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CLINICAL CASE

Irreversible vasoplegia in fatal amlodipine intoxication

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Abstract

Amlodipine poisoning can have serious repercussions since it causes great hemodynamic compromise, and there are no specific antidotes available, with supportive management being the therapeutic pillar. The objective of this study was to describe the clinical characteristics, evolution, and therapeutics used in an adolescents with severe amlodipine poisoning and multiple organ failure.

Keywords: *Amlodipine. Intoxication. Vasoplegia. Cardiogenic shock.*

Introduction

Drug poisoning is a major cause of admission to pediatric emergency departments. It is estimated that about 5% will require intensive care due to some organ failure, which translates into increased morbidity and mortality[1]. It is important for first-contact physicians to recognize potentially lethal medications in pediatrics, including those with minimal doses, such as digoxin, beta-blockers, sulfonylureas, tricyclic antidepressants, and calcium channel blockers (CCBs). The latter occupy the sixth position among the most lethal drugs according to data from the National Poisoning Data System of the United States, since they are drugs prescribed in frequent conditions such as high blood pressure or heart failure[1,2]. The incidence of CCB poisoning is not exact, but it is estimated to be a growing problem, as shown in the report of the Danish Toxicology Information Centre, which showed a 20% increase over a 6-year period (2009-2014). In the United States, in 2020, 6132 cases of IBCC were reported, of which 1159 (18.9%) were in children under 5 years of age; in this group, 1.6% of them developed severe symptoms and 0.47% died[2-4].

Primarily, SCIB causes vasoplegic, cardiogenic, or mixed shock that rapidly progresses to hemodynamic failure. Management represents a challenge since there is no antidote, and specifically in the case of amlodipine (AI), its half-life and elimination are prolonged, which can lead to a poor therapeutic response[5,6]. Even though IBCC is an increasingly common problem, there are controversies in its management, and evidence is limited. The following is a case of AI poisoning that required management in the pediatric intensive care unit.

Case report

A 12-year-old female was previously healthy. 48 h before her arrival at the emergency room, she ingested 10 tablets of 10 mg of AI (1.4 mL/kg of weight) in a self-injurious manner after a family argument and without receiving medical attention. A day later, he began

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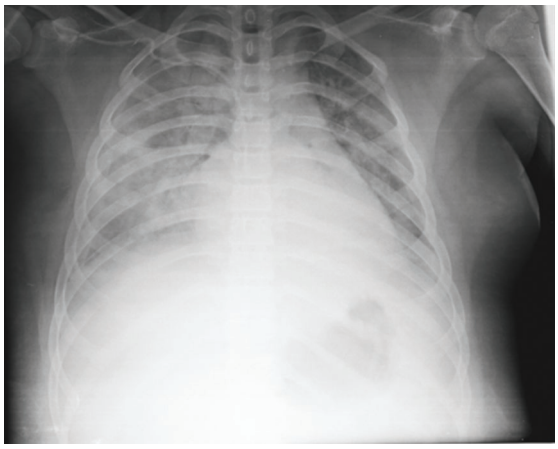


Figure 1. Chest X-ray showing bilateral alveolar infiltrates.

vomiting gastric contents on 20 occasions, unquantified fever, holocranial headache, and generalized abdominal pain. She was treated at a Community Hospital for severe respiratory distress, oxygen saturation of < 75%, and hypotension, where she was intubated and administered norepinephrine. After this, she was transferred to our hospital.

Evolution

On arrival, she was under sedation-analgesia and orointubated, presenting data of vasoplegic shock such as immediate capillary filling, bulging pulses, sinus tachycardia of up to 160 beats/min, and arterial hypotension. Ultrasound was performed at the cardiac and pulmonary point of care, which revealed a high cardiac output of 7 L/min and preserved biventricular function, dilated vena cava with a compliance index of 8%, as well as bilateral pulmonary B pattern. Your laboratory tests are summarized in table 1. Chest X-ray suggested pulmonary edema (Fig. 1) and elevated procalcitonin, so empirical antibiotics with ceftriaxone were initiated, in addition to balanced solutions at 1200 mL/m^2/body surface area and calcium gluconate 1 g every 4 h. He remained stable for 4 h and subsequently presented worsening of the hemodynamic status with greater tachycardia and without being able to achieve mean arterial pressure figures above the 5th percentile. Doses of norepinephrine up to 3 μg/kg/min, and adrenaline at 3 mcg/kg/min were used; on reaching a dose of 0.5 mcg/kg/min of norepinephrine, management with hydrocortisone 100 mg/m^{2}SC/day, vasopressin with a maximum dose of 0.001 units/kg/min, hyperinsulinemia-euglycemia therapy with infusion of rapid-acting insulin up to a maximum dose of 10 international units/kg/h, methylene blue with a loading dose of 2 mg/kg and then infusion at 0.5 mg/kg/h was initiated.

Table 1. Laboratory tests during the stay

Laboratory parameter	Reference values	Income	12 h
Hemoglobin	12.20-18.18 g/dL	10.9	10.40
Hematocrit	36-52%	33.5	31.5
Platelets	142,000-424,000 μL	371,000	338,000
Leukocytes	4,500-11,000 μL	17,600	19,000
Lymphocytes	600-3,400 mm^3	1,500	1,520
Neutrophils	2,000-6,900 mm^3	14,900	14,760
Glucose	20-60 mg/dL	138	121
Urea Nitrogen	4-19 mg/dL	16.0	28.0
Urea	16.60-48.50 mg/dL	34.2	59.9
Creatinine	0.70-1.20 mg/dL	0.7	1.6
Uric acid	3.40-7 mg/dL	5.9	8.6
Sodium	136-144 mmol/L	137	146
Potassium	3.60-5.10 mmol/L	3.8	3.1
Chlorine	101-111 mmol/L	108	110
Calcio	7.60-10.40 mmol/L	8.4	10.8
Phosphorus	2.50-4.50 mg/dL	4.5	1.8
Magnesium	1.70-2.30 mg/dL	2.0	1.7
Procalcitonin	< 0.5 ng/mL	1.870	
pH	7.35-7.45 mmHg	7.36	7.26
pCO_2	3-200 mmHg	35	24
pO_2	83-108 mmHg	60	64
Lactate	0.5-2.2 mmol/L	1.1	5.8
SaO_2	65-75%	88.3	90.9
Base	± 2.5 mmol/L	–5.6	–16
Bicarbonato	21-28 mEq/L	19.8	10.6

Outcome

The patient persists with sinus tachycardia of up to 180 beats/min, and it was never possible to reach perfusive blood pressure figures. He had a fever of 41°C continuously without being able to subside. It persists with irreversible shock, with the addition of refractory metabolic acidosis and hyperlactatemia. He presented ventricular tachycardia without a pulse, for which

cardiopulmonary resuscitation maneuvers were granted without obtaining return of spontaneous circulation, with a fatal outcome 20 h after admission.

Discussion

AI is a selective blocker of vascular smooth muscle calcium channels that causes peripheral vasodilation and is used in cardiovascular diseases. In Mexico, 10 and 5 mg tablets are marketed. IBCC is usually accidental in young children and intentional in adolescents. Any dose in pediatrics is considered toxic and in adults > 0.2 mg/kg. The lethal dose is not established, but deaths have been reported with doses > 100 mg; in this case, the dose was higher than this, which, together with the delay in interventions such as gastric decontamination, monitoring, and timely referral, favored a fatal outcome. Risk factors that can increase toxicity have been described, such as previous heart disease or chronic kidney disease, factors that the patient did not present[7,8].

AI leads to vasoplegia with catecholamine-refractory shock; in addition, pharmacological selectivity is lost with affection to cardiomyocyte contractility, leading to heart failure and arrhythmias. The shock phenotype in the patient was hyperdynamic due to vasoplegia corroborated by elevated cardiac output. Refractory hyperthermia was striking, a symptom that is little described in AI and could be related to the stress response[8-10].

AI has a half-life of 50 h, a plasma concentration of up to 12 h, a volume of distribution of 21 L/kg and is eliminated by the kidneys. These characteristics confer importance and should force us to maintain vigilance with monitoring for at least 12-24 h before the intake of this medication. Another important characteristic is that it binds to 99% plasma proteins, which explains the ineffectiveness of hemodialysis and hemoperfusion, although extracorporeal dialysis with albumin could be considered when there is a failure in conventional symptomatic management, which remains controversial[11].

The recommendations for the management of severe AI in children are derived from the consensus of experts in adults, since no difference in clinical expression has been seen according to age group; it is worth mentioning that most of the evidence is limited to case series. The management is supportive since there is no specific antidote. It is important to maintain ionic and acid-base balance. It has been described that water therapy can be deleterious in the initial management of these patients since precapillary vasodilation causes non-cardiogenic pulmonary edema, as was the case where ultrasound pulmonary B pattern and alveolar infiltrate were seen, in which volume response tests were negative, which tells us about the importance of integrating ultrasound to the point of care in toxicology[11,12].

Calcium administration and hyperinsulinemia-euglycemia therapy are the most documented interventions, although it is not clear when to start them; we use them in unison with vasoactive amines. The administration of calcium is essential since it competes with BCCs by restoring contractility; it has not been established whether the effectiveness in bolus or infusion is greater. On the other hand, hyperinsulinemia-euglycemia therapy is justified since it favors inotropism and lusitropism favoring intracellular calcium metabolism, in addition to improving glucose uptake, a mechanism that is altered in AI. It has been seen that delay in this therapy leads to worse results. The time or dose is not established, but blood glucose should be maintained in the range of 100-150 mg/dL. We had not used such a high dose of rapid-acting insulin infusion as in case 1; It is noteworthy that there was no hypoglycemia[11-13].

Nor has it been possible to establish superiority of one vasopressor over another, emphasizing the individualization of the case according to the hemodynamic pattern. We followed the guidelines for the management of amine-refractory shock and assessed the use of lusotropic or inodilator according to the findings of the echocardiogram. In both cases, supratherapeutic doses of amines were used, which *per se* increases mortality. When there is refractoriness to amines, the use of adjuvants such as lipid emulsion or methylene blue should be considered. The latter has shown efficacy in septic shock or post-cardiac surgery, with successful case reports in AI, since it inhibits the production of nitric oxide, which plays a fundamental role in the pathophysiology of AI. However, it is a drug that is difficult to access in our environment. There are other measures for the treatment of vasoplegia, such as the administration of hydroxycobalamin and angiotensin II, which have not been approved in pediatrics[14].

An alternative to treatment failure is extracorporeal membrane oxygenation (ECMO). Finn et al. in a recent meta-analysis, found a good survival rate in AI with ECMO. In the consensus on resuscitation in severely intoxicated patients in 2023, veno-arterial ECMO is proposed in poisoning with cardiogenic shock or arrhythmias[15]. Finally, the behavior of procalcitonin levels has not been described in AI, unlike other poisonings such as paracetamol or organophosphates, where their elevation has been related to the degree of severity, so it

would be worthwhile to analyze their efficacy as a clinical marker of severity and/or prognosis in subsequent studies[16].

Conclusions

AI leads to cardiovascular collapse quickly and progressively. Early interventions have been shown to change the prognosis. The dose ingested was very high, and she developed irreversible vasoplegia. The use of ECMO should be considered in this type of case with shock secondary to poisoning that does not respond to usual management. Unfortunately, it is still a very limited resource in our region. It is necessary to continue increasing the evidence of this type of case to better establish the clinical profile and therapeutic response in children.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent of the patient's parents, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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