ali nije značajno smanjio smrtnost (9 bolesnika u skupini na amiodaronu odnosno 11 u kontrolnoj skupini). Srednje vrijeme od prijama na intenzivnu njegu do smrti (vrijeme preživljenja), međutim, značajno se produžilo u skupini na amiodaronu (22 h prema 10 h u kontrolnoj skupini; P=0,03). Unatoč jasnim ograničenjima, napose zbog premaloga uzorka, ovo ispitivanje upućuje na to da amiodaron može dovoljno produžiti vrijeme preživljenja i time dati dovoljno vremena antioksidacijskom liječenju da spasi život te iz tog razloga preporučujemo njegovu profilaktičku primjenu u prva 24 sata od otrovanja AlP-om.

KLJUČNE RIJEČI: AlP; antidisritmici; atrijska fibrilacija; EKG; holter; ST-segment; toksičnost; ventrikulska fibrilacija