



CASE REPORT

Successful treatment of aluminium phosphide poisoning by dihydroxyacetone: A two-case report study

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Funding information

This article was supported by Kerman University of Medical Sciences (project no.: 96000536).

Abstract

What is known and objective: Aluminium phosphide (AIP) is an agricultural fumigant which produces phosphine gas in the presence of moisture. Phosphine inhibits oxidative phosphorylation and causes cell death by inhibiting cytochrome C oxidase. Clinical manifestations of AIP poisoning are refractory hypotension, tachycardia, low oxygen saturation and severe metabolic acidosis.

Case summary: Two cases received dihydroxyacetone (DHA) in addition to routine management of AIP poisoning. Administration of DHA (7 gr in 50 mL sodium bicarbonate, gavage) 2 times at a 1-hour interval improved the clinical signs.

What is new and conclusion: This is the first case report to highlight the safe and successful treatment of AIP poisoning with DHA. However, more clinical studies are recommended to determine the precise mechanism of DHA action.

KEYWORDS

antidote, case report, dihydroxyacetone, hypotension, phosphine

1 | WHAT IS KNOWN AND OBJECTIVE

Aluminium phosphide (AIP) or rice tablet is a solid fumigant which is widely used to protect grain stores. It is a cheap method for fumigation of agricultural products during shipping of products and hundred tons of AIP are used worldwide every year.¹⁻³ In contact with moisture, AIP releases a lethal gas called phosphine (PH₃). The characteristics of AIP poisoning include shock, severe metabolic acidosis, dysrhythmia and respiratory distress syndrome causing death within 24 hours, if not treated.^{4,5} Aluminium phosphide disrupts

cellular respiration and ATP production by mechanisms including inhibition of mitochondrial oxidative phosphorylation, inhibition of cytochrome C oxidase, impairment in glucose haemostasis, depletion in cellular oxygen, and toxic effects on cardiovascular and pulmonary system.⁶⁻¹⁰ The mortality rate by AIP poisoning is high in Asian countries¹¹⁻¹⁵ and so far no effective antidote or therapeutic strategy has been introduced for its poisoning.

Generally, management of PH₃ poisoning includes supportive cares such as preventing the hydrolysis of AIP with potassium permanganate, paraffin and coconut oil.⁴ Recently, researches have

focused on the treatment of cardiovascular disorders of AIP poisoning using mechanical methods such as extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump.^{5,16} It has been demonstrated that dihydroxyacetone (DHA) as a simple carbohydrate can overcome hypovolemic hypotension¹⁷ and can reduce toxicity of PH3 in HepG2 cells by increasing ATP production.⁷ In another study, it has been shown that a single dose of DHA completely prevented the death caused by AIP poisoning in rats through improving blood pressure and heart rate.¹⁸

Dihydroxyacetone was first proposed in 1920 as an alternative to glucose replacement for diabetic patients and as a diagnostic method for glycogen storage disease in 1950.¹⁹ In a clinical trial, it was found that consumption of DHA and pyruvate instead of sugar reduced weight in over-weight people²⁰ and DHA was suggested as an over-the-counter weight loss drug.²¹ It was found that, immediately after administration, DHA converts to DHA phosphate and participates in energy production pathways including glycolysis, Krebs cycle and fructose metabolism.^{22,23}

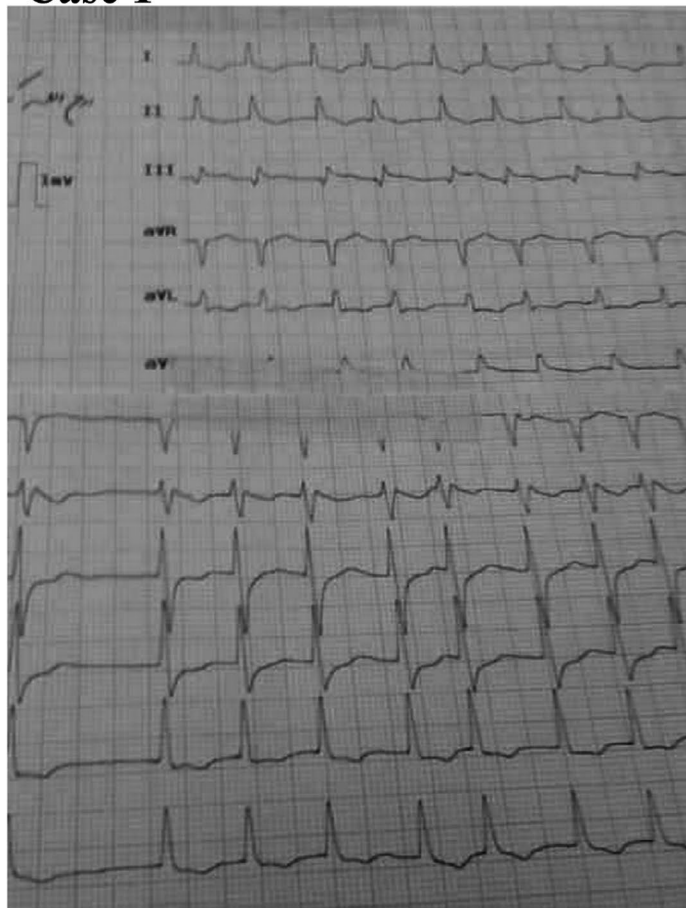
Moreover, DHA as a pharmacological and liquid-injectable compound was recommended for the successful treatment of hemorrhagic shock at the dose of 30-60 mg/kg body weight.²²

Dihydroxyacetone could be an effective antidote for cyanide-induced mitochondrial dysfunction^{24,25} and can be used for the treatment of acute anoxemia in cardiovascular collapse and myocardial infarction.²² It also increased the volume of muscle and the capacity for aerobic endurance.^{20,26} Dihydroxyacetone eliminated the inhibitory effect of PH3 on the mitochondrial respiratory chain, thereby preventing the effect of PH3 on intracellular ATP depletion.⁷

It has been shown that oral administration of DHA is tolerable in human.¹⁹ The European Union stated that no specific clinical signs, mutagenicity and carcinogenicity were observed in chronic exposure to DHA, and oral and intraperitoneal administration of high doses of DHA were associated with reversible symptoms such as dizziness, shortness of breath, temporary pulling of the toe immediately after injection. DHA at the doses higher than 16 000 mg/kg body weight for oral and 6400 mg/kg body weight for intraperitoneal exposure can be toxic.²⁷

As animal and clinical studies have shown beneficial effects of DHA in elevation of blood pressure, in the current study DHA was aimed to be used for prevention of refractory hypotension caused by AIP poisoning as the main cause of mortality in AIP-poisoned patients.

Case 1



Case 2

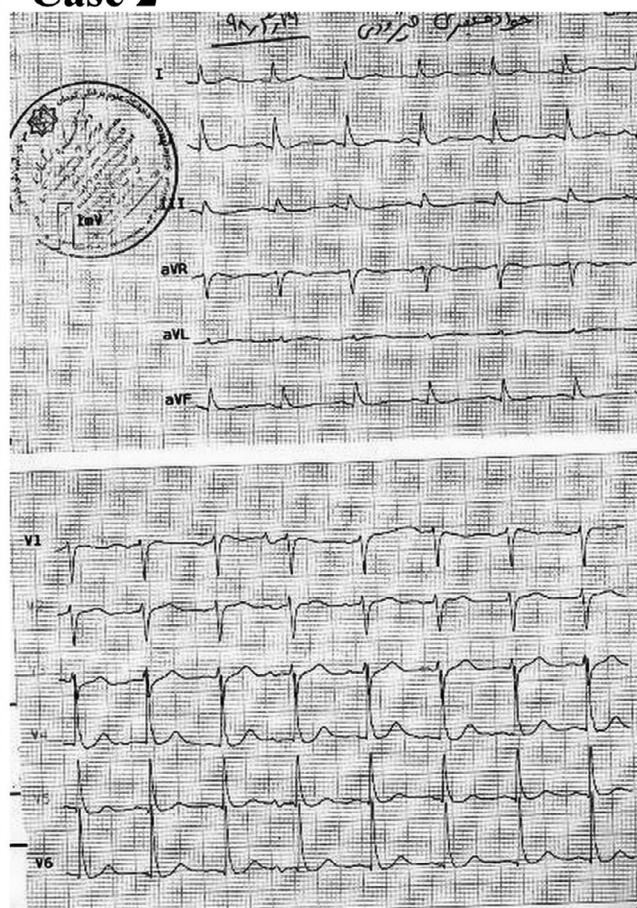


FIGURE 1 Electrocardiography of cases 1 and 2



2 | CASE SUMMARY

2.1 | Case 1

A 39-year-old man was admitted into Afzalipour hospital, the main toxicology centre in Kerman province, after intentional ingestion of half tablet, 1500 mg, of AIP. He was admitted into the emergency department (ED) 1 hour after the ingestion, complaining of nausea, vomiting, abdominal pain, and thirst. Vital signs on the admission were blood pressure, 77/58 mm Hg; pulse rate, 125 beats/min; respiratory rate, 30/min; and core temperature, 36.7°C, with an oxygen saturation of 90% in room air. An initial blood gas analysis showed pH, 6.91; PCO₂, 56.3 mm Hg; PaO₂ 6.2 mm Hg; HCO₃, 10.8 mmol/L; and BE -21.9 mmol/L. In physical examination, he was confused, with cold extremities and non-detectable pulses. He was tachypneic and had tenderness in abdominal examination. Early electrocardiography (ECG) revealed atrial fibrillation (Figure 1), and bedside echocardiography showed a left ventricular ejection fraction (LVEF) of 30%. Serial vital signs and blood gas are shown in Tables 1 and 2. After early intubation and blind insertion of central venous line (because of impenetrable pulses) in ED, the patient was admitted to the poisoned intensive care unit (ICU).

2.2 | Case 2

A 40-year-old man was admitted to a general hospital, after unintentional inhalation of PH3 gas in a closed space without ventilation (a pistachio silo), complaining of chest pain. Early ECG showed ventricular tachycardia. He underwent angiography with the diagnosis of acute coronary syndrome. Coronary angiography was normal. The physician noticed severe metabolic acidosis in the early arterial blood gas. Because of low oxygen saturation, he was intubated, and after incision of CV-line, he was referred to Afzalipour hospital. Vital signs on the admission were blood pressure, 118/64 mm Hg; pulse rate, 107 beats/min; respiratory rate, 26/min; and core temperature, 37.3°C, with an oxygen saturation of 87%. An initial blood gas analysis showed pH, 6.96; PCO₂, 36.7 mm Hg; PaO₂, 51.8 mm Hg; HCO₃, 8.0 mmol/L; and BE, -20.7 mmol/L. The patient was admitted to the ICU.

The patients underwent a gavage of 7 gr of DHA in combination with 50 mEq (50 mL) of sodium bicarbonate (NaHCO₃) through nasogastric tube (repeated 1 hour later), intravenous (IV) crystalloid fluid, norepinephrine; 4 µg/min, IV sodium bicarbonate (100 mEq), IV magnesium sulfate (1 gr stat followed by 1 gr q6h), IV calcium gluconate (1 gr stat followed by 1 gr q6h), IV hydrocortisone (200 mg stat followed by 200 mg q6h), high-dose insulin plus glucose (1 unit/kg of regular insulin along with 0.5 gr/kg of dextrose as bolus dose with a closed control of glucose and potassium; IV infusion of insulin and glucose continued in doses of 0.5 unit/kg and 0.5 gr/kg respectively), and IV N-acetylcysteine (in total dose of 300 mg/kg). All the treatments continued until vital signs, cardiac function and blood gas were normalized and then were tapered gradually. Case 1 was extubated on day 2 and echocardiography on day 4 showed an LVEF of 50%. The patient was discharged from the hospital on

TABLE 1 Serial vital signs of cases 1 and 2

		Time after ingestion															
Vital signs		Cases	On admission	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h	12 h	13 h	14 h	24 h	Day 2	Day 7
Blood pressure (mm Hg)	1		77/58	64/23	97/65	98/44	124/65	107/62	97/63	105/65	100/69	97/67	105/65	130/86	123/94	120/76	127/66
	2		118/64	110/60	91/62	95/60	95/66	98/70	102/65	117/81	116/76	130/84	129/87	122/88	108/67	136/82	128/80
Pulse rate (beat/min)	1		125	58	62	72	95	110	125	98	110	132	98	81	101	84	78
	2		107	105	106	104	101	100	100	95	90	89	88	88	90	78	87
Respiratory rate (breath/min)	1		30	28	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	20 Extube	19 Extube
	2		SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	20 Extube
Oral temperature (°C)	1		36.7	36.3	35.5	35.7	35.1	35.3	36	36.5	36.5	36.8	37.5	37.7	37.2	37.6	37.4
	2		37.3	37.2	37.1	37	37.4	37.5	37.4	37.3	37.2	37/5	37.4	37.5	37.2	37.7	37.5
O ₂ saturation (%)	1		90	90	92	94	95	93	96	95	95	96	95	98	97	93	93
	2		87	85	87	88	83	95	95	96	97	97	98	98	100	96	97

TABLE 2 Serial blood gas analyses of cases 1 and 2

Measurement	Cases	Time after ingestion										Day 2	Day 7
		On admission	1 h	2 h	3 h	4 h	5 h	6 h	8 h	12 h	24 h		
pH	1	6.91	6.94	6.93	7.20	7.19	7.30	7.28	7.37	7.38	7.32	7.45	7.43
	2	6.967	–	7.07	–	7.23	–	7.31	–	7.39	7.44	7.45	7.482
PaCO ₂ (mm Hg)	1	56.3	60	58.8	40.3	51	40.3	60.1	46.6	47.9	58.1	46.8	40.8
	2	36.7	–	33.9	–	38.5	–	33.8	–	35.1	57.6	46.4	37.5
PaO ₂ (mm Hg)	1	26.2	31.2	57	122	46.6	77	60.4	91.8	73	58	61	32.5
	2	51.8	–	55.2	–	48.8	–	74.5	–	89.8	103.7	84.9	67.8
Serum HCO ₃ (mmol/L)	1	10.8	12.3	11.9	15.5	19.1	19.3	28	26.4	27.7	29.6	32.2	26.7
	2	8.0	–	9.4	–	15.9	–	16.8	–	21	25.2	29.6	27.8

day 7 in a good condition after psychiatry consultation. Case 2 was extubated on day 3 and echocardiography on day 4 showed an LVEF of 60%. The patient was discharged from the hospital on day 8 in a good condition.

3 | WHAT IS NEW AND CONCLUSION

Our patients, in addition to low blood pressure, showed metabolic acidosis, tachycardia and high respiration rate. Administration of DHA in these cases increased both systolic and diastolic blood pressure and normalized heart and respiratory rates.

It seems that focusing on maintaining blood pressure and oxygenation to tissues could be a ray of hope in the management of PH3 poisoning. It has been shown that the supportive care of cardiovascular and pulmonary system using vasopressors, inotropic drugs and non-drug methods such as ECMO, hyperbaric oxygenation and intra-aortic balloon pump had beneficial effects on AIP poisoning.^{5,16,28–32} Glucose-insulin-potassium (GIK) therapy improved the outcome of AIP poisoned patients by elevation of glucose uptake and utilization by myocytes.³³ Furthermore, insulin improved inotropy and peripheral vascular resistance.^{34,35} Some researchers have focused on ATP production by administration of magnesium and nutrients including glucose, α -ketoglutarate, fructose, mannitol and DHA to reduce toxicity of PH3.^{7,36}

It has been shown that DHA normalized blood pressure and heart rate in AIP poisoning in rats¹⁸ which might be through activation of cytochrome C oxidase, tissue oxygenation improvement and recovery of blood volume.^{17,37,38} DHA reacts with nitrogen group of amino acids in corneocytes in the upper layers of the stratum corneum and is used as an ingredient in tanning products.^{21,39,40} As phosphorous and nitrogen are in the nitrogen group in periodic table and have similar properties,⁴¹ we can expect that DHA are able to trap PH3 gas. DHA also has a protective role in the acute anoxemia of AIP and has an effective role in improving metabolic acidosis.¹⁷ DHA as an ATP supplier also increased viability of PH3-treated cells through elevation of ATP production in glycolysis process and through reduction of oxidative damage.⁷ Taking together, DHA seems to improve blood pressure, to

prevent cellular damage through improvement of cardiovascular function, to restore mitochondrial respiration and to trap PH3.

Considering the above, DHA as a non-toxic sugar can be used as a treatment without any worries in poisoning with rice tablet. Rescuing these AIP-poisoned patients with DHA can be promising to treat this fatal poisoning. However, more extensive clinical studies are suggested to find out the exact mechanism of DHA.

ACKNOWLEDGEMENTS

We are grateful to Ehsan Mehrabi Kermani for editing the English text.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interests.

ETHICAL APPROVAL

This Research is registered in Ethics Committee of Kerman University of Medical Sciences (Ethics Code: IR.KMU.REC.1396.2005) and Clinical Trial System of Iran (No: IRCT20180114038356N1).

PATIENT CONSENT STATEMENT

The present study was conducted upon the consent of who accompanied the patients.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

We did not use other sources in this article.

DATA AVAILABILITY STATEMENT

All data are presented in the article.

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How to cite this article: Oghabian Z, Ahmadi J, Pakravan S, et al. Successful treatment of aluminium phosphide poisoning by dihydroxyacetone: A two-case report study. *J Clin Pharm Ther.* 2020;00:1-5. <https://doi.org/10.1111/jcpt.13194>