CASE REPORT

Cardiac Arrest Post Voluntary Intoxication with Propafenone

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Abstract

We report the clinical case of a 17-year-old girl, observed in the emergency room 1.5 hours after voluntary ingestion of 6 g of propafenone and 1.5 g of ibuprofen. On arrival, she was conscious and without arrhythmias noted in the electrocardiogram. Gastric lavage was performed and activated charcoal administered. Fifteen minutes later, a convulsive episode was followed by sudden asystole, from which she recovered after four minutes of advanced life support. Subsequently, she had two episodes of asystole. She was then placed on inotropic support, but due to persistent haemodynamically significant bradycardia she required a transvenous temporary pacemaker. She was then admitted to pediatric intensive care unit, where for 72 hours post admission she remained haemodynamically unstable pacemaker-dependent. She was discharged after eight days, fully recovered and without neurological deficits. The favourable outcome was due to fast institution of cardiorespiratory resuscitation measures as well as inotrope support and transvenous temporary cardiac pacing.

Keywords: Adolescent; Anti-Arrhythmia Agents/poisoning; Drug Overdose/complications; Heart Arrest/chemically induced; Propafenone/poisoning; Suicide, Attempted

Introduction

Propafenone is a class 1C lipophilic antiarrhythmic drug that has β-adrenergic and calcium channel blocking activity. It is used in the treatment of supraventricular tachycardia and ventricular arrhythmias.[1-3] Intoxication is rare and is associated with cardiac / ventricular failure with possible QRS extension, atrioventricular blockage and cardiorespiratory arrest.[1,3-6] It is also associated with non-cardiac symptoms such as metabolic acidosis, alteration of state of consciousness, seizures and coma.[1,3,5,6] There is no specific antidote or effective method for removing propafenone from the blood, so the treatment used is supportive, namely with cardiopulmonary resuscitation measures.[3,5] Doses above 4 g can be fatal.[1,7]

The divulgation of this case is important as it highlights the role of rapid implementation of cardiovascular support and implantation of a temporary pacemaker in a favorable prognosis for propafenone intoxication. The combination of drugs that interfere with the metabolization of propafenone may prolong its toxicity. As far as we know, voluntary ingestion of propafenone and ibuprofen has not yet been reported in the literature in pediatric age.

Case Report

We present the clinical case of a 17-year-old adolescent female, pediatric psychiatric outpatient, after a previous voluntary intoxication with paracetamol and psychotic crises in the previous two years. She was admitted to the emergency department of a level II hospital, brought by emergency resuscitation and support vehicle about 1.5 hours after voluntary ingestion of 6 g of propafenone and 1.5 g of ibuprofen (medication of a member of the family household).

On admission to the emergency service, she was conscious and oriented, hemodynamically stable (blood pressure 130/90 mmHg, heart rate 108 bpm), electrocardiogram with sinus rhythm. Normal capillary glycaemia (130 mg/dL) and remaining objective examination with no alterations. A few minutes later, there was a sudden onset of sinus bradycardia (heart rate 62 bpm), without hemodynamic repercussion or altered state of consciousness. Gastric lavage was performed, with no sign of the tablets, and activated charcoal (50 g) was administered. About 15 minutes later, she had a short duration tonic-clonic seizure, with extreme bradycardia (heart rate 20 bpm) followed by cardiorespiratory

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arrest. Advanced life support was started with return of spontaneous circulation after four minutes (atropine and adrenaline were administered), and she was intubated and ventilated. Due to decompensated shock (blood pressure 48/23 mmHg) and severe metabolic acidosis partially compensated - pH 7.2, partial pressure of carbon dioxide (pCO_2) 15.6 mmHg, bicarbonate (HCO3) 11 mmol/L, lactate 6.7 mmol/L, base excess -11 -, cardiovascular support was initiated with noradrenaline (0.1 µg/kg/min) and sodium bicarbonate. About 30 minutes after imposition of these measures, there were two new episodes of cardiorespiratory arrest (asystole) with return of spontaneous circulation after two minutes of cardiovascular resuscitation. Nevertheless, bradycardia was maintained (heart rate ~50 bpm; QT interval 526 ms) (Fig. 1) with hemodynamic repercussion (blood pressure 45/33 mmHg), non-responsive to atropine, so noradrenaline perfusion was replaced by dopamine and it was decided to insert a transvenous temporary pacemaker, procedure that takes place in the radiology department by the team of adult intensivists in collaboration with the pediatric and cardiology emergency team through the catheterization of the femoral vein with fluoroscopic support - VVI pacing mode (ventricular pacing and sensing), heart rate 60 bpm. Since this, hemodynamically stable with no further cardiorespiratory arrest. Focal convulsions ceased with midazolam.

She was subsequently transferred by pediatric interhospital transportation to a pediatric intensive care unit with cardiovascular support - dopamine (10 µg/kg/min) and adrenaline (0.15-0.3 µg/kg/min), and sodium bicarbonate infusion (1 mEq/kg/h).

On admission to the pediatric intensive care unit, despite the pacemaker controlling cardiac rhythm, poor peripheral perfusion continued, Glasgow coma scale was 3 (without sedation) and brief, self-limited seizures, were seen on the amplitude-integrated electroencephalogram (aEEG). The transthoracic

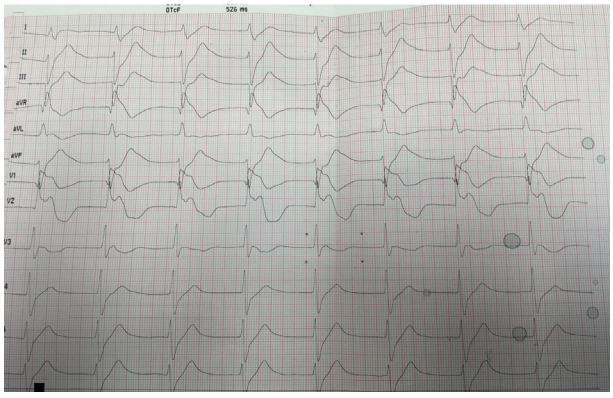

Figure 1. Junctional rhythm, heart rate ~ 50/min, QRS complex widening, diffuse changes in ventricular repolarization, negative T waves in right precordial leads.

echocardiogram showed severe systolic and diastolic dysfunction (cardiac index 1.1 L/min/m^2). Blood analysis showed blood count with no changes and negative inflammatory parameters, hepatic cytolysis enzymes and renal function were normal. There were high cardiac dysfunction markers: N-terminal prohormone of brain natriuretic peptide (NT-proBNP) 1030 pg/mL, troponin I 0.753 ng/mL, compatible with the alterations in electrocardiogram which showed signs of cardiac ischemia (negative T waves in all precordial leads). The toxin scan of blood and urine was negative. Propafenone blood dosing was not available.

In the first 72 hours of hospitalization, she maintained hemodynamic instability, with cardiac activity pacemaker dependent, cardiovascular support by infusion of adrenaline (up to 0.6 µg/kg/min) and dopamine (up to 7.5 µg/kg/min) and invasive mechanical ventilation. It was initiated phenytoin, phenobarbital and midazolam infusion at admission for the convulsive episodes (tonic-clonic seizures), without new episodes. The control electroencephalogram showed no critical activity, so on day three antiepileptic drugs were gradually removed without new seizures. Neuroprotection measures were maintained throughout hospitalization, particularly with temperature control equipment – Criticool® at 35ºC from days one to four of hospitalization. Monitoring with near infrared spectroscopy (NIRS) system was always normal (~60%-70%).

Subsequently, gradual clinical improvement was observed, with greater hemodynamic stability, progressive improvement of contractile function and recovery of consciousness. On the fourth day of hospitalization she was extubated, cardiovascular support was suspended and, as sinus rhythm was maintained so the temporary pacemaker was removed without intercurrences. On the sixth day the echocardiogram showed normal systolic and diastolic functions (cardiac index 3.5 L/min/m^2) and the electrocardiogram was normal (QT interval 410 ms), with no signs of cardiac ischemia.

It should be noted that acute renal injury (creatinine 129 µmol/L and urea 9.30 mmol/L, glomerular filtration rate 42.45 mL/min/1.73 m^2) was found on day one, with progressive improvement and normalization by the fourth day (creatinine 62 µmol/L, glomerular filtration rate 88.5 mL/min/1.73 m^2). There was also transient elevation of alanine aminotransferase (ALT), which was highest on day one (167 U/L).

During hospitalization she was observed by a pediatric psychiatrist. She was transferred on the eighth day, asymptomatic and without neurological deficits, to the pediatric psychiatric service. She currently has regular follow-up as a pediatric psychiatric outpatient.

Discussion

Propafenone is an antiarrhythmic agent widely used in adults and as such this drug is easily available to children and young people.[1,2,7] Intoxications are rare, with few cases described at pediatric age.[1,2] Overdose is mainly associated with changes of cardiac conduction and function and subsequent cardiogenic shock, but also with other symptoms, namely depression of consciousness, seizures and coma, although it is not fully understood whether by direct effect or cerebral hypoperfusion.[1-4,6,8-10] Toxic effects can be fatal, especially at doses higher than 4-6 g, and are due to severe myocardial depression, ventricular dysrhythmias and refractory seizures.[1,2 4,10]

There is no effective antidote or method of serum removal of propafenone, with treatment consisting of supportive measures, for which there are, however, no defined protocols.[3,4] Thus, early diagnosis is essential to implement measures to reduce intestinal absorption, such as gastric lavage, administration of activated charcoal and intravenous hydration.[3,8,11,12] However, these measures are often not sufficient.

Propafenone causes both cardiac depression and decreased peripheral resistance, so it is usually necessary to administer inotropic drugs and vasoconstrictors.[4,5,9] Indeed, in this case was given primacy to dopamine for vascular support due to its strongest inotropic and positive chronotropic effect in the heart as well as being a vasoconstrictor, in high doses, as well as adrenaline. Noradrenaline instead is a more evident vasoconstrictor. In the case described, the effect of propafenone was so marked that, despite cardiovascular support with dopamine and adrenaline and adjuvant therapy with mechanical ventilation and sodium bicarbonate, it was necessary to insert a temporary pacemaker to maintain cardiac electrical activity, a treatment recommended when there is a lack of response to others.[4] The pacemaker was programmed in VVI pacing mode, with a frequency of 60/min. In VVI pacing mode, the ventricle is the chamber stimulated and also the place where the generator captures or senses the electrical activity that inhibits it, in this case a ventricular heart rate above 60/min. The lack of response to atropine probably derives from the presence of junctional rhythm. Although in our case this measure was adequate, the survival rate in patients with propafenone intoxication requiring cardiovascular support is low, as even a pacemaker may prove ineffective in the case of severe electrical and mechanical cardiac depression.[3-5,8,9] In this situation, the placement of an intra-aortic balloon pump should be considered to maintain circulation support, as well as extracorporeal membrane oxigenation.[9,13] There are few reported cases in the literature of intoxications greater than 4-6 g, above which dose fatal cases are described and reports of survival at pediatric age are scarce.[1,4,7,8] Similar cases to ours are described, in which pacemaker support was required in pediatric age, also with good results.[1,8]

For adjuvant therapies that inhibit or reduce the effects of propafenone, sodium bicarbonate, as an adjunct to cardiovascular support, appears to be the most effective, with reports of cardiac stabilization and recovery from arrhythmia.[1,2,9,10,12] Sodium bicarbonate seems to be beneficial by reducing metabolic acidosis and due to its effect on sodium channels.[1,2,9-11]

Other therapeutic alternatives, such as lipid infusion or the use of calcium gluconate, glucagon and insulin have been described successfully in isolated cases; however, there is insufficient data to establish an actuation protocol.[3,4,6,10-12,14,15]

Lipid infusion in persistent shock has been consistently proposed, probably because it is a lipophilic drug. However, the administration period and dosage are not fully established, and the adverse effects described, such as pancreatitis, respiratory distress by fat embolism and coagulopathy, limit its use, which is why it is used only in the absence of response to other therapies.[4,10-12,14,15]

Insulin is successfully used in beta blocker and calcium channel blocker intoxications, promoting the release of catecholamines and increasing the uptake of calcium by the cells, with a consequent positive inotropic effect. For this reason, it has been proposed in the treatment of propafenone intoxications.[3] in a case of recovery of cardiac activity with insulin without sequelae in an adolescent with propafenone intoxication.[3-5,10-12,14,15] However, its effectiveness has not been adequately proven.[3-5,10-12,14,15]

It is estimated that propafenone is absorbed rapidly and greedily (approximately 100%), its half-life ranges from 2-12 hours, with serum peak 2-3 hours after ingestion.[2,6,8,16] Cardiac effects start after 30-120 minutes, as occurred in our case.[8,16]

Propafenone is metabolized by the enzyme complex encoded by the gene *CYP2D6* in the liver, and the mean time to elimination of propafenone varies depending on whether the patient is a slow or rapid metabolizer.6 The mean elimination time of propafenone ranges from 17 ± 8 hours for slow metabolizers, to 5 ± 2 for rapid metabolizers.[6] Slow metabolizers are more susceptible to therapeutic and toxic effects.[9,16] So implicitly, earlier clinical improvement was expected, as described in the literature, around the second day after ingestion.[1,4,8,9] We believe that the late recovery in our case may due to

the fact that the patient was a slow metabolizer, as well as the fact that the acute renal injury may have caused a delay in its clearance. The activity of *CYP2D6* can also be modified by the presence of other drugs, and it may be inhibited or stimulated and consequently the elimination time of propafenone may be extended or reduced, as well as competition may occur with different drugs, thus increasing its half-life in a similar way.[17] Ibuprofen is primarily metabolized by *CYP2C8*; however, when in high serum concentrations, as in our case, it may be metabolized by the same enzyme complex.[18] Thus, simultaneous overdose with ibuprofen, though innocuous on its own, may have caused competition of both drugs for *CYP2D6* and consequently caused an increase in the nefarious effect of propafenone.[19] Ischemic hepatitis, a standard secondary liver injury, defined by levels of ALT ≥ 100 IU/L, may be induced by hemodynamic instability or arterial hypoxia. As in the literature, it occurred within 24 hours after the insult.[20] The acute renal injury was also explained as secondary to renal hypoperfusion.[21]

In summary, the main clinical and laboratorial findings in our case were bradycardia, seizures, shock and metabolic acidosis. The rapid and early treatment with gastric lavage, resuscitation and cardiovascular support, including the implantation of a temporary pacemaker, mechanical ventilation and administration of alkalinizing solutions were essential for the favorable clinical evolution of this case. The authors highlight the collaboration of several medical specialties, in a level II hospital, in the emergent approach to a critical patient.

WHAT THIS CASE REPORT ADDS

- Cardiovascular drugs, as propafenone, are widely used in adults, so are easily available to children and young people and should be considered in voluntary intoxications.
- The main clinical and laboratorial findings in propafenone intoxications are changes of cardiac conduction and function and subsequent cardiogenic shock, as well as depression of consciousness, seizures and coma.
- The rapid and early treatment with gastric lavage, resuscitation and cardiovascular support, including the implantation of a temporary pacemaker, mechanical ventilation and administration of alkalinizing solutions are important in clinical prognosis.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Paragem Cardíaca Consequente a Intoxicação Voluntária com Propafenona

Resumo:
Reportamos o caso de uma adolescente de 17 anos, acompanhada em consulta de pedopsiquiatria. Transportada à urgência pela VMER, 1,5 horas após ingestão voluntária de 6g de propafenona e 1,5g de ibuprofeno. À chegada Escala de Coma de Glasgow (ECG) 15, hemodinamicamente estável, sem arritmias no eletrocardiograma. Feita lavagem gástrica e administrado carvão ativado. Cerca de 15 minutos depois, episódio convulsivo rápido seguido de paragem cardiorrespiratória (PCR), revertida após 4 minutos de suporte avançado de vida (SAV). Posteriormente, 2 episódios de assistolia. Iniciou suporte cardiovascular e bicarbonato. No entanto, bradicardia persistente com repercussão hemodinâmica, sendo colocado pacemaker provisório transvenoso com apoio fluroscópico e transferida para uma Unidade de Cuidados Intensivos Pediátricos. Nas primeiras 72 horas manteve instabilidade hemodinâmica e ritmo cardíaco dependente de pacemaker. Alta em D8, assintomática, sem défices neurológicos.
A boa evolução clínica deveu-se à rápida instituição de reanimação cardiorrespiratória, incluindo suporte cardiovascular, bicarbonato e pacemaker provisório.

Palavras-Chave: Adolescente; Antiarrítmicos/envenenamento; Paragem Cardíaca/induzida quimicamente; Overdose de Medicamentos/complicações; Propafenona/envenenamento; Tentativa de Suicídio