Propofol Infusion Syndrome in a refractory epileptic status case

Síndrome por Infusión de Propofol en un caso de estatus epiléptico refractario

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Abstract

Introduction: Propofol Infusion Syndrome (PRIS) is a rare but potentially lethal adverse reaction secondary to the continuous intravenous infusion of this drug. The diagnosis is based on the combination of metabolic acidosis, rhabdomyolysis, hyperkalemia, hepatomegaly, renal failure, hyperlipidemia, arrhythmias, and rapidly progressive heart failure. Objective: To report a case of PRIS and literature review. Clinical case: A 6-year-old female patient with history of epilepsy secondary to large malformation of cortical development of the right hemisphere. The patient presented a refractory status epilepticus that required admission to the Intensive Care Unit for life support and treatment, which included continuous intravenous infusion of propofol at 10 mg/kg/h. She developed hemodynamic instability, and after 24 h of treatment an increase of creatine phosphokinase (CPK) levels, metabolic acidosis and elevated lactacidemia were observed. After ruling out other causes, PRIS was diagnosed; therefore, the drug was suspended, achieving hemodynamic stabilization after 24 hours. Discussion: The diagnosis of PRIS is complex and should be considered in patients who are receiving this drug and present metabolic acidosis or heart failure. The factors that most influence mortality are the cumulative dose of the drug, the presence of fever, and cranial brain injury. In the case described, the patient received a dose higher than 4 mg/kg/h, which is the maximum recommended dose, and responded favorably 12 hours after stopping the drug.

Keywords:
Propofol; Infusion Syndrome; Sedatives; Hypnotics; Metabolic Acidosis Epileptic status
**Introduction**

Since its introduction in 1986, propofol has become one of the drugs frequently used in surgical procedures and sedation of critically ill patients. In cases of refractory epileptic status in adult and pediatric patients, it is used as a third-line drug by some experienced health centers.

Propofol Infusion Syndrome (PRIS) is a rare condition, often diagnosed by a discard process, with variable clinical manifestations, being metabolic acidosis the most frequent among them. The factors that most influence mortality are the cumulative dose of the drug, the presence of fever and craniocerebral trauma.

Due to the wide range of manifestations of the syndrome, it becomes very important to consider it within the differential diagnoses of patients with metabolic acidosis, since early diagnosis and intervention can prevent a fatal outcome.

In this context, the case of a 6-year-old patient with diagnosis of refractory epileptic status is discussed, who received sedation with propofol and developed lactic acidosis associated to the use of this drug.

**Clinical case**

6-Year-old female patient with history of cerebral cortical dysplasia with neuronal migration disorder and right hemisphere sulci malformation, secondary epilepsy, scoliosis, and mild-moderate intellectual disability, treated with valproic acid, levetiracetam, and clonazepam.

In September 2016, she presented an automatism crisis (blinking type), associated with periods of increased muscle tone of the upper limbs and disconnection from reality. After multiple consultations, she was admitted on October 13 and treated with midazolam and levetiracetam. The patient persisted with more than 30 crises per day and was transferred to a tertiary health care center with consciousness compromise, she was admitted in the Pediatric Intensive Care Unit (PICU) and treated with a dose of valproic acid and adjusted dose of levetiracetam.

After 24 hours, the electroencephalogram (EEG) showed a pattern of electrical status, therefore, it was added to the treatment midazolam, topiramate, and phenobarbital. The EEG control showed persistence of the electrical status pattern associated with consciousness compromise and areflexia, which led to the connection of the patient to mechanical ventilation, and the start of continuous intravenous infusion of midazolam and an increase in the phenobarbital dose (up to 80 mg/kg), without stopping electrical crises identified in a new EEG record. On October 16, the medical team decided to initiate intravenous infusion of propofol in progressive doses up to 10 mg/kg/h, which was maintained for 24 hours, reducing the frequency of electrical crises. Subsequently, a progressive dose reduction to 5 mg/kg/h was initiated, which triggered the re-initiation of the electrical activity with EEG status pattern.

On October 17, a simple brain CT scan was performed, which showed no evidence of cerebral edema or ischemic lesions and no new brain lesions. The next day, ketamine was added in continuous intravenous infusion at 2 mg/kg/h and continued propofol at 5 mg/kg/h, topiramate, and valproic acid.

After the beginning of propofol infusion, the patient presented hemodynamic compromise characterized by alteration of distal perfusion, tachycardia and arterial hypotension, which was interpreted as septic shock requiring support with two vasoactive drugs (iv adrenaline at 0.3 µg/kg/min and iv noradrenaline at 0.4 µg/kg/min) and first-line antibiotic treatment (cefotaxime + amikacin) and pan-cultures. In this context, it was decided to transfer the patient to Carlos Van Buren Hospital as a neurosurgical reference center for assessment and possible surgical resolution of her structural neurological pathology.

On admission to the PICU at this hospital, the patient was acutely ill, intubated, with hemodynamic compromise, tachycardia, hypotension, with poor distal perfusion, and green urine, supported by the aforementioned vasoactive drugs. Laboratory tests showed metabolic acidosis, increased lactacidemia, and elevated CPK and CPK-MB levels. A retrospective review of the clinical tests and findings described before the transfer showed that 24 hours after starting treatment with propofol, the patient presented, along with the hemodynamic compromise, an increase in total CPK up to 22,822 U/L associated with metabolic acidosis (pH 7.27 BE:-6.6) and elevated lactacidemia (44 mg/dL). Propofol infusion syndrome was proposed as diagnosis and the administration of the drug was suspended, achieving hemodynamic stabilization after 24 hours, normalizing heart rate, reaching adequate blood pressure values and improving the signs of distal perfusion (pulse and capillary filling). The control echocardiogram showed no pathological findings. After 48 hours, the support with vasoactive drugs was suspended, while antibiotic treatment was suspended after 72 hours with negative cultures, low CRP, and without leukocytosis, which made it possible to rule out the diagnosis of septic shock suggested in the hospital of origin.

A new EEG showed there was no electrical status pattern. A progressive decrease in lactic acid and CPK was achieved, registering a value of 5193 U/L on October 22. Table 1 shows the results of the laboratory tests and their progression in relation to propofol infusion.

On October 19, brain MRI showed multiple hy-
perintense lesions of the cerebellar white matter, subcortical ones, lesions of the corpus callosum and both internal capsules, with magnetic susceptibility artifact associated to multiple bilateral and supratentorial cortical-subcortical cerebellar microbleeding foci.

After the suspension of propofol, the anticonvulsant treatment was adjusted, increasing doses of valproic acid and topiramate, and re-initiating iv midazolam infusion progressively. The patient had a torpid evolution, and required immunomodulation therapy with methylprednisolone boluses, responding favorably on the fifth day with recovery of consciousness, achieving extubation on October 26 without difficulties.

Discussion

Propofol infusion syndrome (PRIS) is a rare and potentially lethal adverse reaction described by the use of this drug in continuous intravenous infusion in high doses. As a result of the widespread use of propofol, cases of metabolic acidosis without other identifiable causes have been reported. The first cases were documented in the pediatric population since 1990 and later in the adult population. In 1998, PRIS was recognized as a diagnostic entity by Bray RJ through a collection of cases within the pediatric population in intensive care units (ICU), which is where the greatest number of publications appear, however, there are cases described in other areas such as anesthesiology, such as the report of a clinical case of PRIS in an adult patient after an intraoperative high-dose propofol infusion for a short period of time.

Due to case reports in 2001 and mainly motivated by the collection of adult PRIS cases published in The Lancet by Cremer (10), the Food and Drug Administration (FDA) warns of the risks of long-term sedation (>48 h) with propofol. In 2006 the FDA again updated the label information and limited the maximum iv dose of propofol to 4 mg/kg/h.

There are currently no unified criteria for the diagnosis of this syndrome, which is based on the combination of metabolic acidosis, rhabdomyolysis, hyperkalemia, hepatomegaly, renal failure, hyperlipidemia, arrhythmias, and rapidly progressive heart failure. The occurrence of at least one of these signs in a patient who is receiving continuous high-dose propofol infusion should raise suspicion of this complication.

In the case described, propofol was used as a third line treatment for refractory status epilepticus which

<table>
<thead>
<tr>
<th>Laboratory exams</th>
<th>15/10/16</th>
<th>16/10/16</th>
<th>17/10/16</th>
<th>18/10/16</th>
<th>19/10/16</th>
<th>20/10/16</th>
<th>Units and normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.37</td>
<td>7.30</td>
<td>7.29</td>
<td>7.27</td>
<td>7.37</td>
<td>7.43</td>
<td>(7.35 – 7.45)</td>
</tr>
<tr>
<td>PCO₂/PO₂</td>
<td>40/131</td>
<td>37/113</td>
<td>39/122</td>
<td>37/158</td>
<td>40.9/107</td>
<td>37.1/87</td>
<td>(35-35 / 83-108)</td>
</tr>
<tr>
<td>HCO₃</td>
<td>23</td>
<td>21.3</td>
<td>19</td>
<td>18</td>
<td>19</td>
<td>21</td>
<td>mmol/L (20 – 24)</td>
</tr>
<tr>
<td>BE</td>
<td>-2.0</td>
<td>-3.5</td>
<td>-6.6</td>
<td>-6.4</td>
<td>-5.2</td>
<td>-2.0</td>
<td>mmol/L (-2.0 + 3.0)</td>
</tr>
<tr>
<td>Lactid acid</td>
<td>44</td>
<td>26.8</td>
<td>18</td>
<td>18</td>
<td>16.7</td>
<td>16.7</td>
<td>mg/dl (4.5 – 19.8)</td>
</tr>
<tr>
<td>Na/K</td>
<td>137/3.9</td>
<td>138/3.8</td>
<td>142/3.4</td>
<td>140/3.4</td>
<td>136/3.7</td>
<td>134/3</td>
<td>mmol/L (135 – 145 / 3.5 – 5.1)</td>
</tr>
<tr>
<td>Total CK</td>
<td>87</td>
<td>6974</td>
<td>22.822</td>
<td>15.678</td>
<td>229</td>
<td>224</td>
<td>U/L (29-168)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>289</td>
<td>247</td>
<td>224</td>
<td>224</td>
<td>150</td>
<td>150</td>
<td>mg/dl (&lt; 150)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.45</td>
<td>0.42</td>
<td>0.41</td>
<td>mg/dl (0.53 – 0.85)</td>
</tr>
<tr>
<td>Total bilirubin/Direct bilirubin</td>
<td>0.2/0.1</td>
<td>0.2/0.1</td>
<td>0.2/0.1</td>
<td>0.2/0.1</td>
<td>0.2/0.1</td>
<td>0.2/0.1</td>
<td>mg/dl (0.1 – 0.4)</td>
</tr>
<tr>
<td>GOT</td>
<td>23</td>
<td>18</td>
<td>22</td>
<td>309</td>
<td>505</td>
<td>651</td>
<td>U/L (5-34)</td>
</tr>
<tr>
<td>GPT</td>
<td>13</td>
<td>15</td>
<td>12</td>
<td>64</td>
<td>129</td>
<td>224</td>
<td>U/L (0-55)</td>
</tr>
<tr>
<td>FA</td>
<td>145</td>
<td>131</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>148</td>
<td>U/L (&lt; 500)</td>
</tr>
</tbody>
</table>

was difficult to manage. The choice of propofol or other anesthetics in these situations is not without controversy since the evidence is based primarily on case reports and small series, the therapeutic decision is usually made based on the experience of the medical team in charge. It is important to consider that in refractory status epilepticus, the doses of propofol reported to stop seizures tend to far exceed the recommended doses of 4 mg/kg/h in an average time limit of 48 hours. These two factors (dose and time) have been identified in the different publications as the main risk factors for developing adverse effects to propofol and PRIS. In the case of this patient, the electrical crisis was stopped only when 10 mg/kg/h of iv propofol was reached, a dose that was maintained for 24 hours after which it was reduced to 5 mg/kg/h in the following 36 hours.

In addition, other risk factors for the development of PRIS have been described, such as the presence of upper respiratory infection, traumatic brain injury, use of corticoids, catecholamine infusions, congenital errors of mitochondrial fatty-acid oxidation, among others. The presence of severe traumatic brain injury has been associated with an increased incidence of PRIS due to elevated levels of endogenous catecholamines and exogenous administration of these drugs. Patients with refractory status epilepticus are considered a population at risk due to the treatment required (propofol infusion at high doses and prolonged time) which, along with the presence of risk factors that all critical patients have in common (low carbohydrate reserve and high endogenous catecholamine discharge), makes them a group that requires special attention in the presence of any manifestation of PRIS.

Physiopathology

The physiopathological mechanisms described are multiple, among them the effect of the drug on the mitochondrial level and on lipid metabolism:

<table>
<thead>
<tr>
<th>1. Mitochondrial Effects</th>
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<tr>
<td>They are explained by the similarity between coenzyme Q and propofol. The latter interferes with the respiratory chain generate a decoupling in the formation of ATP, producing an imbalance between the supply and the energy demand.</td>
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<th>2. Effects on lipid metabolism:</th>
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<tr>
<td>The alteration of beta-oxidation is the main effect of propofol on lipid metabolism. This leads to an energy imbalance mainly in myocardial and skeletal muscle cells that are highly dependent on critical catecholamine-mediated lipolysis and beta-oxidation of free fatty acids (FFA). This explains why patients with PRIS have some degree of cardiac and skeletal muscle myocytolysis.</td>
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</tbody>
</table>

Associated with this, in critical patients as in the case presented above, lipolysis is increased by increased sympathetic outflow and high concentrations of cortisol, resulting in an additional increase in free fatty acids, that associated with the alteration on lipid metabolism, generates a higher accumulation of FFA, which has been shown to have arrhythmogenic properties.

In patients with critical illnesses, such as those with refractory status epilepticus, carbohydrate reserves are generally low or may even be depleted by high intake or insufficient supply. In the absence of carbohydrates, phosphorylated citrate levels fall and lipid metabolism slows down. Carbohydrate reserves deplete faster in children than in adults, which may explain the higher prevalence of PRIS in this population. If a propofol infusion is added to this, triglyceride accumulation will begin quickly.

Table 2 shows the clinical correlation of each physiopathological event.

Understanding the multiple physiopathological factors involved, it is not surprising that the clinical manifestations are variable what makes diagnosis even more difficult. In this case, the initial manifestation was metabolic acidosis and consequently heart failure determined by hemodynamic compromise. Among
the other manifestations described are hypertriglyceridemia, which in this patient rose to 320mg/L, hyperkalemia, and renal failure, among others. It is important to point out that within the cardiovascular manifestations of PRIS, there is a compromise of myocardial contractility due to beta receptor antagonism, a direct energy crisis due to the low mitochondrial ATP production. On an electrical level, in more severe cases, acute bradycardia, and refractory ventricular arrhythmias that may progress to asystole may occur. In this patient, it was not possible to evidence echocardiographic or electrocardiographic alteration during the administration of propofol since the medication was suspended on admission to Carlos Van Buren Hospital and these tests were not performed in the hospital of origin.

Patients with refractory epileptic seizures receive a large number of antiepileptic drugs for their management, making them susceptible to pharmacological interactions, which was in the case analyzed the association of valproic acid and propofol one of many to consider. A synergistic anticonvulsant effect between the two drugs is proposed partly because of their diverse action on gamma-aminobutyric acid (GABA) receptors and the inhibition of glutamate NMDA receptors of valproate. However, this phenomenon becomes more complex to explain in cases of refractory status epilepticus, since modifications of the GABA receptor have been described according to the subtype of unit that constitutes it. At the same time, it is possible to suggest that patients receiving valproic acid could achieve higher plasma doses of propofol than expected due to inhibition of cytochrome P450 2C9 and the enzymatic system UDP-Glucuronosyltransferase by valproate, leading to a decrease in propofol metabolism. In the literature there are no case reports of PRIS in which the simultaneous administration of propofol and valproic acid is analyzed, however, it seems to be something to be taken into account as a factor that could contribute to the generation of adverse effects and/or PRIS.

As for any other anesthetic used in refractory status epilepticus, it is recommended to administer the lowest effective dose of propofol, titrated according to the response of electroencephalographic monitoring (continuous or serial), in other words, increasing the dose of the drug until the desired effect is obtained or until adverse effects such as hypotension and/or cardiopulmonary depression are detected that lead to suspicion of the presence of PRIS, forcing the suspension or change of therapy as has been described in up to 6% of the cases described in the literature.

In relation to the imaging findings, there is a pediatric case of PRIS in which alterations were reported in the brain MRI, characterized by an extensive hyper-intensity in T2 of the supra and infratentorial white matter, with restriction of diffusion and complete regression in follow-up, with defects in the beta-oxidation of very long-chain fatty acids as a mechanism. This differs from what was found in our patient, since multiple infra and supratentorial bleeding foci was observed in the patient, which persist as small areas of magnetic susceptibility artifact, suggesting a hemosiderin deposition of residual nature. In the clinical context of severely ill patients hospitalized in ICU, similar findings have been reported, but of lesser extension in relation to the use of extracorporeal membrane oxygenation (ECMO), heat stroke, and, as in our case, in relation to refractory epileptic status, suggesting as physiopathology an alteration of the blood-brain barrier secondary to the crises themselves, inflammation or angiogenesis. Considering the clinical evolution of the patient in relation to PRIS, the larger extension of the bleeding foci in relation to what has been reported in literature, as well as the little recognition of microbleeds as a finding in post convulsive changes, makes it possible to propose the probable multifactorial origin of the alterations in our case.

There is no specific treatment for PRIS, it is recommended to establish a support therapy associated with the suspension of the drug as in this case. Regarding the physiopathological role of carbohydrates, it has been recommended to maintain an optimal intake of carbohydrates (6-8 mg/kg/min) in order to provide an adequate substrate for defective mitochondria and suppress lipid oxidation. Exceptionally, the use of plasmapheresis has been documented to be effective, however, there is no evidence to support its routine use, as the use of renal replacement therapy and ECMO has been recommended to maintain an optimal intake of carbohydrates (6-8 mg/kg/min) in order to provide an adequate substrate for defective mitochondria and suppress lipid oxidation.

On the other hand, it is important to mention that due to the national reality, patients with complex pathologies are often transferred to other services within the same health care center, and then to others of greater complexity, thus, the transfer of information on the use of drugs and doses used should be very rigorous in order to not delay the diagnosis of cases such as PRIS, in which suspicion and early management are key to avoiding outcomes that could be fatal.

**Conclusion**

The diagnosis of propofol infusion syndrome remains complex due to the severity of the patients who receive this drug. This clinical case illustrates the diversity of scenarios in which the syndrome may appear, with particular emphasis on patients with refractory status epilepticus, who due to the difficulty in their management require multiple drugs and among them...
may require propofol in doses that often exceed those recommended, which requires continuous monitoring and maintaining a high degree of suspicion of the appearance of symptoms and early signs of PRIS.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

References