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Case Report

CASE REPORT

Single dose of propofol causing propofol infusion syndrome in a newborn

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Abstract

Propofol infusion syndrome (PRIS) is a rare syndrome originally described in critically ill children undergoing long-term (> 48 h) propofol infusion at high doses (> 4 mg/kg/h). Severe metabolic acidosis, rhabdomyolysis, renal failure and fatal cardiac failure are the features. Herein, we present a case of a newborn who developed PRIS after a single bolus dose of propofol at 3.2 mg/kg/do, developing rhabdomyolysis and severe metabolic acidosis, with a successful outcome after medical therapy.

INTRODUCTION

Propofol related infusion syndrome (PRIS) is a rare syndrome originally described in critically ill children undergoing long-term (> 48 h) propofol infusion at high doses (> 4 mg/kg/h) and is defined as the occurrence of acute bradycardia resistant to treatment and progressing to asystole associated with propofol infusion [1, 2]. Severe metabolic acidosis, rhabdomyolysis, renal failure and fatal cardiac failure are other features [2]. It is not clear what the underlying pathophysiologic mechanism is, although the majority of observations point into the direction of interference with the energy production in the mitochondria [3].

Herein we present a case of PRIS described in a newborn who received significantly lower dose of propofol compared to those reported in the literature causing PRIS.

CASE REPORT

A 38.2 weeks gestation, a 3095 g female infant was born by vaginal delivery to a 19-year-old mother. Prenatal diagnosis of congenital cystic adenomatoid malformation was established at 27 weeks. The infant had Apgar scores of 8 and 9 at 1 and 5 min, respectively. On Day 7 of life, an angiotomography was performed confirming prenatal diagnosis of type 2 Congenital Cystic Adenomatoid Malformation (CCAM) of the left lung. She was transferred to the NICU for surgical intervention (left superior lung lobectomy), which was performed on Day 12 of life, finding multiple cysts on 3, 4 and 5 segment of the lung. No complications during the procedure were reported. Anesthetic intervention included 25 μg of fentanyl, 10 mg of propofol and 200 μg of vecuronium (total doses).

In the immediate postsurgical period, she presented mixed acidosis (pH 6.75 pCO_2 68 mmHg, HCO_3 11.3 mmol/L, BD 13.4), requiring high frequency oscillatory ventilation (HFOV), reaching up to 26 of paw and amplitude of 80 due to hypercarbia up to 107 mmHg. She also presented hemodynamic instability with sudden bradycardia and hypotension, for which atropine 0.01 mg/kg/do and normal saline as volume expander were administered. As hypotension was unresponsive to volume, dopamine was started at a 10 μg/kg/min rate. Hyperkalemia of 8.2 mmol/L was also seen, requiring polarized solution and calcium gluconate due to cardiac toxicity. The patient also showed hyperglycemia (303 mg/dL) for which insulin was started. Uric acid was elevated (6.5 mg/dL) as well as creatine phosphokinase enzyme (768.6 UI/L) and aldolase (24.8 UI/L). Urine dipstick

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testing showed a positive result for blood (inferring myoglobinuria) and pH of 5. Urine sediment was examined observing renal epithelial cells and the absence of red blood cells. Presumptive diagnosis of PRIS was established. Adequate state of hydration and intravenous bicarbonate was warranted to enhance uric acid excretion. After ~5 h, HFVO was weaned to pressure control ventilation and the patient was finally extubated 36 h later. She showed hemodynamic stability and no further electrolyte derangements were observed over the next few days. At follow up, she remains asymptomatic.

DISCUSSION

Since its description in 1990, PRIS has been reported at lower doses and shorter periods of administration, from 8.8 to 17.5 mg/kg/h for more than 44 h to 2.6 mg/kg/h for 52 h reported by Merz *et al.* recently in adults [4, 5]. In children, doses as low as 4.8 mg/kg/h have reported to cause PRIS [5]. To our knowledge, this is the first case of PRIS reported in a term newborn after a single bolus of propofol at a dose of 3 mg/kg.

Ghanta *et al.* [6] showed the efficacy and safety of propofol as an induction agent to facilitate neonatal endotracheal intubation with a low dose (2.5 mg/kg) and administered in a single bolus. In our patient there is no other explanation for rhabdomyolysis, bradycardia, hypotension and metabolic acidosis. Despite the fact that the slight elevation of creatine kinase (CK) could be attributed to surgery, other features of rhabdomyolysis present in our patient such as lactate dehydrogenase of 2150 UI/L, symptomatic hyperkalemia of 8.2 mmol/L, myoglobinuria and elevated uric acid can only be attributed to propofol-related bioenergetic failure in skeletal muscle cells [7–9]. Furthermore, there is not a recognizable risk factor for PRIS, as catecholamines were administered after appearance of PRIS. Krajcova *et al.* observed patterns in the relationship between time and dose of propofol infusion and reported signs of the syndrome; symptoms that could be caused by mitochondrial uncoupling occurred relatively early and after high doses of propofol. On the other hand, signs, which would be consistent with accumulation of nonesterified fatty acids, such as rhabdomyolysis of arrhythmias, occurred after protracted propofol infusions irrespective of doses [9].

Multiple studies indicate that propofol has an effect on the respiratory chain [1–3]. A decrease in mitochondrial transmembrane electrical potential was detected in liver mitochondria isolated from control rats incubated with propofol. The rate of oxygen consumption was increased suggesting that propofol acts as an uncoupler [3]. Kam *et al.* hypothesized that the inhibitory action of propofol is caused by inhibition of coenxyme Q [2, 10]. In humans, muscle cytochrome oxidase deficiency was demonstrated in a child who received prolonged high-dose propofol infusion without a genetic defect of cytochrome oxidase [2]. Vanlander *et al.* [3] reported a patient in which the existence of a previous defect in complex I can explain why he was most vulnerable to the administration of propofol. Krajcova *et al.* [9] demonstrated that 96 h of exposure of human skeletal muscle cells to concentrations of propofol found in plasma of propofol-sedated patients reduced the spare capacity of electron transfer chain and caused a profound inhibition of fatty acid oxidation. The analysis of acylcarnitines has become widely accepted as a helpful instrument to confirm the diagnosis of PRIS. Elevated levels of acylcarnitines indicate the impairment of mitochondrial fatty acid oxidation as the probable main cause of this syndrome [11]. Propofol also inhibits protein carnitine palmitoyl transferase I and uncouples the mitochondrial respiratory chain via high levels of C5-acylcarnitine, which has an effect on short chain and medium-chain fatty acids that freely diffuse into the mitochondria, but cannot be utilized [11].

Low carbohydrate supply is a risk factor for PRIS because energy demand is satisfied by lipolysis if carbohydrate supply is low [1, 10]. Children are more prone to the development of PRIS due to low glycogen storage and high dependence on fat metabolism. Fat overload associated with propofol infusion may also contribute to increased plasma fatty acids [1]. Propofol inhibits cardiac beta-adrenoreceptor binding and calcium channel protein function. It suppresses the activity of sympathetic nerves and the baroreceptor reflex, thus deteriorating cardiac failure in PRIS [11].

Large plasmatic increases of CK and myoglobinuria have been documented both in children and adults receiving propofol, and they have been interpreted as proof of a direct necrotizing effect of propofol on peripheral and cardiac muscles [2]. Histological studies showed signs of severe myocytolysis in the skeletal muscle and myocardium of affected patients [2]. Recently, Vollmer *et al.* reported a fatal case of PRIS, in which electron dense bodies found in association with mitochondria in muscle and liver cells probably correspond to accumulation of free fatty acid and provide direct morphological evidence for the mitochondrial damage in PRIS [12]. Furthermore, Sumi *et al.* concluded that propofol suppresses mitochondrial function, causes reactive oxygen species (ROS) generation and induces a metabolic switch from oxidative phosphorylation to glycolysis, by targeting mitochondrial complexes I, II and III *in vitro*. Also, data from their study indicated that predisposition to mitochondrial dysfunction, caused by genetic mutations or the pharmacological suppression of electron transport chain by biguanides promotes propofol-induced cell death and caspase activation; these mechanism constituting the molecular basis of PRIS [13].

In conclusion, in patients who present propofol infusion syndrome at low doses of propofol, a pre-existing defect in the respiratory chain could be present. Care should be taken in the administration of propofol in neonates with risk factors to present PRIS (SIRS, RDS, state of shock, steroid treatment), and an alternative agent for sedation should be considered.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

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ETHICAL APPROVAL

The study was approved by the Ethics Committee of National Institute of Perinatology, Mexico.

CONSENT

Authors confirm to have written patient consent to publish findings.

GUARANTOR

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