REVIEW ARTICLE

Propofol-Related Infusion Syndrome in Critically Ill Pediatric Patients: Coincidence, Association, or Causation?

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Over the past two decades numerous reports have described the development of a propofol-related infusion syndrome (PRIS) in critically ill adult and pediatric patients who received continuous infusion propofol for anesthesia or sedation. The syndrome is generally characterized by progressive metabolic acidosis, hemodynamic instability and bradyarrhythmias that are refractory to aggressive pharmacological treatments. PRIS may occur with or without the presence of hepatomegaly, rhabdomyolysis or lipemia. To date, the medical literature contains accounts of 20 deaths in critically ill pediatric patients who developed features consistent with PRIS. These reports have generated considerable discussion and debate regarding the relationship, if any, between propofol and a constellation of clinical symptoms and features that have been attributed to its use in critically ill pediatric patients. This paper reviews the literature concerning PRIS, its clinical presentation, proposed mechanisms for the syndrome, and potential management should the syndrome occur.

KEYWORDS adverse effect, lipemia, metabolic acidosis, pediatric intensive care, propofol infusion syndrome, sedation

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INTRODUCTION

Propofol is approved by the Food and Drug Administration (FDA) for induction of general anesthesia in patients older than 3 years of age, and maintenance of general anesthesia in patients older than 2 months of age.[1] Although it is also approved for sedation in critically ill adults who are intubated and mechanically ventilated, it is not labeled for this purpose in infants and children.[1] In fact, the manufacturer's product information stresses the fact that the drug lacks this approved labeling.[1] Despite the absence of FDA labeling, prolonged sedation with propofol has been used in critically ill pediatric patients who are mechanically ventilated.

see related article page 10

ABBREVIATIONS CK, creatine phosphokinase or creatine kinase; CK-MB, creatine phosphokinase myocardial band; CPT I, carnitine palmitoyl transferase; CPT II, carnitine acyltransferase II; ECMO, extracorporeal membrane oxygenation; EEG electroencephalogram; FDA, Food and Drug Administration; FFA, free fatty acids; MSOF, multi-system organ failure; PRIS, propofol-related infusion syndrome; PICU, Pediatric Intensive Care Unit; RBBB, right bundle branch block

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In 1997 Hatch reported that propofol was

being prescribed in virtually all pediatric intensive care units (PICU) in the United States.[2] Forty-five physicians from 12 PICUs in Australia and New Zealand completed a survey regarding their use of propofol for sedation.[3] Eighty-two percent reported its use in the PICU. Thirty-nine percent used propofol in ventilated children requiring longer-term sedation, 67% used maximum doses that might be considered large (≥ 10 mg/kg/hr), and 19% used propofol for more than 72 hours. The drug's use is also described in studies that evaluated propofol pharmacokinetics in neonates, infants, and children who required sedation while critically ill.[4-7]

In the last 15 years, numerous reports have described the development of a propofol-related infusion syndrome (PRIS) in critically ill patients who received continuous infusion propofol for anesthesia and sedation. The syndrome is characterized by progressive and refractory metabolic acidosis, lipemia, bradyarrhythmias, hepatomegaly, rhabdomyolysis, hemodynamic instability, culminating in cardiovascular collapse (Table 1). Although PRIS has been reported in all ages, its examination in adults is beyond the scope of this paper; hence, the reader is referred to a review of the topic in that population.[8]

PRIS was first commented on in 1990 when The Danish Side Effect Committee reviewed an adverse effect in a child.[9,10] This case involved a previously healthy 2-year-old admitted to an intensive care unit (ICU) with croup. The child developed hypotension, hepatomegaly, multisystem organ failure (MSOF) and subsequently died after receiving 10 mg/kg/hr of propofol for 4 days. Since the initial report, 29 cases of PRIS have been described in critically ill pediatric patients. It has been suggested that propofol may have been a factor in the deaths of 20 of those children.

To date, 10 peer-reviewed cases[11-20] and seven letters to the editor[21-27] have described PRIS in 22 infants and children. Two papers described another seven children whose information was obtained via anonymous personal communication.[9,10] Two retrospective studies[28,29] and one prospective study[30] reported the safe administration of propofol to critically ill pediatric patients. Although completed over five years ago, the results of a large multi-center, randomized, controlled trial of the safety of propofol for sedation in critically ill children have not been published.

Table 1. Presentation of the propofol-related infusion syndrome

Clinical Features
Asystole
Bradycardia (sudden onset)
Dysrhythmias
Greenish color to urine
Hypotension
Multi-System Organ Failure (enlarged liver, oliguria, anuria)
Laboratory Findings
Multi-System Organ Failure (hepatic transaminases and serum creatinine)
Hyperlipemia (serum triglycerides)
Metabolic acidosis (lactate, base deficit, anion gap)
Rhabdomyolysis (urinary myoglobin, serum creatine phosphokinase)
Fatty-Acid oxidation (total carnitine, C5-acylcarnitine, malonylcarnitine)
Autopsy Findings
Hepatic steatosis
Myoglobin casts in the renal tubules
Rhabdomyolysis of peripheral and cardiac muscles
Muscle Biopsy Findings
Basophilic fibers and histocytes
Decreased complex IV activity
Focal necrosis

These reports have generated considerable discussion and debate regarding the relationship, if any, between propofol and a constellation of features attributed to its use for sedation or general anesthesia in critically ill pediatric patients. This paper reviews the literature concerning propofol and a potentially fatal infusion syndrome in children that is characterized by progressive metabolic acidosis, lipemia, hypotension, MSOF and rhabdomyolysis that may culminate in cardiovascular collapse. The paper will also review proposed mechanisms and potential management options should the PRIS occur.

REVIEW OF THE MEDICAL LITERATURE

Case Series

To our knowledge, only two peer-reviewed

Table 2. Peer reviewed case series

Ref	Age* (Sex)	Diagnosis	Dose† (Duration) [max dose†]	Clinical Features	Treatment	Outcome	Autopsy‡ (Muscle Biopsy)
11	2.7 (F)	LTB	7.5§ (115 hr) [11.5]	MA, Lipemia, Hepatomegaly, BC, RBBB, Asystole	Dobutamine, Dopamine, Isoproterenol, Adrenaline, Atropine,Tris buffer‖	Died	Myocytolysis of cardiac muscle, No myocarditis. Microvesicular fatty changes in the liver (ND)
	1.33 (F)	LTB	7.4§ (66 hr) [8.0]	MA, Lipemia, Oliguria, ↑K, Hepatomegaly, BC, RBBB, Asystole	Dopamine, Adrenaline, Furosemide, Dobutamine, Isoproterenol, Dexamethasone, PD, AV hemofiltration‖	Died	ND (ND)
	1.83 (F)	LTB	10§ (76 hr) [13.6]	MA, Lipemia, BC, Asystole	Bicarbonate, High dose inotropic support, Pacing electrodes‖	Died	Hepatic steatosis, No myocarditis (ND)
	0.08 (F)	Bronchiolitis	8§ (74 hr) [10.7]	MA, Lipemia, Hepatomegaly, RF, ↓Ca, BC	Atropine, Isoproterenol, PD	Died	ND (ND)
	6 (M)	LTB	8.1§ (104 hr) [9.2]	MA, Lipemia, Anuria, BC, ↓BP, Asystole	Dobutamine, Adrenaline, Atropine, TVP‖	Died	Hepatic steatosis,Tubular debris in kidney (ND)
12	17 (M)	SZ	NR (44 hr) [17.5¶]	MA, ↑K , ↓Ca, Rusty brown urine, Anuria, ↑CPK, BC, ↓BP, Asystole	Sodium bicarbonate, Calcium gluconate, Atropine, Dopamine, Phenylephrine, Dialysis (type NR)‖	Died	Rhabdomyolysis of the diaphragm and other muscles, Myoglobin casts in the renal tubules (ND)
	7 (M)	SZ	NR (63 hr) [26.9¶]	MA, Tea-colored urine, ↑CPK, Anuria, ↓BP, TC, Asystole	Hydrocortisone, Dobutamine, Dopamine, Epinephrine, Phenylephrine, Dialysis (type NR)‖,#	Died	Rhabdomyolysis of limb muscles, Myoglobin casts in renal tubules, (ND)

AV, arteriovenous; BC, bradycardia; BP, blood pressure; Ca, calcium; CPK, creatine phosphokinase; F, female; K, potassium; LTB, laryngotracheobronchitis; M, male; MA, metabolic acidosis; ND, not done; NR, not reported; PD, peritoneal dialysis; PRIS, propofol-related infusion syndrome; RF, renal failure; RBBB, right bundle branch block; SZ, seizures; TC, tachycardia

** Years*

† mg/kg/hr

‡ Findings pertinent to clinical features noted in the PRIS

§ Average rate of infusion (mg/kg/hr)

‖ Given concurrent antibiotics

¶ Although dose reported as mg/kg/min, assumed µg/kg/min

 # Ketogenic diet prior to admission

case series have been published (Table 2).[11,12] The first publication described five previously healthy pediatric patients who developed signs of PRIS.[11] Patients were between the ages of 4 weeks and 6 years (80% < 3 years) and were hospitalized in three separate PICUs. Four children had laryngotracheobronchitis and one had bronchiolitis due to an upper respiratory tract infection. Three of the five children had blood cultures that were positive for *Branhamella catarrhalis*, respiratory syncytial virus, or parainfluenza virus 2, and all received antibiotics.

Within a day of the onset of respiratory disease each patient presented with pulmonary obstruction that required intubation and sedation. Average propofol infusion doses ranged between 7.4 to 10 mg/kg/hr with a maximum range of 8–13.6 mg/kg/hr. Total infusion times ranged from 66 to 115 hours. Metabolic acidosis

was noted within 24 hours of beginning propofol in three patients and within 72 and 98 hours in the remaining two. All five children had lipemic serum, bradyarrhythmia and myocardial failure that progressed to asystole. Resuscitation efforts were unsuccessful despite aggressive use of pharmacological therapies. It is unclear if propofol was discontinued prior to death in four of the patients; however, it was stopped 3 hours prior to death in the remaining patient. Autopsy was performed in three children and revealed myocytolysis of cardiac muscle without evidence of myocarditis, hepatic steatosis and tubular debris in the kidney. The authors noted that these findings rarely occur with laryngotracheobronchitis and that the clinical and pathological findings were inconsistent with sepsis or viral myocarditis. Because the patients had no underlying heart or other concomitant diseases, the authors concluded that propofol might have been a contributing factor. Cook, an intensivist who cared for two patients described in this report, noted that one child died almost 3 days after propofol was discontinued and that another had septicemia,[31] lending additional doubt as to any causative link of propofol with the patients' demise.

Hanna and Ramundo reported two cases of possible PRIS (Table 2).[12] The first occurred in a 17-year-old male hospitalized with seizures despite adequate anticonvulsants. Four days after admission, he was transferred to the PICU for general anesthesia and was given a 2 mg/kg loading dose of propofol that was followed by a continuous infusion (10 mg/kg/hr). Burst suppression on electroencephalogram (EEG) occurred within one hour and he was maintained with doses between 7.5–13.7 mg/kg/hr for 18 hours. Complex partial seizures occurred each time propofol was discontinued; hence, it was restarted and continued for an additional 44 hours at doses up to 17.5 mg/kg/hr. The child's urine became "rusty brown" in color and he developed metabolic acidosis, hyperkalemia, and hypotension by 48 hours. A transient fever with elevated WBC count occurred, and antibiotics were started. The patient became anuric requiring dialysis. He developed hypoxia and ultimately asystole that was refractory to bicarbonate, calcium gluconate and atropine. He died 84 hours after starting propofol. An autopsy revealed rhabdomyolysis of the diaphragm and other muscles, which was accompanied by myoglobin casts that filled the renal tubules.

The second case involved a 7-year-old male with seizures refractory to anticonvulsants and the ketogenic diet.[12] The child was transferred to the PICU and given propofol at a starting dose of 2 mg/kg/hr. The dose was titrated to 11 mg/kg/hr at which point clinical seizures terminated; however, EEG seizures continued despite aggressive propofol dosing of 26.9 mg/kg/hr. Thirty-eight hours after beginning propofol his urine became a "tea-color" and he developed anuria that required dialysis. Progressive hypotension, hypoxia and acidosis ensued and propofol was discontinued 63 hours after it was begun. The child died 78 hours after beginning propofol from dysrhythmias and subsequent asystole that was unresponsive to conventional therapy. Rhabdomyolysis of limb muscles, renal tubular myoglobin casts, and patchy aspiration bronchopneumonia were noted on autopsy. Hanna and Ramundo concluded that propofol should not be used to sedate children until it is proven safe.

Case Reports

Eight publications have described individual cases of PRIS (Table 3).[13-20] Strickland and Murray reported a case of fatal metabolic acidosis in an 11-year-old female with a three week history of lethargy and headache.[13] She developed increasing somnolence, decreased responsiveness and urinary incontinence due to possible seizures. A right temporal lobe astrocytoma was identified and an emergency posterior frontotemporal craniotomy was performed. The child was given vecuronium, isoflurane and propofol (2.3 mg/kg followed by 7 mg/kg/hr) for anesthesia. Six hours after surgery significant cerebral edema required resection of the right temporal lobe, and the child was given methylprednisolone. On day three urine output significantly decreased and the child developed hypotension and profound metabolic acidosis. The acidosis significantly improved following sodium bicarbonate, but marked hyperkalemia occurred. Ventricular tachycardia and fibrillation led to cardiac arrest. Cardiopulmonary resuscitation was unsuccessful despite aggressive therapy and the child died. Pertinent laboratory studies at

Table 3. Single peer reviewed case reports

Ref	Age* (Sex)	Diagnosis	Dose† (Duration) [max dose†]	Clinical Features	Treatment	Outcome	Autopsy‡ (Muscle Biopsy)
13	11 (F)	Astrocytoma	9.4§ (38 hr) [12]	MA, Lipemia, Oliguria, ↑K, Myoglobinuria, ↓BP, VT, VF, Asystole	Methylprednisolone, Dopamine, Bicarbonate, Glucose and insulin, Atropine, Lidocaine, Calcium chloride, Epinephrine, Bretylium‖	Died	NA (ND)
14	0.83 (M)	Viral URI	10§ (50.5 hr) [12.8]	MA, RAL, Lipemia, Oliguric, Enlarged liver, ↑LFT, ↑CPK, Myoglobinuria, RBBB, ↓BP, BC	Sodium bicarbonate, Dopamine, Isoproterenol, Epinephrine, Atropine, Carnitine, External cardiac pacing, Plasmapheresis, CVVH‖	Survived	NA (Myonecrosis, ↓ Cytochrome C oxidase activity)
15	13 (F)	CHI	6§ (96 hr) [6]	MA, ↑LFT, ↑SCr, Green urine, ↓BP, ↑CPK, RBBB, Wide QRS	Mannitol, Dopamine, Epinephrine‖	Died	Rhabdomyolysis of muscle, Myoglobin casts in renal tubules, No hepatic steatosis (ND)
16	2 (M)	CHI	5.2 (72 hr) [5.4]	MA, ↑K, ↑SCr, Oliguria, BC	Isoproterenol, Transverse pacing, Hemofiltration	Survived	NA (ND)
17	13 (M)	AVM	NR (74) [11.4]	MA, ↑SCr, Oliguria, Myoglobinuria, Dysrhythmias, Asystole	Magnesium, Potassium, Bicarbonate, Lidocaine, Amiodarone, Epinephrine, Norepinephrine, ECMO	Survived	NA (ND)
18	3 (F)	Choking	20§ (15 hr) 4.2§ (8 hr)	MA, RA, ↑CPK, ↑LFT, Enlarged liver, Bronchospasm, Lipemia, ↓BP, BC, ↓CO, Wide QRS, Dysrhythmias	Epinephrine, Dopamine, External cardiac pacing	Died	ND (ND)
19	0.42 (M)	Cleft lip repair	11.7 (61.75 hr) [15]	MA, Hepatic failure, Oliguria, ↑K, Lipemia, Rhabdomolysis, BC, ↓BP	Isoproterenol, Dopamine, Epinephrine, Transcutaneous pacing, Charcoal hemoperfusion, Hemodialysis	Survived	NA (ND)
20	10 (M)	SZ	5.5 (> 48 hr) 6-9 (NS)	MA, Lipemia, Enlarged liver, Rhabdomyolysis, PHT, ↓BP, VT, VF, RBBB	Lidocaine, Magnesium, Dopamine, Esmolol, Adrenaline#	Died	ND (ND)

AVM, arteriovenous malformation; BC, bradycardia; BP, blood pressure; CHI, closed head injury; CO, cardiac output; CPK, creatine phosphokinase; CVVH, continuous venovenous hemodialysis; ECMO, extracorporeal membrane oxygenation; K, potassium; LFT, liver function tests; MA, metabolic acidosis; NA, not applicable; ND, not done; NR, not reported; PHTN, pulmonary hypertension; RA, respiratory acidosis; RAL, respiratory alkalosis; RBBB, right bundle branch block; RF, renal failure; SCr, serum creatinine; SZ, seizures; URI, upper respiratory track infection; VF, ventricular fibrillation; VT, ventricular tachycardia

** Years*

† mg/kg/hr

‡ Findings consistent with the infusion syndrome

§ Average rate of infusion (mg/kg/hr)

‖ Given concurrent antibiotics

 # Ketogenic diet

the time of her arrest included lipemic serum, leukocytosis with a left shift and an elevated urine myoglobin. Although cultures of tracheal secretions were positive for *Haemophilus influenzae*, blood and urine cultures showed no growth. An autopsy was not performed. With

the exception of one hour when hypotension occurred, the average dose of propofol was 9.9 mg/kg/hr (8–12 mg/kg/hr). Although the duration of therapy was not reported, the child was hospitalized for 38 hours. The authors noted that hyperkalemia was exacerbated by the acidosis and significantly contributed to her cardiac arrest. With the exception of possible septic shock, the authors concluded that other causes of a metabolic acidosis were unlikely. The authors suggested that propofol might have contributed to the child's death, despite their inability to show that propofol was a causative factor.

The case reported by Cray et al. describes a healthy 10-month-old male with fever and lethargy due to a viral upper respiratory infection.[14] Although blood cultures were negative, leukocytosis was noted and cefotaxime was started. The infant was intubated after development of a croupy cough and difficulty swallowing. Sedation was inadequate despite scheduled and as needed midazolam and morphine, and propofol was begun (3.5 mg/kg/hr) and rapidly titrated to 7 mg/kg/hr. The next morning his urine was "olive green" and he had significantly elevated serum triglycerides. Except for 5 hours when he was given 12.8 mg/kg/hr, he received a mean propofol dose of 10 mg/kg/hr for 50.5 hours. The patient experienced a leak around the endotracheal tube and was taken to the operating room where he was extubated and propofol was discontinued. Over the next two hours his condition deteriorated. He had atrioventricular block with right bundle branch block (RBBB) accompanied by respiratory alkalosis and metabolic acidosis for which he was given sodium bicarbonate and dopamine. During transport to the PICU he developed bradycardia unresponsive to atropine and external pacing. On PICU admission he was hypotensive and had an enlarged liver. Twelve hours after propofol was stopped, the acidosis, hypocalcemia, hypoglycemia, and mild elevations in hepatic transaminases persisted. He had no response to bicarbonate, or large doses of isoprotenerol, dopamine and epinephrine. The child also failed cardiac pacing; however, cardiac index and ejection fraction were normal. Plasmapheresis did not improve his clinical status, but the acidosis did resolve following hemofiltration with bicarbonate predilution fluid. Hypotension also improved and pressors were stopped. Muscle necrosis characteristic of a single episode of myonecrosis was noted on muscle biopsy. Although he made a complete recovery, the authors concluded that propofol is not a safe agent for prolonged sedation when used at high doses in critically ill children.

Cannon et al. described a 13-year-old female found unconscious following a bicycle accident.[15] The patient had a closed head injury (Glascow Coma Score 3) with elevated intracranial pressure, diffuse cerebral edema and a small subarachnoid hemorrhage. The authors did not report the use of any corticosteroid, but did administer mannitol. Propofol was begun (6 mg/kg/hr) and continued for about four days. Prior to transfer to another facility, the patient became febrile, had an elevated WBC and was given broad-spectrum antibiotics. Upon admission to the PICU her serum creatinine and hepatic enzymes were elevated, she had "green urine," was acidotic and had significantly elevated cardiac enzymes. She was given dopamine, epinephrine and intravascular volume support for RBBB with widened QRS complexes and hypotension. Despite aggressive measures, the cardiac abnormalities and hypotension persisted and the child died. Subdural hemorrhage, diffuse cerebral edema, bilateral uncal herniation, right lower lobe pneumonia, bilateral pulmonary thromboemboli in the peripheral pulmonary vasculature of both lungs and rhabdomyolysis of skeletal muscle were reported on postmortem examination. Hepatic steatosis was not found. Tracheal aspirate cultures were positive for *Staphylococcus aureus* that was sensitive to vancomycin. The authors concluded that this was PRIS and suggested that agents other than propofol be used for long-term sedation.

A 2-year-old male who sustained an air pellet gun shot to the head was ventilated and sedated using an average of 5.2 mg/kg/hr (4–5.4 mg/kg/hr) of propofol over 72 hours.[16] Bradycardia and oliguria were noted on day four and propofol was discontinued. The cardiac dysfunction responded to isoproterenol and transverse pacing. Creatine kinase (CK), troponin T and myoglobin were all elevated. Although he developed metabolic acidosis, he made a complete recovery following hemofiltration.

Culp et al. described a 13-year-old male

admitted for elective craniotomy due to an arteriovenous malformation.[17] The child was given 3–8.4 mg/kg/hr of propofol intraoperatively for general anesthesia and admitted to the neurosurgical ICU where he was placed on a ventilator. Propofol was then used for sedation in doses ranging from 6–11.4 mg/kg/hr, which was discontinued 74 hours after surgery when he developed a prolonged QT interval, inverted T-wave, and hemodynamic instability. Subsequent ventricular tachycardia was unresponsive to cardioversion, magnesium, potassium, lidocaine, amiodarone and his metabolic acidosis did not resolve following aggressive sodium bicarbonate. Cardiogenic shock was refractory to epinephrine and norepinephrine. Renal dysfunction and rhabdomyolysis ensued. CK was significantly elevated, but CK-MB and troponin were normal. The patient was started on extracorporeal membrane oxygenation (ECMO). Forty-eight hours later both cardiac rhythm and ejection fraction had normalized and the ECMO was discontinued after a total of 60 hours with full recovery. The authors concluded that the features noted in their patient were consistent with PRIS and stressed the role of ECMO as a treatment option.

A healthy 3-year-old female was intubated and mechanically ventilated after choking on a piece of bread.[18] On admission she had aspiration pneumonia and new onset seizures. Midazolam, fentanyl and propofol were used for sedation. The child inadvertently received a large dose of propofol (20 mg/kg/hr) for 15 hours. Bronchospasm and combined respiratory and metabolic acidosis developed and propofol was discontinued. Lumbar puncture and EEG were normal and blood cultures were negative. Within 13 hours the child recovered; however, she continued to require sedation and propofol was reinstituted (4 mg/kg/hr). Eight hours later she developed resistant bradycardia, dysrhythmias and a metabolic acidosis. Although echocardiography noted normal contractility, she had a significant decrease in cardiac output and an external pacemaker was inserted. Despite a functioning pacemaker and aggressive pharmacological therapies the child died. Hepatic enzymes, CK and lactate were elevated and the serum was lipemic. Ten hours after the drug was stopped the plasma propofol concentration was 190 μg/L. The authors noted that a concentration of 400 μg/L is generally associated with a pharmacodynamic effect. Although an autopsy was performed, the autopsy and toxicology results were not reported.

A 5-month-old male with a history of gastroesophageal reflux, managed with cisapride and ranitidine, was admitted for surgical correction of a cleft lip and palate.[19] Propofol (1 mg/kg/hr) was used for sedation and was increased to 11 mg/kg/hr. Despite "grossly" lipemic serum the propofol dose was increased (15 mg/kg/hr) on the second postoperative day. Later that day the urine became a "green brown" color and a profound metabolic acidosis was noted. Although propofol was discontinued, the patient became hypotensive, oliguric and developed a variety of cardiac arrhythmias that were resistant to drug therapy and pacing. Hepatic failure, coagulopathy, acute renal failure, hyperkalemia, hyperphosphatemia and rhabdomyolysis developed 24–96 hours after propofol was stopped. The child survived following charcoal hemoperfusion and hemodialysis. The authors concluded that this case was similar to those previously reported and noted the successful use of dialysis.

Baumeister and colleagues reported PRIS in a 10-year-old male with intractable epilepsy who was given 5.5 mg/kg/hr of propofol.[20] The propofol was tapered over two days and the child began the fasting phase of the ketogenic diet. Twenty-four hours later seizures recurred and he was placed on 9 mg/kg/hr of propofol. The child developed a metabolic acidosis, hyperlipemia, rhabdomyolysis and cardiac instability including RBBB and ventricular arrhythmias. Serum CK and CK-MB were both markedly elevated. During this time he received 6 mg/kg/hr of propofol. Although the total duration of propofol infusion was not specified, it was continued for more than 48 hours. He died from myocardial failure. The authors concluded that propofol and the ketogenic diet should not be used concurrently.

Non-Peer-Reviewed Reports

Many of the above reports served as the impetus for several Letters to the Editor. We chose to present these in a separate section because many do not provide an in-depth review of the case and were not peer-reviewed. Seven cases involving patients ranging in age

Table 4. Cases published as letters to the editor

Ref	Age* (Sex)	Diagnosis	Dose† (Duration)	Clinical Features	Treatment	Outcome	Autopsy‡ (Muscle Biopsy)
21	0.083 (F)	Whooping Cough	10 mg/hr§ (96 hr)	Lipemia	NR	Survived	NA (NR)
22	1.67 (F)	Epiglottitis	5-10 (56 hr)	MA, BC, Lipemia, ↓BP, ↑LFT, Oliguria, Urine "dark," ↑CPK, Rhabdomyolysis, Asystole	Adrenaline, Dopamine Bicarbonate, Calcium, CVVH	Survived	NA (Focal necrosis with basophilic fibers and histocytes)
23	9 (M)	Stridor, Subglottic Stenosis	4.5‖ (72 hr)	BC, ↓BP, Enlarged liver, Heart block, Asystole	Atropine, Isoprenaline, Dobutamine, Adrenaline	Died	Mild hepatic steatosis (NR)
24	4 (M)	Laryngitis, Subglottic Stenosis	8.6 (96 hr)	Lipemia, PHT, ↑LFT, Urine dark, ↑CPK, Myoglobinuria, Rhabdomyolysis	Hyperhydration, Bicarbonate, Nitric oxide, Nitroglycerin, CVVH	Survived	(5% Fiber necrosis)
25	6 (M)	Acute laryngitis, Stridor	5-10 (60 hr)	MA, ↓BP, BC, VT, RBBB, ↑CPK, Myoglobinuria	Various inotropes, Dantrolene	Died	ND (NR)
26	1.5 (F)	Arthrogryposis Multiplex Congenita	6‖ (5 hr)	MA, BC, Lipemia, Dysrhythmias, Oligoanuria	Fluid restriction, Bicarbonate, Inotropic support, PD	Survived	NA (↓ Complex IV activity¶)
27	5 (F)	AVM	6-15 (10 hr)	MA	Glucocorticoids, Insulin, Labetalol	Survived	NA (NR)

BC, bradycardia; BP, blood pressure; CPK, creatine phosphokinase; CVVH, continuous venovenos hemodialysis; LFT, liver function tests; MA, metabolic acidosis; NA, not applicable; NR, not reported; PD, peritoneal dialysis; PHT, pulmonary hypertension; RBBB, right bundle branch block; VT, ventricular tachycardia

** Years*

† mg/kg/hr

‡ Findings consistent with the infusion syndrome

§ Units of 10 mg/hr confirmed per original publication

‖ Average dose; assumes a weight of 40 kg

¶ Suggestive of possible mitochondrial respiratory-chain enzyme deficiency

from 1 month to 9 years are described in Table 4.[21-27] All but two patients were admitted to the hospital with a diagnosis of respiratory difficulty. Propofol doses ranged from 4–15 mg/kg/hr and were infused from 5 hours to 4 days. The predominant clinical features were metabolic acidosis and cardiovascular events. Five patients recovered, two were treated with hemodiafiltration and one was managed with peritoneal dialysis.

Kirkpatrick and Cole described a 1-month-old female admitted for whooping cough (*Bordatella pertussis*).[21] Her serum became lipemic after four days of propofol 10 mg/hr (weight not provided) and the infusion was stopped. No metabolic acidosis or hemodynamic instability occurred and the infant made a full recovery. The second letter described a 20-month-old female with acute epiglottitis (negative cultures), who was intubated and sedated with chloral hydrate and propofol.[22] The propofol dose of 5–10 mg/kg/hr was continued for 56 hours. Metabolic acidosis and lipemic serum were noted on the third day and she developed bradycardia, hypotension, oliguria and asystole. The infant's cardiac arrest responded to adrenaline and dopamine; however, bradycardia continued despite treatment. A sodium bicarbonate infusion did not correct the acidosis. She developed myoglobinuria and was started on venovenous hemodiafiltration. The patient's condition improved over the next 24–48 hours and dialysis was discontinued. Symptoms recurred and hemodiafiltration was reinstituted

and continued for 21 days. Plasma carnitine concentrations were normal. Focal necrosis, basophilic fibers and histocytes were noted on muscle biopsy. The child was discharged on day 54 and there were no signs of neurological complications at 6 months follow-up. The authors concluded there were similarities between this case and those reported by others.

A 9-year-old male was admitted for stridor and subglottic stenosis. After receiving midazolam and morphine, he was changed to propofol and fentanyl.[23] The drug was stopped on the morning of the fourth day as the child improved. Later that day he developed T-wave inversion and a widening QRS. He was given a 50 mg bolus (1.25 mg/kg estimated) and was restarted on an average dose of 4.5 mg/kg/hr for 72 hours. The child rapidly developed bradycardia, complete heart block, and hypotension that did not respond to atropine or dobutamine. Impairment of ventricular function was noted on echocardiogram and his heart was enlarged on x-ray. He had an enlarged liver on physical examination, but did not develop a metabolic acidosis or lipemic serum. Within hours he developed asystole unresponsive to epinephrine and died. Microvesicular hepatic steatosis was noted on autopsy and there was no histological evidence of myocarditis. A nasopharyngeal culture was positive for influenza A. Bray concluded that this was a case of PRIS and that propofol should not be used in children.

Van Straaten et al. described a previously healthy 4-year-old male who was hospitalized with laryngitis and subglottic stenosis.[24] He was intubated and sedated for three days with 8.6 mg/kg/hr of propofol. On the third day progressive respiratory failure occurred and lipemic serum was noted; however, he did not have metabolic acidosis. The urine was dark in color, but no myoglobin was present. Propofol was stopped on the fourth day when he was diagnosed with pulmonary hypertension and rhabdomyolysis. He also had elevated CK and hepatic transaminases. Over the next seven days he developed worsening rhabdomyolysis with myoglobinuria. Five percent muscle fiber necrosis was noted on muscle biopsy. Serum total and free carnitine levels were slightly elevated; however, fatty acid oxidation was normal. The patient fully recovered following "hyperhydration," sodium bicarbonate and venovenous hemodiafiltration. The author concluded that propofol should not be used until there is a better understanding of the dosing relationship to a possible syndrome.

A previously healthy 6-year-old presented with progressive stridor due to acute laryngitis.[25] Propofol was given in doses ranging from 5 to 10 mg/kg/hr over 60 hours. Two days later a metabolic acidosis and a variety of cardiac dysrhythmias with progressive myocardial failure occurred. The patient's CK was elevated, but the CK-MB fraction was normal. Myoglobinuria was noted and his central body temperature increased to 41.5°C for which he was given dantrolene for suspected malignant hyperthermia. Within hours his blood pressure and body temperature normalized and his cardiac rhythm stabilized; however, despite these measures the child was pronounced brain dead.

Mehta and colleagues described an 18-month-old female with arthrogryposis multiplex congenita who was admitted for elective surgery.[26] Propofol was initiated at 6 mg/kg/hr and was continued for only five hours. Metabolic acidosis was noted after surgery and bicarbonate was given continuously for 36 hours. Arrhythmias developed and were treated with fluids and inotropic agents. Although the infant had lipemic serum, it was unclear if this was present before or after propofol was begun. Serum concentrations of amino- and organic- acids were normal; however, decreased cytochrome c oxidase activity was found on muscle biopsy. Oligoanuria ensued and peritoneal dialysis was started. There was no myoglobinuria. The patient completely recovered.

In a Letter to the Editor, Young and Manara describe a retrospective review of the use of propofol in 158 children over a three year period.[28] Seventy-one received propofol for sedation and 75% received an additional sedative. Median age was 9.5 years (range, 10 months–15 years). Patients with evidence of a respiratory tract infection did not receive propofol, and it was discontinued if lipemia was noted. Propofol was given alone or in combination with an opioid (74.6%). The median propofol dose was 3.1 mg/kg/hr (range, 0.6–6 mg/kg/hr) and the median duration of administration was 16 hours (range, 2–149 hr). There were no unexplained cases of metabolic acidosis, lipemia, hepatic, or cardiac failure.

Table 5. Cases published using personal communication

Ref	Age*	Diagnosis	Dose† (Duration)	Clinical Features	Outcome (Autopsy‡)
9,§ 10‖	2	Croup	10# (96 hr)	↓BP, Hepatomegaly, Multi-System Failure	Died (NR)
9¶	3.83	NR	200 mg/hr** (48 hr)	MA, Unspecified arrhythmia, Respiratory failure	Died (NR)
	1.08	Laryngitis, Encephalitis	6.3# (96 hr)	MA, BC, Hepatomegaly, Atrioventricular block	Died (Fatty changes to the liver)
9¶	1.83 or 2.5	Epiglottitis	5.2# (96 hr)	MA, BC, Hepatomegaly, Asystole	Died (Fatty changes to the liver)
	2.17	Croup	10.23# (96 hr)	MA, Hepatomegaly, Heart failure	Died (NR)
	0.5	CHD	1–6 (>72 hr)	BC, Hepatomegaly, Respiratory failure	Died (NR)
	8	SZ	15.2# (29 hr)	MA, BC, Asystole, ↑CPK, Myoglobinuria	Died (NR)

BC, bradycardia; BP, blood pressure; CHD, congenital heart disease; CPK, creatine phosphokinase; MA, metabolic acidosis; NR, not reported; SZ, seizures
** Years*
† mg/kg/hr
‡ Findings consistent with the infusion syndrome
§ Secondary reference from Danish Side Effect Committee
‖ Secondary reference from the Committee on Safety of Medicines
¶ Personal communication
 # Average propofol dose
*** Units correct per report*

Other Reports

Bray reported seven cases of PRIS.[9] One case has not been published in English and six were obtained via confidential personal communications with other practitioners. Patient demographics for these children are noted in Table 5. Although ages were provided, the age for one infant is unclear, but was either 1.8 or 2.5 years. The children presented with a URI (e.g., croup, epiglottitis, laryngitis), central nervous system disorders (e.g., seizures, encephalitis) or congenital heart disease. Dose and duration of therapy were unclear in two patients. One child was given 1–6 mg/kg/hr of propofol, but the authors failed to provide information regarding the time various doses were infused and simply listed duration as > 72 hours. The dose in the second child was reported as 200 mg/hr for 48 hours; however, the child's weight was not specified. The third patient received 15 mg/kg/hr for less than 48 hours.

Five of the patients developed metabolic acidosis, four became bradycardic, and four developed hepatomegaly. The oldest child was the only one to have muscle involvement (muscle rigidity, elevated CK, and myoglobinuria). Information regarding the presence of lipemic serum was not available for any patient. The author also failed to provide concurrent medications or pharmacological interventions. All children died. Autopsy was performed in two children; both had fatty changes in the liver.

Retrospective Studies

Pepperman et al. compared the safety of propofol to other sedatives in 198 critically ill patients who were admitted to two PICUs over a two year period.[29] Medical records of patients who required sedation and mechanical ventilation, with or without analgesia, were reviewed. Propofol was given to 106 patients, while 92 received other agents. Most patients also received morphine. Propofol was given at a mean dose of 3.39 mg/kg/hr (range, 0.4–30 mg/kg/hr) for 30

minutes to 156 days. Thirteen children in the propofol and 14 in the non-propofol group died. Patients were stratified by primary diagnosis as either respiratory (n = 46), cardiac (n = 110) or neurological (n = 42). Although 10 deaths occurred in patients with a primary respiratory diagnosis, there was no difference in the number of deaths in those given propofol (n = 6) versus other sedatives (n = 4).

Clinically significant metabolic acidosis occurred in 41 patients (38.7% propofol, 26.1% other). Patients in the propofol group ranged from 0.1–5 years of age; 62% were < 3 years old. Primary diagnoses in these patients included respiratory (n = 9), cardiac (n = 8) and neurological conditions (n = 1). Propofol doses ranged from 0.4–9 mg/kg/hr (45% > 4 mg/kg/hr) with a duration ranging from 16 to 144 hours (59% > 48 hours). Four patients who received propofol and six patients who did not developed a marked metabolic acidosis and died. The acidosis was not associated with either dose or duration of therapy. Only four patients with a metabolic acidosis also had lipemia. Three received propofol in doses (duration) of 1.3 mg/kg/hr (24 hr), 5.15 mg/kg/hr (13 days) and 5.2 mg/kg/hr (127 hr). Two of the three were receiving concurrent fat emulsions as part of their nutritional support. The authors concluded that there was no association between propofol and lipemia, metabolic acidosis or mortality; hence, propofol "compared favorably" to other sedatives used in critically ill pediatric patients.

Bray retrospectively reviewed the medical records of patients less than 12 years who had a primary diagnosis of a respiratory infection and were admitted to the PICU for more than 2 days. The study period occurred over a seven year period.[9] Only 44 patients were intubated for ≥ 48 hours and 26 of these received non-propofol sedatives. The author focused on 9 patients who had clinical features consistent with PRIS and received propofol for ≥ 48 hours at > 4 mg/kg/hr. Mean age, propofol dose and duration of therapy for the nine patients were 2.8 ± 3.0 years (median,1.3 years; range:,0.08–9.1 years), 7.27 ± 2.84 mg/kg/hr (median, 4.55 mg/kg/hr; range, 4.5–12.8 mg/kg/hr), and 123.3 ± 88.9 hours (median, 94 hr; range, 54-342 hr), respectively. Although three of these children developed signs consistent with PRIS and died, it is important to note that all three had been described previously.[11,23] These children received propofol in doses of 4.5, 8, and 8.1 mg/kg/hr for 72, 74, and 104 hours, respectively. Bradycardia resistant to treatment was accompanied by metabolic acidosis, lipemia, enlarged liver or liver with fatty changes. None of the patients developed rhabdomyolysis or myoglobinuria. The remaining six children, who survived, received 4.5 to 12.8 mg/kg/hr of propofol for 54–342 hr. Although none of these children developed bradycardia, lipemia, rhabdomyolysis or myoglobinuria, two patients had an enlarged liver and two developed metabolic acidosis. Clinical features of the syndrome did not occur in any of the 26 patients who did not receive propofol. Although the sample size was extremely small and included previously published data, Bray concluded that while he could not establish a direct causation there was an association between large doses and a prolonged duration of propofol and cardiac toxicity.

Cornfield and colleagues conducted a study in 142 critically ill children who were consecutively admitted to the PICU or bone marrow transplant unit over an 18-month period.[30] Although this was a retrospective study, data were collected concurrent with hospitalization. Propofol was used if conventional regimens (e.g., midazolam and morphine) failed to produce adequate sedation or if the addition of propofol would enable the doses of other sedatives to be decreased. Children who were hypotensive, bradycardic, had a low cardiac index, or a prior history of hypersensitivity to propofol were excluded. Propofol was infused at < 3 mg/kg/hr with an option for an additional 1 mg/kg bolus each hour; hence, the propofol dose never exceeded 4 mg/kg/hr. Efficacy was determined subjectively via nursing or physician notes and was measured using the incidence of accidental extubation and inadvertent removal of central venous or indwelling arterial catheters. Safety measures included assessment of heart and respiratory rates, blood pressure, and blood gas determinations.

The mean age of these 148 patients was 5.8 years (2 months–18 years). Admitting diagnoses included congenital heart disease, acute hypoxemic respiratory failure, leukemia or solid tissue tumor, sepsis, cystic fibrosis, tracheal reconstruction, epilepsy, renal insufficiency,

metabolic disease and other. All patients were adequately sedated and accidental extubation or unintentional removal of a central venous or arterial catheter did not occur. Additional sedation with a benzodiazepine or a combination of opiates was used in 62% of patients. There was no clinically important change in systolic or diastolic blood pressure or heart rate. Thirty-one percent of patients were on at least one vasoactive agent (i.e., dopamine, dobutamine, epinephrine or milrinone). Within the first 12 hours of propofol infusion vasoactive therapy did not change in 60% of patients, while 24% had an agent discontinued and 16% had one added.

Although a metabolic acidosis was noted in 10 patients, it was attributed to the primary diagnosis and resolved without pharmacological intervention or discontinuation of propofol. Only three of the ten children had a metabolic acidosis for more than one hour. The vast majority of patients received < 3 mg/kg/hr of propofol for < 48 hours, leading the investigators to conclude that 4 mg/kg/hr was a safe dose. Ten children died within one week of receiving propofol; however, all deaths were attributed to the patient's underlying disease.

Prospective Studies

Martin and colleagues conducted a trial in nine children (2.2 months to 8.7 years) who required concurrent propofol and fentanyl for sedation.[32] Continuous propofol infusion was administered in conjunction with fentanyl. Neither neuromuscular blocking agents nor other lipid products (e.g., parenteral nutrition) were given. The mean dose and duration of propofol infusion was 2.1 (1.5–2.8) mg/kg/hr and 35.3 hours, respectively. One child received propofol for 144 hours. No patient developed clinically important changes in heart rate, mean arterial pressure or central venous pressure. Likewise, there were no clinically important alterations in serum triglycerides, serum lactic acid, BUN, serum creatinine, or hepatic enzymes. Although the authors agreed that additional studies are needed, they concluded that propofol may be used safely in postoperative cardiac patients.

A multicenter, randomized, controlled clinical trial was conducted to evaluate the safety and efficacy of propofol for sedation during mechanical ventilation in critically ill children.[33-35] Patients were randomized to receive either 1% or 2% Diprivan (AstraZenca) or standard sedative agents. Patients were enrolled if they were between the ages of newborn through 16 years and were intubated and expected to receive sedation for at least 24 hours. Those with croup and epiglottitis were excluded.

A total of 327 children (205 males) were studied. Admitting diagnoses included: respiratory distress syndrome/pneumonia (50.2%), cardiac surgery (12.5%), sepsis (10.1%), and central nervous system disorders (8%). One-hundred thirteen patients received 2% Diprivan, 109 received 1% Diprivan and 105 received a standard sedation regimen. There was no difference in the mean PRISM score for the three groups. Patients at all but one center also received continuous infusion fentanyl. Lorazepam was the most frequently administered standard sedative (80%). Propofol dose was initiated at 5.5 mg/kg/hr and was titrated as needed to maintain a COMFORT score between 17 and 26.

Primary safety measures were assessed by blood gases and base excess at various time points. Secondary safety measures important to the assessment of the infusion syndrome included vital signs, hematology, serum chemistries, and urinalysis. There was no difference in blood gases, hemodynamic parameters, and renal function measures among the three treatment groups. Mean triglyceride and free fatty acid concentrations were higher in the propofol groups than in patients receiving standard sedative agents. The 1% propofol group generally had the highest values. A total of 25 patients died from the time of enrollment until the 28 day follow-up period (Table 6). Although statistical significance was not reported, the majority of these deaths occurred in those receiving propofol (n = 21), with the largest numbers of deaths occurring in the 2% group (n = 12). Eleven deaths in the propofol group occurred during sedation or within 24 hours of the end of sedation. Ten of the twenty-one deaths in the propofol groups (47.6%) and 1 death in the standard sedation group (25%) occurred at a single center. When the data was adjusted for the exclusion of this center, mortality for propofol (6% vs 3%) was significantly lower than observed with the standard sedative agents (compared to 19% and 4%).[36] Blumer

Table 6. Summary of clinical features reported in the 25 patients who died during the multi-center study

	2% Diprivan	1% Diprivan	SSA*
During Sedation or Within 24 hr After Discontinuing Sedation (n = 13)†			
Deaths	7	4	2
Multi-System Organ Failure	3	1	1
Hepatorenal Syndrome	1		
Cardiac Failure or Asystole	1	2	1
Sepsis or CNS Infection	3		
Respiratory Disorder or Failure	2	1	
Renal Failure	1		
Intraventricular Hemorrhage			1
7-day Follow-up Period (n = 7)†			
Deaths	4	3	
Multi-System Organ Failure	1	1	
Cardiac Failure or Asystole	1		
Sepsis or CNS Infection	1	2	
Respiratory Disorder or Failure	1	1	
Intraventricular Hemorrhage	1		
Deaths During the 28-day Follow-up Period†			
Deaths	1	2	2
Multi-System Organ Failure	1		1
Cardiac Failure or Asystole		1	
Respiratory Disorder or Failure		1	
Sepsis or CNS Infection			1

** Standard sedative agents*
† Patients included in more than one category

et al. also reported that "the overall mortality rate of 7.6% is comparable to values from other databases of mechanically ventilated PICU patients."[34] Although the study ended in July of 1998, the data have yet to be published. It is our understanding that the manuscripts describing the findings from the clinical trial are undergoing final revisions and should be submitted for publication in a peer-reviewed publication in the very near future (J Blumer, personal communication. May 2006).

In an American Academy of Pediatrics newsletter, Kelly and Bojko summarized the response of Dr. Jeff Blumer,[34,35] the lead investigator in the propofol trial, to the FDA.[36] Blumer noted that: 1) there was no statistically significant difference in mortality between the groups; 2) more than half of the deaths occurred 7 days after propofol was discontinued; 3) the primary investigators did not attribute any of the deaths to propofol; 4) mortality was not an endpoint of the study; and 5) patients who were "do not resuscitate" were included.

CRITICAL ANALYSIS

Similarities in Presentation

Reports describing PRIS have emanated from over 20 centers in the UK, Netherlands, Germany and the United States. Twenty-two cases have been described in 10 peer-reviewed reports[11-20] and seven letters to the editor.[21-27] An additional seven cases have been described anonymously via personal communication.[9,10] Mean ± SD age of 29 patients was 4.7 ± 4.5 years (median, 2.7 y; range, 0.08-17 y) with 52% being younger than 3 years. Gender was reported in 22 patients with 50% being male. Although there was no consistent diagnosis at hospitalization, 14 were admitted with an upper respiratory infection (i.e., laryngotracheobronchitis, epiglottitis, stridor, subglottic stenosis, or croup), 9 had some type of CNS insult (i.e., tumor, AVM, seizures), and 2 children had a foreign body obstruction.

Patients were prescribed propofol for both sedation and general anesthesia. The mean ±

SD dose of propofol was 9.2 ± 3.6 mg/kg/hr (median, 8.8 mg/kg/hr), and all patients received more than 4 mg/kg/hr (range, 5.2–20 mg/kg/hr). Dosage was unclear in two children.[21,23] Units of the propofol dose in one report were clearly in error (mg/kg/min)[12] and dose was not adjusted for weight in one child (200 mg/hr).[9] Although the duration of infusion was 66.4 ± 30 hours (median, 72 hr; range, 6-115 hr), duration in two patients was simply reported as > 48 and > 72 hours,[20] and many papers failed to note the duration of infusion for the maximum dosage rate. Most reports failed to note the patients' nutritional status, carbohydrate intake, or administration of fat emulsion as part of nutritional support.

The nature of some of the publications makes it difficult to determine if the clinical feature was simply not reported because the practitioners failed to make the assessment or if the feature was not present. For example, one report noted that their patient developed rhabdomyolysis, but failed to report any change in urine color, CK values, or urine studies.[19] The most common clinical features included metabolic acidosis, cardiovascular instability, lipemia, hepatomegaly and rhabdomyolysis (Table 7). Signs of rhabdomyolysis included a change in urine color, myoglobinuria, and elevated CK. Myocytolysis was confirmed by autopsy or muscle biopsy in some individuals. Not all reports were careful to note the time that clinical features appeared in relation to the duration of therapy or discontinuation of propofol. If one assesses the duration of therapy and the day on which a symptom/sign was first reported, most features of PRIS tended to cluster between days 2 to 4; however, there does not appear to be a time when any specific feature presented (Figure 1).

Concurrent medications were not reported for any of the seven patients described via personal communication. When reported, the majority of children (n = 17) were unsuccessfully managed with aggressive catecholamine therapies; however, the largest doses used were not reported. Only three reports noted administration of glucocorticoids.[12,13,28]

To date, the role of propofol has been questioned in the deaths of 20 of the 29 above cases. Autopsy was only performed in 7 of the 29 patients. Hepatic steatosis was noted in 6 patients, rhabdomyolysis was noted in 3 patients, and myoglobin casts were found in the renal tubules of 4 patients. Most reports failed to provide specific information concerning the duration of propofol therapy before the onset of symptoms and the initial presenting symptoms or signs of PRIS. Importantly, many authors failed to note when in the course of the disease the propofol was discontinued or when death or survival occurred in relation to discontinuation of propofol. For example, one child received propofol for 4 days prior to transfer to the author's institution.[15] The drug was discontinued when the child failed to awaken, but the reader is unaware of when it was discontinued in relation to hospital transfer or the child's death.

Table 7. Clinical features* of propofol-related infusion syndrome reported in 29 children and autopsy findings noted in nine

Cardiac Manifestations	
Bradycardia	19 (66%)
Hypotension	12 (41%)
Arrhythmia	15 (52%)
Asystole	12 (41%)
Hepatic Manifestations	
Increased liver enzymes	5 (17%)
Enlarged liver	12 (41%)
Hepatic steatosis	
Hepatic dysfunction	2 (7%)
Lipemia	14 (48%)
Metabolic acidosis	24 (83%)
Renal Manifestations	
Increased serum creatinine	2 (7%)
Oliguria	8 (28%)
Anuria	5 (17%)
Rhabdomyolysis	8 (28%)
Change in urine color	5 (17%)
Increased CPK	9 (31%)
Myoglobinuria	5 (17%)
Autopsy (n = 9)	
Hepatic steatosis/fatty liver	6 (67%)
Myoglobin casts in renal tubules	4 (44%)
Rhabdomyolysis	3 (33%)

** Patients may be included in more than one category*

Possible Mechanisms for PRIS

If there is an association between propofol and an infusion syndrome, it would be important to determine the mechanism(s) that might explain the spectrum of clinical features noted in these patients. Because many of the

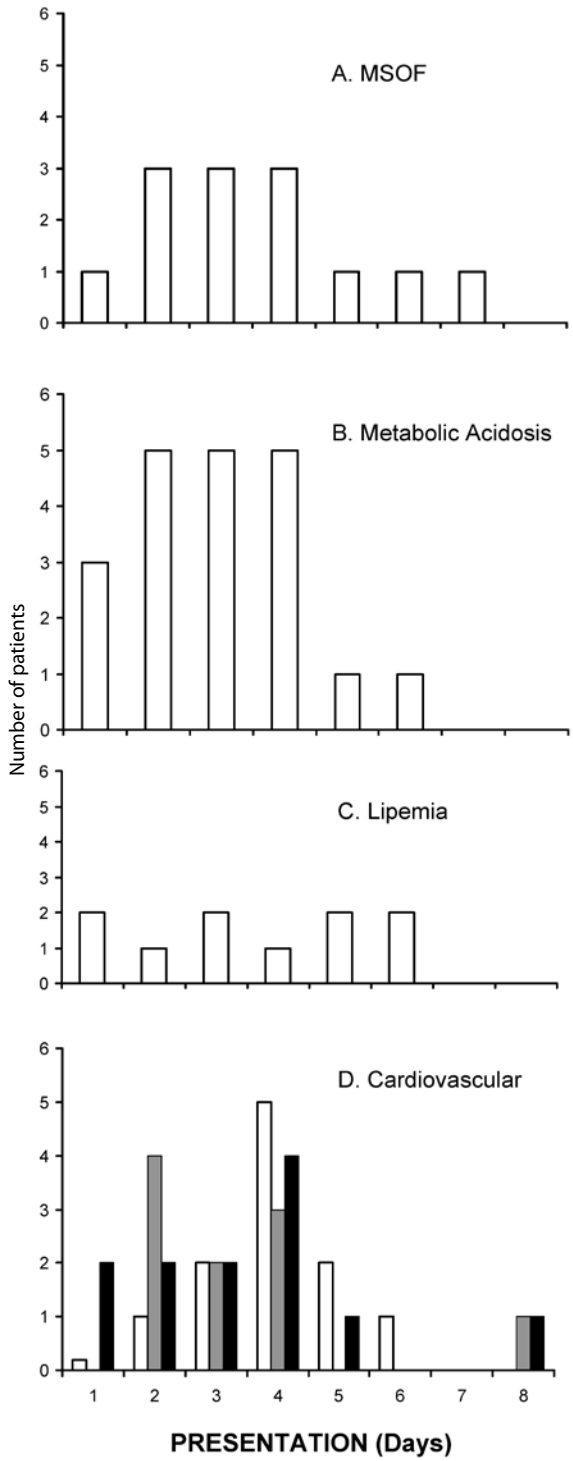

Figure 1. Description of clinical findings associated with PRIS in 29* patients and day the sign or symptom was first described. MSOF, multi-system organ failure. Panel D. Cardiovascular; □ = bradycardia; ▒ = hypotension; ■ = dysarrhythmia
* some patients developed more than one symptom

features (e.g., acute CNS injury, multi-system organ failure, sepsis/infection) and some of the concurrent medications (e.g., catecholamines, steroids) have all been associated with the signs and symptoms of PRIS makes it very difficult to assign causation to any one variable. Several authors have hypothesized a variety of mechanisms for PRIS including a pharmacological basis, a propofol metabolite, product formulation, contamination of the propofol emulsion, and malignant hyperthermia. Others have speculated that endogenous catecholamine and glucocorticoids may serve as "priming factors" for muscle injury and that propofol and exogenous catecholamine and corticosteroids may "trigger" the syndrome.[37]

Pharmacological Effect of Propofol

Propofol is capable of producing various pharmacological effects that may play a role in PRIS. The drug can directly or indirectly affect 1) cardiovascular hemodynamics, 2) cardiac contractility, 3) cardiac conduction, and 4) peripheral and cardiac muscle function and production and use of energy. The primary cardiovascular pharmacodynamic effect of propofol is its ability to cause hemodynamic instability via dose- or infusion rate-dependent peripheral vasodilatation that can markedly decrease systemic vascular resistance. An effect of propofol on myocardial contractility is controversial, but the drug can have a negative inotropic effect that may diminish cardiac contractility.[38] In rats, it appears to work in a dose-dependent manner to antagonize both cardiac voltage-gated calcium channels[39] and β-receptor binding.[40] These effects impair left ventricular force[38] and stroke volume,[41] all of which can reduce myocardial contractility. Clearly, propofol does decrease systemic vascular resistance and cardiac output to cause hypotension particularly in patients who are volume depleted. Although many of the patients with PRIS developed decreases in blood pressure, propofol-induced hypotension generally occurs very early (i.e., 2–3 minutes post-induction) in a course of therapy and does not present days after the drug is begun.

Although numerous patients with PRIS developed bradycardia, heart block or other arrhythmias, propofol exhibits little to no chronotropic effect. While bradycardia was seen in

animals, it was only noted in concentrations above those expected in vivo.[42,43] Bradycardia during propofol infusion is generally attributed to vagal stimulation and not propofol. Propofol serum concentrations have been shown to directly correlate with decreases in atrioventricular conduction times in rabbit and guinea pig hearts,[42,43] however, the drug has little effect on conduction in humans. Even when underlying conduction defects were present, the use of propofol had no effect on sinus node function or atrioventricular conduction.[44] However, propofol might indirectly affect cardiac conduction by inhibiting the transport and oxidation of short-, medium- and long-chain free fatty acids (FFA). The accumulation of high concentrations of these substances has the potential to be arrhythmogenic.[45,46] Bonnet evaluated clinical features of inherited disorders of fatty acid oxidation in 107 children.[45] Arrhythmia was the predominant presenting feature in 24 cases.[46] Patients with defects of long-chain fatty acid transport across the inner mitochondrial membrane (CPT l or CPT ll deficiency) presented with conduction disorders and atrial tachycardias, whereas ventricular tachycardias were observed in patients with any type of fatty acid oxidation deficiency.

Another possible pharmacological mechanism involves FFA.[16,33] This mechanism would appear to be the most likely one for the observed lipemic serum, metabolic acidosis, hepatic steatosis and peripheral or cardiac muscle damage noted in PRIS. FFA are an essential source of energy for cardiac and skeletal muscle since they yield relatively large quantities of ATP. Propofol alters energy production at the subcellular level by reducing the entry of long-chain FFA into the mitochondria. It accomplishes this by increasing the activity of malonyl coenzyme A, thereby inhibiting carnitine palmitoyl transferase I (CPT I) from transporting the long-chain fatty-acids across the outer mitochondrial membrane (Figure 2). An accumulation of fats causes a substantial increase in non-esterified fatty acids. The liver then converts excess FFA to ketones, which in turn contributes to the development of metabolic acidosis. The excess fats may also be deposited in the liver. Although some patients were noted to have hepatic steatosis on autopsy, this has not been a universal finding in all patients with PRIS.

Once acylcarnitine is within the mitochondrial matrix it is converted to fatty acyl-CoA by carnitine acyltransferase II (CPT II). Small- and medium-chain FFA do not require a transporter protein, but diffuse across the mitochondrial membrane. Normally the acyl-CoA and small and medium chain fatty acids are transformed by β-spiral oxidation to yield ATP via the mitochondrial respiratory chain (i.e., Complex II or succinate dehydrogenase). Propofol inhibits β-spiral oxidation thereby decreasing the availability of ATP, which generates energy necessary for cellular function. This creates a situation of underproduction of energy in a patient that already has an increased demand due to illness. It is hypothesized that the inability of muscle fibers to use FFA leads to lactic acidosis and acute cardiomyopathy and skeletal myopathy seen in PRIS.

In order to assess the plausibility of this theory Wolf and colleagues collected blood from a patient with PRIS.[47] They noted a slight elevation in total serum carnitine and more than a 10-fold increase in serum C5-acylcarnitine and malonylcarnitine. The authors concluded that these findings are consistent with impaired fatty-acid oxidation, reduced entry of long-chain acylcarnitine esters into the mitochondria, and failure of the respiratory chain at Complex II. Repeat assessment of serum after recovery was consistent with normal lipid metabolism. Van Straaten also reported a slight elevation in total and free serum carnitine concentrations; however, no abnormalities in fatty acids were noted.[24] Cray and colleagues homogenized skeletal muscle obtained by biopsy from a patient who developed rhabdomyolysis while receiving propofol and found a decrease in cytochrome C oxidase activity in muscle.[14] Because cytochrome C oxidase activity was normal in skin fibroblasts they concluded that the reduced activity in muscle was due to propofol and could not be attributed to a genetic defect. Another report also noted elevated concentrations of acylcarnitine intermediates (i.e., acetyl and hydroxyl-butyryl) and medium-chain unsaturated and dicarboxylic species in a sample obtained during PRIS.[19] The authors concluded that these aberrations were either diet or drug induced since the values were normal in a subsequent specimen.

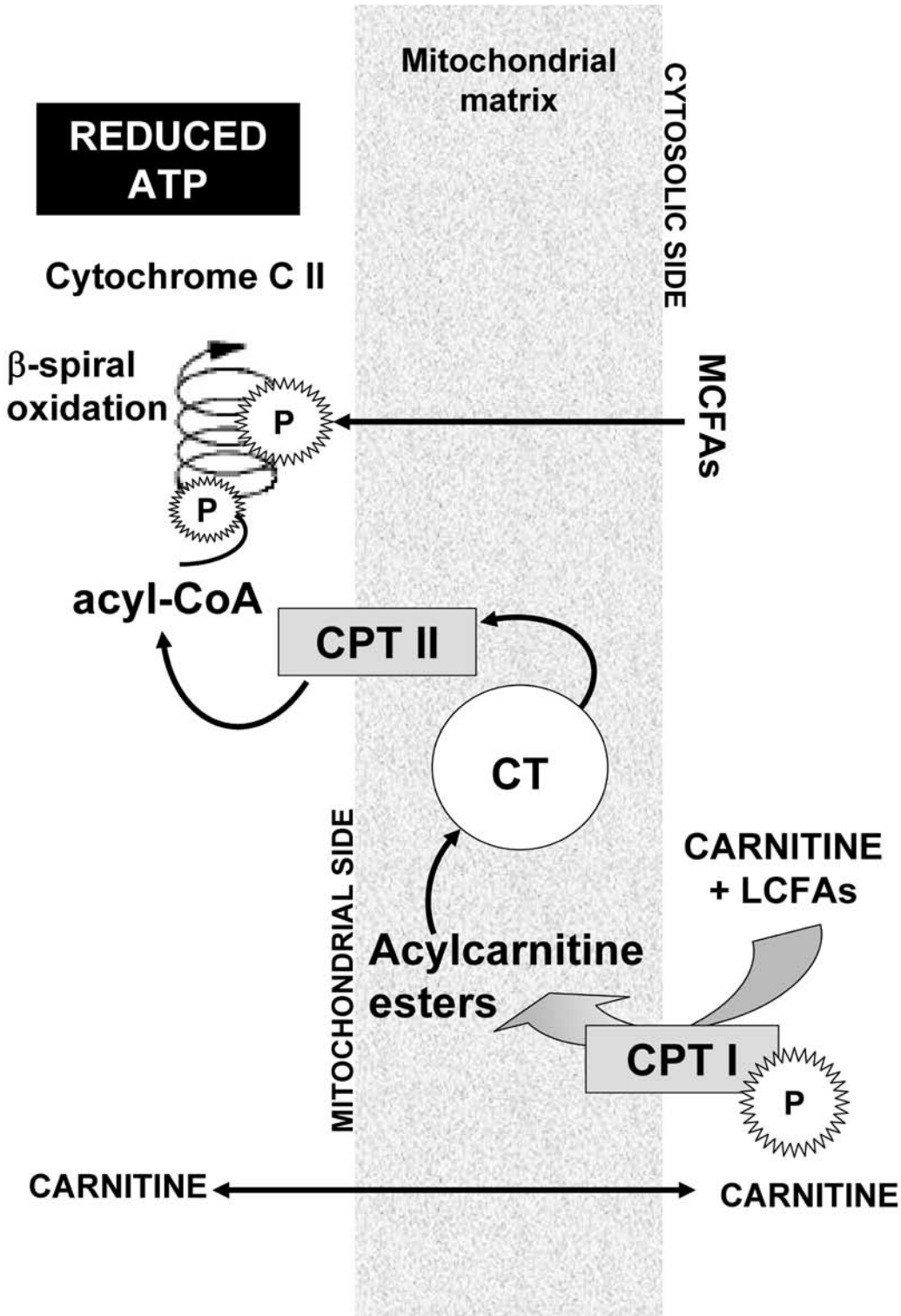

Figure 2. Propofol increases malonyl coenzyme A (not shown) to decrease the activity of carnitine palmitoyl transferase I (CPT I), which transports long chain fatty acids (LCFAs) across the cytosolic side of the mitochondria. Acylcarnitine esters are transported into the mitochondrial matrix membrane via carnitine translocase (CT). The acyl group is cleaved by carnitine acyltransferase II (CPT II) to yield acyl CoA. Medium chain fatty acids (MCFAs) freely diffuse across the mitochondrial membrane. Normally, Acyl CoA and MCFAs are transformed by β-spiral oxidation via the respiratory chain at cytochrome C II to yield ATP. Propofol uncouples β-spiral oxidation to reduce the formation of ATP. The state of low energy production may contribute to cardiac and peripheral muscle damage.

Propofol Metabolite(s)

Propofol is extensively metabolized and excreted in the urine as sulfate and/or glucuronide conjugates of the parent compound or its hydroxylated metabolite. Several reports have suggested that the observed metabolic acidosis may be due to accumulation of propofol metabolites, specifically propofol glucuronide, quinol glucuronides, and 4-quinol sulfate.[11-13] This theory is based on 1) the presence of a "possible" propofol metabolite noted on gas chromatography in the serum of one child who developed PRIS[14] and 2) survival of patients with PRIS who were treated with AV[11] or VV[14] hemofiltration, an unspecified type of dialysis,[12] hemofiltration[11,16] or charcoal hemoperfusion.[19] Propofol itself has a very large volume of distribution and would not be effectively cleared using plasmapheresis, ECMO or CVVH; hence, some have speculated that extracorporeal methods may have removed an offending metabolite or agent. Others have concluded that this mechanism is not plausible because of the water solubility of the metabolites, their very short half-lives, and persistent metabolic acidosis following the discontinuation of propofol.[6,19,23] Acylcarnitine and lactic acid are water soluble and can be removed by dialysis. However, the possibility remains that the elimination of these substances by these measures may have contributed to survival in patients receiving various forms of dialysis.

Propofol Formulation

Propofol is an intravenous sedative-hypnotic anesthetic that is formulated in a lipid emulsion vehicle.[1] There are currently three propofol products available in the United States. The first product (Diprivan, AstraZeneca Pharmaceuticals, Wilmington, DE) has been used in virtually all reports describing PRIS. The patent for Diprivan expired in 1999 and two other generic formulations (Baxter Pharmaceutical Products, Inc., New Providence, NJ and Parenta Pharmaceuticals, Inc., West Columbia, SC) were marketed. Each product exists as a 1% or 2% soybean oil-in-water emulsion. The pH of the Diprivan product has been adjusted with sodium hydroxide to produce a higher pH (7–8.5) than that of generic propofol (4.5–6.4). We were able to identify only one published case report of PRIS in an adult while receiving the generic product.[48] The generic formulations are preserved with 0.25 mg/mL sodium metabisulfate, while Diprivan is preserved with disodium edetate (0.005%). Both products are emulsified with 1.2% purified egg phospholipids. Holzki and colleagues described an atypical case of PRIS in a 3-year-old who received a large dose (20 mg/kg/hr) of propofol. The child developed bronchospasm, hypotension and dysrhythmias within 15 hours of beginning propofol. Although the clinical presentation might suggest an allergic reaction, the authors did not note if the child was allergic to eggs or sulfites.

Three reports have suggested that the lipid vehicle may have contributed to the observed metabolic acidosis by causing lipemia with subsequent impairment in lactate metabolism.[11,13,14] The oil-in-water emulsion used in each of the propofol formulations has been used as a substrate in parenteral nutrition regimens for over 30 years. The oil-in-water emulsion has been associated with lipemia, elevations in triglycerides, respiratory distress and hepatic steatosis.[49] However, it does not appear to cause bradycardia, cardiac arrhythmias or rhabdomyolysis. Only one report of a patient with metabolic acidosis due to Intralipid has been published.[50] This occurred in a 2.16 kg infant who accidentally received 250 mL of Intralipid (24 g/kg) over one hour.[50] Serum triglyceride concentrations rose to 12,900 mg/dL. Although the infant developed metabolic acidosis, no bradycardia or dysrhythmias were described, and the child made a full recovery.

The mean ± SD dose of propofol reported in 12 pediatric patients who died due to PRIS was 8.5 ± 2.8 mg/kg/hr.[9] Use of a 1% Diprivan product would result in the delivery of 2 g/kg/day of soybean emulsion. This dose is about 50-60% of the maximum dose of fat emulsion (3–4 g/kg/day) that is currently used in pediatric parenteral nutrition support. While the fat emulsion may have contributed to lipemia, it is unlikely that the lipid dose played a role in the PRIS.

Bacterial Contamination of the Propofol Infusion

Several reports have mentioned the possibility that bacterial contamination of the lipid emulsion might be responsible for PRIS.[11,12,14,27] The authors speculated that the fat emulsion

vehicle may serve as a medium for bacterial and fungal growth, which may subsequently predispose a patient to sepsis. Between June 1990 and February 1993, the Centers for Disease Control and Prevention conducted case-controlled and/or cohort studies to investigate unusual outbreaks of bloodstream infections, surgical-site infections, and acute febrile episodes after surgical procedures at seven hospitals.[51] Sixty-two cases were identified and 79% of those had undergone surgery during the time in question. Propofol was the only variable that was significantly associated with the postoperative complications at all seven hospitals. *Staphylococcus aureus, Moraxella osloensis, Enterobacter agglomerans, Serratia marcescens or Candida albicans* were found in 6 of the outbreaks. Cultures of unopened containers of propofol were negative; however, cultures from propofol syringes currently in use were positive at two hospitals. Several incidences of bacterial contamination have been reported following repackaging or improper storage of propofol[52] and Intralipid.[53] With the exception of one report describing PRIS,[13] other reports failed to provide information related to the method of administration (i.e., repackaging and hang times).

The manufacturer stresses that strict aseptic technique must always be maintained during handling of propofol.[1] Although 0.005% disodium edetate has been added to the Diprivan injectable product as a bacterial growth retardant, it is not an antimicrobially preserved product under USP standards. The manufacturer recommends that administration should be completed within 12 hours after the vial has been spiked and that tubing and any unused portions of Diprivan Injectable Emulsion must be discarded. If the product is transferred to a syringe or other container prior to administration, aseptic technique is essential and the product and administration lines should be changed after 6 hours. Strickland and colleagues reported the syndrome in two patients despite exchange of the administration set every 4 hours.[13]

Several arguments can be made against bacterial contamination of the propofol product as a cause for PRIS. While some of the patients had fever, most reports failed to mention abnormalities in body temperature or WBC with differential, and only 10 noted the use of antibiotics. Although some patients had positive viral cultures from an upper respiratory sample, a positive blood culture was not described in any patient. Some patients developed varying degrees of renal dysfunction, but thrombocytopenia was not mentioned in any report. Virtually all patients had bradycardia, not tachycardia. Finally, few authors attributed the clinical features described in their patients to infection.

Malignant Hyperthermia

Many of the signs and symptoms associated with PRIS are also observed in patients who develop malignant hyperthermia from other medications used for general anesthesia. These patients rapidly develop a high fever with sustained muscle contractions. As muscle tissue is destroyed the breakdown products damage the kidneys causing acute renal failure and myoglobinuria. Acidosis, tachycardia, hypercarbia, glycolysis, and hypoxemia may also be present. Neff et al. hypothesized that "a loss of calcium ion homeostasis leading to impairment of mitochondrial respiration, enhanced generation of cellular toxins (free radicals, prostaglandins, leukotrienes) and activation of proteases and phospholipases" might be a possible mechanism for the syndrome.[54] Dantrolene has been used to treat malignant hyperthermia. It may alter calcium flux across the sarcoplasmic reticulum of skeletal muscle by inhibiting abnormal excitation-contraction coupling.

One report described the use of dantrolene in a 6-year-old male who received 5–10 mg/kg/hr of propofol for 60 hours.[25] The child developed metabolic acidosis and cardiac dysrhythmias, which progressed to myocardial failure that was unresponsive to conventional therapies. The CK was elevated, but the CK-MB was normal. His core body temperature increased to 41.5°C. Following administration of dantrolene, cardiac improvement occurred and his body temperature returned to normal. However, brain death occurred due to the prolonged hypotension.

Although many of the patients reported with PRIS were febrile, most authors failed to report the maximum temperature, leading the reader to assume that most temperatures were neither excessive nor persistent. Unlike malignant

hyperthermia where symptoms appear within hours of exposure, the onset of the symptoms in patients with PRIS did not appear in some patients until days after propofol was begun and continued after propofol was discontinued. Although tachycardia is a common finding in patients with malignant hyperthermia, the majority of those with PRIS had bradycardia. Perhaps the strongest argument against propofol-induced malignant hyperthermia is its safe use for anesthesia in patients susceptible to malignant hyperthermia.[55,56]

Possible Priming and Triggering Factors

Vasile and colleagues propose that "the term PRIS is misleading and that a more descriptive term of critical illness cardiac failure and rhabdomyolysis associated with high-dose propofol, catecholamines or steroids seems more appropriate."[37] This group of authors suggests that critical illness is a "priming factor" that causes release of endogenous proinflammatory cytokines or inadequate response of anti-inflammatory cytokines, which in turn produces an increased secretion of catecholamines and glucocorticoids. This catecholamine surge produces sympathetic overactivity that can have a direct cardiotoxic effect (i.e., human stress cardiomyopathy). The persistence of this state also creates a hypercatabolic environment. These authors speculate that high-dose propofol, exogenous catecholamines and corticosteroids are "triggering factors," which may contribute to the cardiac features, rhabdomyolysis and eventual metabolic acidosis and organ failure.

RECOMMENDATIONS FOR PREVENTION AND TREATMENT

Several international committees and organizations have reviewed the available data and made recommendations regarding the use of propofol and PRIS. In response to reports of the Danish Side Effect Committee and the case series of Parke et al.,[10,11] the United Kingdom Committee on Safety of Medications issued a warning regarding the possibility of serious propofol-associated adverse reactions.[2,9] In 1992, the Anesthetic and Life Support Drugs Advisory Committee to the FDA concluded there was no identifiable link between propofol and adverse cardiac events in either children or adults.[57] After reviewing data from the 327 patients enrolled in the multicenter trial,[34,35] the FDA concluded that there was no evidence of a correlation between propofol and the adverse reactions noted in this study; however, they requested that AstraZeneca conduct an additional study on the safety of Diprivan when used for sedation in high-risk PICU patients. Subsequent to this FDA review in March 2001, AstraZeneca issued a "Dear Doctor" warning letter regarding safety concerns when propofol was used for sedation of critically ill patients admitted to the PICU.[57] The warning letter emphasized that propofol is not FDA labeled for sedation in PICU patients and should not be used for this purpose. The Canadian Health Protection Board also issued a notice stressing the use of propofol only for approved indications.[58]

Prevention

If PRIS exists, its etiology is likely multifactorial. A review of the literature suggests that admitting diagnosis, propofol dose and duration of therapy, nutritional status and available substrate, and concurrent medications should be considered when propofol is given to critically ill children.

Admitting Diagnosis

Many of the children reported to have PRIS were admitted with a primary respiratory diagnosis. It should be noted that the majority of isolated organisms on culture were viral; seven patients had positive cultures from a tracheal aspirate (*Branhamella catarrhalis*, parainfluenza virus 2, *Haemophilus influenzae*), nasopharyngeal aspirate (respiratory syncytial virus, parainfluenza virus 3, Influenza virus A) or sputum (*Pseudomonas aeruginosa*). While the number of patients is small, two studies arrived at different conclusions.[9,29] Bray retrospectively reviewed the medical records of 128 patients < 12 years of age who had a primary diagnosis of a respiratory infection and were admitted to the PICU for more than 2 days.[9] Nine children received propofol in doses larger than 4 mg/kg/hr for more than 48 hours. Three patients, who were previously described in a separate publication, died from what was attributed to PRIS. Only three of the remaining

six had either an enlarged liver or a metabolic acidosis. None of the six survivors had lipemic serum or cardiovascular manifestations of PRIS. Pepperman et al. also noted 10 deaths in patients with a primary respiratory diagnosis. There was no difference in mortality in those given propofol (23%) versus other sedatives (19%). It remains unclear if admitting diagnosis is a factor in PRIS. Until more definitive information is available the practitioner should consider the possible ramifications of using short- or long-term propofol in a child admitted with a coexisting upper respiratory tract infection.

Nutritional Status and Adequate Carbohydrate Substrate

Adults may experience a decreased incidence of this syndrome as they generally require smaller propofol doses for sedation and tend to maintain a greater store of carbohydrates compared to children.[3] Wolf and colleagues not only suggested that inadequate carbohydrate stores or insufficient supplementation of calories might contribute to this syndrome in children, but theorized that adequate carbohydrate intake might prevent the syndrome.[16] The authors recommended that a minimum of 6–8 mg/kg/min of carbohydrate should be sufficient to suppress fat metabolism in critically ill pediatric patients. Most case reports failed to note the child's nutritional status prior to admission or whether or not the patient was receiving parenteral nutrition. Interestingly, clinical features of the syndrome appeared in a 5-month-old on propofol during the initial fasting phase of the ketogenic diet (see above)[20] and in another who was on the diet prior to admission.[12] Withington and colleagues also reported the syndrome in an infant who received 1.53–2.7 mg/kg/min of dextrose.[19]

Dose and Duration of Propofol

Cremer and colleagues used a retrospective analysis of 67 head-injured adults to determine a crude odds ratio for PRIS.[59] They estimated that the likelihood of the syndrome increased by 1.93 for every mg/kg/hr of propofol administered above 4.98 mg/kg/hr. Rigby-Jones et al. reported that doses ≤ 4 mg/kg/hr produced adequate sedation in pediatric patients[7] and Cornfield and colleagues reported the safe use of propofol in 142 pediatric patients who received < 4 mg/kg/hr.[30] For these reasons, the lowest effective dose should be used and the dose should not exceed 4 mg/kg/hr. Although some have suggested that the duration of infusion should not exceed 48 hours, lactic acidosis and lipemia have been reported following short-term exposure.[18,26,28] To date no one has speculated on the role that total cumulative dose might play.

When propofol must be used, the smallest possible dose that produces the desired pharmacodynamic effect should be given. The patient should be switched to a benzodiazepine (i.e., midazolam or lorazepam) if adequate sedation can not be achieved with ≤ 4 mg/kg/hr or if prolonged therapy (≥ 48 hours) is required. While on propofol the patient should be monitored for clinical features and laboratory findings that have been attributed to the syndrome (Table 1).

Monitoring and Assessment

Although many critically ill pediatric patients have a variety of conditions that may cause symptoms consistent with PRIS, patients receiving propofol should be closely monitored for complications suggestive of the syndrome. However, it is unclear if early identification of PRIS and discontinuation of propofol would affect outcome.

Given the suggested clinical features of PRIS the practitioner should closely monitor vital signs, especially blood pressure for hypotension. Continuous ECG should be assessed for dysrhythmia including bradycardia, ventricular tachycardia or fibrillation, RBBB, and a widened QRS. Although no guidelines have been proposed for laboratory monitoring in patients while receiving propofol it would seem prudent to assess the following on a daily basis in any patient who is administered more than 4 mg/kg/hr and/or receives an infusion for longer than 48 hours. Laboratory tests should include serum lactic acid, serum triglycerides, serum creatinine, CK and hepatic enzymes. Although visual inspection of the serum for lipemia should be done, clear serum does not preclude hypertriglyceridemia. Serum CK, CK-MB and troponin I have been elevated in some patients, but have not been universal findings in those with rhabdomyolysis. The urine should

also be visually assessed for changes in color and should be screened for myoglobin. Should PRIS be suspected, the practitioner may also consider obtaining serum to assess carnitine and acylcarnitine status and possibly even a muscle biopsy. If the patient recovers, a follow-up assessment of carnitine status and a second muscle biopsy would enable one to evaluate the role of propofol versus the contribution of preexisting disease or diet. If an autopsy is performed, the pathologist should note the presence of hepatic steatosis, myoglobin casts in the renal tubules, and rhabdomyolysis of the peripheral or cardiac muscles.

Treatment

If PRIS is suspected, propofol should be discontinued and the child should not be re-challenged. The cardiac features noted with the syndrome have generally failed to respond despite aggressive pharmacological therapies and cardiac pacing. In animals, administration of catecholamines increased cardiac output causing an increase in first pass removal of propofol, and an overall increased clearance of the drug resulting in the need for large doses of propofol.[60] The negative inotropic effect of propofol may also alter a patient's response to catecholamines and/or their doses. Similarly, since propofol can antagonize beta-receptor binding by catecholamines its use may also necessitate larger catecholamine doses to produce an effect. Vasile and colleagues describe this as a "vicious cycle in which propofol and catecholamines drive each other in a progressive myocardial depressive effect."[37]

Only one report noted the addition of carnitine to a patient's therapeutic regimen; however, the authors failed to report the dosage or response, if any, to the agent.[14] Although the role of carnitine supplementation has not been explicitly discussed, the signs and symptoms described in many of the case reports have also been associated with primary and secondary carnitine deficiency syndromes.[61] For this reason the practitioner might consider adding carnitine in the treatment of any child who develops symptoms consistent with PRIS.

Free fatty acid intermediaries are water soluble and these are easily dialyzed. This might explain the therapeutic benefit of various forms of hemodiafiltration reported. Several practitioners have successfully managed PRIS with venovenous hemodiafiltration,[14,16,22] charcoal hemofiltration[19] or ECMO.[17] Plasmapheresis did not appear to be beneficial.[14]

SUMMARY AND CONCLUSIONS

For over a decade, there has been speculation about the existence of an infusion syndrome attributed to the use of propofol in critically ill pediatric patients. The mere existence of the syndrome itself remains controversial and evokes passionate opinions among PICU practitioners. Although the syndrome is intriguing, our review of the literature provides only anecdotal evidence of an association between propofol and an infusion syndrome in critically ill pediatric patients. Although several plausible theories exist, to date no one has been able to show that propofol or the lipid emulsion causes the myriad of clinical features reported with the syndrome.

Kang noted that proponents of a PRIS would suggest that: 1) PRIS has been reported by 20 different groups at various institutions worldwide, 2) its features have not been linked to other agents and are therefore unique to propofol, 3) signs and symptoms appear to be related to the presence or absence of propofol and display a dose- and duration-dependent relationship with propofol, 4) the symptoms generally occur within days of beginning propofol, and 5) several mechanisms might provide a rational basis for a relationship with propofol.[62]

Others would argue that the case reports provide only circumstantial evidence and have failed to prove either association or causation. About half of the reports in children were described via a Letter to the Editor or confidential personal communication, which were not peer-reviewed and did not provide ample information to allow scrutiny. Published retrospective and prospective studies have not noted the infusion syndrome in any patient. Although unpublished data from a clinical trial suggests an increased mortality in children given propofol, the conclusions from this study have been highly criticized by investigators who conducted the study.[34] Proponents of the safety of propofol in critically ill children would also note that the majority of patients described in reports had a multitude of reasons for the signs

and symptoms displayed and for subsequent death. Finally, they would stress that millions of children worldwide have received propofol without adverse effects.

If the syndrome does occur, it remains unclear whether it is associated with any predisposing factors. Historically, we have learned that certain drugs (anesthetic agents) may trigger a life-threatening event (malignant hyperthermia) in a genetically susceptible individual. Advances in pharmacogenomics and histochemistry of various muscle enzymes may enable a better understanding of the role, if any, that genetics may play in PRIS. At this time, the lack of a clearly defined mechanism(s) that causes the syndrome would preclude anything but a fishing expedition for a gene.

If this therapeutic controversy is to be resolved, basic science researchers will need to identify a valid animal model reflective of humans and conduct studies in a simulated critically ill pediatric model. These studies should be designed to determine if the signs and symptoms ascribed to propofol can be reproduced. Assuming they can be replicated, identification of the cause(s), possible mechanisms, risk factors, and successful approaches to medical management is essential. Although plasma carnitine concentrations were normal in one patient, the signs and symptoms reported with the infusion syndrome have also been noted in those with primary and secondary carnitine deficiency syndromes. Research evaluating carnitine status of critically ill pediatric patients who receive long-term propofol might prove most informative. Likewise, the use of a fat emulsion vehicle that contains medium-chain triglycerides in place of long-chain triglycerides should be investigated.

The available literature is fraught with cases described via informal, non-peer-reviewed methods. It is imperative that practitioners publish any case of a suspected PRIS as a manuscript that appears in a refereed journal. A large multi-center, prospective, randomized, double-blind controlled trial designed to address safety concerns of propofol for sedation should be conducted in critically-ill infants and children who receive doses ≤ 4 mg/kg/hr for ≤ 48–72 hours. The ethics of such a study are debatable and are discussed in a paper published in this issue of JPPT.

Finally, reports of the syndrome should not preclude the use of propofol as a sedative in critically ill pediatric patients. However, these reports do raise concerns about its use and the caution issued by the manufacturer may serve to increase practitioners' liability should they elect to use propofol "off-label." Until the needed data are available, practitioners must contemplate the benefit to risk ratio of using propofol for sedation in critically ill infants and children. If used, the practitioner should institute close monitoring paradigms and at the earliest evidence of possible initiating/evolving PRIS, stop the propofol infusion and provide any necessary therapy promptly.

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