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# Syndrome due to propofol infusion in an adolescent

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**Abstract:** The case report of an 18 years adolescent with history of apparent health is described. He was assisted in the emergency service of Roberto Rodríguez Fernández Teaching General Hospital from Morón, Ciego de Ávila, with suggestive symptoms of acute appendicitis, reason why he was surgically intervened. Once finished the procedure he had a cardiac arrest, which was interpreted as a syndrome due to propofol. It was decided to referred him to the Intensive Cares Unit, where he had a favorable clinical course, with improvement of all parameters. Six days later he was transferred to the Intermediate Cares Unit and later on he was discharged from the hospital institution without complications.

**Key words:** adolescent; operation; propofol; syndrome due to propofol; general anesthesia; sedation

## 1 Introduction

Propofol (2,6-diisopropylphenol) is a hypnotic-sedative drug commonly used to induce general anesthesia and sedation in intensive care units. Propofol infusion syndrome (PIS) is a rare but potentially fatal complication. Although there is no widely accepted definition, the clinical presentation generally consists of metabolic acidosis with an increased anion gap that cannot be explained by any other cause, in addition to cardiac arrhythmias (especially Brugada-type), rapidly progressive heart failure, rhabdomyolysis, hyperkalemia, and a history of prolonged infusion of the drug [1].

The first cases were described in children in the early 1990s and later in adults [1]. As a result, the U.S. Food and Drug Administration (FDA) issued a warning against the use of propofol in continuous infusions, and in 2006 recommended a maximum dose of 4 mg/kg/h [2]. In turn, the European Medicines Agency recommended monitoring for clinical manifestations suggestive of this syndrome in patients receiving prolonged infusions [3].

Although this condition is always related to the dose and duration of the infusion, we are sharing with the medical community the case of a patient with a typical clinical presentation in whom propofol was administered via bolus injections.

## 2 Clinical case

We present the clinical case of an 18-year-old patient with no prior medical history who was admitted to the emergency department of the Roberto Rodríguez Fernández General Teaching Hospital in Morón, Ciego de Ávila province, with symptoms suggestive of acute appendicitis, which was confirmed, and an appendectomy was performed. General anesthesia was administered, with induction using propofol (2 doses) and midazolam; relaxation with succinylcholine; maintenance with sevoflurane, midazolam (3 doses), and fentanyl (3 doses); and relaxation with vecuronium (1 dose), all

calculated based on the patient's weight, for an approximate operative time of 45 minutes.

Once the surgical procedure was completed, the adolescent developed a decreased heart rate, which did not improve with the administration of atropine, and went into asystolic cardiac arrest. Resuscitation was performed until he regained a normal rhythm, but the same event recurred on two further occasions, prompting a request for evaluation by the intensivists.

The patient was bradycardic and experiencing hemodynamic deterioration, so he was placed on an inotropic agent (dobutamine 10 mcg/kg/min); he also presented with oxygenation abnormalities, as his pulse oximetry saturation was 80%, with an asystole-controlled mode and an inspired oxygen fraction ($FiO_2$) of 0.6.

It was decided to transfer him to the Intensive Care Unit, where a series of additional tests were performed, namely:

- Hematocrit: 0.46/L
- Blood glucose: 6.6 mmol/L
- Creatinine: 83.9 µmol/L
- Remaining blood chemistry tests: normal
- Blood gases:
- pH: 7.18 (mixed acidosis)
- Partial pressure of oxygen ($pO_2$): 76.3 mmHg
- Partial pressure of $CO_2$: 48.7 mmHg
- Bicarbonate ($HCO_3$) : 18.9 mmol/L
- Negative base excess: -7.3 mmol/L
- Anion gap: 19 mEq/L
- Lactate: 3.1 mmol/L
- Kirby index ($pO_2$ /$FiO_2$): 127 mmHg
- Ionogram: Potassium (K): 5.8 mmol/L (mild hyperkalemia)
- Electrocardiogram: first-degree atrioventricular block; ST-segment depression in leads DII, DII, and aVF; V2–V6; negative T waves in leads DI, aVL, and V2–V4, attributable to hemodynamic compromise (Figure 1)

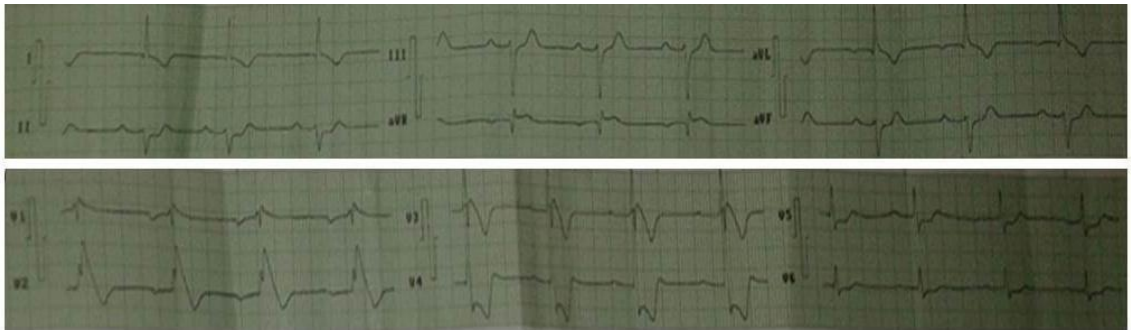

Figure 1. Electrocardiogram

- Echocardiogram: no acute abnormalities
- Anteroposterior chest X-ray: bilateral diffuse homogeneous opacities consistent with non-cardiogenic pulmonary edema (Figure 2).

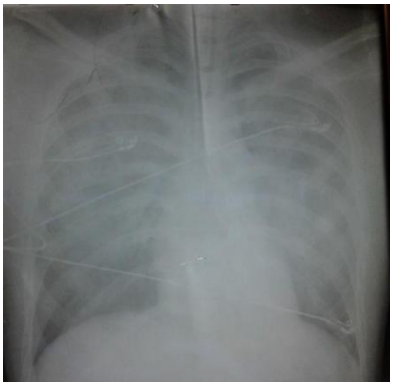

Figure 2. Anteroposterior chest X-ray. Note bilateral diffuse homogeneous opacities consistent with non-cardiogenic pulmonary edema

Based on all these findings, it was concluded that the patient was experiencing propofol syndrome, and the following treatment was indicated:

- Treatment for oxygenation impairment and pulmonary edema, initially involving an increase in $FIO_2$ and the use of alveolar recruitment maneuvers through adjustment of positive end-expiratory pressure (PEEP).
- Provide care for post-cardiac arrest syndrome.
- Maintain adequate hemodynamics with dobutamine, which normalized all electrocardiographic changes.
- Prophylactic antibiotic therapy, as used in patients with uncomplicated appendicitis.
- Organ and system-specific care.

The patient progressed favorably, with improvement in clinical, electrocardiographic, radiographic, and blood gas parameters. At 72 hours, he was weaned from the ventilator and remained on noninvasive ventilation for 48 hours. On the sixth day, he was transferred to the Intermediate Care Unit and subsequently discharged from the hospital without complications.

## 3 Comments

PIS is rare but extremely serious. It is characterized by shock and multiple organ dysfunction attributable to the infusion of the drug [4]. Its true incidence is unknown, as most data come from case reports, and there are no standardized criteria for its diagnosis. Some authors [5,6] reported an incidence of 10% in neurocritical care adults treated with propofol and 31% in those receiving doses higher than 6 mg/kg/h; whereas in a more recent prospective study, the incidence was much lower (1.1%), but the included patients had received lower doses [7,8].

Furthermore, mortality ranges from 30-80%, and key risk factors include: cumulative propofol dose, cardiac symptoms, hypotension, fever, metabolic acidosis, renal failure, advanced age, and traumatic brain injury [5,8,9].

In this adolescent, who had no history of disease that could be considered a risk factor for this complication, and in whom propofol was not administered via high-dose or prolonged infusion but rather as a bolus, and taking into account, in addition, the blood gas, electrocardiographic, and pulmonary abnormalities, the most likely diagnosis was PIS.

The pathophysiology of this syndrome is uncertain and likely multifactorial. The primary cause of cellular injury and death appears to be an imbalance between energy supply and demand. This anesthetic agent interferes with oxidative phosphorylation, thereby causing uncoupling of the mitochondrial respiratory chain and inhibiting the beta-oxidation of fatty acids by blocking the activity of type 1 carnitine palmitoyltransferase [7].

This results in a cellular energy deficit and promotes the accumulation of free fatty acids in various organs, which particularly affects skeletal and cardiac muscle cells, while causing cell lysis, the development of rhabdomyolysis, and

myocardial dysfunction, respectively [8].

Furthermore, rhabdomyolysis leads to the release of intracellular substances such as myoglobin, creatine phosphokinase (CPK), potassium, and lactic acid, which can cause or exacerbate renal failure. Meanwhile, propofol inhibits beta-adrenergic receptors and blocks cardiac calcium channels, thereby promoting the development of cardiovascular manifestations [9]. Cardiac arrhythmias are common, primarily bradycardia and electrocardiographic abnormalities similar to those observed in Brugada syndrome (ST-segment elevation in V1-V3) [10].

Other factors that may contribute to the development of PIS include decreased carbohydrate reserves and the stress associated with critical illness itself. Therefore, neurocritical care patients appear to be highly susceptible to developing lethal forms of PIS, which may be linked to high endogenous release and exogenous administration of catecholamines [5,10].

High doses of propofol (infusion rate and duration) constitute the main risk factor for PIS and increased mortality from this cause [5,8]. Consistent with the above, the authors recommend that the dose should not exceed 4 mg/kg/h for no more than 48 hours [7,8,9]; however, propofol-induced syndrome can develop following the administration of lower doses over shorter periods of time. Thus, a review of the literature revealed that this patient presented with the typical clinical picture of propofol-induced syndrome, as described above. Other possible risk factors include the presence of serious illnesses, particularly neurological conditions, the use of vasopressors or glucocorticoids, carbohydrate deficiency, and a history of heart disease [10]; similarly, underlying mitochondrial disorders represent an increased risk [9], which could not be confirmed in this patient.

There is no established specific treatment. The first step is to discontinue administration of the drug; hemodynamic support includes vasopressor therapy with catecholamines, which may require the use of an external pacemaker in cases of refractory bradyarrhythmias [10].

Regarding the latter, it is suggested that in the most severe cases, the use of milrinone, glucagon, or calcium should be considered, as well as extracorporeal membrane oxygenation. Similarly, renal replacement therapy is often required for renal injury and hyperkalemia; however, it is suggested that both hemodialysis and hemofiltration could be useful for removing propofol and its metabolites. It is recommended to maintain a carbohydrate infusion rate of 6-8 mg/kg/minute [9,10].

Propofol infusion syndrome is rare but potentially life-threatening. Although the risk increases with the infusion rate and duration of treatment, the clinical picture can develop with short infusions at doses lower than 4 mg/kg/h, which necessitates suspecting the presence of this syndrome even after propofol has been used as a bolus; Furthermore, all patients treated with propofol should be monitored for signs suggesting its onset (electrocardiogram, blood lactate, CPK, and triglyceride levels, among others).

## Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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