

## Dihydroxyacetone as a definitive treatment for aluminium phosphide poisoning in rats

Jafar Ahmadi<sup>1,2</sup>, Siyavash Joukar<sup>3,4</sup>, Hussein Anani<sup>5</sup>, and Somayyeh Karami-Mohajeri<sup>1,2</sup>

Pharmaceutics Research Center, Institute of Neuropharmacology<sup>1</sup>, Department of Toxicology and Pharmacology<sup>2</sup>, Physiology Research Center, Institute of Basic and Clinical Physiology Sciences<sup>3</sup>, Department of Physiology and Pharmacology<sup>4</sup>, Faculty of Allied Medical Sciences<sup>5</sup>, Kerman University of Medical Sciences, Kerman, Iran

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Aluminium phosphide (AIP), a very toxic pesticide also known as the *rice tablet*, releases phosphine gas upon contact with water, moisture, or gastric acid. Its mortality rate in humans is 70-100 % due to cardiogenic shock and refractory hypotension. Dihydroxyacetone (DHA) is a simple ketonic carbohydrate, mainly used for sunless skin tanning. It also plays a beneficial role in the treatment of hypotension and cardiogenic shock by restoring blood volume and cellular respiration. The aim of this study was to investigate the its effect on the haemodynamics and electrocardiogram (ECG) in male rats poisoned with AIP. The animals were divided into the following groups: control (received 1 mL corn oil, orally), AIP (received 15 mg kg<sup>-1</sup> AIP solved in corn oil, orally), AIP plus DHA (treated with 50 mg kg<sup>-1</sup> of DHA 30 min after receiving AIP), and AIP plus *N*-acetyl cysteine (NAC) (treated with 200 mg kg<sup>-1</sup> of NAC 30 min after receiving AIP). The animals were then anaesthetised and ECG, blood pressure, and heart rate were recorded for 120 min. Treatment with AIP alone and in combination with NAC was associated with progressive hypotension, tachycardia, and ECG disturbances in rats, resulting in 100 % mortality 3 h after poisoning. However, DHA achieved 100 % survival in the poisoned rats and prevented AIP-induced ECG and haemodynamic abnormalities. The main mechanism of DHA in the treatment of AIP poisoning is unclear, but the findings suggest the promising therapeutic potential of DHA against AIP poisoning.

KEY WORDS: *acute toxicity; AIP; DHA; N-acetyl cysteine; NAC; pesticides; refractory hypotension; rice tablet*

While the application of pesticides in agriculture has improved the quality and quantity of agricultural products around the world (1), its death toll as a result of deliberate, accidental, occupational, or criminal poisoning has become an important issue (2).

Aluminium phosphide (AIP), also known as the *rice tablet*, is a highly effective and accessible solid fumigant widely used to protect agricultural products from pests (3). It is the most common cause of death among the residents of developing countries such as Iran and India, with the rate of 70-100 %. Death often occurs during the first 12 to 24 h of poisoning (4, 5).

On contact with moisture, water, or gastric acid, AIP releases a lethal gas called phosphine (6). Its absorption begins immediately after ingestion, and the symptoms are nonspecific, including nausea, vomiting, abdominal pain, pulmonary oedema, cardiovascular changes, seizure, hypoglycaemia, and lactic acidosis (1, 7, 8). The exact mechanism of phosphine gas poisoning has not yet been determined, but previous studies suggest inhibition of cellular respiration through the inhibition of cytochrome C oxidase, induction of oxidative stress via over-production of free radicals, and reduction of antioxidant enzymes (4).

Although phosphine is a non-specific poison affecting most organs, it particularly affects the cardiovascular system with electrocardiogram (ECG) disturbances, myocardial damage, collapse of vessels, congestive heart failure, arrhythmia, cardiogenic shock, and refractory hypotension (3, 9).

The management of AIP poisoning has mostly been supportive and, unfortunately, no specific antidote has been discovered so far. The strategies that have been proposed include preventing the hydrolysis of AIP and reducing the absorption of phosphine with gastric lavage with potassium permanganate, paraffin, and coconut oil. Management also includes the use of vasopressors, anti-arrhythmic drugs, digoxin, temporary cardiac pacing, and antioxidants such as *N*-acetyl cysteine (NAC) and vitamins E and C (1). Mechanical methods such as extracorporeal membrane oxygenation and balloon pump in the aorta have been shown to increase the survival time (10-12). Several *in vitro* studies reported that intravenous hydroxyethyl starch (13) prevented the leaking of intravascular fluids, that milrinone and vasopressin managed hypotension (14), and that *N*(ω)-nitro-L-arginine methyl ester (L-NAME) inhibited nitric oxide synthesis (15). However, no research so far has come up with a successful method or pharmacological compound for the definitive treatment of AIP poisoning.

Yet, some hope looms from most unexpected places with a cosmetic tanning product dihydroxyacetone (DHA)

Correspondence to: Somayyeh Karami-Mohajeri, Faculty of Pharmacy, Haft Bagh-e-Alavi Highway, Kerman, 7616911319, Iran  
Email: [s\\_mohajeri@kmu.ac.ir](mailto:s_mohajeri@kmu.ac.ir) or [somayyehkarami@gmail.com](mailto:somayyehkarami@gmail.com)

(16-20). This simple ketonic carbohydrate has been shown to effectively treat haemorrhagic and hypovolemic shock induced by lactic acidosis (21) and to restore mitochondrial respiration by suppressing cytochrome C oxidase inhibition by cyanide in mice and rabbits (22, 23). It also countered phosphine gas toxicity in the HepG2 cell line by increasing the production of ATP through glycolysis (24) and proved helpful in the treatment of acute anoxia in cases of cardiovascular collapse, myocardial infarction, general metabolic acidosis, and fatigue-induced lactic acidosis by restoring the phagocytic activity (21).

All these findings have prompted us to investigate the efficiency of DHA in the treatment of cardiac shock, blood pressure, and ECG in male rats poisoned with AIP.

## MATERIALS AND METHODS

### *Chemicals*

AIP in the form of granules packed in moisture-resistant sachets was purchased from the pesticide manufacturing company Samiran (Tehran, Iran). DHA was obtained from Merck Co. (Darmstadt, Germany). Other chemicals, all of high purity, were purchased from Sigma Aldrich (St. Louis, MO, USA).

### *Determination of LD<sub>100</sub> of AIP*

Based on earlier reports of the AIP LD<sub>50</sub> and LD<sub>100</sub> in rats of 8.7-12 mg kg<sup>-1</sup> (25) and 20 mg kg<sup>-1</sup>, respectively (26), we reran the tests with the range of 8-20 mg kg<sup>-1</sup> of AIP dissolved in corn oil and administered it orally (to six rats in each group) to mimic real-life mortality with a single dose. Mortality rates were calculated after 24 h of AIP administration using the probit analysis.

### *Animals*

All animal experiments were performed in accordance with relevant ethical guidelines for animal use, which was approved by the Ethics Committee of the Kerman University of Medical Sciences (Ethics code: IR.KMU.REC.1396.1964). Male Wistar rats weighing 250±20 g were purchased from the animal house of the Kerman University of Medical Sciences. Before the experiments started, the animals were kept in the laboratory for 7 days in order to adapt to the environment. During the study, the animals were kept in a controlled environment with a temperature of 22-24 °C and a 12-hour darkness / light cycle, with free access to food and water.

### *Study design*

Thirty rats were randomly divided into four groups (six rats in each group), as follows. Group 1 consisted of healthy control rats which received a single oral dose of 1 mL of corn oil alone through gavage (control group). Group 2

included healthy rats poisoned with a single oral dose of 15 mg kg<sup>-1</sup> of AIP in 1 mL of corn oil (AIP group). Group 3 consisted of AIP-poisoned rats treated with a single oral dose of 50 mg kg<sup>-1</sup> of DHA in 1 mL of 5 % dextrose 30 min after AIP administration (AIP+DHA). Group 4 consisted of AIP-poisoned rats treated with a single intraperitoneal dose of 200 mg kg<sup>-1</sup> of NAC in 1 mL of 5 % dextrose 30 min after AIP administration (AIP+NAC).

The animals were anaesthetised with ketamine/xylazine (60/6 mg kg<sup>-1</sup>) 30 min after administration of AIP (27). To maintain anaesthesia, ketamine/xylazine dosing (30/3 mg kg<sup>-1</sup>) was repeated 60 and 90 min after AIP poisoning.

### *Monitoring of survival time*

Survival was monitored continuously by direct observation of rats in all groups for the first 6 h. After that, the groups were checked for survival every 6 h for more than 24 h.

### *Recording of ECG, systolic blood pressure, heart rate, shock index, and survival*

The anaesthetised animals were immediately monitored for ECG, systolic blood pressure (SPB), and heart rate (HR) and the readings forwarded to a PowerLab data acquisition instrument (ML870, AD Instruments, Bella Vista, Australia). More specifically, the electrodes for recording lead II ECG were subcutaneously connected to the limbs of animals (14, 25), and ECG and HR monitored and recorded for 2 h. The ECG data were then analysed using LabChart Pro Modules (AD Instruments). Baseline RR interval (i.e. the time between two successive R waves) and QT interval (i.e. the time from the beginning of the Q wave to the end of the T wave) were calculated based on 2-minute ECG-recorded strips. To obviate the dependence of the QT interval on HR, corrected QT (QTc) intervals were calculated using Bazett's formula, normalised as QTc = QT / (RR / f)<sup>1/2</sup>, where f = 150 ms (28).

SBP was also measured using a non-invasive method through a cuff attached to the rat tail. Shock index (SI) was calculated by dividing HR by SBP (29). Several studies have shown that SI is a better indicator of haemorrhagic shock than blood pressure or HR alone (30, 31). A rise in SI precedes hypotension and is an early sign of haemodynamic instability due to cardiovascular diseases such as cardiac ischaemia, myocardial infarction, and heart failure (32, 33).

### *Statistical analysis*

All analyses were performed using the GraphPad-Prism 5.0 software (San Diego, CA, USA). Survival curves were plotted using the Kaplan-Meier method and its statistical significances were determined using the post hoc log-rank test. All data were normally distributed, as confirmed by the Shapiro-Wilk's test. Two-way repeated measure

ANOVA test followed by Tukey's *post-hoc* test was used for data analysis. P values of less than 0.05 were considered statistically significant.

## RESULTS

### *Probability of survival and survival time*

No mortality was reported in the control and AIP-poisoned animals treated with DHA. However, the untreated poisoned animals and those that received NAC after poisoning died after an average of  $148.1 \pm 32.2$  min and  $136.2 \pm 21$  min, respectively. Figure 1 shows the probability (%) of survival in all four groups.

### *HR, SBP, and ECG*

Table 1 shows the SPB and HR findings in the four groups. Animals poisoned with AIP (group 2) exhibited a time-dependent systolic hypotension that became significant in respect to control 60 min after the poisoning. Tachycardia became significant 90 min after the poisoning.

The AIP+DHA animals (group 3) showed no significant change in SBP or in HR in respect to control.

In the AIP+NAC rats, SBP decreased and HR increased with time.

The shock index (Figure 2) reinforces the SPB and HR findings of time-dependent and significant increase in in the AIP and AIP+NAC groups. In the AIP+DHA group it was similar to control.

ECG abnormalities such as shorter RR, ST elevation (Table 2), and prolonged QTc (Figure 3) were also observed

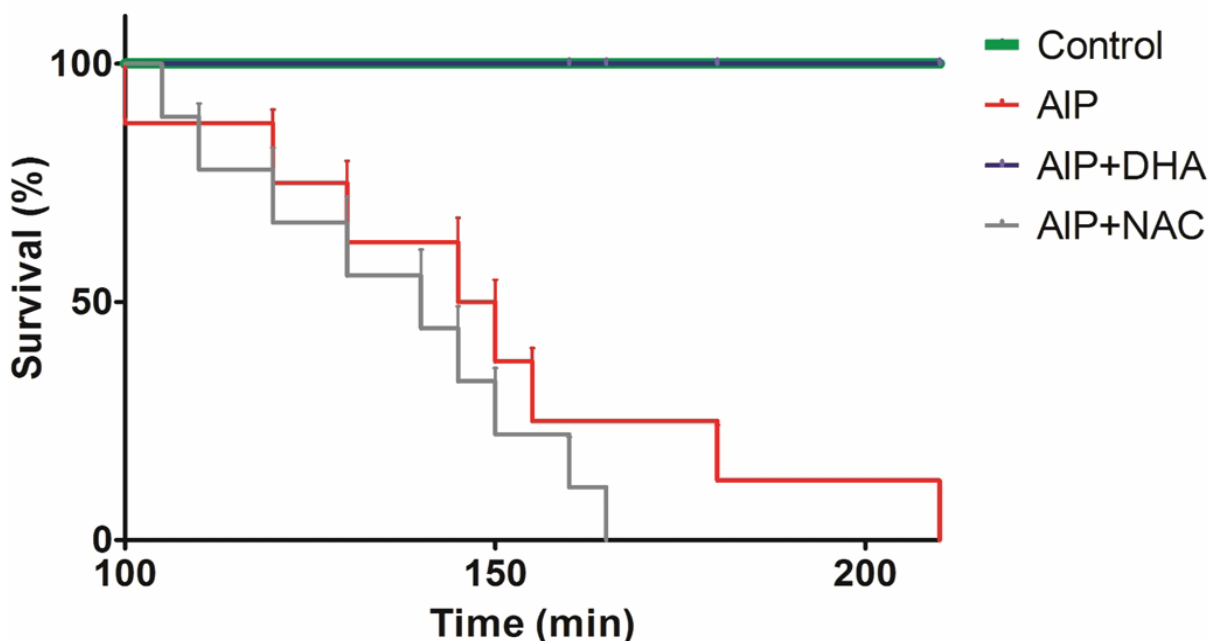
in the AIP-poisoned rats. In contrast, DHA significantly eliminated ECG abnormalities. The lethal dose of AIP caused a non-significant drop in the QRS interval, but it dropped significantly in the AIP+NAC group (Table 2).

## DISCUSSION

The results of our study are pretty straightforward and conclusive: DHA completely eliminated tachycardia in AIP-poisoned rats, probably because it prevented severe hypotension. It is well known that HR is affected by changes in oxygen levels in the body to compensate for its lack through greater cardiac output (34). However, high HR can result in cardiac ischaemia, ventricular arrhythmias, and left ventricular dysfunction (35), which eventually led to death in groups 2 and 4.

SI showed a significant increase in the AIP-poisoned rats (group 2) early compared to controls and it grew with time, which can be associated with left ventricular dysfunction and myocardial damage. SI can also be a good indicator of the quality of treatment and cardiovascular status in the early stage of poisoning with AIP.

ECG parameters reinforced the findings of tachycardia, hypotension, and SI in the poisoned rats. The ST elevation was first recorded 60 min after AIP poisoning and continued to rise with time until the rats died. This is in line with earlier reports that AIP poisoning leads to ST elevation (36, 37). In acute poisoning with AIP, ST elevation correlates closely with mortality, and its lowering can indicate successful treatment (3, 36). The case in point is the ST segment in DHA-treated AIP-poisoned rats, which was consistent with the one in the control group. DHA

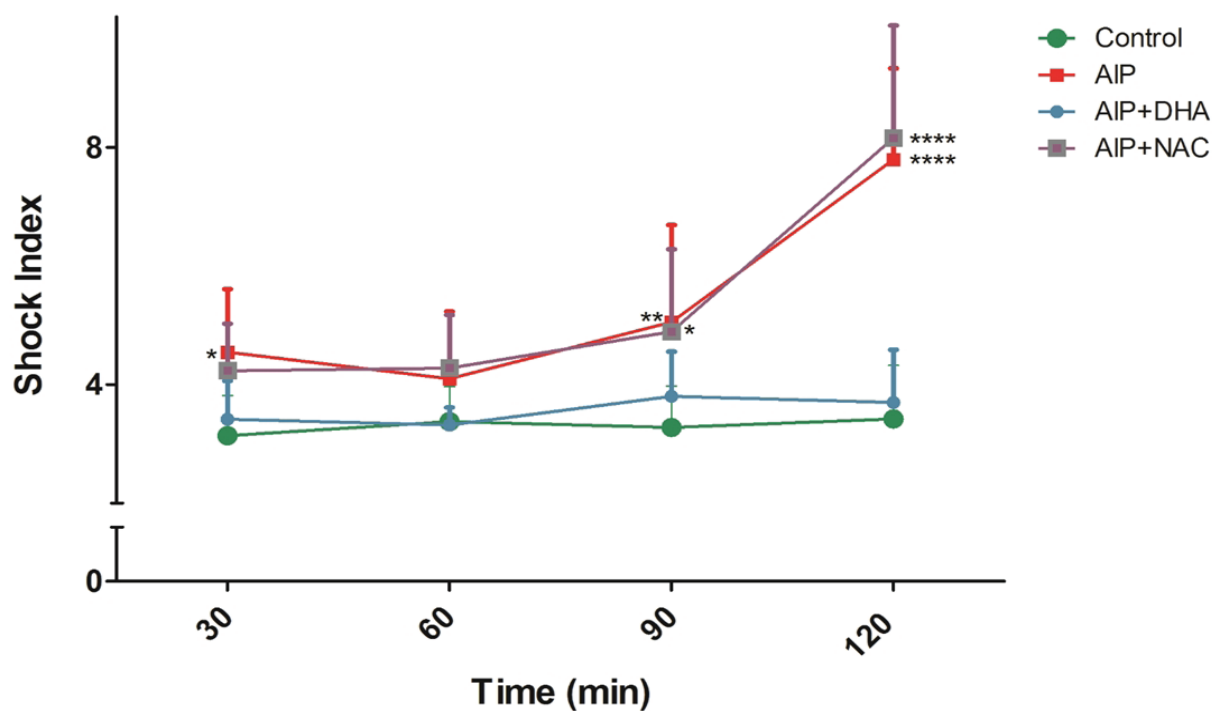


**Figure 1** Overall survival across study groups (in percentages). Control - rats receiving only corn oil; AIP - rats poisoned with a single aluminium phosphide dose ( $15 \text{ mg kg}^{-1}$ ); AIP+DHA - AIP-poisoned rats treated with a single DHA dose ( $50 \text{ mg kg}^{-1}$ ); AIP+NAC - AIP-poisoned rats treated with a single NAC dose ( $200 \text{ mg kg}^{-1}$ )

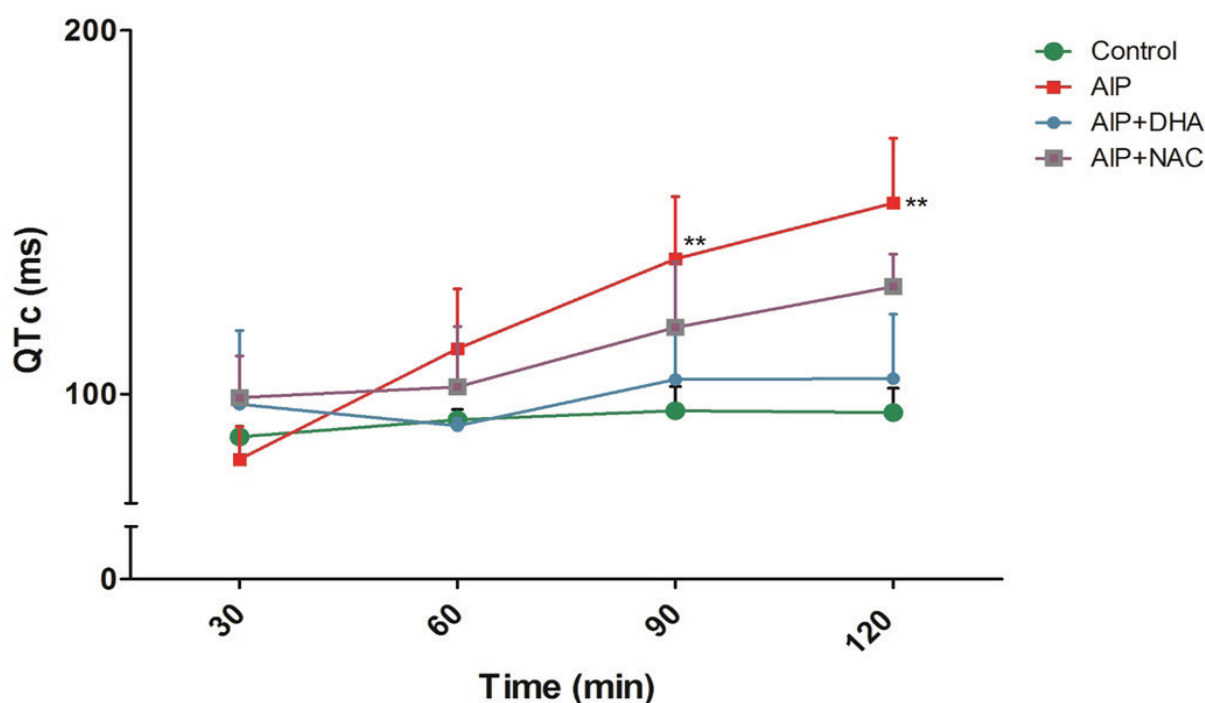
**Table 1** Changes in systolic blood pressure (SBP) and heart rate (HR) by study groups (six rats in each)

Variables	SBP				HR				
	30	60	90	120	30	60	90	120	
Control	Mean±SD	78.7±10.3	76.4±14.0	78.1±12.1	76.0±7.5	243.7±17.4	254.8±17.3	249.2±21.0	251.1±22.0
AIP	Mean±SD	65.1±18.2	62.8±18.7	54.1±13.2	48.3±7.4	270.4±18.9	273.4±34.1	263.1±54.0	363.9±29.1
	p <sup>1</sup>	0.28	0.35	<b>0.01</b>	< <b>0.00</b>	0.13	>0.99	>0.99	< <b>0.00</b>
AIP+ DHA	Mean±SD	79.8±11.5	79.2±9.7	73.5±11.9	80.6±22.5	256.5±18.8	256.0±15.6	262.3±31.0	278.2±24.2
	p <sup>1</sup>	1	1	0.97	0.98	>0.99	>0.99	>0.99	>0.99
AIP+ NAC	Mean±SD	68.0±13.1	70.0±10.1	55.0±11.3	47.0±5.5	286.5±16.3	299.9±39.8	325.4±53.3	387.0±21.6
	p <sup>1</sup>	0.52	0.88	<b>0.01</b>	< <b>0.00</b>	<b>0.05</b>	<b>0.03</b>	< <b>0.00</b>	< <b>0.00</b>
Control - rats receiving only corn oil; AIP - rats poisoned with a single aluminium phosphide dose (15 mg kg <sup>-1</sup> ); AIP+DHA - AIP-poisoned rats treated with a single DHA dose (50 mg kg <sup>-1</sup> ); AIP+NAC - AIP-poisoned rats treated with a single NAC dose (200 mg kg <sup>-1</sup> ). Significant values are bolded. <sup>1</sup> significant difference from control; <sup>2</sup> significant difference from the AIP group	p <sup>2</sup>	0.99	0.88	>0.99	1	>0.99	>0.99	>0.99	>0.99

Control - rats receiving only corn oil; AIP - rats poisoned with a single aluminium phosphide dose (15 mg kg<sup>-1</sup>); AIP+DHA - AIP-poisoned rats treated with a single DHA dose (50 mg kg<sup>-1</sup>); AIP+NAC - AIP-poisoned rats treated with a single NAC dose (200 mg kg<sup>-1</sup>). Significant values are bolded. <sup>1</sup> significant difference from control; <sup>2</sup> significant difference from the AIP group



**Figure 2** Changes in shock index (SI) across study groups (6 rats in each). Control - rats receiving only corn oil; AIP - rats poisoned with a single aluminium phosphide dose ( $15 \text{ mg kg}^{-1}$ ); AIP+DHA - AIP-poisoned rats treated with a single DHA dose ( $50 \text{ mg kg}^{-1}$ ); AIP+NAC - AIP-poisoned rats treated with a single NAC dose ( $200 \text{ mg kg}^{-1}$ ). Data are shown as means $\pm$ SD. \*\*\*\* $P < 0.001$ ; \*\* $P < 0.01$ ; \* $P < 0.05$



**Figure 3** Changes in QTc across study groups (6 rats in each). Control - rats receiving only corn oil; AIP - rats poisoned with a single aluminium phosphide dose ( $15 \text{ mg kg}^{-1}$ ); AIP+DHA - AIP-poisoned rats treated with a single DHA dose ( $50 \text{ mg kg}^{-1}$ ); AIP+NAC - AIP-poisoned rats treated with a single NAC dose ( $200 \text{ mg kg}^{-1}$ ). Data are shown as means $\pm$ SD. \*\* $P < 0.01$

**Table 2** Electrocardiogram parameters by study groups (six rats in each)

Variables	RR (ms)			QRS (ms)			ST (ms)						
	30	60	90	30	60	90	30	60	90	120			
Control	Mean±SD	244.4±18.4	241.9±15.4	244.3±18.9	242.1±20.1	20.2±3.9	20.4±3.9	20.4±3.2	20.8±2.9	22.8±3.1	22.6±3.7	21.8±4.0	21.5±3.8
AIP	Mean±SD	221.5±16.9	224.1±38.2	258.4±49.2	167.5±15.2	15.02±3.1	15.1±2.6	15.5±4.2	14.0±2.5	22.9±10.6	31.2±14.4	43.9±20.1	54.4±6.5
	p <sup>1</sup>	0.25	0.5	0.72	<0.00	0.2	0.22	0.39	0.07	0.23	0.27	0.01	<0.00
ALP+	Mean±SD	226.3±23.6	231.1±16.8	232.1±32.2	213.7±23.3	13.8±1.7	13.9±2.0	13.2±1.8	13.6±1.4	41.5±22.4	31.1±5.1	33.±7.3	32.5±14.5
	p <sup>1</sup>	0.58	0.9	0.88	0.2	0.07	0.08	0.05	0.11	1	1	0.95	1
AIP+NAC	Mean±SD	210.7±11.5	204.5±30.1	190.2±41.1	163.8±21.2	14.3±2.1	13.5±1.7	13.0±1.8	12.9±1.3	31.2±12.0	36.9±20.5	43.7±17.2	43.5±9.7
	p <sup>1</sup>	0.04	0.01	<0.00	<0.00	0.08	0.02	0.01	0.01	0.19	0.33	<0.00	<0.00
	p <sup>2</sup>	0.92	0.55	<0.00	1	1	0.92	0.66	0.99	>0.99	>0.99	0.4	0.73

Control - rats receiving only corn oil; AIP - rats poisoned with a single aluminium phosphide dose (15 mg kg<sup>-1</sup>); ALP+DHA - AIP-poisoned rats treated with a single DHA dose (50 mg kg<sup>-1</sup>); AIP+NAC - AIP-poisoned rats treated with a single NAC dose (200 mg kg<sup>-1</sup>). Significant values are bolded. <sup>1</sup>significant difference from control; <sup>2</sup> significant difference from the AIP group

successfully reversed RR interval shortening to normal. The QRS complex and the QTc interval are indicative of electrical conductivity in the heart tissue (37, 38). Prolonged QTc interval is associated with ventricular tachyarrhythmias due to premature action potential in the late stages of depolarisation, which increases the risk of ventricular arrhythmias or fatal ventricular fibrillations and is associated with ECG findings called Torsades de pointes (39). In this study, ALP poisoning caused a significant increase in the QTc interval with a non-significant decrease in QRS complex interval 60 min after the poisoning. This increase in the QTc interval could be a sign of deadly arrhythmias in animals. Administration of DHA and NAC restored it to normal.

NAC administration, however, had no significant effect on blood pressure and survival time. In fact, instead of lowering SI, NAC increased it above all other groups. According to Akturi et al. (40) one plausible reason for high SI could be the anaphylactic shock associated with NAC. Anaphylactic shock seems to be a result of the activation of histamine receptors, stimulation of endothelial cells, and the release of nitric oxide (41).

NAC was also inferior to DHA in correcting the ST elevation. It led to a significant drop in the QRS complex and, ultimately, did not save the rats from death. Yet a number of poisoning treatment centres currently use NAC as an antioxidant in ALP poisoning management. Our findings warn against its use as it may exacerbate the symptoms and even accelerate death caused by ALP poisoning. Clearly, even though oxidative stress is involved in ALP toxicity, it certainly is not the main mechanism of its action.

Speaking of the mechanism of action, we still do not know through which mechanisms DHA normalised the ECG parameters and stabilised the haemodynamics in the poisoned rats. Some authors (21, 42) point to the recovery of blood volume, improved tissue oxygenation, and restored cell respiration through the activation of cytochrome C oxidase.

Whatever the mechanism(s), the most important goal in poisoning management is to prevent death, which has been ignored by many animal studies of ALP poisoning. Most of them were focused on alleviating symptoms instead of addressing this key issue (5, 10, 11, 27, 43, 44). Our study, in turn, has identified DHA as a promising treatment for patients poisoned with rice tablets.

#### *Conflict of interest*

None to declare.

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### Dihidroksiaceton kao definitivni lijek za trovanje aluminijevim fosfidom u štakora

Aluminijev fosfid (AIP) je pesticid koji u dodiru s vodom, vlagom ili želučanom kiselinom oslobađa iznimno toksičan plin fosfin. Smrtnost u ljudi je od 70 do 100 % zbog srčanog šoka i refraktorne hipotenzije. Dihidroksiaceton (DHA) jednostavan je ketonski ugljikovodik koji se mahom rabi kao preparat za tamnjenje kože. Osim toga, rabi se u liječenju niskog krvnog tlaka i srčanog šoka, a djeluje tako što volumen krvi i stanično disanje vraća na normalnu razinu. Cilj je ovoga istraživanja bio ispitati njegov utjecaj na hemodinamiku i elektrokardiogram (EKG) u mužjaka Wistar štakora otrovanih aluminijevim fosfidom. Životinje su podijeljene u sljedeće skupine: kontrolnu (koja je jednokratno primila 1 mL kukuruznog ulja na usta), AIP (koja je jednokratno primila 15 mg kg<sup>-1</sup> AIP-a otopljenog u kukuruznom ulju na usta), AIP plus DHA (koja je jednokratno primila 50 mg kg<sup>-1</sup> DHA 30 min nakon trovanja AIP-om) te AIP plus *N*-acetilcistein (NAC) (koja je jednokratno primila 200 mg kg<sup>-1</sup> NAC-a 30 min nakon trovanja AIP-om). Životinje su potom anestezirane i u idućih 120 min mjereni su im EKG, sistolički krvni tlak i broj otkucaja srca. Primjena AIP-a samog ili u kombinaciji s NAC-om bila je povezana s progresivnom hipotenzijom, tahikardijom i poremećajima u EKG-u te je dovela do 100-postotne smrtnosti unutar tri sata od trovanja. S druge pak strane, DHA je osigurao 100-postotno preživljenje otrovanih štakora i spriječio poremećaje u EKG-u i hemodinamici izazvane trovanjem AIP-om. Još nije jasan osnovni mehanizam djelovanja DHA, ali naši rezultati upućuju na obećavajući terapijski potencijal DHA u liječenju otrovanja AIP-om.

**KLJUČNE RIJEČI:** akutna toksičnost; AIP; DHA; pesticidi; refraktorna hipotenzija; *N*-acetilcistein