Renal Replacement Therapy

CASE REPORT

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Propofol infusion syndrome as a cause for CRRT circuit malfunction: a case report with literature review

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Abstract

Background Propofol is commonly used for sedation in the Intensive Care Unit (ICU). When administered in high doses and for a prolonged time, it can cause a rare but hazardous complication: Propofol Infusion Syndrome (PRIS). Along with other findings, PRIS can cause lipemia and clotting of the Continuous Renal Replacement Therapy (CRRT) circuit.

Case presentation A 62-year-old woman admitted to the ICU after an acute ischemic stroke was sedated with Propofol for neuroprotection. On the sixteenth day of infusion (mean daily dose: 4 mg/kg/h), she presented with hyperlactatemia (7.7 mg/dL), acute kidney injury, metabolic acidosis (pH: 7.23 / HCO_3–: 12.2 mEq/L), hyperkalemia (6.9 mEq/L), and hypotension requiring high doses of norepinephrine. CRRT and corticosteroids were initiated. After 15 min of CRRT, the blood in the circuit had a milky color, and the therapy was interrupted because of high transmembrane pressure, despite adequate anticoagulation with heparin. Laboratory tests showed hypertriglyceridemia (782 mg/dL), increased transaminases, and creatine phosphokinase (5008 U/L), suggesting the rare and fatal PRIS.

Conclusion There is no established guideline for treating PRIS other than early discontinuation of Propofol and supportive care. Although CRRT is an important tool in managing PRIS, hypertriglyceridemia can cause circuit malfunction. Clinical hypervigilance and serial monitoring in at-risk patients are advised to minimize potentially lethal complications.

Keywords Acute kidney injury, Continuous renal replacement therapy, Dialysis, CRRT, Propofol, Propofol infusion syndrome, Hypertriglyceridemia, Case report

Background

Propofol is commonly used for sedation in the intensive care unit (ICU). Although generally considered a safe drug, when administered in high doses and for a prolonged time, it can cause a rare but extremely dangerous complication: Propofol Infusion Syndrome (PRIS), first described in 1992 [1]. Along with other findings, PRIS can cause lipemia, leading to clotting of the CRRT (continuous renal replacement therapy) [2].

We describe a case of Propofol-induced hypertriglyceridemia causing CRRT dysfunction.

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Case presentation

A 62-year-old woman with no previously reported comorbidities other than a smoking history was admitted to the Intensive Care Unit with hypoxemic respiratory failure, right hemineglect, and hemiparesis secondary to an acute ischemic stroke. The patient was intubated and sedated with Propofol (average dose: 4 mg/kg/h) via continuous intravenous drip trough a central venous catheter for neuroprotection. On the sixteenth day of infusion, she presented with hyperlactatemia (7.7 mg/dL), acute kidney injury, metabolic acidosis (pH: 7.23/HCO_3–: 12.2 mEq/L), hyperkalemia (6.9 mEq/L), and hypotension requiring high doses of norepinephrine and corticosteroids administration. A computed tomography (CT) of the abdomen and pelvis showed no dilatation of biliary ducts and no abnormalities of the liver, pancreas, or kidney.

Continuous renal replacement therapy (CRRT) was initiated through a double-lumen venous dialysis catheter placed in the patient's left internal jugular vein. After 15 min of CRRT, the blood in the circuit had a milky color (Fig. 1), and the therapy was interrupted because of high transmembrane pressure, despite adequate anticoagulation with heparin (Fig. 2).

Laboratory tests showed hypertriglyceridemia (782 mg/dL), increased transaminases, and creatine phosphokinase (5008 IU/L). The laboratory data at admission and during Propofol infusion are summarized in Table 1. A presumptive diagnosis of PRIS was made and Propofol was discontinued.

Potassium-lowering therapy was maintained, however, the hyperkalemia worsened (K: 8.0 mEq/L) and the patient died due to hyperkalemia-induced cardiac arrest, with ventricular fibrillation followed by ventricular tachycardia and asystole.

Discussion and conclusions

Propofol (2,6 diisopropilfenol), a sedative and hypnotic drug approved by the Federal Drugs and Administration (FDA) in 1989, is widely used in the ICU [3]. Although it may have appealing properties as a first-line drug for sedation, Propofol infusion is not without risks. In rare cases, it can cause a fatal condition known as Propofol Infusion Syndrome (PRIS), more likely to occur with high-dose infusion (> 5 mg/kg/h) for over 48 h [4].

PRIS is characterized by clinical symptoms and abnormalities such as metabolic acidosis, rhabdomyolysis, hyperlipidemia, cardiac dysfunction, liver, and kidney failure [5]. The pathophysiology behind its development is yet unclear. However, it seems to include impaired free fatty acid utilization and mitochondrial activity,

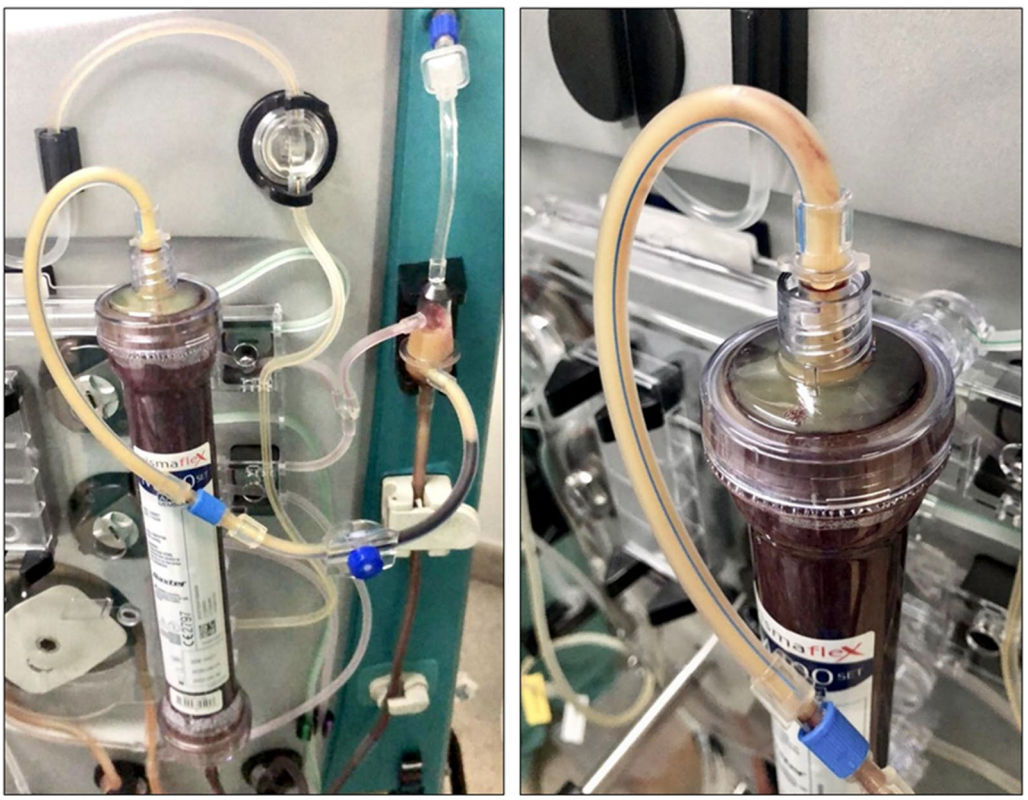

Fig. 1 Continuous renal replacement therapy circuit showing milk-colored plasma

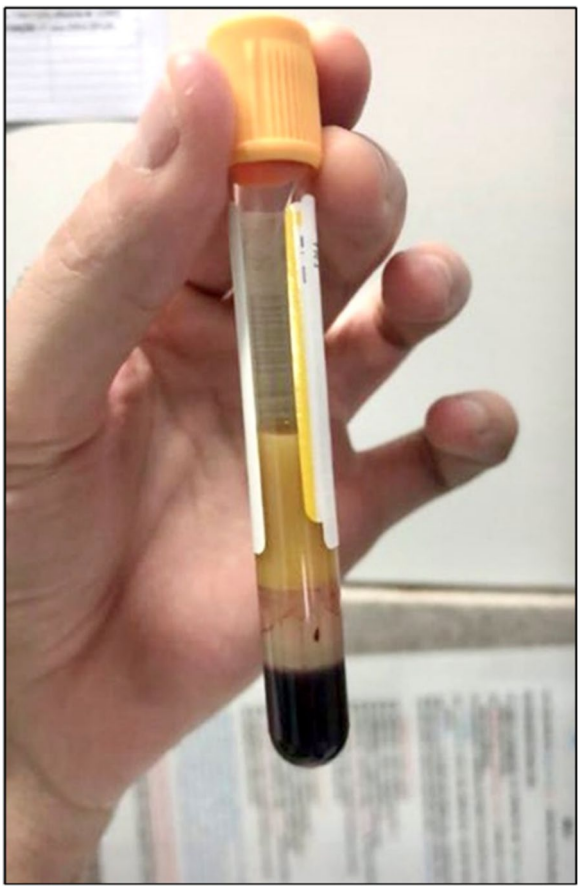

Fig. 2 Blood sample showing lipemia

Table 1 Laboratory data at admission, after 10 days and 16 days of Propofol infusion

Test (unit)	Admission	After 10 days	After 16 days
Hemoglobin (g/dL)	11.9	7.8	9.6
Hemoglobin (g/dL)	36.2	23.6	28.2
White blood cell (/μL)	13,100	41,800	23,700
Platelet count (/μL)	21.8×10^4	25.2×10^4	26.4×10^4
Creatinine (mg/dL)	1.23	1.45	4.01
Blood urea nitrogen (mg/dL)	28.4	54.6	99.4
Sodium (mEq/L)	134	135	128
Potassium (mEq/L)	3.8	3.2	6.9
Blood pH	7.41	7.45	7.23
PaO_2 (mmHg)	79.3	76.1	115.2
$PaCO_2$ (mmHg)	26.4	34.4	29.8
HCO3- (mmol/L)	19.1	26	12.2
Lactate (mg/dL)	1.9	1.5	7.7
T-Bil (mg/dL)	0.7	1.2	1.0
AST (IU/l)	39	562	1485
ALT (IU/l)	25	799	441
aPTT (sec)	42	30,3	76
PT (sec)	98	62	84.5
INR	1.0	1.28	1.08
CPK (IU/L)	19	23	5008
Triglyceride (mg/dL)	202	152	782

aPTT, activated partial thromboplastin time; ALT, alanine transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; INR, international normalized ratio; PT, prothrombin time; T-Bil, total bilirubin

disruption of the electron transport chain, and blockage of beta-adrenoreceptors and cardiac calcium channels [6]. Those metabolic derangements create a disproportion between energy demand and utilization, leading to cardiac and peripheral muscle necrosis [7].

In a multicenter, retrospective study, the incidence of PRIS was 2.9%, with a mortality rate of 36.8% [5]. Concomitant administration of vasopressors or corticosteroids, young age, as well as critical illness have been proposed as risk factors for its development [6]. A meta-analysis by Fong et al. found that death from PRIS was more likely if the patient developed any of the following symptoms: cardiac arrhythmias, rhabdomyolysis, impairment in renal function, metabolic acidosis, or dyslipidemia [4].

The likelihood of critically ill patients developing hypertriglyceridemia while receiving Propofol is still unknown. One observational study found that 28% of patients developed triglyceride (TG) levels greater than 400 mg/dL, with a median time to development of 47 h [8]. Devaud et al. observed hypertriglyceridemia in 45% of patients; however, the cutoff used for TG was considerably lower (≥180 mg/dL). Also, it is still not well-established whether the change in TG levels is due to the drug itself or its lipid vehicle [9].

Although CRRT is an important tool in managing PRIS, hypertriglyceridemia can cause the circuit to malfunction. The exact mechanism for that is unknown, but there is evidence supporting that an increased blood viscosity, correlated with serum TG levels, and hypercoagulability due to elevated coagulation factors, may induce the formation of fibrin fragments, obstructing the fibers and circuit clotting [10].

Reports of CRRT malfunction in patients with hypertriglyceridemia associated with other factors can be found, such as lipid emulsion infusion and liver graft dysfunction [10–13]. In our search, we found six prior reports of CRRT malfunction attributed to PRIS. The summary is shown in Table 2.

Screening for PRIS during Propofol infusion is recommended and may include monitoring the levels of creatinine, creatinine phosphokinase (CPK), troponin, triglycerides (TG), and serum lactate. However, the utility and sensitivity of those biomarkers is, at this time, questionable [20]. Although a prospective observational study

Table 2 Review of the literature on CRRT malfunction secondary to Propofol Infusion Syndrome

Case	Age (years)/sex	Propofol infusion rate (mg/kg/h)	Duration of propofol infusion	Serum triglycerides (mg/dL)	Intervention	Outcome
[14]	31/male	NA	10 days	1772	Propofol discontinued	CRRT resumption; Patient, recovered
[15]	55/NA	3.6	40 h	NA	NA	NA
[16]	41/male	NA	NA	3286	Propofol discontinued; Heparin drip; Lipopheresis	CRRT resumption
[17]	54/female	NA	NA	1132	Propofol discontinued	NA
[18]	81/male	3.1–3.75	7 days	1876.11	Propofol discontinued; dialysis line replaced	CRRT resumption
[19]	42/male	2.4	50 h	1155	NA	Patient died
Our case	62/female	4	16 days	782	Propofol discontinued	Patient died

NA, not available / CRRT, continuous renal replacement therapy

suggested that serum TG should be measured at least twice weekly [9], healthy patients receiving Propofol can have significant rises in TG levels without any adverse effects, questioning its value as a screening tool [20]. One study found that daily monitoring creatine phosphokinase (CPK) may reduce the incidence of PRIS, advising that Propofol is stopped if CPK reaches levels > 5000 IU/L [21].

There is no established guideline for treating PRIS other than early recognition, and discontinuation of Propofol. Supportive care should be provided, including hemodialysis, hemodynamic support, and extracorporeal membrane oxygenation in refractory cases [6, 22]. Since lipemia can lead to CRRT circuit clotting and malfunction, early detection of hypertriglyceridemia in patients receiving Propofol can improve maintaining hemofilter patency.

When it comes to acute triglyceride lowering therapy in PRIS, there are no preferred treatment or clinical practice guidance. Insulin or heparin infusions may lower serum triglyceride by enhancing lipoprotein lipase activity. Plasmapheresis can also be considered, as it can rapidly reduce the levels of chylomicrons and triglycerides. While some studies demonstrated its feasibility, limited clinical evidence exists for either of these therapies [23–25].

Given the high mortality of PRIS, the best management lies in prevention. Propofol administration, if possible, should be limited to 48 h and the dose should not be higher than 4 mg/kg/h. Strategies such as daily weaning of sedation and other alternatives to sedative drugs should be encouraged. When prolonged infusion of Propofol is needed, using minimal doses possible, limiting the amount of lipid content delivered to patients and maintaining adequate carbohydrate intake could help reduce the risk of PRIS [6, 22].

Although our patient had several risk factors which may have contributed to the development of PRIS, including corticosteroid and vasopressor use, critical illness and duration of Propofol use, earlier identification and discontinuation of the inciting agent could have had a positive impact on the outcome.

This report, added to previous cases, evidences hypertriglyceridemia as a possible cause of filter clotting during CRRT in patients receiving Propofol and reinforces the importance of PRIS prompt diagnosis, as well as the need for further research on early markers, pathophysiology and possible specific therapies.

Abbreviations

ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CPK	Creatine phosphokinase
CRRT	Continuous renal replacement therapy
CT	Computed tomography
FDA	Federal Drugs and Administration
ICU	Intensive Care Unit
INR	International normalized ratio
PRIS	Propofol Infusion Syndrome
PT	Prothrombin time
T-Bil	Total bilirubin
TG	Triglyceride

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MGZ reviewed and wrote the paper; LCMGB and ISG reviewed the references; MAL conceived, designed, and wrote the paper.

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