

## REVIEW ARTICLE

# Propofol infusion syndrome

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### Summary

The clinical features of propofol infusion syndrome (PRIS) are acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis (base deficit  $> 10 \text{ mmol.l}^{-1}$ ), rhabdomyolysis, hyperlipidaemia, and enlarged or fatty liver. There is an association between PRIS and propofol infusions at doses higher than  $4 \text{ mg.kg}^{-1}.\text{h}^{-1}$  for greater than 48 h duration. Sixty-one patients with PRIS have been recorded in the literature, with deaths in 20 paediatric and 18 adult patients. Seven of these patients (four paediatric and three adult patients) developed PRIS during anaesthesia. It is proposed that the syndrome may be caused by either a direct mitochondrial respiratory chain inhibition or impaired mitochondrial fatty acid metabolism mediated by propofol. An early sign of cardiac instability associated with the syndrome is the development of right bundle branch block with convex-curved ('coved type') ST elevation in the right praecordial leads (V1 to V3) of the electrocardiogram. Predisposing factors include young age, severe critical illness of central nervous system or respiratory origin, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake and subclinical mitochondrial disease. Treatment options are limited. Haemodialysis or haemoperfusion with cardiorespiratory support has been the most successful treatment.

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Accepted: 5 February 2007

Propofol is commonly used in anaesthesia and in intensive care where its favourable pharmacokinetics and rapidly reversible sedation make it an ideal drug for short-term sedation. However, propofol has been associated with a number of serious adverse effects such as metabolic acidosis, cardiac asystole, myocardial failure, rhabdomyolysis, and death [1–33]. Although previous reports have described severe metabolic acidosis during propofol infusion in children, cases have been described in adult patients more recently [3, 4, 6–8, 10, 13–23]. In 1998, Bray proposed the term 'propofol infusion syndrome' (PRIS) to describe this clinical state associated with propofol infusions in children [5]. The clinical features of PRIS that were originally described in children include acute refractory bradycardia leading to asystole in the presence of one or more of the following: metabolic acidosis (base deficit  $> 10 \text{ mmol.l}^{-1}$ ), rhabdomyolysis, hyperlipidaemia and an enlarged or fatty liver. There is a

strong association between PRIS and propofol infusions at doses greater than  $4 \text{ mg.kg}^{-1}.\text{h}^{-1}$  of longer than 48 h duration [5]. The mechanisms by which this syndrome occurs have not been elucidated but there is in vitro evidence that suggests impaired mitochondrial function [27]. The management of patients with this syndrome involves cardiovascular support with cardiac pacing and haemofiltration [27–33].

The aim of this article is to review the clinical features, pathophysiology and management of propofol infusion syndrome (PRIS).

### Methods

An electronic search was performed using the Ovid interface for Medline (1963–2006), CINAHL and EMBASE database. The following terms were searched separately and then combined to identify relevant articles:

propofol, arrhythmias, metabolic acidosis, lipidaemia, head injuries, and rhabdomyolysis. The titles and abstracts of the generated references were examined for relevance. The bibliographies of the articles were also scanned for additional references, i.e. 'reference dredging'.

## History

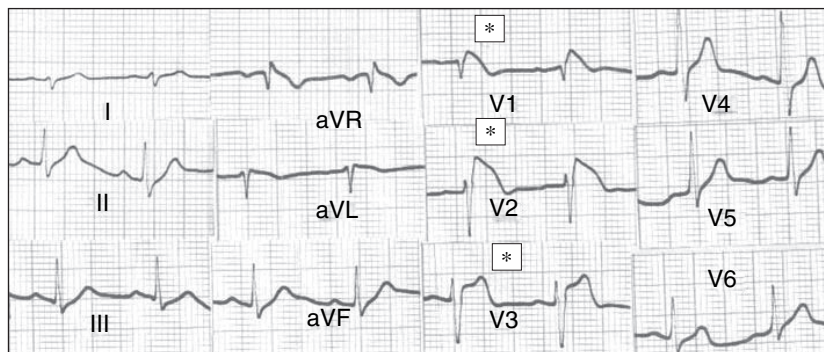
The first case of PRIS-related death was in Denmark in 1990, and the Danish Side-effects Committee issued a warning about the use of propofol infusions in children [1]. The patient was a 2-year-old girl with croup who was sedated for 4 days with a propofol infusion ( $10 \text{ mg.kg}^{-1}.\text{h}^{-1}$ ) and developed metabolic acidosis, heart failure, hypotension and hepatomegaly. However, this case report did not receive much attention because the syndrome had not been identified at the time. In 1992, it was a report by Parke et al. [2] that caused real concern. The authors reported five deaths in children aged 4 weeks to 6 years who were admitted to the paediatric intensive care unit for the management of severe respiratory tract infections. The children, who were ventilated and sedated with propofol infusion ( $7\text{--}10 \text{ mg.kg}^{-1}.\text{h}^{-1}$  for between 66 and 115 h), developed metabolic acidosis, hyperlipidaemia, hepatomegaly, bradyarrhythmias and, ultimately, progressive cardiac failure. This was a hallmark publication and proposed a link between propofol infusions and mortality. Following this, a child (20 months old) with epiglottitis developed PRIS associated with a propofol infusion (mean rate  $7.4 \text{ mg.kg}^{-1}.\text{h}^{-1}$ ) over 56 h [28]. Unlike the previous reports, this patient, the first recorded survivor of PRIS, was resuscitated from asystolic cardiac arrest and veno-venous haemofiltration was undertaken to treat the acidosis. Cornfield et al., in a retrospective review of a case series of 142 critically ill children who were sedated with continuous propofol infusion at doses less than  $3 \text{ mg.kg}^{-1}.\text{h}^{-1}$ , found no association between propofol infusion doses and metabolic acidosis or haemodynamic instability. They concluded that propofol could be safely and effectively used to provide sedation in the paediatric intensive care unit [34]. However, the dose range was below the dose ( $4 \text{ mg.kg}^{-1}.\text{h}^{-1}$ ) associated with propofol toxicity. Statistically, this study was limited by the small sample size [35].

In 2001, an unpublished randomised controlled trial of the use of propofol infusions involving 327 patients in a paediatric intensive care unit in the US recorded an increase in the 28-day mortality in propofol-treated patients with a trend toward statistical significance [36]. The group that did not receive propofol had a mortality of 4%, whereas those who received 1% propofol infusion had an 8% mortality, and those who received 2% propofol infusions had an 11% mortality. The baseline disease

severity scores were similar for the three groups. The trial was terminated early and the United States Food and Drug Agency issued a warning against the use of propofol for long-term sedation in the paediatric population.

However, in 1996, a case report described the occurrence of severe metabolic acidosis in a 30-year-old woman with acute respiratory failure (caused by asthma) who was sedated with a propofol infusion [37]. The patient developed a worsening metabolic acidosis (increased anion gap) despite the absence of hypoxia, hypotension, sepsis, shock, diabetes or catecholamine administration. Lactic acidosis resolved 12 h after the propofol infusion was ceased and she was extubated without event. This case suggested that an early metabolic acidosis may signal the onset of PRIS. The first recorded death from PRIS in an adult was in 1998 in a patient with refractory epilepsy who received a propofol infusion (rate  $8.8\text{--}17.5 \text{ mg.kg}^{-1}.\text{h}^{-1}$  over 44 h). Metabolic acidosis, hypotension, hyperkalaemia and rhabdomyolysis preceded a wide complex bradycardia and ultimately asystole despite resuscitation [4]. In 2001, Cremer et al., in a retrospective cohort study from an adult neurosurgical intensive care unit, reported that seven of 67 adult patients with head injury who received propofol infusion for sedation showed signs of PRIS and died [3]. The authors estimated that the odds ratio for the occurrence of PRIS for every  $\text{mg.kg}^{-1}.\text{h}^{-1}$  increase in mean propofol dose above  $5 \text{ mg.kg}^{-1}.\text{h}^{-1}$  was 1.93 (CI 1.12–3.32,  $p = 0.018$ ). When the investigators retrospectively reanalysed the ECGs of these seven patients, they found that six patients had developed right bundle branch block with convex-curved ('coved type') ST segment elevation in the right praecordial leads (V1–V3) similar to that observed in patients with the Brugada syndrome [38] (Fig. 1). Brugada syndrome is an inherited sudden cardiac death syndrome caused by a defect in ion channels in the myocardium which causes electrical instability by augmenting outward currents and/or reducing inward currents at the end of phase 1 in the cardiac action potential. These electrocardiographic changes precede the malignant ventricular arrhythmias that cause sudden cardiac death in these patients.

More reports of unexplained early metabolic acidosis developing in patients who were not critically ill on high dose propofol infusions of short duration emerged [13, 17, 18, 39]. A 31-year-old woman received propofol sedation for a radiofrequency ablation procedure for chronic atrial fibrillation [16]. Metabolic acidosis occurred ( $\text{pH } 7.3$ ,  $\text{BE } -8 \text{ mmol.l}^{-1}$ ) after 395 min of propofol infusion and this resolved gradually upon cessation of the infusion. The authors concluded that the metabolic acidosis was caused by propofol alone because no other causes for the metabolic acidosis existed. They suggested



**Figure 1** Right bundle branch block with convex-curved ('coved') ST elevation [\*] in V1 to V3 usually precedes malignant ventricular arrhythmias in propofol infusion syndrome.

that PRIS may be reversible in the early stages, and emphasised that high dose, prolonged infusions of propofol should be avoided.

In 2004, the Australian Adverse Drug Reactions Committee issued a warning concerning the use of propofol for sedation in adult intensive care units and recommended that propofol should not be infused at rates greater than  $4 \text{ mg.kg}^{-1}.\text{h}^{-1}$  [40].

### Cases recorded

Cases recorded in the literature are summarised in Tables 1–4. Although PRIS was initially considered a syndrome associated with paediatric patients, it is now evident that it can occur in adults. To date, 32 paediatric and 29 adult cases have been recorded in the literature. Of these, 20 paediatric and 18 adult patients died, and 12 paediatric and 11 adult patients survived. Seven of the 12 paediatric patients and one of the 11 adult patients who survived had the hallmarks of PRIS, whereas the other patients had either metabolic acidosis or other early signs of PRIS. Seven of 61 cases reported occurred during general anaesthesia using propofol infusions. Most of the cases reported had either respiratory or central nervous system (CNS) illness (22 with respiratory disease, and 33 with neurological disease).

### Mechanism of PRIS

Early theories about the cause of acidosis in PRIS included impaired hepatic lactate metabolism caused by intralipid present in propofol leading to lactate accumulation and acidosis, accumulation of inactive propofol metabolites, and lipid microembolisation [2, 5, 37]. However, recent research has focused on impaired mitochondrial respiratory chain function. Whether the mitochondrial defect caused by propofol is mediated by an unidentified metabolite [29, 41] or by an underlying neuromuscular defect is widely debated. Cray et al. supported the theory that a propofol metabolite caused

a biochemical lesion that disrupted the respiratory chain (as evidenced by a reduction in mitochondrial muscle cytochrome C oxidase), causing a failure of ATP production, cellular hypoxia and metabolic acidosis [29]. Mehta et al. demonstrated a reduced complex IV activity and cytochrome oxidase ratio in the mitochondria in in-vitro studies [41]. Studies utilising guinea pig heart tissue confirmed that propofol either impairs oxygen utilisation or inhibits electron flow along the mitochondrial electron transport chain in cardiomyocytes [42] (Fig. 2).

Wolf et al. reported raised serum levels of malonylcarnitine, C5-acylcarnitine, creatine kinase, troponin T, triglyceride, lactate and myoglobinaemia in a 2-year-old child with PRIS. They postulated that propofol caused a disruption of mitochondrial fatty-acid oxidation [27] (Fig. 3). Long-term propofol infusion was associated with an increase in malonylcarnitine, which inhibits carnitine palmitoyl transferase, a mitochondrial transport protein. Consequently, the entry of long chain acylcarnitine esters in muscle tissue is impaired. Medium chain and short chain fatty acids diffuse into the mitochondria and inhibit the respiratory chain (at complex II), resulting in a rise in C5, C4 or C2-acylcarnitine [27, 30, 43]. This causes a failure of ATP production in the mitochondria, leading to a build up of long chain, medium chain and short chain fatty-acid metabolic by-products. Soya bean (added to propofol to enhance its solubility) increases the medium and long chain triglyceride fat load. As a consequence of impaired fatty-acid oxidation, a rapid build up of toxic fatty-acid intermediates results and when this is coupled with cellular hypoxia, it worsens the acidosis [30, 43]. Excess serum fatty-acid concentrations cause ventricular arrhythmias [31, 44]. A case report speculated that PRIS was precipitated by the commencement of a ketogenic diet (high fat, low carbohydrate) as adjuvant therapy for refractory status epilepticus in a 10-year-old boy sedated with propofol [11]. It suggested that the fat load, coupled with propofol-mediated impairment of mitochondrial fatty-acid oxidation, caused the metabolic acidosis.

**Table 1** Deaths in Paediatric PRIS patients.

Case No.	Sex (M/F)	Age; years	Diagnosis [Reference]	Mean dose; mg.kg <sup>-1</sup> .h <sup>-1</sup> (duration)	Clinical features	Treatment
1	F	2.17	Laryngotracheobronchitis (Croup) [1]	10.2 (4 days)	Cardiac failure, metabolic acidosis,	NA
2	F	2.75	Laryngotracheobronchitis (Croup) [2]	7.5 (115 h)	RBBB, bradycardia, asystole Metabolic acidosis, BE – 11.8 Lipidaemia, hepatomegaly, fever	Atropine, inotropes
3	F	1.33	Laryngotracheobronchitis (Croup) [2]	7.4 (66 h) l <sup>-1</sup>	Bradycardia, heart block, asystole Metabolic acidosis, BE – 10.5 Lipidaemia, hepatomegaly, acute renal failure Bilateral lung consolidation	Inotropes Propofol ceased Peritoneal dialysis Haemofiltration
4	F	1.83	Laryngotracheobronchitis (Croup) [2]	10 (76 h)	Bradycardia, asystole Metabolic acidosis, BE – 9.2, lipidaemia	Inotropes Cardiac pacing
5	F	0.08	Bronchiolitis [2]	8 (64 or 74 h)	Fever, lung consolidation Bradycardia, atrial ectopics Metabolic acidosis, BE – 22.8, lipidaemia Hepatomegaly, acute renal failure respiratory failure	Propofol infusion ceased Atropine, Isoprenaline Peritoneal dialysis
6	M	6	Laryngotracheobronchitis (Croup) [2]	8.1 (104 h)	Bradycardia, asystole Metabolic acidosis, BE – 16 Lipidaemia, acute renal failure Sepsis	Inotropes Transvenous pacing Propofol ceased
7	NA	NA	Laryngitis, epiglottitis [62]	Range 5–9 (>48 h)	Metabolic acidosis Hepatomegaly	NA
8	M	9	Upper respiratory infection Influenza A [24]	4.5 (72 h)	Bradycardia, VT, asystole Cardiac failure, hepatomegaly, fever	Atropine, Inotropes
9	NA	<2.6	Epiglottitis [5]	5.2 (4 days)	Bradycardia, asystole Metabolic acidosis Hepatomegaly with fatty change	NA
10	NA	1.08	Laryngitis, encephalitis [5]	6.3 (4 days)	Bradycardia, AV block Metabolic acidosis Hepatomegaly with fatty change	NA
11	F	11	Brain tumour resection PICU sedation post-op [25]	9.4 (38 h)	Junctional rhythm, VT, VF Hypotension Metabolic acidosis, BE – 21 Lipidaemia, acute renal failure hyperkalaemia, fever	Propofol infusion ceased Inotropes, bicarbonate Glucose and insulin Lidocaine, bretylium Cardioversion
12	NA	3.83	NA [5]	200 mg.h <sup>-1</sup> (2 days)	Cardiac arrhythmia, respiratory failure Metabolic acidosis	NA
13	NA	1.08	Laryngotracheobronchitis (Croup) [5]	NA (2 days)	Cardiac failure	NA
14	NA	0.5	Congenital heart disease [5]	? 6 (> 72 h)	Bradycardia, hepatomegaly, respiratory failure	NA
15	NA	8	Status epilepticus [5]	15.2 (29 h)	Bradycardia, asystole Metabolic acidosis Fever 38.4 °C CK 38770 U.l <sup>-1</sup> Myoglobinuria	NA
16	M	6	Laryngitis [26]	? 5–10 (60 h)	Nodal bradycardia and tachycardia, VT Heart failure, metabolic acidosis Lipidaemia, fever, CK > 33 000 U.l <sup>-1</sup> Myoglobinuria	Inotropes Dantrolene
17	M	7	Focal motor status epilepticus [4]	20 (63 h)	Tachycardia, bradycardia, asystole Metabolic acidosis Rhabdomyolysis, CK 49992 U.l <sup>-1</sup> Acute renal failure, fever, hypoxia	Propofol infusion ceased inotropes, phenylephrine Dialysis

Table 1 (Continued).

Case No.	Sex (M/F)	Age; years	Diagnosis [Reference]	Mean dose; mg.kg <sup>-1</sup> .h <sup>-1</sup> (duration)	Clinical features	Treatment
18	F	13	Closed head injury [9]	6 (96 h)	RBBB, circulatory failure SAH, SDH Metabolic acidosis, fever, pneumonia Rhabdomyolysis	Propofol infusion ceased Inotropes
19	F	3.08	Aspiration pneumonia [12]	20 (15 h) ceased for 13 h, then 4.2 (8 h)	Bradycardia, VEB's, Incomplete RBBB Metabolic acidosis, BE < -10 lipidaemia, fever, hepatomegaly Rhabdomyolysis, CK 2000 U.l <sup>-1</sup>	Inotropes Propofol infusion ceased External pacemaker Transvenous pacemaker
20	M	10	Status epilepticus [11]	NA (>48 h)	RBBB, polymorphic VT, Torsades de pointes Cardiac failure, hyperlipidaemia, fever Metabolic acidosis, hepatomegaly	Lidocaine, Magnesium, Propofol infusion ceased Esmolol, inotropes

NA, not applicable; RBBB, right bundle branch block; BE, base excess; VF, ventricular fibrillation; VT, ventricular tachycardia; CK, creatine kinase; SAH, subarachnoid haemorrhage; SDH, sub-dural haematoma; VEB, ventricular ectopic beats.

PRIS mimics the mitochondrial myopathies in which there are specific defects in the mitochondrial respiratory chain associated with mitochondrial DNA abnormalities [45]. The clinical features of a mitochondrial myopathy result from a disturbance in lipid metabolism in cardiac and skeletal muscle. The patients are well until stressed by infection or starvation, when they metabolise fat to produce energy. Under these conditions, they develop severe rhabdomyolysis, cardiac and hepatic insufficiency associated with hypoglycaemia [45, 46]. Steiner et al. [47] and Farag et al. [48] recommended that propofol should not be used in patients with an inborn error of mitochondrial fatty-acid metabolism (very long chain acyl-coenzyme A dehydrogenase deficiency) because it interfered with fatty-acid oxidation and caused severe metabolic acidosis.

### Pathophysiological features of PRIS

One common feature of PRIS is myocardial failure and cardiovascular collapse. Several cellular mechanisms have been postulated to explain how propofol alters cardiac contractility and rhythm. Propofol causes bradycardia (as it reduces sympathetic more than parasympathetic tone) and decreased myocardial contractility due to antagonism of beta adrenoreceptors and calcium channels [7,31]. Excess serum fatty acids have pro-arrhythmic effects, and this may explain the ventricular arrhythmias associated with PRIS [44]. Histological studies of the myocardium and skeletal muscle of patients who have died from PRIS showed signs of severe myocytolysis causing cardiac and skeletal muscle rhabdomyolysis [49]. On microscopy, skeletal muscle

showed a disorganisation of myofibrils and sarcomeres with an acute necrosis of the muscle fibres (swelling, loss of striations and vacuoles, and degenerate nuclei). Histopathological examination of the heart revealed numerous focal areas of myofibril degeneration surrounded by an acute inflammatory reaction with macrophages and neutrophils [8]. The imbalance between cellular energy production and utilisation in peripheral and cardiac muscle is the key pathogenic mechanism that causes peripheral and cardiac muscle necrosis, and the accumulation of toxic fatty acids. Rhabdomyolysis causes myoglobinuria, acute renal failure and secondary hyperkalaemia [45].

During the publication of the early cases of PRIS, it was suggested that the syndrome may be caused by untreated sepsis; or that metabolic acidosis was a consequence of renal failure and the ensuing arrhythmias were due to acidosis alone [50–52]. Ahlen et al., in a review sponsored by AstraZeneca (the manufacturers of Diprivan<sup>TM</sup>), argued that the cardiovascular features of PRIS could be explained by sepsis and systemic inflammatory response in most of the case reports [53]. In a large number of reports involving patients with head injuries and cerebral oedema, they suggested that the use of fluid restriction and vasopressors were relevant causative factors as these ultimately impaired tissue perfusion. They also suggested the rhabdomyolysis could be explained by inadequate oxygen supply to the skeletal muscle, which leads to anaerobic metabolism and, if severe, causes muscle cell death with rhabdomyolysis and increased serum creatinine levels. Rhabdomyolysis may be associated with the administration of high doses of steroids in some of the case reports.

**Table 2** Survivors in paediatric PRIS patients.

Case No.	Sex (M/F)	Age; years	Diagnosis [Reference]	Mean dose; mg.kg <sup>-1</sup> .h <sup>-1</sup> (duration)	Clinical features	Treatment
1	F	1.67	Epiglottitis [28]	7.4 (56 h)	Bradycardia, asystole Metabolic acidosis, BE – 17 Lipidaemia, renal failure, fever Rhabdomyolysis, CK > 100 000 U.l <sup>-1</sup>	Propofol infusion ceased Adrenaline, dobutamine, Ca <sup>++</sup> Bicarbonate infusion Veno-veno haemofiltration
2	M	4	Laryngitis with sub-glottic stenosis [33]	8.6 (3 days)	Lipidaemia, elevated serum carnitine Rhabdomyolysis, CK 127 000 U.l <sup>-1</sup> Pulmonary hypertension	Propofol infusion ceased Bicarbonate Veno-veno haemofiltration
3	F	0.83	Upper respiratory tract obstruction due to oesophageal foreign body [29]	10 (50.5 h)	RBBB, 1st degree HB, bradycardia Metabolic acidosis, BE – 13 Lipidaemia, fever, hepatomegaly Rhabdomyolysis, CK 31785 U.l <sup>-1</sup>	Propofol infusion ceased Cardiac pacing Plasmapheresis Veno-veno haemofiltration
4	NA	1.5	Bilateral talipes repair under GA [41]	6 (5 h)	Bradyarrhythmias Cardiac failure, acute renal failure Metabolic acidosis, BE – 17	Bicarbonate infusion Inotropes Peritoneal dialysis
5	M	2	Gunshot wound to head [27]	5.2 (72 h)	Nodal bradycardia, cardiac failure acute renal failure Metabolic acidosis, BE – 10 Rhabdomyolysis, myoglobinaemia Lipidaemia, Troponin 0.04 µg.l <sup>-1</sup> Elevated total carnitine 66 µmol.l <sup>-1</sup> Elevated C5 acylcarnitine 8.4 µmol.l <sup>-1</sup> Elevated manonylcarnitine 3.3 µmol.l <sup>-1</sup>	Propofol infusion ceased Isoprenaline Transvenous pacing Haemofiltration
6	M	13	AVM resection PICU sedation post op [32]	NA (4 days)	Cardiac failure, Rhabdomyolysis ARF	Propofol infusion ceased ECMO Haemodialysis
7	M	7	Osteogenesis imperfecta ORIF femur under GA Respiratory tract infection [55]	13.5 (2.4 h)	Metabolic acidosis, BE – 8.3	Propofol infusion ceased
8	F	5	Embolisation of cerebral AVM, PICU post op [54]	Range 6–15 (10 h)	Metabolic acidosis, BE – 5.6	Propofol infusion ceased
9	M	0.42	Cleft lip repair PICU sedation post op [30]	11.7 (approx. 72 h)	Tachy- and bradyarrhythmias, VT Cardiac failure, metabolic acidosis Lipidaemia, rhabdomyolysis Acute renal failure, liver failure Coagulopathy Elevated free acylcarnitine intermediates	Propofol infusion ceased inotropes External pacing Charcoal haemoperfusion Dialysis
10	M	13	Parietal AVM resection PICU sedation post op [31]	Range 3–8.4 (> 74 h)	Increased QT interval, polymorphic VT Cardiac failure Metabolic acidosis Rhabdomyolysis ARF, myoglobinuria Pulmonary Oedema	Propofol infusion ceased Cardioversion Lidocaine, amiodarone Inotropes, bicarbonate ECMO Haemodialysis
11	F	11	Recurrent seizures [42]	4.7 (130 h)	Elevated C4 acyl-carnitine 2.1 µmol.l <sup>-1</sup>	Propofol infusion ceased
12	M	7	Craniosynostosis PICU sedation post op [50]	NA (0.66 h)	Metabolic acidosis, BE – 7.8	Propofol infusion ceased

Abbreviations – see Table 1. Plus PICU, paediatric intensive care unit; ARF, acute renal failure; ECMO, extra-corporeal membrane oxygenation; AVM, arterio-venous malformation; GA, general anaesthesia.

Hepatomegaly and fatty change associated with PRIS may be mediated by several mechanisms. Bray [5] suggested it is caused by hepatic congestion secondary to cardiac failure. Fat infiltration of organs may be caused

by the high lipid content of propofol [5]. Parke et al. proposed that, in critically ill patients, enhanced sympathetic nervous system stimulation, cortisol and growth hormone increased lipolysis and fat oxidation, resulting in

**Table 3** Deaths in adult PRIS patients.

Case No.	Sex (M/F)	Age; years	Diagnosis [Reference]	Mean dose; mg.kg <sup>-1</sup> .h <sup>-1</sup> (duration)	Clinical features	Treatment
1	M	17	Refractory epilepsy [4]	11.2 (44 h)	Wide complex bradycardia, asystole Hypotension, hypoxia, metabolic acidosis Rhabdomyolysis, hyperkalaemia, fever	Propofol infusion ceased Bicarbonate, calcium Atropine
2	NA	>18	Closed head injury [14]	7.6 (55 h)	Cardiovascular collapse Metabolic acidosis, acute renal failure	NA
3	F	47	Asthma [8]	12 (> 48 h)	VT, asystole, metabolic acidosis Myoglobinuria, ARF, hyperkalaemia CK 762 000 U.l <sup>-1</sup> , troponin I 4 mg.l <sup>-1</sup>	Dopamine, phenylephrine Haemodialysis
4	M	18	Closed head injury Intracerebral haemorrhage [10]	Range 5.8–7.6 (98 h)	LBBB, bradycardia, PEA, asystole Cardiac failure, lipidaemia, fever Metabolic acidosis, BE – 24 Myoglobinuria, hyperkalaemia	Atropine, adrenaline
5	NA	16–55	Head injury [3]	7.3 (> 58 h)	VT, rhabdomyolysis, hyperkalaemia	NA
6	NA	16–55	Head injury [3]	5.7 (> 58 h)	Sinus tachycardia, SVT Cardiac failure, metabolic acidosis, Rhabdomyolysis, hyperkalaemia	NA
7	NA	16–55	Head injury [3]	6.6 (> 58 h)	AF, VT, metabolic acidosis, lipidaemia	NA
8	NA	16–55	Head injury [3]	5.5 (> 58 h)	Metabolic acidosis, hyperkalaemia ST, idioventricular rhythm, cardiac failure	NA
9	NA	16–55	Head injury [3]	7.4 (> 58 h)	Metabolic acidosis, rhabdomyolysis SVT, VT, cardiac failure, metabolic acidosis	NA
10	NA	16–55	Head injury [3]	5.8 (> 58 h)	Rhabdomyolysis, hyperkalaemia SVT, Nodal rhythm, VT, lipidaemia	NA
11	NA	16–55	Head injury [3]	6.9 (> 58 h)	Metabolic acidosis, hyperkalaemia Sinus tachycardia, idioventricular rhythm Metabolic acidosis, lipidaemia, hyperkalaemia	NA
12	F	21	AVM embolisation [6]	4.5–9 (>48 h)	Cardiac failure Metabolic acidosis, BE – 19.1, lactate 15 mmol.l <sup>-1</sup>	Propofol infusion ceased Dopamine
13	F	23	Status epilepticus [15]	12 (106 h)	Tachycardia, cardiac failure, metabolic acidosis Acute renal failure, hyperkalaemia	NA
14	M	31	Closed head injury and seizure [7]	4.1 (157 h)	Polymorphic VT, VF, metabolic acidosis Hyperlipidaemia, rhabdomyolysis Acute renal failure, CK 11 000 U.l <sup>-1</sup>	NA
15	M	42	Cerebral sinus thrombosis [13]	0–8.6 (>120 h)	Cardiac failure, metabolic acidosis acute renal failure, CK 22426 U.l <sup>-1</sup>	Propofol infusion ceased Phenylephrine
16	F	27	Seizures after AV malformation embolisation [20]	dose NA; 36 h	Metabolic acidosis, hypotension bradycardia	Inotropes, pacing, fluids
17	M	64	Status epilepticus [20]	dose NA; 24 h	Metabolic acidosis, rhabdomyolysis hypotension, raised CPK, cardiac arrest	Inotropes, bicarbonate
18	F	24	Status epilepticus, encephalitis [20]	dose NA; 44 h	Bradyarrhythmias, hypotension Metabolic acidosis	Inotropes, cardiac pacing

Abbreviations – see previous tables plus LBBB, left bundle branch block; PEA, pulseless electrical activity; SVT, supraventricular tachycardia; VT, ventricular tachycardia; AF, atrial fibrillation; CPK, creatinine phosphokinase.

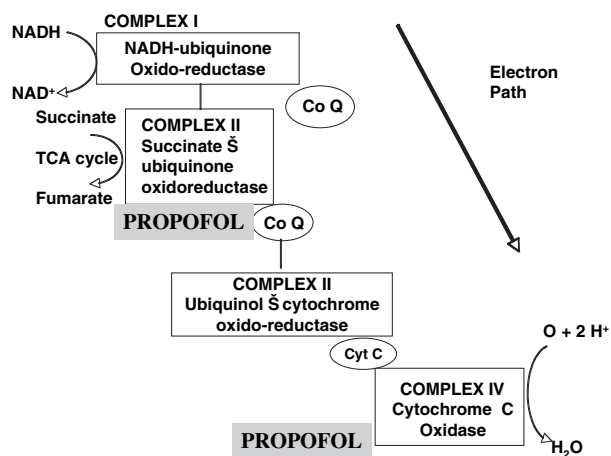
a large increase in circulating non-esterified fatty acids [2]. Ahlen et al. [53] suggest that hypoperfusion, hypoxia, sepsis, hypermetabolic states, and vasopressor therapy impair liver function and exacerbate hyperlipidaemia. Normal lipid metabolism in the liver requires carbohydrate substrates. The authors postulated that as a result of depletion of carbohydrate stores in the critically ill

patient, lipid accumulation associated with the high propofol infusion rates is not a direct toxicity of propofol but rather a consequence of exhaustion of carbohydrate stores. However, this cannot explain the occurrence of the syndrome in some patients who developed signs of PRIS during a relatively short anaesthetic. The possibility of a genetic predisposition cannot be excluded.

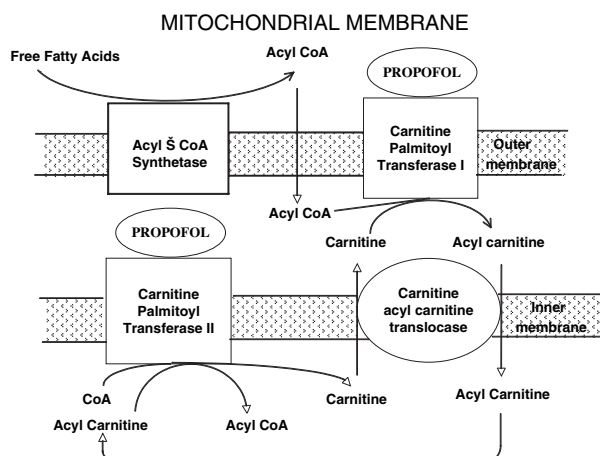
**Table 4** Survivors in adult PRIS patients.

Case No.	Sex (M/F)	Age; years	Diagnosis [Reference]	Mean dose; mg.kg <sup>-1</sup> .h <sup>-1</sup> (duration)	Clinical features	Treatment
1	F	30	Asthma [37]	NA (12.75 h)	Metabolic acidosis, lactate 8.6 mmol.l <sup>-1</sup>	Propofol infusion ceased
2	M	41	Asthma [8]	NA (ca 144 h)	Cardiac failure Rhabdomyolysis, CK 204 000 U.l <sup>-1</sup> Myoglobinuria acute renal failure Troponin I 46 µg.l <sup>-1</sup>	NA
3	F	31	Propofol TIVA RFA pulmonary vein [17]	4.98 (6.6 h)	Metabolic acidosis	Propofol infusion ceased Bicarbonate
4	M	64	Propofol TIVA Laparoscopic radical prostatectomy [17]	7.8 (ca 4.5 h)	Tachycardia Metabolic acidosis	Propofol infusion ceased
5	F	17	Closed head injury Intra-abdominal haemorrhage [13]	> 4 (> 48 h)	Metabolic acidosis Rhabdomyolysis	Propofol infusion ceased Haemodialysis
6	M	42	Brainstem resection of cavernous angioma [18]	Range 2.3–9 (21 h and 7.5 h)	Metabolic acidosis ARF Rhabdomyolysis Myoglobinuria	Propofol infusion ceased
7	M	40	C-spine stabilisation (TIVA propofol) Post op sedation in ICU [19]	3 (72 h)	Metabolic acidosis Rhabdomyolysis ARF Fever 41 °C	Dantrolene Propofol infusion ceased Veno-veno haemofiltration
8	F	18	Status Asthmaticus [37]	NA (3 h)	Metabolic acidosis, BE – 10, lactate 12 mmol.l <sup>-1</sup>	Propofol infusion ceased
9	M	45	Cardiac surgery [21]	2.6 (8 h)	Metabolic acidosis, VT, cardiac failure	Propofol ceased, inotropes Amiodarone
10	M	30	Quadriplegia, sepsis [22]	5.5 ( 56 h)	Atrial fibrillation, lactic acidosis, raised CPK Cardiac ischaemia	Propofol ceased
11	M	21	Head injury [23]	6.8 (42 h)	Tachycardia, cardiac dysfunction, metabolic acidosis BE 13.4; renal failure	Acidosis improved when propofol ceased

Abbreviations – see previous tables plus TIVA, total intravenous anaesthesia.

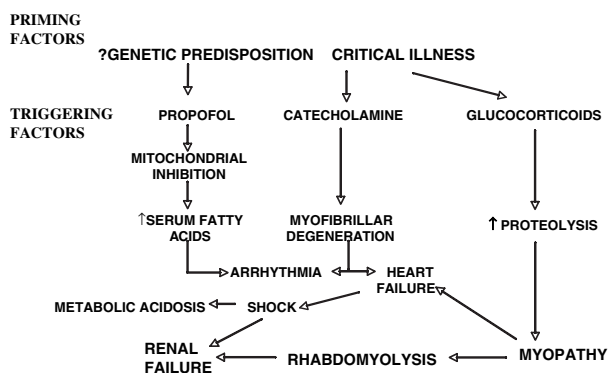


**Figure 2** Inhibitory actions of propofol at the mitochondrial electron transport chain. Inhibition of coenzyme Q at Complex II and cytochrome c at Complex IV causes a failure of ATP production. Co Q = coenzyme Q; Cyt C = cytochrome c.



**Figure 3** Effects of propofol on fatty acid metabolism at the mitochondria. Sites where propofol inhibits the conversion of free fatty acids to acyl-coA causing a failure of fatty acid oxidation and ATP production.





**Figure 4** Factors that predispose to the propofol infusion syndrome. Critical illness or genetic factors may be ‘priming’ factors, and propofol, catecholamines and glucocorticoids are triggering factors that precipitate the systemic disturbances of propofol infusion syndrome.

Vasile et al. proposed ‘priming factors’ and ‘triggering factors’ that contribute to PRIS [49]. The ‘priming factors’ include endogenous catecholamines, glucocorticoids, systemic inflammation and cytokine production in critically ill patients [Fig. 4]. High dose propofol and exogenous catecholamines and corticosteroids are the ‘triggering’ factors. In the critically ill patient, endogenous and exogenous catecholamines contribute to cardiac and peripheral muscle injury. Vasile et al. [49] noted that myofibrillar degeneration (or coagulative myocytolysis) in cardiac and skeletal muscle was associated with high blood levels of exogenous and endogenous catecholamines. In addition, catecholamine-induced lipolysis increases the circulating free fatty-acid load, and this compounds the pathology. Steroids may also have a triggering role in acute muscle damage. Several critically ill patients who presented with PRIS received high dose steroids during the treatment in the ICU. It is suggested that steroids induce proteolysis of the cardiac contractile myofilaments.

### Preventing PRIS in the critically ill

Carbohydrate stores are depleted more rapidly in children than in adults and this may explain the higher prevalence of PRIS in children. In critically ill patients, an inadequate supply of carbohydrate to the patient promotes the mobilisation of fat stores and increases fat metabolism [43]. This increases the circulating fatty-acid load and predisposes to PRIS. It is suggested that early adequate carbohydrate intake can prevent PRIS by preventing the switch to fat metabolism [27, 46]. Certainly the larger carbohydrate stores in adults may explain the lower incidence of this syndrome in adults. Wolf et al. suggested

that a carbohydrate intake of  $6\text{--}8\text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  can suppress fat metabolism in critically ill children and thus prevent PRIS [27].

A major concern with propofol is the lipid load owing to its formulation. A daily intravenous lipid load of  $2\text{--}3\text{ g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  is regarded as adequate for children on total parenteral nutrition (TPN). This is equivalent to a fat load conferred by a 1% propofol infusion running at  $4\text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ . As most of the reported cases of PRIS were associated with infusion rates greater than  $4\text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ , it is postulated that the excessive lipid load may be a contributory factor [43]. The use of a more concentrated propofol solution ( $60\text{ mg}\cdot\text{ml}^{-1}$ ) can reduce the lipid load [54].

### Early markers of PRIS

There is much interest in the identification of an early marker of PRIS. Unexplained metabolic acidosis, elevated serum lactate, creatine kinase and myoglobin levels or hyperlipidaemia may all herald the onset of PRIS. Three case reports suggested that early onset lactic acidosis after the start of propofol infusions in the absence of other causes may be an early marker of PRIS. Koch et al. described the clinical course of a 5-year-old girl who was sedated with high dose propofol infusion in the ICU after embolisation of a cerebral arteriovenous malformation (AVM). She developed lactic acidosis (peak values: lactate  $5.3\text{ mmol}\cdot\text{l}^{-1}$ , BE  $-5.6\text{ mmol}\cdot\text{l}^{-1}$ , pH 7.31) 6 h after a propofol infusion was started at  $15\text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ . The acidosis resolved when propofol was ceased. No other features of PRIS were present [55]. Kill et al. reported that a 7-year-old boy with osteogenesis imperfecta undergoing surgery to the distal femur developed lactic acidosis following a 150-min propofol anaesthetic (mean infusion rate of  $13.5\text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) [56]. Haase et al. reported that elevated serum lactate levels ( $2.7\text{ mmol}\cdot\text{l}^{-1}$ ) were detected only 1 h after a short 40-min propofol infusion (total dose  $6.1\text{ mg}\cdot\text{kg}^{-1}$ ). The patient had an uneventful general anaesthetic but was transferred to PICU post-operatively. Serum lactate levels peaked at  $9.4\text{ mmol}\cdot\text{l}^{-1}$  7 h after admission to PICU, then returned to near normal over the next 10 h [57].

Onur et al. investigated the effect of propofol infusion on acid-base status and liver and myocardial enzyme levels during short-term anaesthesia in children. The only statistically significant findings were a lower pH and higher triglyceride level in the propofol group ( $p < 0.05$ ). However, the changes were not clinically important [58]. Elevated malonylcarnitine or acylcarnitine levels (C2, 4, or 5) indicate impaired fatty-acid metabolism and may be potential early makers of the onset of PRIS, but these

tests are not readily available in most hospital laboratories [27, 43].

Hypertriglyceridaemia is well documented in many PRIS patients [2, 43]. A significant rise in serum triglyceride occurs even in short-term propofol infusions in healthy patients without adverse effects [59]. A role of serum triglycerides as an early marker of PRIS is therefore unlikely. Monitoring serum creatine kinase and myoglobin levels has been suggested but its utility as an early marker of PRIS is questionable [60].

Electrocardiographic changes in a patient receiving a propofol infusion may warn the clinician of an impending PRIS. The development of coved ST elevations in the right precordial leads (V1 to V3), similar to that seen in the Brugada syndrome, may be the first sign of cardiac instability that is commonly associated with PRIS [38].

## Management

The successful management of PRIS relies on a prompt recognition of the early signs. The propofol infusion should be stopped and an alternative sedation agent should be used. Cardiorespiratory support and haemodialysis or haemofiltration are required. Conventional circulatory support measures have had limited success in the treatment of patients with PRIS. Many case reports highlight the refractory nature of this condition to intravenous fluid volume support and the use of escalating doses of inotropes [2, 4, 6, 8–10, 12, 24]. Limited success has been achieved with cardiac pacing (both transvenous and external) [2, 12, 27–32]. Two reports have recorded the successful use of extracorporeal membrane oxygenation (ECMO) for oxygenation and circulatory support [31, 32]. Haemodialysis or haemofiltration has been advocated to decrease the blood levels of metabolic acids and lipids, and has been the most effective treatment of severe PRIS when combined with cardiorespiratory support [13, 19, 27–32].

The heterogeneity of the details and the lack of good metabolic and cardiovascular data has made it more difficult to accept PRIS as a distinct clinical entity. There is great uncertainty surrounding PRIS and much debate has been stimulated [33, 60–64]. There are now adequate data that suggest that infusion rate and duration of propofol administration can be relevant factors for the development of the syndrome, especially in critically ill patients treated in the intensive care units. Precautionary statements about propofol use in intensive care [64] and anaesthesia can be made. It is recommended that a propofol infusion rate of greater than  $4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  for longer than 48 h should be avoided. However, there are reports which indicate that PRIS can occur with high dose infusions of a shorter duration. Early metabolic

acidosis has been reported 1–4 h after the commencement of infusion [17, 56], and one patient reportedly developed PRIS after 5 h of infusion [41]. An idiosyncratic reaction or a genetic predisposition must be considered a possibility. Predisposing factors include young age, severe critical illness of central nervous system or respiratory origin, exogenous catecholamine or glucocorticoid administration, inadequate carbohydrate intake and subclinical mitochondrial disease [49]. Future research should be directed at establishing the precise pathophysiological cellular mechanisms of the syndrome, and the identification of a genetic predisposition, so that PRIS can be avoided in susceptible patients.

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