Open Journal of Clinical & Medical Images

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Case Series

Open Access, Volume 3

Propofol infusion syndrome (PRIS) in neuropatients: Early initiation of renal replacement therapy: Case series and literature review

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Received: Oct 25, 2023
Accepted: Dec 05, 2023
Published: Dec 12, 2023
Archived: www.jclinmedimages.org

Keywords: Propofol infusion syndrome; Propofol toxicity; Renal replacement therapy; Metabolic acidosis.

Abstract

Propofol-Related Infusion Syndrome (PRIS) is a rare, lethal adverse event of propofol, characterized by acute, severe metabolic acidosis, circulatory collapse and finally multiple organ dysfunction. The management of the syndrome consists of immediate discontinuation of propofol and supportive treatment including hemodynamic support, hemodialysis and, in refractory cases, extracorporeal membrane oxygenation. However, given the high mortality rates, prevention, increased awareness and early aggressive, supportive treatment could improve the outcome. Clinicians should consider alternative regimens when prolonged sedation is needed and remain within recommended maximal dose limits. Early initiation of renal replacement therapy (RRT), even in absence of absolute indications, could be beneficial and lifesaving. The aim of this paper is to present a case series of 4 neuropatients, who suffered from PRIS and were treated effectively with early RRT.

Cases presentation

A 21-year-old multi-trauma male patient was transferred to the hospital for neurosurgical treatment, because of posttraumatic subarachnoid hemorrhage, brain contusions and subdural hematoma. Additionally, he had thoracic trauma and multiple fractures of the spine and long bones of both lower limps. The patient underwent craniectomy, hematoma drainage and stabilization of limp fractures. He was then admitted to the intensive care unit (ICU) and put on mechanical ventilation, propofol and remifentanil for sedation and analgesia respectively, prophylactic antiseizure, antiedematous and antibiotic medications, intravenous fluids and vasopressors to maintain an appropriate cerebral perfusion pressure (Table 1). On the 6th day, he deteriorated, as he developed metabolic acidosis, hemodynamic destabilization, hyperpyrexia (>39,5°C) and new creatinine phosphokinase raise. Suspecting Propofol Related Infusion Syndrome (PRIS), propofol was replaced with midazolam and although there was no absolute indication, we started early Continuous Veno-Venous HemoDiaFiltration (CVVHDF) (Table 2).

The second patient was a 49-year-old female with an acute subarachnoid hemorrhage due to brain aneurysm rupture, HUNT-HESS scale V, Fisher grading scale IV. After she was operated, she was admitted to the ICU and she was treated with mechanical ventilation, propofol and remifentanil, prophylactic antiseizure and antibiotic treatment, intravenous fluids and vasoactive drugs (noradrenaline and nimodipine) (Table 1). On the 3rd day, she developed severe rhabdomyolysis and hemodynamic collapse, with no electrocardiographic or echocardiographic abnormalities. As intrahospital sepsis proved to be unlikely, we considered PRIS. Therefore, we discontinued propofol infusion and we started CVVHDF (Table 2).

The third patient was a 22-year-old male, with a severe brain injury due to trauma. He suffered from diffuse brain injury, brain contusions, posttraumatic subarachnoid and intraventricular hemorrhage. After an intraventricular catheter was placed for drainage and intracranial pressure monitoring, he was transferred to the ICU. On the 4th day of sedation with propofol, with a mean rate of 5 mg/kg/h, he presented unexplained hyperthermia, acute hemodynamic destabilization, rhabdomyolysis and hypertriglyceridemia (Table 1). Propofol was replaced with midazolam and dexmedetomidine and continuous renal replacement therapy (CRRT) was started, although there was no absolute renal indication (Table 2).

The last patient was a 35-year-old multi-trauma man, who had a history of alcohol abuse and bipolar disorder. He was intubated with a low Glascow Coma Scale (GCS: 4) because of brain contusions, mild brain edema and alcohol intoxication. Moreover, he had serious facial skeleton fractures and severe hypoxemia due to pulmonary contusions and probable blood aspiration. He was admitted to the ICU, where he was sedated with midazolam, propofol and remifentanil. Although, we considered of the many risk factors for PRIS and we tried to maintain the recommended doses, on the 5th day he developed hemodynamic instability, metabolic acidosis and paroxysmal atrial fibrillation (Table 1). After propofol was replaced with dexmedetomidine, CRRT was started (Table 2). All four patients rapidly improved after propofol was discontinued and CRRT started. Although the mortality of PRIS is reported to be over 50% [6], our case series suggests that early propofol withdrawal and aggressive resuscitation driven only by the suspicion of PRIS may be lifesaving.

Table 1: Presentation of the four neuropatients with PRIS.

	Patient' Number			
	1	**2**	**3**	**4**
Demographic characteristics				
Age	21	49	22	35
Sex	Male	Female	Male	Male
Underlying disease (cause of Brain Injury)	Multi-trauma patient	Acute subarachnoid hemorrhage	Brain trauma	Multi-trauma patient
BMI (kg/m^2)	20,1	24	22	28
APACHE II score upon ICU admission	17	28	24	30
SOFA score upon PRIS onset day	13	12	14	14
Noradrenaline dose before PRIS onset (mcg/kg/min)	1,2	1	0,8	1
Corticosteroids before PRIS onset (mg/kg/h)	No	No	No	No
Features				
Metabolic acidosis*	Yes	Yes	Yes	Yes
Lactic acidosis** (mg/dL)	5	7,1	6,5	6,8
Hyperkalemia† (mEq/dL)	5,4	4,5	5,8	6
Rhabdomyolysis ‡ (mgr/dL)	25618	>40000	28700	36700
Lipaemia § (mg/dL)	199	221	198	240
ECG changes	ST, T elevation	ST	ST	ST, T elevation
Cardiac dysrhythmias	No	No	No	AF
Cardiac failure	No	No	No	No
Hypotension	Yes	Yes	Yes	Yes
Acute Respiratory Distress Syndrome (P_aO_2/F_iO_2)	138	250	150	180
Acute Kidney Injury (oligoanuria§)	No	No	No	No
Acute Kidney Injury (serum creatinine mg/dL)	2,6	1,0	1,8	2,2
AKIN stage	2	1	1	2
Liver dysfunction#	Yes	Yes	Yes	Yes
White Blood Cells (WBC)	5100	17930	12400	13600
C-Reactive Protein (CRP) (mgr/dL)	32,85	18,44	16	14
Procalcitonin (PCT) (μgr/L)	2,6	< 0,12	<0,12	1,5
Unexplained fever (Temperature >38,5°C)	Yes	No	Yes	Yes
Mean propofol dose (mg/kg/h)	4,5	5	5	4,2

Duration of propofol administration (hours) before PRIS was diagnosed	144	64	92	120
Treatment				
Time of propofol infusion termination (hours after PRIS diagnosed)	6	6	6	6
Noradrenaline (mcg/kg/min)	2	3	2,5	3,2
Sodium bicarbonate 8%	No	No	No	No
Antibiotic escalation	Yes	Yes	Yes	Yes
CVVHDF (dose, mg/kg/h)	26	28	26	28
Duration of CVVHDF (hours)	120	44	48	144
Outcome				
Days of mechanical ventilation	24	12	20	25
Days of ICU stay	27	16	24	28
ICU outcome (survived/died)	survived	survived	survived	survived
Days of hospital stay	35	32	34	42
Final outcome (survived/died)	survived	survived	survived	survived

AF: Atrial fibrillation; NR: Nodal rhythm; ST: Sinus tachycardia; SVT: Supraventricular tachycardia; VR: Idioventricular rhythm; VT: Ventricular tachycardia.

*Base deficit >8 mmol/L once or >5 mmol/L for >24 h continuously.

**Lactic acid >2 mmol/L

†Potassium concentration >5,5 mmol/L.

‡Creatine kinase concentration >4000 U/L or myoglobin concentration >1000 g/L.

§Triglyceride concentrations >3,0 mmol/L.

$Diuresis <30 ml/h for more than 6 hours

#Transaminase or/and γ-GT elevation

Table 2: Indications for CRRT treatment in our patients.

	Patients Number			
	1	2	3	4
Absolute Indications				
Metabolic acidosis (pH < 7,0)	No	No	No	No
Hyperkalemia (> 6,5 mEq/dL)	5,4	4,5	5,8	6
Hypernatremia (>160 mEq/dL)	155	142	150	158
Serum urea (mg/dL)	123	20	54	133
Serum creatinine (mg/dL)	2,6	1,0	1,8	2,2
Diuresis (< 200 ml/12 hours)	No	No	No	No
Fluid overload (ml/days)	9000 ml/6 days	10000 ml/3 days	6500/4 days	7500/5 days
Intracranial hypertension	No	No	No	No
Hypoxemia	Yes	No	Yes	Yes
Relative Indications				
Lactic acidosis (mg/dL)	5	7,1	6,5	6,8
Hyperthermia	Max 39,8 °C	Max 38,6°C	Max 39,6 °C	Max 39,8 °C
Blood purification	Yes	Yes	Yes	Yes
Rhabdomyolysis	Yes	Yes	Yes	Yes
Hemodynamic deterioration	Yes	Yes	Yes	Yes

Introduction

Propofol is one of the most common intravenous anaesthetic drugs used for maintaining sedation and hypnosis in intubated mechanically ventilated patients in ICUs, since 1986, when it was first introduced [1]. Its pharmacokinetic characteristics, fast onset of action (within seconds after administration), brief half-life (up to 15 minutes), easily adaptable dosage to maintain an optimal degree of sedation and rapid regain of consciousness after discontinuation, make it a useful option, particularly in neuropatients [2]. It possesses sedative, anxiolytic, anticonvulsant and neuroprotective properties, since it reduces intracranial pressure. It enhances the neuro-inhibitory activity of the gamma-aminobutyric acid-A (GABA-A) receptor by prolonging the duration of the opening period of its chloride channels, leading to hyperpolarization of the postsynaptic neuron membrane and its subsequent inhibition [2,3].

Propofol-related infusion syndrome (PRIS) is a potentially fatal condition caused by extended exposure to propofol and it is primarily characterized by acute severe metabolic acidosis and circulatory failure [1]. It was first reported in a 3-year-old Danish girl in 1990 [4], while the first case of PRIS in an adult was reported in 1996 [5]. It was a 30-year-old female with exacerbation of bronchial asthma who developed an unexplained severe lactic acidosis that was attributed to propofol infusion [5]. Since then, most of the literature on PRIS consists of case reports and case series [6].

Pathophysiology: The mechanism responsible for PRIS remains obscure [1]. Generally, PRIS is thought to result from the disruption of the mitochondrial respiratory chain that inhibits adenosine triphosphate (ATP) synthesis and causes cellular hypoxia. Propofol decouples oxidative phosphorylation and impairs the electron flow along the electron transport chain in the inner-mitochondrial membrane. This reduces the mitochondrial capacity for energy production and affects the balance between energy demand and utilization, leading to the production of a large amount of long, medium and short-chain fatty acid (FFA) metabolites [7].

Further, in the setting of serious concurrent metabolic insults, such as critical illness, excess lipolysis of the adipose tissue occurs and FFAs become the basic energy providers for the musculoskeletal and cardiovascular cells, instead of carbohydrates. Normally, FFAs undergo beta-oxidation inside the mitochondria to generate acetyl-coenzyme A, which further feeds ATP-generating processes, particularly the Krebs Cycle. This cycle generates free electrons, which enter the mitochondrial electron transport chain. As propofol disrupts the latter process and represses ATP production, cellular hypoxia and metabolic acidosis ensues [7].

On the other hand, propofol increases serum malonylcarnitine, responsible for the repression of carnitine palmitoyl transferase-1 (CPT-1) which is a mitochondrial transporter. This protein is crucial for the transfer of long-chain FFA into the mitochondrial matrix. Hence, the impairment of long-chain FFA transportation leads to their accumulation in the mitochondrial matrix affecting the respiratory chain and further worsening the cellular hypoxia and metabolic acidosis, which ultimately result in muscle necrosis and rhabdomyolysis. Moreover, the respiratory chain is affected by an excess medium and short-chain FFA that are part of propofol itself and diffuse into the mitochondria. Overall, the impaired fatty acid oxidation produces toxic fatty acid intermediates, which worsen acidosis, particulalrly when cellular hypoxia coexists [1,7].

Main clinical features: Propofol-related infusion syndrome presents a wide range of features with multi-organ involvement. The most commonly involved systems are the metabolic and cardiovascular, while more rarely liver, kidneys and musculoskeletal system can be affected [1,6]. The metabolic manifestations are a result of tissue-level hypoxia. The high FFAs and triglycerides lead to a "fat overload syndrome" wherein the hydrolysis is not able to balance out the triglycerides in circulation. As a result, these lipids accumulate in the blood and are taken up by the reticuloendothelial system leading to hepatomegaly [1,7].

The cardiovascular system suffers from ATP insufficiency and FFAs accumulation, which directly affect cardiomyocytic function. Due to its antagonistic effects on beta-adrenoreceptors and calcium channels, propofol diminishes sympathetic tone, causing bradycardia and impairing myocardial contractility. Further, the ventricular arrhythmias associated with PRIS can be attributed to the pro-arrhythmic effects of excess serum FFAs. Several cardiovascular manifestations may occur, such as right bundle branch block, hypotension, Brugada-like syndrome ECG (elevated ST segment and widening of the QRS complex), ventricular arrhythmia, ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, cardiogenic shock and asystole [8,9].

The metabolic manifestations include metabolic and lactic acidosis, hyperkalaemia, hypertriglyceridemia and hyperthermia. Secondary to cardiac failure, hepatic congestion may develop. Also, the high levels of lipid deposition from propofol and free circulating fatty acids are further responsible for hepatomegaly, steatosis, elevated liver enzymes and liver dysfunction [10,11]. Besides, hypoperfusion, hypoxia, sepsis, hypermetabolic states, and vasopressor therapy that may be employed in the treatment of this syndrome, can further impair liver function [10,11]. Moreover, PRIS causes extreme lysis of myocytes of the musculoskeletal system due to defective beta-oxidation of FFAs. On histological examination necrosed myocytes with disorganized myofibrils, sarcomeres, degenerated nuclei, absence of striations and swelling can be seen. These are typical signs of rhabdomyolysis, leading to myoglobinuria and renal dysfunction. It is also suggested that decreased oxygen supply, leading to anaerobic metabolism, is another cause of myocyte death that eventually causes serum creatinine elevation and rhabdomyolysis [11].

Risk factors: Poor oxygen saturation, sepsis, traumatic brain injury, critical illness, young age, elevated catecholamines, inborn errors of metabolism, corticosteroids, an imbalance between lipid and carbohydrate stores of the body and high propofol dosages are the main risk factors for the emergence of PRIS [12].

According to evidence provided by case reports and studies, the proposed infused propofol dosage is less than 4 mg/kg/hour (or 67 mcg/kg/minute) for less than 48 hours [6]. Higher dosages for longer durations are not recommended and it is better to switch to alternative drugs, if required. The increased levels of endogenous catecholamines observed in patients with cerebrovascular injuries and sepsis can lead to the acceleration of propofol clearance. An increase in the drug dosage, could, therefore lead to PRIS [2].

On the other hand, acidosis brought on by PRIS may decrease vasomotor tone, raising the need for vasopressors [1]. In addition, corticosteroid use, can activate the ubiquitin-proteasome pathway that causes muscle rupture because of myofilament disturbance, while they minimize mitochondrial energy output by affecting the mitochondrial enzymatic activity [6]. Furthermore, catecholamines and glucocorticoids peak due to the neuroendocrine stress response to critical illnesses (acute neurological injury, status epilepticus, sepsis, etc.), which forms one of the major predisposing factors for PRIS. These hormones regulate the activity of lipase, which facilitates the breakdown of triglycerides into glycerol and FFAs [6]. Additionally in critically ill patients, the energy production in the body shifts from carbohydrates to lipids, which further results in an increase in FFAs. On the other hand, patients can develop a lipid excess state because of parenteral feeding, propofol infusion (as propofol is itself a lipid emulsion), or a combination of both. If glucose infusion is not used to regulate excess lipolysis and maintain a balance, then an overload of FFAs in the body and

a depletion of the glycogen stores could take place, giving rise to PRIS [1,6]. Finally, it seems that idiosyncratic factors are also implicated in PRIS manifestation, since patients suffering from inborn errors of metabolism, particularly mitochondrial diseases, are at a greater risk for developing PRIS upon exposure to propofol [1,10].

Diagnosis: Propofol-related infusion syndrome lacks specific signs and symptoms, other than propofol administration. Its presentation overlaps with other conditions leading to critical illness [10]. Therefore, clinicians should keep a broad differential diagnosis in mind, while managing a patient with PRIS.

Electrocardiogram (ECG), serum creatine kinase, lipase, amylase, lactate, liver enzymes, and myoglobin levels in urine should be monitored under propofol sedation (Figure 1).

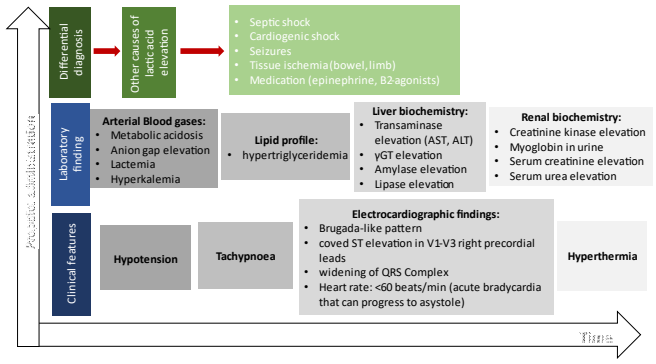

Figure 1: Clinical and laboratory findings in PRIS.

Treatment: Therapeutic options for PRIS are limited and mainly supportive [13]. The first step in managing PRIS is withdrawal of propofol immediately after recognizing the syndrome and replacement with another sedating agents [6]. Metabolic and lactic acidosis and hyperkalemia can be treated with haemodialysis and hemofiltration, although this approach cannot remove the excess lipids from the blood [13]. More specificly, propofol undergoes hepatic metabolism and is rapidly cleared by the kidneys as propofol-glucuronide and 2,6-diisopropyl-1,4-quinol sulfo-and glucuro-conjugates [14]. Unlike the highly lipophilic parent drug, these toxic water-soluble metabolites can be eliminated by CRRT [14].

The cardiac manifestations can be managed with cardiac pacing, inotropes, and vasopressors, which could improve contractility of heart muscle and counteract low blood pressure and manage cardiogenic shock [1,6]. Prolonged PRIS-related cardiogenic shock with severely compromised hepatic and muscle perfusion may dramatically reduce mitochondrial citrate metabolism and result in citrate accumulation. As citrate is increasingly used for regional anticoagulation during CRRT, tight monitoring of the ionized/total calcium ratio is imperative to prevent metabolic complications related to citrate intoxication [15].

Propofol dosages should be kept as low as possible and within the therapeutic margin. Other medications should be considered for critically ill patients in ICU who need prolonged sedation. When a long duration of propofol infusion is necessary, it is advised to closely monitor the useful markers of PRIS, such as arterial blood gas, lactic acid levels, electrolyte levels, and signs of cardiac dysfunction. Apart from this, maintaining a balanced load of carbohydrates can help to counter the increased FFA levels preventing PRIS [11].

Discussion

It is important to notice that most of the clinical data on PRIS originates from case reports and case series, while there is a lack of specific criteria for PRIS diagnosis [6]. PRIS continues to be reported in the literature as a potential lethal side effect of propofol, although mortality trends to a reduction [10]. Cremer et al. in 2001 first published a landmark paper in the Lancet of seven neurosurgical patients with PRIS, which was associated with the additive dose of infusion propofol [9]. According to Krajčová et al. who reviewed 153 published equivalent case reports, fatality rates in included cases were 51% and decreased over time. This reduction in mortality was associated with the cumulative dose of propofol, being represented by both mean infusion rate and the duration of infusion. In this paper authors reviewed only pathophysiology and risk factors of the syndrome and did not relate the outcome to the treatment [10].

Therapeutic options for PRIS are limited and mainly supportive [13]. There are only a few reported cases that include treatment options [6,11,12,16]. Mirrakhimov et al. in 2015 reviewed 35 reported PRIS cases in adult patients. The 28 reviewed articles included 36 cases with PRIS, of which 29 died (80,5% mortality). From these 36 patients, only 13 were treated with RRT (36,1%) and 1 had plasma exchange (2,77%). From these 14 patients, 10 finally died (71,4% mortality). According to this review, RRT could improve PRIS prognosis, although it is not clarified the time and the indication of RRT in every case [6]. Moreover, Levin et al recently reported a case describing rapid hemodynamic improvement and resolution of lactic acidosis and rhabdomyolysis after one single session of plasma exchange [16].

Equally, all four patients treated in our ICU, rapidly improved after propofol was discontinued and CRRT started. Although, we used classic hemofiltration membranes with standard delivered RRT dose [17], rapid hemodynamic and metabolic acidosis improvement and ideal fluid control was observed. Our case series suggests that early propofol withdrawal and aggressive resuscitation driven enclouding early RRT initiation may be beneficial.

Conclusion

PRIS is a rare but often fatal complication of propofol administration. The best management of PRIS is its prevention. Manifestations of PRIS such as hyperkalemia, acute renal failure, cardiovascular dysfunction and malignant arrhythmias should be aggressively treated. Early initiation of CRRT, even in the absence of well-established indications, such as acute kidney injury, metabolic acidosis, or hyperkalemia, might offer a survival benefit.

Declarations

Funding: No applicable.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Authors' contributions: S.E. Collected the patients' files, reviewed the literature and wrote the manuscript.

P.V. Reviewed the manuscript and approved the final version.

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