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Sepsis and Propofol Related Infusion Syndrome in a 19-Year-Old Male Patient

Sogunro O[1]*, Mikesell C[2] and Stausmire J[3]

[1]Department of Surgery, St. Vincent's Medical Center, Bridgeport, USA
[2]Department of Pediatric Intensivities, Mercy Health Children's Hospital, Toledo, USA
[3]Department of Nursing, Mercy Health St. Vincent Medical Center, Toledo, USA

Abstract

Propofol Related Infusion Syndrome (PRIS) involves cardiac failure, rhabdomyolysis, metabolic acidosis, and renal failure in critically ill patients receiving long-term propofol infusions at high doses. It carries a high mortality rate of up to 81%. We present a case of a young adult who developed PRIS and survived. A 19-year-old male involved in a motor vehicle collision was intubated and sedated with Propofol. On hospital day 7, the patient suddenly became hypotensive, tachycardic, hyperkalemic, had cardiac arrhythmias, and profound metabolic acidosis. PRIS was suspected and propofol discontinued. The patient was managed expectantly and ultimately discharged on hospital day 22. PRIS is a complex syndrome and requires prompt recognition of its key features including changes in cardiac rhythm, decreased blood pressure, increased oxygenation requirements and derangements in laboratory data. A high clinical suspicion of PRIS should most readily be recognized by the critical care team.

Keywords: Propofol; Intensive care unit; Complications; Trauma; Sedation

Introduction

Propofol is a potent hypnotic used as an induction agent for anesthesia, it is also used as an easily titratable sedative in intensive care units [1,2]. It was approved by the Food and Drug Administration (FDA) in 1989 and has many advantages including a rapid onset and short duration of action, anxiolytic, and anticonvulsant properties [3]. Propofol's mechanism of action is suspected to be through the stimulation of gamma-aminobutryic acid (GABA) receptors. Propofol Related Infusion Syndrome (PRIS) is a rare and complex syndrome. It presents with acute cardiac failure, rhabdomyolysis, metabolic acidosis, and renal failure in critically ill patients receiving long term propofol infusions (>48 hours) at high doses (>4 mg/kg/hour or 67 mcg/kg/min). The true incidence of PRIS has not been well-defined, various studies show an incidence anywhere from 1.1% to as high as 17 to 31%. A 2015 clinical update reported 37 adult cases of PRIS with only 7 survivors, for a mortality rate of 81% [2]. We present a case of a young adult with sepsis, orthopedic trauma and traumatic brain injury who demonstrated signs and symptoms of PRIS and survived. The patient's family reviewed the case and gave written informed consent for publication of this report.

Case Description

A 19-year-old male presented to the emergency department after a motor vehicle collision involving multiple victims. His Glasgow Coma Scale (GCS) upon arrival was 3, he was intubated and propofol was started for sedation at 30 micrograms/kilogram/minute (mcg/kg/min). He sustained a right femur fracture, multiple areas of intraparenchymal cerebral hemorrhage, and diffuse axonal injury (DAI). He was taken to the operating room for an intramedullary nail of the right femur and subsequently admitted to the pediatric intensive care unit, where others involved in the accident were also hospitalized. Trended laboratory values during key moments of the hospital stay are depicted in Table 1. On hospital days 2 through 6, he remained on propofol titrated between 20 to 70 mcg/kg/min. On hospital day 6, he had increased respiratory secretions, oxygen desaturations, and increased ventilation support requirements. A computerized tomography (CT) scan of the chest revealed a left lower lobe consolidation, pneumonia was diagnosed, and he was started on intravenous antibiotics. In the early evening of hospital day 7, he became agitated, tachypneic, tachycardic, and febrile. Propofol was increased from 50 mcg/kg/hr to 70 mcg/kg/hr to help with agitation.

The patient became hypotensive with systolic blood pressure of 80mmHg and mean arterial pressure of 28 mmHg, unresponsive to fluids, and with oxygen desaturations into the low 80% range (Table 2). Labs revealed hyperkalemia of 7.8 mmol/L, severe metabolic and respiratory acidosis, elevated troponins, and peaked T-waves on EKG. He had progressive and changing ventricular arrhythmias seen on his rhythm strip (Figure 1). He was given 2 ampules of bicarbonate and a norepinephrine drip was initiated for persistent hypotension. Propofol was discontinued, central venous access obtained, and an arterial line was placed.

His hyperkalemia was managed with a total of 25 units of insulin, 5 ampules of dextrose 50, 1 gram of calcium gluconate, and 1 additional ampule of bicarbonate. He was also given 40 mg of intravenous lasix and started on an insulin drip. A temporary dialysis catheter was placed, but never required use. He progressed from ventricular tachycardia to ventricular fibrillation for less than 3 seconds then spontaneously returned to sinus rhythm. Approximately 5 hours from the onset of the acute change in clinical picture, his blood pressure and hyperkalemia significantly improved. Additional laboratory values obtained include elevated creatine kinase, myoglobinemia, hypertriglyceridemia, elevated liver enzymes, leukocytosis, and azotemia. He was managed conservatively for the next several days with midazolam for sedation. He was successfully extubated with minimal cognitive deficits. He ultimately was discharged on hospital day 22 to a rehabilitation facility.

Discussion

Parke et al. first described PRIS in the literature in 1992 in a case

***Corresponding author:** Sogunro O, General Surgeon, Department of Surgery, St. Vincent's Medical Center, Bridgeport, USA, Tel: +1-8602241197; E-mail: olutayosogunro@gmail.com

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Lab	Reference Range	HD 1	HD 3	HD 6	HD 7 am	HD 7 pm	HD 8	HD 11	HD 17	HD 22
K	3.7-5.3 mmol/L	3.7	3.6	4.3	4.3	7.8*	3.8	4.3	4.2	4.5
CK	39-308 U/L	697	-	-	-	21,675	26, 454	71, 744	3, 932	-
Mygb	28-72 ng/mL	1331	-	-	-	4, 945	4,345	19, 520	979	-
Trop	<0.03 ng/mL	-	-	-	-	0.81	1.05	0.34	-	-
Trygl	<150 mg/dL	-	-	-	-	331	-	211	-	-
BUN	6-20 mg/dL	10	7	9	16	12	30	43	53	34
Cr	0.7-1.20 mg/dL	0.81	0.76	0.57	0.57	0.99	1.59	1.11	1.16	0.98
Gluc	70-99 mg/dL	98	132	149	114	244	247	96	111	93
Hgb	13.5-17.5 g/dL	14.4	9.9	7.4	12.6	9.1	8.0	6.7	6.8	8.2
WBC	4.5-13.5 k/uL	22.4	7.9	7.5	7.8	33.8	18.9	30.6	11.4	14.2
AST	<40 U/L	-	68	-	-	-	>7000	1,076	-	-
ALT	5-41 U/L	-	31	-	-	-	2879	1,990	-	-
ALP	40-129 U/L	-	52	-	-	-	127	180	-	-
Tbil	0.3-1.2 mg/dL	-	0.75	-	-	-	3.18	4.01	-	-
pH	7.35-7.45	7.25	7.43	7.40	7.41	7.09	7.29	7.44	-	-
PaO_2	75-95 mmHg	533	70	62	69	63	171	104	-	-
$PaCO_2$	32-45 mmHg	57	38	41	39	67	38	34	-	-
SaO_2	%	100	94	92	94	81	99	98	-	-
HCO_3	22-27 mmol/L	25.2	25.2	22.9	24.2	20.3	18.1	23.4	-	-
BE	0.0-2.0	-2	1	-2	0	-10	-9	1	-	-

HD: Hospital Day; K: Serum Potassium; CK: Creatine Kinase; Mygb: Myoglobin; trygl: Triglyceride; Trop: Troponin-T; BUN: Blood Urea Nitrogen; Cr: Creatinine; Gluc: Glucose; Hgb: Hemoglobin; WBC: White Blood Cells; AST: Aspartate Transaminase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; Tbil: Total Bilirubin; PaO_2: Partial Pressure Arterial Oxygen; $PaCO_2$: Partial Pressure Carbon Dioxide; SaO_2: Oxygen Saturation; HCO_3: Bicarbonate; BE: Base Excess
*The highest lab value of multiple tests during the same period is documented.
-Indicates a value that was not obtained on this day.

Table 1: Laboratory values from key hospital days.

Vital Sign	HD 1	HD 6	HD 7AM	HD 7PM	HD 8	HD 22
Temperature (°C)	38.3	36.4	36.8	38.1	37.3	37.2
Blood pressure (mmHg)	100/56	138/76	115/58	87/51	110/62	137/88
Heart Rate (beats/min)	56	128	104	126	120	96
Respiratory Rate (breaths/min)	20	32	25	29	29	22
Oxygen Saturation (%)	100	94	92	81	99	98

Changes in vital signs during hospital stay, HD7 is when the event of PRIS occurred, HD: Hospital Day

Table 2: Vitals signs from key hospital days.

review of 5 children with upper respiratory tract infections who received propofol during their treatment. They developed metabolic acidosis, bradyarrhythmias, lipemic serum, progressive myocardial failure and all eventually died, with propofol considered as the contributing factor [4,5]. PRIS risk factors include sepsis, acute head trauma, critically ill patients on vasopressors and glucocorticoids, carbohydrate depletion, carnitine deficiency, and subclinical mitochondrial disease. In 1998, Bray et. al. coined the term propofol related infusion syndrome in a summary of propofol related deaths in 18 children who suffered serious side effects. He added an enlarged liver with fatty changes to the clinical syndrome [4]. Nine of them received long term (>48 hours) and high dose (>4 $mg/kg^{-1} h^{-1}$) infusions of propofol and three died from progressive myocardial failure [6]. In 1998, PRIS was described in an adult patient and featured symptoms nearly identical to the pediatric population and included hypoxia, metabolic acidosis, rhabdomyolysis, renal failure, and cardiac dysfunction [4].

The pathophysiology of PRIS is complex. It involves an energy imbalance between demand and supply at the intracellular level caused by propofol-mediated impairment of fatty acid oxidation in the mitochondrion. It affects cardiac and peripheral muscle through a direct necrotizing effect as evidenced by increased plasma levels of creatine kinase, troponin, and myoglobin. Free fatty acids (FFAs) are an important fuel for skeletal muscle and the myocardium. Medium and short chain FFAs freely cross the mitochondrial membranes while long chain free fatty acids enter through an integral membrane protein called carnitine palmitoyl transferase 1 (CPT1). The FFAs undergo beta-spiral oxidation which generates electrons for the electron transport chain for cellular respiration [7-9]. Any obstacle to free fatty acid utilization in the mitochondrion will lead to myocytolysis.

Propofol affects FFA utilization in two ways (Figure 2). First, it inhibits CPT1, which inhibits long chain free fatty acid entry into the mitochondrion. Second, it uncouples the process of beta-spiral oxidation from the electron transport chain, specifically at complex II. This uncoupling leads to an inability to utilize the medium and short chain FFAs leading to disruption of cellular respiration. PRIS has been described with sepsis as a known risk factor [7,8]. As in sepsis, a catecholamine surge occurs in acute neurological conditions, which decreases the anesthetic effects of propofol. The relationship between propofol and catecholamines, such as epinephrine and norepinephrine, is antagonistic. Propofol has a negative inotropic, or weakened

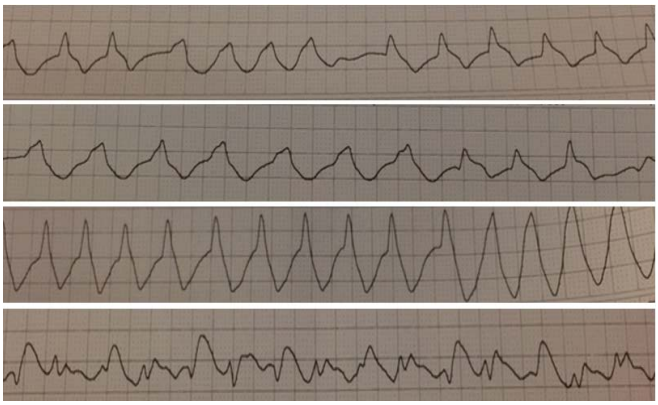

Figure 1: Rhythm strips of acute cardiovascular collapse, progressive and changing ventricular arrhythmias between ventricular tachycardia, ventricular fibrillation and unspecified.

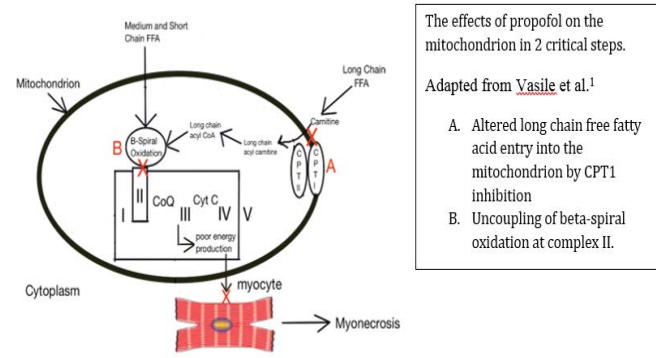

Figure 2: The mitochondrion propofol pathophysiology, propofol-mediated impairment of fatty acid oxidation.

force of cardiac muscular contraction, effect. This causes increased catecholamine requirements during times of stress, as evidenced by this patient's poor cardiac response to a norepinephrine drip while on the propofol. Catecholamines increase cardiac output and decrease propofol concentrations and its anesthetic properties. The stimulation of inflammatory cytokines from sepsis led to a hypermetabolic state, increasing energy demand without an associated increase in supply secondary to propofol's inhibition of mitochondrial cellular respiration. Together, propofol and catecholamines progressively depress myocyte activity eventually leading to organ failure.

PRIS is a clinical diagnosis of exclusion. Management involves discontinuation of propofol and management of the individual systemic derangements. The differential diagnosis includes Brugada syndrome, a mitochondrial disorder known as medium chain acylcoa dehydrogenase deficiency (MCAD), sepsis, and diabetic ketoacidosis [4]. This otherwise healthy young male had no previous history of cardiac abnormalities, no family history of mitochondrial diseases or diabetes. Of note, a Brugada-like syndrome has been described in PRIS. In a review by Mirrakhimov et al., six adult patients with PRIS displayed Brugada syndrome-like EKG patterns. Many times, as physicians we are asked if our training truly makes a difference in the way we care for our patients. We add, that our training cannot be the sole determinant of patient care but that it is extremely important to understand and appreciate that we cannot give the best patient care without the outstanding care given by nurses, especially in those critically ill. Earlier that evening of hospital day 7, when the bedside critical nurse noted increased oxygenation requirements of the patient, she notified our physician team. All the derangements in his vitals signs and oxygenation were well tracked and reported by her. As a team of physicians and nurses were able to give great care to this patient in eventually diagnosing PRIS. After prolonged instability and resuscitation efforts, the parents began to consider a comfort care only treatment plan. Two key factors came together in the clinical course at this point; the high index of suspicion for PRIS and the direct communication with the family. Both us as the treating physician team and the critical care nurses were able to reassure and provide compassion to the family. We were able to provide rational treatment and we realized a favorable outcome as a team.

This patient had risk factors for both sepsis and for PRIS being sedated on propofol for 6 days at a rate of up to 70 mcg/kg/min. He had metabolic acidosis, rhabdomyolysis, renal failure, hypoxia, cardiac dysfunction, lipemia, and liver dysfunction all consistent with PRIS. The rapid improvement of life-threatening cardiac arrhythmias and other acute symptoms after the discontinuation of propofol lends to the diagnosis of PRIS. Sepsis cannot be completely excluded as a cause of this patient's sudden decline, however, the likelihood of PRIS is high. It is also quite likely that both etiologies were at work. Waele et al. reported a similar case of sepsis precipitating PRIS in Belgium in a 30-year-old male who developed respiratory failure from pneumonia after abdominal surgery and was intubated and sedated with propofol [8,9].

Conclusion

PRIS is a complex syndrome and requires prompt recognition. Early identification of its key features including cardiac arrhythmias, acute changes in heart rate, decreased blood pressure, increased oxygenation requirements, and derangements in laboratory data including hyperkalemia, elevated CK and Myoglobin, elevated troponins, and metabolic acidosis is crucial by the critical care nurse. From the foregoing, caution should be used with long-term propofol infusion (>48 hours) at high doses (>67 mcg/kg/min). In the acute trauma patient that is septic, a benzodiazepine may have fewer undesirable systemic effects.

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References

1. Vasile B, Rasulo F, Candiani A, Latronico N (2003) The pathophysiology of propofol infusion syndrome: A simple name for a complex syndrome. Intens Care Med 29: 1417-1425.
2. Mirrakhimov AE, Voore P, Halytskyy O, Khan M, Ali AM (2015) Propofol infusion syndrome in adults: A clinical update. Crit Care Res Pract 2015.
3. Fodale V, La-Monaca E (2008) Propofol infusion syndrome: An overview of a perplexing disease. Drug Saf 31: 293-303.
4. Diaz JH, Roberts CA, Oliver JJ, Kaye AD (2014) Propofol infusion syndrome or not. Ochsner J 14: 434-437.
5. Parke TJ, Stevens JE, Rice AS, Greenaway CL, Bray RJ, et al. (1992) Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five Case Rep 305: 613-616.
6. Bray RJ (1998) Propofol infusion syndrome in children. Paediatr Anaesth 8: 491-499.
7. Ahlen K, Buckley CJ, Goodale DB, Pulsford AH (2006) The propofol infusion syndrome: The facts, their interpretation and implications for patient care. Eur J Anaesthesiol 23: 990-998.
8. De-Waele JJ, Hoste E (2006) Propofol infusion syndrome in a patient with sepsis. Anaesth Intens Care 34: 676-677.
9. Yeagle PL (1989) Lipid regulation of cell membrane structure and function. FASEB J 3: 1833-1842.