neurocritical care society Neurocrit Care (2011) 15:139–145
DOI 10.1007/s12028-010-9385-7

PRACTICAL PEARL

Propofol Infusion Syndrome During Refractory Status Epilepticus in a Young Adult: Successful ECMO Resuscitation

Christophe Guitton · Laurence Gabillet · Patrick Latour · Jean-Christophe Rigal · David Boutoille · Ousama Al Habash · Pascal Derkinderen · Cédric Bretonniere · Daniel Villers

Published online: 25 May 2010

Abstract
Background Propofol infusion syndrome (PRIS) is a rare but serious complication of propofol administration consisting of metabolic disorder with acidosis, often leading to fatal cardiovascular collapse.
Methods A case of PRIS is described in a 17-year-old female with refractory status epilepticus (RSE) who was receiving high-dose propofol for seizure control and sedation.
Results Metabolic syndrome was observed with renal failure, severe metabolic acidosis, and rhabdomyolysis after 58 h of propofol infusion at a maximum dose of 8.8 mg/kg/h. It was not initially associated with circulatory failure. Propofol was stopped immediately, and brief bradycardia was observed. The patient was started on continuous hemofiltration resulting in correction of the metabolic disorder. However, cardiocirculatory failure occurred a few hours later. Her clinical evolution and biological assessments were typical of PRIS. Extracorporeal membrane oxygenation (ECMO) was initiated despite the presence of cardiocirculatory arrest. Cardiocirculatory function improved rapidly, and the patient was weaned off ECMO after 5 days. No severe neurologic effects were observed, and she left the intensive care unit after 36 days, returning home after 2 months.
Conclusions Careful consideration should be given before prescribing propofol as first-line therapy for RSE, and this drug should be avoided altogether if high doses are required. Close biochemical monitoring is needed if propofol is used for more than a few hours, so that PRIS can be recognized promptly. Immediate discontinuation of propofol is essential, and early hemofiltration should be initiated. ECMO should be considered in cases of cardiocirculatory failure.

Keywords Status epilepticus · Propofol · Propofol infusion syndrome · Metabolic acidosis · Rhabdomyolysis · Extracorporeal membrane oxygenation

C. Guitton · L. Gabillet · C. Bretonniere · D. Villers
Service de Réanimation Médicale, Centre Hospitalier Universitaire, 44093 Nantes, France

P. Latour
Laboratoire d'Explorations Fonctionnelles, Centre Hospitalier Universitaire, 44093 Nantes, France

J.-C. Rigal
Service de Réanimation de Chirurgie Thoracique et Cardio-Vasculaire, Centre Hospitalier Universitaire, 44093 Nantes, France

D. Boutoille
Service des Maladies Infectieuses, Centre Hospitalier Universitaire, 44093 Nantes, France

O. Al Habash
Service de Chirurgie Thoracique et Cardio-Vasculaire, Centre Hospitalier Universitaire, 44093 Nantes, France

P. Derkinderen
Service de Neurologie, Centre Hospitalier Universitaire, 44093 Nantes, France

C. Guitton (✉)
Service de Réanimation Médicale, Hôtel Dieu CHU de Nantes, 30 Boulevard Jean Monnet, 44093 Nantes Cedex 1, France
e-mail: christophe.guitton@chu-nantes.fr

Introduction

Propofol (2,6-diisopropylphenol) is used increasingly for the treatment of refractory status epilepticus (RSE) in

adults due to its short half-life [1–4]. However, its use is limited by a rare complication known as propofol infusion syndrome (PRIS). Initially described in children, numerous cases have now been reported in adults, notably during the sedation of brain injured patients. This severe syndrome is associated with varying degrees of metabolic abnormality (metabolic acidosis, lactacidemia, hyperlipemia, rhabdomyolysis, and acute anuretic renal insufficiency) and cardiovascular failure with ventricular dysfunction, which is often fatal [5]. The pathogenesis of this syndrome is still unclear [6].

We describe a case of PRIS occurring during the care of a patient with RSE. This case shows that propofol can be used effectively to manage RSE, but also highlights the care required when using high doses of this drug for prolonged periods of time. It also highlights the aggressive approach required to treat PRIS.

Case Report

This case did not meet the criteria for research, and formal review was waived by the University Hospital Scientific Research Board in Nantes.

A previously healthy 17-year-old girl, weighing 51 kg and without any significant medical history, presented with signs of viral disease. She was still febrile 48 h later, and was also confused. She suffered three generalized tonic-clonic epileptic seizures (GTCS), without recovery of consciousness between them. During this prehospital phase, diazepam (10 mg) was administered followed by 500 mg of phenobarbital. The GTCS stopped, but there was no return to normal consciousness, and she remained with a Glasgow Coma Score (GCS) of 3. She did not have circulatory failure at this stage.

The patient was transferred to the emergency room with a GCS = 3 and normal reactive pupils. Her temperature was 37.6°C, and blood pressure was normal. Slight petechial hemorrhaging was noticed on the face, hands, and right knee (probably due to respiratory and circulatory phenomena during seizures similar to those observed during the Valsalva maneuver). Antibiotic therapy with ceftriaxone was initiated because of suspected bacterial meningitis.

Her blood biochemistry, reported in Table 1 (H-5), showed mild renal failure (creatinine 1.4 mg/dL) with dehydration. Her electrocardiogram (ECG) (Fig. 1) and chest X-ray were normal. No toxicology screening was performed. Because of persistent coma, the patient was intubated using etomidate and suxamethonium, ventilated, and transferred to the medical intensive care unit (MICU) where she was sedated with continuous infusion of midazolam (10 mg/h) and fentanyl.

Brain computed tomography (with intravenous contrast) was normal. Analysis of cerebrospinal fluid (CSF) showed raised protein (1.24 g/L), three leukocytes/mL, and no bacteria. A diagnosis of aseptic meningoencephalitis was suspected. Neurologic examination showed a GCS = 5, paroxysmic right horizonto-rotational rhythmic nystagmic eye movements, and some axial tonic contractions.

Continuous electroencephalographic (EEG) monitoring showed a partial epileptic focus localized in the left occipital lobe. Under continuous EEG monitoring, sedation and anti-convulsants were adjusted to midazolam (20 mg/h) and propofol (Fresenius®) to prevent EEG evidence of seizure activity (H0). Propofol was chosen, so that it could be titrated for later rapid awakening. During the first 4 h, four boluses of 100 mg propofol and a progressive increase to 400 mg/h (7.8 mg/kg/h) were required to obtain burst-suppression on the EEG, without seizure activity into the bursts.

The increase in sedation led to arterial hypotension requiring fluid challenge and infusion of norepinephrine (0.3 μg/kg/min). Urine output was maintained during these first hours of care. Echocardiography was normal, without any changes in left ventricular function. Blood testing on admission (H0) to the MICU showed some minor changes (Table 1), including slightly altered renal function, elevated aspartate aminotransferase (AST; 38.3 U/L), and serum lactate of 2.9 mmol/L. Respiratory alkalosis after 2 h of artificial ventilation (pH 7.51) led to adjustment of the ventilator settings.

Empiric antibiotic treatment consisting of ceftriaxone (6 g/day), rifampicin (1,200 mg/day), and acyclovir (15 mg/kg, three times/day) was initiated while awaiting the CSF results.

Brain magnetic resonance imaging was performed at H18 and was considered normal. A second CSF analysis at H48 was unchanged (protein 1.29 g/L, three leukocytes/mL, no bacteria, and negative culture).

A full infection screen with bacteriologic, parasitologic, and viral assessments (Lyme disease, toxoplasmosis, *Mycoplasma*, Epstein Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus, human herpes virus 6, human immunodeficiency virus, respiratory syncytial virus, enterovirus, adenovirus, parainfluenza, influenza A or B, B19 parvovirus) was negative. All antibiotic and antiviral treatments were discontinued.

After administering propofol for 12 h at 400 mg/h, continuous EEG revealed critical paroxysmic activity in the left posterior regions requiring an increase in propofol dose to 450 mg/h (8.8 mg/kg/h) from H12 to H32. Oral carbamazepine (200 mg/day) was started, and the propofol dose was reduced progressively in view of the EEG improvement [to 400 mg/h (7.8 mg/kg/h) from H32 to H39; to 350 mg/h (6.8 mg/kg/h) from H39 to H56; and to 300 mg/h (5.8 mg/kg/h) from H56] (Fig. 2).

Table 1 Time points for biochemical and hematologic data

Parameter (unit)	Range	Hours														
		−5 ER	0 Medical intensive care unit	10	12	18	32	34	39	40	56	58	60	65	72	74	78
			Day 1				Day 2				Day 3				Day 4		
WBC ($\times 10^9$/L)	*4–10*	11.1	14.4	8.0				16.8				20.6		16.6			13.5
Hb (g/dL)	*12–16*	15.3	11.1	11.3				10.9				15		11.8			11.4
Plt ($\times 10^3$/mL)	*150–400*	311	196	178				168				247		160			165
Prothrombin ratio	*80–120*	70	57	57				60				74		66	70		70
TCA ratio	*0.8–1.2*	1.22	1.22	1.16				1.16				1.03		1.31	5.4		1.34
Fib (mg/dL)	*200–400*	520	320	330				380				620		470			480
pH	*7.36–7.42*		7.51	7.52		7.39		7.38				7.24	7.35	7.36	7.41	7.43	7.51
Bic (mmol/L)	*23–27*		17	18.3		19.4		19.5				12.2	20.7	19.1	21.3	22.4	25.7
BE (mmol/L)	*−2* to *2*		−4.4	−2.9		−4.8		−5				−13.7	−4.4	−5.5	−2.4	−1.2	3.0
$PaCO_2$ (torr)	*36–43*		22	23		33		35				29	38	35	35	35	31
PaO_2 (torr)	*75–97*		137	129		97		98				126	125	151	134	130	129
SaO_2 (%)	*95–98.5*		98	98		97		97				97	99	99	97	98	98
Lactate (mmol/L)	*0.6–2.4*		2.9									7.2		7.5	5.2	4.5	11.6
K (mmol/L)	*3.3–5*	4.5	3.2	2.7		3.7		3.5				5	5.3	4.7	4.4	4.4	4.1
Protein (g/L)	*64–83*	93.0	59.0	56.0				48.0				59.0	46.0	46.0	47.0	43.0	38.0
Glucose (mmol/L)	*4–6*	4	11.6	4				4.5				6.3	7	5.9	5.7	5.6	5.6
Urea (mg/dL)	*8–23*	12.0	12.9	9.5				8.1				13.7	17.4	19.0	17.1	16.2	19.0
Creat (mg/dL)	*0.4–0.9*	1.4	1.1	1.0				1.7				2.3	2.7	2.7	2.4	2.2	2.1
CPK (U/L)	*0–188*												168,000				
Tropo (ng/ML)	*0–0.03*															0.14	0.15
Myoglobin (μg/L)	*14–58*											>30,000			>30,000		>30,000
Tot Bili (mg/dL)	*0–1*		0.5	1.0								4.2		3.0			2.7
Conj Bili (mg/Dl)	*0–0.3*		0.2	0.6								2.0		2.3			2.3
AST (U/L)	*0–30*		38	29								1,577		4,571			
ALT (U/L)	*0–42*		21	81								245		627			1,048
GGT (U/L)	*0–60*		11	11								28		20			17
Alk Ph (U/L)	*0–98*		62	60								172		109			117
Norepi(μg/kg/mn)		0	0	0.3	0.2	0.05	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3	0.4
Propofol (mg/kg/h)		0.0	7.8	7.8	8.8	8.8	7.8	7.8	6.8	6.8	5.8	0.0	0.0	0.0	0.0	0.0	0.0
Propofol (mg/h)		0	400	400	450	450	400	400	350	350	300	0	0	0	0	0	0

ER emergency room, *WBC* white blood cells count, *Plt* platelet count, *ACT* activated clotting time, *Bic* bicarbonate, *BE* base excess, *K* potassium, *CPK* creatine phosphokinase, *Tot Bili* total bilirubin, *Conj Bili* conjugated bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyltranspeptidase, *Alk Ph* alkaline phosphatase

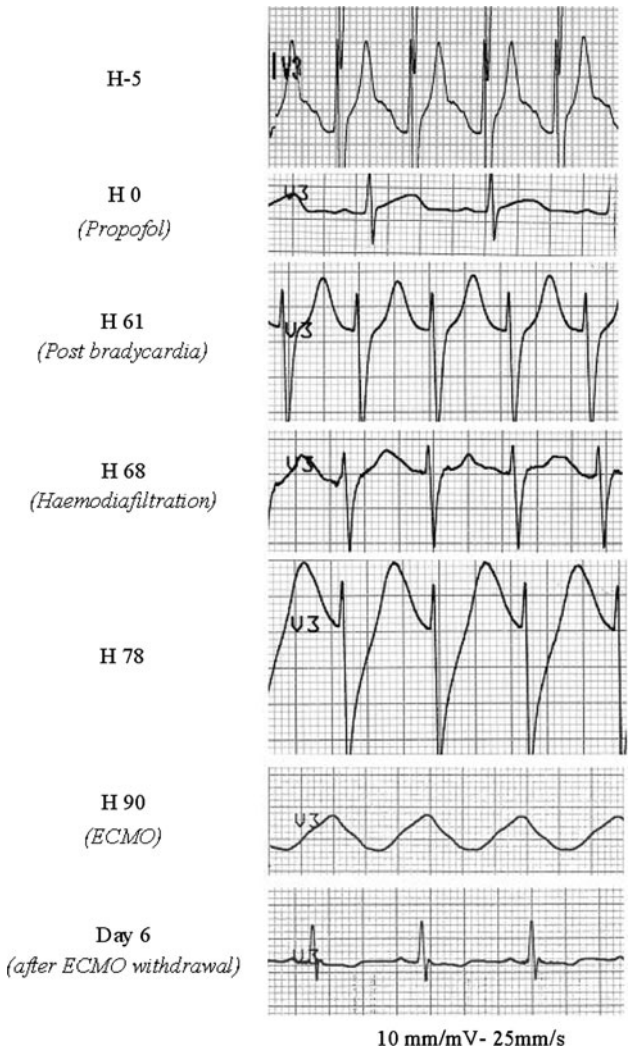

Fig. 1 Serial ECG evolution of precordial V3 lead. *H* hour, *ECMO* extracorporeal membrane oxygenation

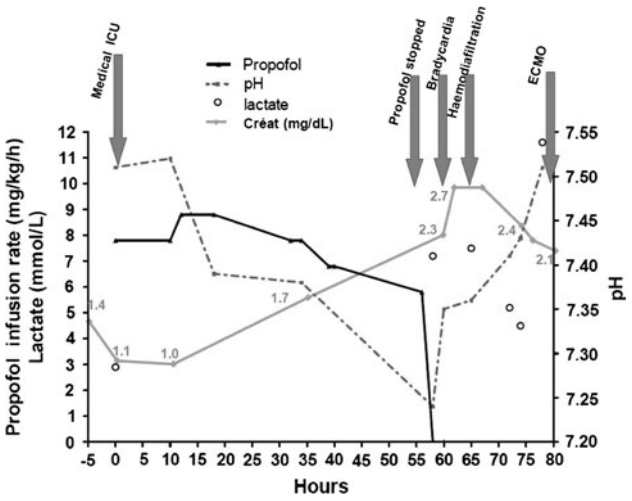

Fig. 2 Changes in propofol infusion rate related to blood pH, lactate, and creatinine levels. *ICU* intensive care unit, *ECMO* extracorporeal membrane oxygenation

There was a slight worsening of renal function (urea 8.1 mg/L and creatinine 1.7 mg/dL) at H34, despite good urine output. This deterioration was attributed to fluid restriction (to prevent cerebral edema) and high-dose acyclovir (which was then decreased).

The patient became anuric at H58, with major worsening of her biological parameters and severe metabolic acidosis (pH 7.24, $PaCO_2$ 29 mmHg, and bicarbonate 12.2 mmol/L). Lactates were 7.2 mmol/L. Her renal failure worsened (potassium 5 mmol/L, urea 13.7 mg/dL, and creatinine 2.3 mg/dL), and rhabdomyolysis was detected [myoglobin $>30{,}000$ µg/L, creatine phosphokinase (CPK) 168,000 U/L, AST 1,577 U/L, and alanine transaminase 245 U/L]. No prior myoglobin or CPK levels were available. The rhabdomyolysis was associated with inflammatory lower limb edema. Abdominal and hepatic ultrasounds were normal, and there were no signs of infection. The metabolic syndrome was isolated, and there were no signs of hemodynamic failure at this stage.

The PRIS was suspected, and propofol was stopped immediately. All potentially hepatotoxic drugs including paracetamol were discontinued. Propofol was replaced with thiopental (1 g/day), and carbamazepine was replaced with levatiracetam (250 mg/day).

A short episode of bradycardia (20 s) to about 30 beats/min was observed at H60, with prolonged QRS associated with transient hypotension. This was treated with 20 mL of 10% calcium gluconate and 250 mL of 8.4% bicarbonates. An ECG recorded a few minutes later showed normal QRS with sinus rhythm (Fig. 1). Cardiac rhythm and hemodynamic status returned to normal. Cardiac ultrasound carried out at this time revealed a normal ejection fraction.

To correct the metabolic disorder, and as the patient was anuric with a potassium level of 5.3 mmol/L and creatinine of 2.7 mg/dL, continuous veno-venous hemofiltration was initiated. In spite of the progressive correction of lactic acidosis (pH 7.36, lactates 7.5 mmol/L to H65; pH 7.41, lactates 5.2 mmol/L to H72; and pH 7.43, lactates 4.5 mmol/L to H74), cytolysis and hemodynamic status worsened. Troponin was increased, but the response was difficult to interpret because of acute renal failure. After H72, the QRS waves gradually widened (Fig. 1) in a refractory way despite the administration of calcium gluconate, bicarbonate, and molar lactate infusions. Left ventricular function measured by trans-thoracic echocardiography gradually decreased from H78.

After multidisciplinary discussions, it was decided to urgently implement rescue circulatory bypass with arteriovenous extracorporeal membrane oxygenation (ECMO). The patient was transferred to the cardiovascular surgery

ICU. Management on admission was complicated by cardiocirculatory arrest with refractory ventricular fibrillation which required external cardiac massage for 30 min, at the same time as femoral access for implementation of femoro-femoral arterio-venous cardiopulmonary bypass. A reperfusion catheter was also inserted into the femoral artery. Unfractionated heparin was used for anticoagulation with target anti-Xa activity in the range of 0.15–0.25 units.

Once ECMO had been started, her improvement was immediate and impressive. Just after ECMO initiation, epinephrine (which replaced norepinephrine) was infused at a rate of 2.7 μg/kg/min, and was then quickly decreased and stopped 24 h later. ECMO flow was maintained at 3.5 L/min for 48 h, with near absence of native cardiac function. The patient was closely monitored using ECMO flow sensors and echocardiography. Progressive improvement of left ventricular function and correction of rhythmic conduction disorders allowed discontinuation of ECMO 5 days later, and the metabolic disturbance normalized.

Her remaining hospital stay was relatively uneventful: awakening allowed extubation 18 days after cardiocirculatory arrest, and renal dialysis was stopped on D26. The patient left the ICU on D36, and returned home at 2 months. Her neurologic course was satisfactory with a restored neuropsychologic state. At 3 months, she had returned to a normal life except for a mild left foot drop. Neurologic examinations were normal at 2-year follow-up. Acylcarnitine levels, ammonemia, and urinary amino acid chromatography were normal, and there was no evidence of a defect in beta-oxidation or urea cycles, ruling out any associated mitochondriopathy or muscular enzymopathy.

Discussion

This report describes a case of PRIS complicating the care of a young woman with RSE. The clinical presentation with metabolic acidosis followed by cardiocirculatory failure was typical of PRIS [5]. Indeed, despite the possibility of a viral infection, a diagnosis of myocarditis was unlikely as metabolic decompensation (acidosis and anuria) had clearly preceded hemodynamic failure, as shown by several echocardiographs. The case cannot be explained by rhabdomyolysis alone, even though GTCS can provoke some degree of muscle damage. Blood CPK and myoglobin levels on admission were not available, but lactates were just above the normal range, and the patient only presented with three general seizures before admission, without recurrence. The patient's metabolic syndrome and the severe clinical signs of rhabdomyolysis were delayed for several hours after admission. Moreover, the metabolic disorder was corrected by hemodialysis and cannot therefore explain the hemodynamic failure. Furthermore, this case is unlikely to be due to acyclovir toxicity which usually results in renal failure and neurotoxicity and not hemodynamic failure.

Propofol is used increasingly for the treatment of status epilepticus due to its short half-life and ease of use [3, 4]. It was chosen for our patient because it offered the possibility of rapid neurologic assessment after discontinuation in the context of possible encephalitis. Although this syndrome has been described during sedation for brain injury, there are few reports of patients developing severe metabolic acidosis and rhabdomyolysis during the treatment of RSE with propofol [7–9]. Cases may be becoming more common as the use of propofol is increasing for this indication, although only a minority of cases are recognized or reported [5]. Initially described in children, PRIS also affects adults irrespective of the indication for propofol (including RSE).

Although the risk is greater with higher doses of propofol, notably >5 mg/kg/h for more than 48 h [10, 11], this dose cannot be considered to be safe as PRIS has also been described with lower doses for a much shorter duration [12–16].

It has also been suggested that newer formulations of propofol are more likely to cause PRIS [17] although we are unable to incriminate the formulation used in our patient, namely propofol Fresenius®. This formulation is very similar to Diprivan® (Astrazeneca), and PRIS has been described with different brands and formulations of propofol.

Careful monitoring of clinical and laboratory parameters is vital in critically ill neurologic patients treated with propofol. However, exactly which parameter is appropriate and necessary to monitor remains unclear. Renal failure, rhabdomyolysis [18], and lactic acidosis [13, 16, 19] are early and common signs of PRIS. In our patient, the deterioration of renal function seen at H38 should have been considered an early sign of PRIS rather than a complication of acyclovir and dehydration. These biological parameters have previously been identified as independent predictive factors of severity and mortality in PRIS [5]. It therefore seems justified to regularly and repeatedly monitor these biological parameters (pH, bicarbonate, CPK, myoglobin, and troponin associated with lipidemia) during the administration of propofol for more than a few hours [6, 13, 20, 21].

Monitoring should also focus on possible electrocardiographic abnormalities. An ECG appearance of right bundle branch block with convex-curved ("coved type") ST elevation in right precordial leads (V1–V3) is often the first indication of electric instability and high risk of sudden death. In our case, early abnormalities were seen with short-lived bradycardia and progressive QRS complex widening. The role of propofol in the development of arrhythmias remains unclear. The main mechanisms suggested include

impairment of oxidative phosphorylation, energy production, and mitochondrial respiration. Propofol also seems to have a direct effect on ventricular function [22–25].

Successful management of PRIS relies on the prompt recognition of this syndrome. Propofol infusion should be discontinued immediately, and aggressive support implemented. Renal support such as continuous hemofiltration is beneficial to remove propofol metabolites and correct metabolic abnormalities such as acidosis [9, 26, 27]. This treatment is sometimes adequate alone and may prevent death in some cases. In our case, early initiation of hemofiltration did not prevent delayed cardiovascular complications despite partial correction of the severe metabolic abnormalities. This scenario has also been described previously [20].

In the case of severe cardiovascular failure and shock, refractory to vasopressive agents, aggressive treatment with extracorporeal life support (ECLS) such as ECMO should be considered, as used in our patient. Only two cases of ECMO use in PRIS have been published; both described the successful use of ECMO in children as a last-ditch attempt to save life [28, 29]. Placement on ECLS allows time for cardiac recovery, which seems to occur quickly within a few days. An increase in number of mobile circulatory assistance devices would facilitate the care of this type of patient and would avoid the need to transport these extremely unstable patients to hospital at the risk of further destabilization [30].

In conclusion, care must be taken when administering propofol to patients with RSE [31]. Current recommendations should be respected, particularly concerning the maximum dose administered during prolonged continuous infusion (4 mg/kg/h). This case of severe PRIS highlights the need for strict biological monitoring during prolonged propofol therapy. In the case of circulatory failure associated with PRIS, invasive and aggressive care with ECMO should be considered.

References

1. Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J. Propofol treatment of refractory status epilepticus: a study of 31 episodes. Epilepsia. 2004;45(7):757–63.
2. Prasad A, Worrall BB, Bertram EH, Bleck TP. Propofol and midazolam in the treatment of refractory status epilepticus. Epilepsia. 2001;42(3):380–6.
3. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus. Eur J Neurol. 2006;13(5):445–50.
4. Lowenstein DH. The management of refractory status epilepticus: an update. Epilepsia. 2006;47(1):35–40.
5. Fong JJ, Sylvia L, Ruthazer R, Schumaker G, Kcomt M, Devlin JW. Predictors of mortality in patients with suspected propofol infusion syndrome. Crit Care Med. 2008;36(8):2281–7.
6. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med. 2003;29(9):1417–25.
7. Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. Neurology. 1998;50(1):301–3.
8. Friedman JA, Manno E, Fulgham JR. Propofol. J Neurosurg. 2002;96(6):1161–2.
9. Zarovnaya EL, Jobst BC, Harris BT. Propofol-associated fatal myocardial failure and rhabdomyolysis in an adult with status epilepticus. Epilepsia. 2007;48(5):1002–6.
10. Cremer OL, Moons KG, Bouman EA, Kruijswijk JE, de Smet AM, Kalkman CJ. Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet. 2001;357(9250):117–8.
11. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med. 2002;30(1):119–41.
12. Burow BK, Johnson ME, Packer DL. Metabolic acidosis associated with propofol in the absence of other causative factors. Anesthesiology. 2004;101(1):239–41.
13. Koch M, De Backer D, Vincent JL. Lactic acidosis: an early marker of propofol infusion syndrome? Intensive Care Med. 2004;30(3):522.
14. Liolios A, Guerit JM, Scholtes JL, Raftopoulos C, Hantson P. Propofol infusion syndrome associated with short-term large-dose infusion during surgical anesthesia in an adult. Anesth Analg. 2005;100(6):1804–6.
15. Merz TM, Regli B, Rothen HU, Felleiter P. Propofol infusion syndrome—a fatal case at a low infusion rate. Anesth Analg. 2006;103(4):1050.
16. Salengros JC, Velghe-Lenelle CE, Bollens R, Engelman E, Barvais L. Lactic acidosis during propofol-remifentanil anesthesia in an adult. Anesthesiology. 2004;101(1):241–3.
17. Badr AE, Mychaskiw G 2nd, Eichhorn JH. Metabolic acidosis associated with a new formulation of propofol. Anesthesiology. 2001;94(3):536–8.
18. Stelow EB, Johari VP, Smith SA, Crosson JT, Apple FS. Propofol-associated rhabdomyolysis with cardiac involvement in adults: chemical and anatomic findings. Clin Chem. 2000;46(4):577–81.
19. Marinella MA. Lactic acidosis associated with propofol. Chest. 1996;109(1):292.
20. Perrier ND, Baerga-Varela Y, Murray MJ. Death related to propofol use in an adult patient. Crit Care Med. 2000;28(8):3071–4.
21. Kumar MA, Urrutia VC, Thomas CE, Abou-Khaled KJ, Schwartzman RJ. The syndrome of irreversible acidosis after prolonged propofol infusion. Neurocrit Care. 2005;3(3):257–9.
22. Vernooy K, Delhaas T, Cremer OL, et al. Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. Heart Rhythm. 2006;3(2):131–7.
23. Schenkman KA, Yan S. Propofol impairment of mitochondrial respiration in isolated perfused guinea pig hearts determined by reflectance spectroscopy. Crit Care Med. 2000;28(1):172–7.
24. Fudickar A, Bein B. Propofol infusion syndrome: update of clinical manifestation and pathophysiology. Minerva Anestesiol. 2009;75(5):339–44.
25. Kam PC, Cardone D. Propofol infusion syndrome. Anaesthesia. 2007;62(7):690–701.
26. Cray SH, Robinson BH, Cox PN. Lactic acidemia and bradyarrhythmia in a child sedated with propofol. Crit Care Med. 1998;26(12):2087–92.
27. Wolf A, Weir P, Segar P, Stone J, Shield J. Impaired fatty acid oxidation in propofol infusion syndrome. Lancet. 2001;357(9256):606–7.

28. Culp KE, Augoustides JG, Ochroch AE, Milas BL. Clinical management of cardiogenic shock associated with prolonged propofol infusion. Anesth Analg. 2004;99(1):221–6.
29. Abrahams JM, Reiter GT, Acker MA, Sinson GP. Propofol. J Neurosurg. 2002;96(6):1160–1.
30. Megarbane B, Leprince P, Deye N, et al. Emergency feasibility in medical intensive care unit of extracorporeal life support for refractory cardiac arrest. Intensive Care Med. 2007;33(5):758–64.
31. Parviainen I, Kalviainen R, Ruokonen E. Propofol and barbiturates for the anesthesia of refractory convulsive status epilepticus: pros and cons. Neurol Res. 2007;29(7):667–71.