Case Report

Restarting propofol following successful management of propofol infusion syndrome: a case report

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Abstract: Propofol infusion syndrome (PRIS) is a rare and potentially fatal complication seen in high-dose (>5 mg/kg/h) or prolonged (>48 h) propofol infusions. PRIS presents as a constellation of symptoms, including anion-gap metabolic acidosis, elevated lactate, cardiogenic shock, rhabdomyolysis, arrhythmia, among other biochemical abnormalities. The current standard of care focuses on early recognition, propofol cessation, and supportive management. Case reports have shown evidence for several novel therapeutic interventions, including plasmapheresis, dialysis, and extracorporeal membrane oxygenation. There has yet to be a documented case demonstrating a trial of reinitiating propofol following successful PRIS management. We present the case of a previously healthy 20-year-old male that presented to the emergency department with new-onset refractory status epilepticus, secondary to suspected autoimmune encephalitis. Despite multiple immunomodulators, anesthetic therapies, and anti-epileptic agents, he exhibited ongoing refractory seizure activity on continuous electroencephalogram monitoring. Propofol boluses were the only therapy to offer seizure burst suppression, prompting uptitration of the infusion. The patient subsequently developed hemodynamic instability and multiple biochemical abnormalities consistent with PRIS. He was managed with one round of plasmapheresis, later followed by a session of sustained-low efficiency dialysis (SLED). This therapeutic combination was successful in managing PRIS and restoring hemodynamic stability. After stopping the propofol infusion, he developed near constant electrographic seizures, with breakthrough clinical seizures despite multiple other therapeutic interventions. Propofol was later restarted for seizure control, with no further recurrence of PRIS. This case provides support for novel therapeutic modalities, plasmapheresis and SLED, when managing PRIS. This case also marks the first successful attempt at restarting propofol following PRIS.

Keywords: Propofol infusion syndrome (PRIS); status epilepticus; plasmapheresis; dialysis; case report

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Introduction

Propofol infusion syndrome (PRIS) is a rare and potentially fatal complication that occurs in critically ill patients, with higher incidence amongst those receiving propofol at doses greater than 5 mg/kg/h or infusions longer than 48 hours (1). The pathophysiology of PRIS remains unclear, but is believed to involve intracellular mitochondrial disruption with impairment of the electron transport chain (1,2). PRIS is a constellation of multiple clinical findings, including elevated anion-gap metabolic acidosis and lactate, cardiogenic shock, rhabdomyolysis, bradycardic arrhythmias, acute kidney injury, hyperkalemia, hypertriglyceridemia, and elevated liver enzymes (1). In current literature, elevated anion-gap metabolic acidosis

is described as the most common finding (3). The largest risk factor for developing PRIS is the dose exposure (1). Use of vasopressors or glucocorticoids, young age, as well as systemic inflammation and cytokine release secondary to critical illness have been proposed as other risk factors (2,4). Studies have shown increased mortality in adults that present with hyperkalemia, hypotension, electrocardiogram (ECG) changes, a mean infusion rate greater than 5mg/kg/h, or a total cumulative dose greater than 240 mg/kg (1).

The present standard of care for PRIS involves early propofol cessation and supportive management (5). Current novel therapies focus on enhancing propofol elimination from the body and treating the complications of PRIS (1). These modalities are based on case report level of evidence and include plasmapheresis, dialysis, and extracorporeal membrane oxygenation (ECMO) (1,6-8). There is currently a lack of literature regarding safely restarting propofol after successful management of PRIS. To date, no published evidence comments on this topic.

We present the case of a patient with new-onset refractory status epilepticus (NORSE) who underwent successful management of PRIS and subsequently had propofol reinstituted without signs of PRIS recurrence, in accordance with the CARE reporting checklist (available at http://dx.doi.org/10.21037/jeccm-20-145). This case demonstrates the severity of PRIS, lends further support to novel therapeutic interventions, and outlines the first successful attempt at restarting a propofol infusion following PRIS.

Case presentation

A previously healthy 20-year-old male presented to the emergency department (ED) with altered mental status after being found unresponsive and posturing in his home. Prior to this, he experienced a 1-week history of flu-like symptoms, cough, and malaise, with antecedent behavioural changes noted by his parents over the previous months. His past medical history revealed remote concussions, as well as recreational vaping, alcohol, and marijuana use. Initial investigations completed in the ED, including bloodwork and a non-contrast computed tomography (CT) of the head, were unremarkable. A lumbar puncture performed in the ED demonstrated a mild pleocytosis of 16 (63% neutrophils, 26% lymphocytes) with normal cerebrospinal fluid (CSF) protein and lactate. Initial management consisted of meningitic doses of broad-spectrum antibiotics, empiric acyclovir for possible viral encephalitis, and an anti-epileptic, levetiracetam. Gadolinium-enhanced magnetic resonance imaging of the brain performed during the first day of admission was unremarkable. Over the course of the first 48 h in hospital, the patient had several witnessed seizures, both generalized tonic-clonic and focal motor seizures with impaired awareness, requiring escalating doses and classes of anti-epileptic medications. Due to recurrent convulsive seizures without return to baseline in between the events, the patient was transferred to the intensive care unit (ICU) for ongoing management of status epilepticus.

In the ICU, the patient was intubated and started on a first-line anesthetic agent, propofol, for management of NORSE. Further investigations, including viral serology, serum and CSF autoimmune encephalitis panels, and paraneoplastic markers were unremarkable. A malignancy screen consisting of a testicular ultrasound and CT scans of the chest, abdomen, and pelvis with intravenous contrast also did not reveal any pertinent findings. Continuous electroencephalogram (EEG) monitoring demonstrated ongoing non-convulsive status epilepticus despite multiple therapeutic agents. Oral anti-epileptic medications consisted of phenytoin, valproic acid, levetiracetam, and lacosamide. Anesthetic infusions included propofol (5 mg/kg/h), midazolam (10 mg/h), phenobarbital (2 mg/kg/h), ketamine (90 mg/h), and inhaled isoflurane. Given persistent non-convulsive status epilepticus on EEG, anesthetic infusions were up-titrated in attempt to achieve burst-suppression. Suppression of epileptiform activity on EEG was only seen with bolus doses of propofol. The effects of near constant seizure activity were deemed more harmful than the risk of developing PRIS, prompting propofol to be titrated to this dose.

Given the high dose and extended duration of the propofol infusion, routine bloodwork monitoring for signs of PRIS was initiated. Five days after originally starting propofol, the patient developed an anion-gap metabolic acidosis, as well as elevated lactate, liver transaminases, triglycerides, and creatine kinase. These findings were concerning for early PRIS, prompting immediate cessation of the infusion and initiation of plasmapheresis for potential benefit in managing both PRIS and NORSE. Bloodwork at the time also demonstrated an elevated serum phenobarbital level, measuring 497 μmol/L, with an elevated osmolar gap of 21.8 mmol/L. These findings suggested a possible concurrent propylene glycol toxicity, given its use as a diluent in phenobarbital (9) and the presence of an osmolar gap associated with the wide anion-gap metabolic acidosis (10),

Table 1 Trend of hemodynamic instability with vasopressor and ionotropic requirements

Time (hours)	Heart rate (beats per minute)	Blood pressure (mmHg)	Norepinephrine (mcg/min)	Epinephrine (mcg/min)	Vasopressin (units/min)	Dobutamine (mcg/kg/min)	Dopamine (mcg/kg/min)
1[a]	46	88/46	20	2	0	0	0
2	57	88/46	30	8	0	0	0
3	61	79/43	30	10	0.08	5	0
4	59	91/49	30	15	0.08	0	0
5	60	87/47	30	13	0.08	0	5
6[b]	65	92/60	30	6	0.08	0	5
7	67	88/57	30	2	0.08	0	5
8	60	111/62	28	0	0.08	0	5
9	73	110/66	12	0	0.08	0	0
10	72	109/67	10	0	0.08	0	0

[a], the onset of hemodynamic instability; [b], the initiation of sustained-low efficiency dialysis.

Table 2 Trend of biochemical abnormalities associated with propofol infusion syndrome

Time (days)	pH	Bicarbonate (mEq/L)	Lactate (mmol/L)	Triglyceride (mmol/L)	AST (U/L)	ALT (U/L)	CK (U/L)
0[a]	7.41	29	1.6	1.02	39	24	829[b]
1[c]	7.46	29	5.6	1.8	54	32	455
2[d]	7.29	18	9.8	2.02	87	74	479
3	7.08	12	17	2.16	110	97	329
4	7.47	26	3.7	2.59	104	91	571
5	7.41	25	/	2.94	126	111	1,088
6	7.44	25	/	2.27	76	75	495
7	7.41	26	/	1.73	37	35	292

[a], the patient's baseline values, taken upon initial assessment in the emergency department; [b], baseline elevation secondary to uncontrolled seizures upon presentation; [c], the day prior to the development of propofol infusion syndrome; [d], the onset of symptoms.

prompting discontinuation of the phenobarbital infusion. Despite early identification and initiation of one course of plasmapheresis, the patient progressively deteriorated developing refractory bradycardia and shock. Management with multiple vasopressor and ionotropic infusions at increasing dosages, including norepinephrine, vasopressin, epinephrine, dobutamine, and dopamine, were unsuccessful in stabilizing the patient (*Table 1*). An arterial blood gas revealed a pH of 7.04, a partial pressure of carbon dioxide of 44, a bicarbonate of 12, and a lactate of 18. New ECG findings of diffuse T-wave inversions and a junctional bradycardia were now present. Emergent sustained-low efficiency dialysis (SLED) was ordered, with a bicarbonate infusion and a cyanokit given as temporizing measures for refractory vasoplegia (11). Significant clinical improvement was noted hours after initiating SLED with resolution of the acidosis and a gradual correction of the other laboratory abnormalities (*Table 2*). He continued a 5-day course of plasmapheresis and nine days of SLED with successful resolution of PRIS. He was weaned off epinephrine, dobutamine, and dopamine in 1 day, vasopressin in 2 days, and norepinephrine in 11 days.

Following the discontinuation of propofol, the patient's electrographic seizure frequency increased on continuous EEG with minimal to no periods of burst suppression. Despite escalating immunotherapy, anti-

epileptic medications, and anesthetic infusions, there was no improvement in his super-refractory NORSE. In addition to his near constant electrographic seizures, he began to develop breakthrough clinical seizures. As propofol was the only medication to result in any amount of burst suppression, the idea of restarting the infusion was considered. A literature search revealed no studies to help guide this decision. Multiple intensivists thoroughly debated this option, extensively discussing the benefits and risks with the family. Given the failure of multiple other therapies following propofol cessation, it was decided to restart the infusion at a low dose, with gradual titration, while vigilantly monitoring for signs of PRIS. Sixteen days after developing PRIS, the infusion was restarted at 1 mg/kg/h with careful monitoring for signs of recurrence. The infusion ran intermittently over the next 80 days ranging from 0–3 mg/kg/h, without evidence of recurrent PRIS. During this time, the patient developed significant encephalomalacia, multiple deep vein thromboses, numerous endocrinopathies, and persistent bacteremia preventing further treatment of NORSE. Given the multiple life-threatening illnesses and the poor clinical prognosis, the patient was palliated and passed peacefully with family at his bedside.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's guardian.

Discussion

We present the case of a previously healthy 20-year-old male admitted to the ICU with NORSE, requiring invasive mechanical ventilation, immunomodulating therapy, as well as multiple anti-epileptics and high-dose anesthetic infusions, who subsequently developed PRIS. He presented with hemodynamic instability, bradycardia, lactic acidosis, hypertriglyceridemia, raised liver transaminases, and elevated creatine kinase, consistent with other reported cases of PRIS. Despite the elevated osmolar gap thought to be secondary to propylene glycol, the diluent in phenobarbital (9), we believe that PRIS represents the primary insult in his presentation. Both PRIS and propylene glycol toxicity can present with a wide anion-gap metabolic acidosis, an elevated lactate, and hypotension (1,10). However, the presence of elevated creatine kinase, triglycerides, and liver transaminases are features uniquely described with PRIS (1,12). Furthermore, the phenobarbital infusion was restarted the day after restoring hemodynamic stability at the same rate (2 mg/kg/h), with later additions of scheduled doses peaking at 600 mg every 6 h, and serum concentrations reaching 820 µmol/L, without further deterioration. The risk factors for developing PRIS in his case included critical illness, vasopressor and glucocorticoid use, as well as a propofol infusion rate greater than 5 mg/kg/h, with a duration longer than 48 h, and a total dose exposure greater than 240 mg/kg.

Optimal management for PRIS remains unclear. Aside from propofol cessation and supportive therapy, the benefit of most other suggested treatment modalities remains experimental, with case report level of evidence. A literature review conducted by Walli *et al*. examined patients with NORSE that subsequently developed PRIS and found this cohort to respond favourably to plasmapheresis, dialysis, and ECMO (5). In this case, the decision was made to initiate plasma exchange therapy, given the potential benefit in both PRIS and NORSE. Evidence for managing PRIS with plasmapheresis has been supported by two adult case reports, both demonstrating clinical improvement as a monotherapy (7,8). Levin *et al*. successfully managed PRIS with a single session of plasmapheresis in a 16-year-old patient with status epilepticus following a head injury (7). Faulkner *et al*. found similar success treating PRIS with one round of plasmapheresis in the case of a 23-year-old patient with refractory status epilepticus secondary to a traumatic brain injury (8).

In this case, plasmapheresis did not offer the same level of success as monotherapy. Despite early identification and initiation of plasmapheresis, the patient continued to deteriorate and became unstable. ECMO was considered, however the patient was deemed an unsuitable candidate. Emergent SLED was subsequently organized. While propofol itself cannot be excreted by the kidneys, it undergoes hepatic metabolism and its resulting toxic water-soluble metabolites can, thereby suggesting the theoretical benefit of dialysis (1). The patient significantly improved shortly after initiating SLED. The severe anion-gap metabolic acidosis resolved within hours, and his vasopressor and inotropic requirements decreased over the following days. Plasmapheresis and SLED were continued over the subsequent days, achieving complete hemodynamic stability and biochemical resolution.

Similar to other case reports, this case supports the trial of suggested novel therapeutic modalities when managing PRIS. Furthermore, this case illustrates the first successful attempt at restarting propofol after PRIS resolution. The suboptimal control of non-convulsive status

epilepticus despite extensive anti-epileptic medications, anesthetic agents, and immune therapy, as well as the initial observation of burst suppression on continuous EEG monitoring with propofol motivated consideration for this decision. However, given the lack of available evidence surrounding this topic, a cautious approach must be used, with vigilant clinical monitoring, if deciding to restart propofol following the management of PRIS.

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Footnote

Reporting Checklist: The authors have completed the CARE Reporting Checklist. Available at http://dx.doi.org/10.21037/jeccm-20-145

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's guardian.

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