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Propofol "Wash-Out" Protocol: Successful Use of Propofol Infusion to Allow for Discontinuation of Multiple High-Dose, Long Duration Infusions of CNS Acting Agents in two Complex Infants.

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Abstract

Background: Clinicians use high-dose narcotics and benzodiazepines for ongoing sedation of chronically ill mechanically ventilated infants undergoing long intensive care unit admissions. Withdrawal symptoms causing cardiopulmonary instability complicates medication weaning and prolongs hospitalization. Intensivists managing adult critically ill patients commonly utilize propofol for continuous sedations, but its utility in pediatrics is limited to older teenagers and short durations due to concern for propofol infusion syndrome. We describe our Infant Propofol Wash-Out protocol in two medically complex infants.

Methods: Case series and literature review.

Results: Propofol Wash-Out Protocol allowed for successful discontinuation of all continuous infusions and minimization of central nervous system acting agents in two complex infants.

Conclusion: Though propofol infusion in pediatric intensive care units carries risk for propofol infusion syndrome which can be fatal, its use in select patients might be considered if appropriate consent procedures and monitoring are in place.

Keywords: Narcotics; Benzodiazepines; Myriad; Narcotic Infusions; Morphine; Hyperalgesia

Background

The term "propofol infusion syndrome" was coined in 1999 to describe the constellation of signs and symptoms identified in some adults and children receiving propofol infusions. This syndrome was rare and potentially fatal, with a poorly understood and likely multifactorial pathophysiology. An unpublished trial by the manufacturer led to black-box warning, rendering propofol contraindicated for use in pediatric intensive care units. Since that time, continuous sedation for critically ill medically complex children has depended upon a myriad of central nervous system (CNS)-acting agents, primarily benzodiazepine and narcotic infusions. Those with extended hospitalizations often receive these infusions at maximal dosing, frequently with concomitant use of other CNS altering medications (i.e., barbiturates, central alpha agonists, anticonvulsants, antipsychotics) and at times neuromuscular blockade. Extremes of dosing and duration may cause paradoxical reactions, hemodynamic compromise and withdrawal symptoms that limit weaning of these agents.

We present two cases of exceedingly complex infants with chronic lung disease and pulmonary hypertension (PHTN) who received extensive dosing and duration of CNS- altering medications. Repeated failure to wean these medications often resulting in pulmonary hypertensive events, and in one case inability to discontinue neuromuscular blockade, led to a multi-disciplinary discussion among pharmacy, neurology, palliative

care, PHTN team and PICU regarding risks and benefits of a propofol "wash-out". The group reached consensus to utilize a propofol infusion to allow for a "wash-out" of other CNS altering medications while preventing withdrawal.

We submit our experience to help guide the pediatric intensivist, as we are unaware of any published literature outlining sustained propofol infusion outside of procedural sedation in critically ill infants.

Case 1

Female infant born with extreme prematurity (27 2/7 weeks) and intrauterine growth restriction (birth weight 455 grams) with 16p microduplication, ventilated since birth (Jet ventilation x 2 months), severe bronchopulmonary dysplasia complicated by pulmonary hypertension and repeated cardiac arrests from hypoxic respiratory insufficiency was transferred from neonatal intensive care until to pediatric intensive care unit at 7 months of age (weighing 4.5kg) for ongoing care. She was GJ tube and chronic ventilator dependent on steroids since birth and sustained repeated infections with multi-drug resistant organisms. At time of transfer her medications included morphine infusion (0.045mg/kg/hr), midazolam infusion (0.35mg/kg/hr), intermittent methadone (0.55 mg/kg Q6 hours), clonidine (0.01mg Q8 hours), and phenobarbital (5 mg/kg daily). Additionally, she received multiple doses of PRN versed, morphine and phenobarbital without affect. Given the inability to maintain her oxygenation and ventilation, dexmedetomidine and cisatracurium infusions were added to her CNS med regimen.

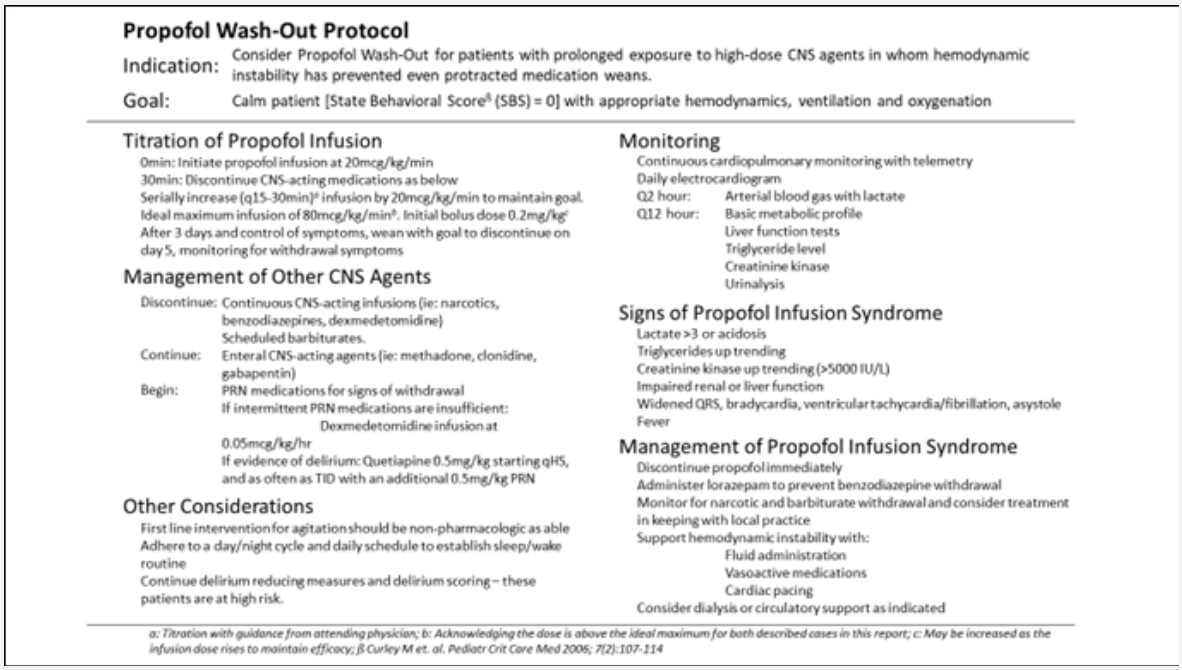
Her status improved once ventilation was adjusted based on arterial blood gases and neuromuscular blockade was discontinued. It became apparent that her ongoing neuro-agitation and underlying poor neurologic function were severe enough to preclude her from tolerating wakefulness while maintaining minute volumes and oxygenation. This problem appeared multifactorial, with etiology including habituation to multiple classes of medication, delirium, underlying lung disease, and pulmonary hypertension. The issue was likely complicated by drug-induced agitation, opioid induced hyperalgesia, and irritability from her many CNS-acting agents (midazolam, methadone, fentanyl, phenobarbital).

Her case was discussed by an interdisciplinary team regarding management options. Considerations included:

i. barbiturate infusion to allow for medication wash-out, risking hemodynamic instability, immune suppression, and ileus, further complicated by long half-life.

ii. Ketamine infusion, with concern for its hemodynamic effects.

iii. Propofol infusion to allow for discontinuation of his other neurologic medications though with risk for propofol infusion syndrome. After extensive discussions it was determined that propofol was the best option despite the risk for propofol infusion syndrome. Risk of propofol infusion, and specifically propofol infusion syndrome (including mortality risk) were held with the family who agreed to move forward with propofol infusion. Informed consent for propofol "wash-out" was obtained and implemented the day following consent (Figure 1).



Propofol Wash-Out Protocol

Indication: Consider Propofol Wash-Out for patients with prolonged exposure to high-dose CNS agents in whom hemodynamic instability has prevented even protracted medication weans.

Goal: Calm patient [State Behavioral Score[§] (SBS) = 0] with appropriate hemodynamics, ventilation and oxygenation

Titration of Propofol Infusion

0min: Initiate propofol infusion at 20mcg/kg/min
30min: Discontinue CNS-acting medications as below
Serially increase (q15-30min)[a] infusion by 20mcg/kg/min to maintain goal.
Ideal maximum infusion of 80mcg/kg/min[b]. Initial bolus dose 0.2mg/kg[c]
After 3 days and control of symptoms, wean with goal to discontinue on day 5, monitoring for withdrawal symptoms

Management of Other CNS Agents

Discontinue: Continuous CNS-acting infusions (ie: narcotics, benzodiazepines, dexmedetomidine)
Scheduled barbiturates.
Continue: Enteral CNS-acting agents (ie: methadone, clonidine, gabapentin)
Begin: PRN medications for signs of withdrawal
If intermittent PRN medications are insufficient:
Dexmedetomidine infusion at 0.05mcg/kg/hr
If evidence of delirium: Quetiapine 0.5mg/kg starting qHS, and as often as TID with an additional 0.5mg/kg PRN

Other Considerations

First line intervention for agitation should be non-pharmacologic as able
Adhere to a day/night cycle and daily schedule to establish sleep/wake routine
Continue delirium reducing measures and delirium scoring – these patients are at high risk.

Monitoring

Continuous cardiopulmonary monitoring with telemetry
Daily electrocardiogram
Q2 hour: Arterial blood gas with lactate
Q12 hour: Basic metabolic profile
Liver function tests
Triglyceride level
Creatinine kinase
Urinalysis

Signs of Propofol Infusion Syndrome

Lactate >3 or acidosis
Triglycerides up trending
Creatinine kinase up trending (>5000 IU/L)
Impaired renal or liver function
Widened QRS, bradycardia, ventricular tachycardia/fibrillation, asystole
Fever

Management of Propofol Infusion Syndrome

Discontinue propofol immediately
Administer lorazepam to prevent benzodiazepine withdrawal
Monitor for narcotic and barbiturate withdrawal and consider treatment in keeping with local practice
Support hemodynamic instability with:
Fluid administration
Vasoactive medications
Cardiac pacing
Consider dialysis or circulatory support as indicated

a: Titration with guidance from attending physician; b: Acknowledging the dose is above the ideal maximum for both described cases in this report; c: May be increased as the infusion dose rises to maintain efficacy; § Curley M et. al. Pediatr Crit Care Med 2006; 7(2):107-114

Figure 1. Infant Propofol Wash-Out Protocol

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While the goal was to be on propofol for 3-4 days, the team recognized the potential for a longer course as needed. The patient remained on full cardiopulmonary monitoring and laboratory surveillance plan was established with management of propofol infusion syndrome discussed on morning and evening rounds with the care team.

The Propofol Wash-Out Protocol was initiated day of life/hospital day 279. Weight at time of initiation was 5.3kg. Propofol infusion was utilized for five days, with dose and details shown in (Table 1). The patient tolerated the propofol infusion without clinical, hemodynamic, or ECG changes, and there was no evidence of propofol infusion syndrome based on laboratory testing. In fact, she had marked an increase in her cardiopulmonary stability, with cessation of events characterized by deep desaturation and loss of minute ventilation predating the propofol wash-out. Following the five days wash out, the propofol infusion was discontinued, methadone wean was initiated, and the patient was able to tolerate being awake and interactive, achieving progress toward neurodevelopmental goals. This success allowed for focus on transition to long term mechanical ventilation, establishment of a feeding and medication regimen, family education and discharge planning. She was ultimately discharged from home ten months later at 19 months of age.

Table 1: Timing and dosing of propofol infusion for Case 1.

Hours	Propofol Dosing	Other Notes
0-24	Infusion initiated at 20mc/kg/min increased serially by 20mg/kg/min over 8 hours to 140mcg/kg/min; bolus 0.2mg/kg	
24-48	Infusion 140mcg/kg/min; bolus 0.4mg/kg	Patient comfortable, SBS goal achieved
48-72	Infusion 140mcg/kg/min; bolus 0.4mg/kg	Weaning initiated after 62 hours
72-96	Infusion 120mcg/kg/min; bolus 0.4mg/kg	
96-120	Infusion 125mcg/kg/min; bolus 0.4mg/kg	Gabapentin increased to 7.5mg/kg TID
120-144	Infusion stopped at 144 hours	Gabapentin increased to 10mg/kg TID Quetiapine qHS added at 0.5mg/kg Lorazepam 0.2mg/kg added PRN severe agitation

SBS = State Behavioral Scale

Case 2

Ex 38-week infant with 15q11.2 chromosomal deletion born by caesarian section for concern for placental abruption postnatally diagnosed with left sided Congenital Diaphragmatic Hernia (CDH). Veno-Arterial Extracorporeal membrane oxygenation (ECMO) was initiated on day of life (DOL) 1. At DOL 19 CDH repair with ECMO decannulation was performed. Post-op day 14, his course was complicated by hypoxic refractory respiratory failure attributed to pulmonary hypertension and he was placed on Veno-Venous ECMO (for 20 days). Cardiac catheterization at 4 months of age documented ¾ systemic right ventricular pressure and mean pulmonary artery pressure of 40 mmHg. His medication regimen was increased to include sildenafil, bosentan, and flolan. He was maintained on prostaglandin infusion for ductus arteriosus patency. A remodulin SQ continuous infusion was initiated at 6 months of age with slow serial dose increase. He underwent tracheostomy at 4.5 months of age for his chronic bronchopulmonary dysplasia and chronic lung disease. His course was further complicated by cardiac arrest at 7 months of age secondary to possible sepsis. He was transferred to the PICU from the Neonatal ICU for ongoing care the following week. His CNS-acting medication on transfer were Methadone (0.7 mg/kg/dose) IV Q6, Ativan (0.5mg/kg/dose) IV Q6, and clonidine (4.5mg/kg/dose) PO Q4 and phenobarbital (5mg/kg/dose) IV BID.

Given his ongoing lability a dexmedetomidine infusion was started and PRN dilaudid and Ativan were added, but he continued to have ongoing severe agitation with resulting desaturation. Patent Ductus Arteriosus stent was placed on 2/11 to allow for discontinuation of the prostaglandin infusion. Brain Magnetic Resonance Imaging demonstrated sequelae of repeated hypoxic injury. He was diagnosed with cortical blindness and chorea secondary to multiple hypotensive events, likely exacerbated by Ativan and gabapentin. To treat his chorea, enteral metoclopramide was added, and he was weaned from Ativan and gabapentin, with eventual transition to enteral tetrabenazine.

Despite these changes, he had severely elevated peak inspiratory pressures on his mechanical ventilator and inadequate ventilation resulting in hypoxia requiring neuromuscular blockade. Ongoing discussions with neurology, pharmacy, cardiology, PHTN, PICU and palliative care teams were held regarding the best plan given his inability to be off muscle relaxant. His labile oxygenation and ventilator failure were thought to be secondary to underlying chronic lung disease and pulmonary hypertension in the setting of habituation to multiple classes of medication, delirium, opioid induced hyperalgesia and chorea. Similar to the first case,

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considerations included barbiturate, ketamine and/or propofol infusion to allow for discontinuation of the other continuous sedating medications and avoid withdrawal. After extensive discussions it was determined that propofol was the best option despite the risk for propofol infusion syndrome and mortality. Informed consent was obtained from the family who agreed to move forward with propofol infusion. The Propofol Wash-Out Protocol was implemented the day following consent. The patient's weight was 9.3kg at time of initiation and the infusion lasted nine days. Details of each day of propofol are outlined in (Table 2).

Table 2: Timing and dosing of propofol infusion for Case 2.

Hours	Propofol Dosing	Other Notes
0-24	Infusion initiated at 20mc/kg/min, increased by 20mcg/kg/min as needed over 10 hours to 250mcg/kg/min; bolus 0.2mg/kg	After 30 minutes: cisatracurium drip, IV lorazepam, phenobarbital, and clonidine discontinued. Infusion and bolus increased with inability to achieve SBS goal. Remaining medications: gabapentin (weaned daily); methadone and quetiapine continued
24-48	Infusion 250mcg/kg/min; bolus 1.5mg/kg	
48-72	Infusion 240mcg/kg/min; bolus 1.5mg/kg	
72-96	Infusion 250mcg/kg/min; bolus 0.4mg/kg	PRN phenobarbital x 1 overnight for irritability
96-120	Infusion 250mcg/kg/min; bolus 0.4mg/kg	Gabapentin discontinued
120-144	Infusion 200mcg/kg/min, weaned to 100mcg/kg/min	
144-168	Infusion increased to 150mcg/kg/min for irritability; subsequently weaned 50mcg/kg/min	
168-192	Increased to 75mcg/kg/min; subsequently weaned to 50mcg/kg/min	Lorazepam x1 for inability to achieve SBS goal
192-216	Infusion 25mcg/kg/min	
216-240	Infusion discontinued at 220 hours	

SBS = State Behavioral Scale

No changes were identified in any of his laboratory parameters, ECG or hemodynamics and there were no signs or symptoms consistent with propofol infusion syndrome. He remained on methadone IV Q6 and Seroquel QHS, as well as tetrabenazine po BID for chorea. Upon conclusion of the propofol wash out, he had no significant agitation and was comfortable while awake and interactive. He demonstrated improved pulmonary status; had no desaturation events or difficulty with ventilation. He was able to sleep overnight and required no PRN medications for agitation. This allowed for focus on establishment of transition to portable ventilator, a feeding and medication regimen, family education and discharge planning. Sixteen weeks later he was able to be discharged home at 13 months of age.

Discussion

Propofol (2, 6-diisopropylphenol) was first introduced into clinical practice in 1977. Propofol is an intravenous hypnotic anesthetic with rapid onset of action and rapid clearance with minimal side effects including a lack of emergence delirium, behavioral changes, nausea, and vomiting [1]. Propofol causes systemic vasodilation and relative bradycardia and undergoes liver metabolism. It is utilized widely for anesthesia induction, procedural sedation and total IV anesthesia (TIVA) [2]. It has neuroprotective and anti-convulsant properties by its GABA-A receptor inactivation that effectively blocks neurotransmitter excitation and lowers intracranial pressure preserving autoregulation [3].

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These favorable properties led to continuation of propofol infusions for post-operative/post-procedural sedation in intensive care units (ICU). Patients' quick anesthesia recovery following propofol discontinuation, and thereby ease of transition to endotracheal extubation, led to adoption of propofol infusions for primary sedation for tolerance of invasive mechanical ventilation. Utilization of propofol infusions as a solo sedating agent enabled minimizing other anxiolytic/sedating agents (i.e., barbiturates, benzodiazepines, anti-psychotics) and narcotics and their side-effects (delirium, hemodynamic effects, and withdrawal), allowing for assessment of extubation readiness.

A case series of metabolic acidosis and fatal myocardial failure in 5 children was published in 1992. The authors describe bradyarrhythmia's, metabolic acidosis, heart failure and lipemic serum after >3 days of propofol infusion [4]. Through the 1990s occurrence of metabolic acidosis, rhabdomyolysis, arrhythmias, myocardial dysfunction, and renal failure continued to be reported in children receiving propofol infusions. This rare but sometimes fatal clinical condition was coined by Bray 1999 as propofol infusion syndrome [5] which over time was recognized to have a complex and multifactorial pathophysiology [6]. The syndrome was characterized as "all or none" with sudden onset after even only a few hours [7]. Most concerning was the lack of identifying features to indicate which patients were vulnerable, although doses exceeding 4mg/kg/hr for >48 hours were thought to be associated with highest risk.

In March 2001 unpublished results of a randomized control trial in pediatric ICU patients receiving propofol were brought to light by the manufacturer AstraZeneca™. The study included 113 children with 12 deaths (11%) in those randomized to 2% propofol, 9 (8%) in the 1% propofol group and 4 (4%) in the non-propofol group [8]. The US Food and Drug Administration (FDA) and Committee on Safety of Medicines in the United Kingdom both reviewed the data. They were unable to find correlation between deaths and underlying disease of the patients, concluding the groups to be reasonably matched. Propofol infusion for sedation in children <16 years of age was therefore contraindicated [9], and the FDA issued a warning against the off-label use of propofol "in pediatric patients in intensive care units [10]. Following this warning, adoption of alternative sedation agents was recommended for pediatric patients.

Use of propofol in adult intensive care units has continued [11] despite published reports of propofol infusion syndrome occurring in adults [12]. These studies have established that propofol infusions are associated with increased risk for hypertriglyceridemia (18%) and hypertriglyceridemia-associated pancreatitis (1.8%). Patients experiencing hypertriglyceridemia were older, had a longer ICU stay, and received propofol for longer duration [13]. Patients with traumatic brain injury appear at increased risk (potentially due to higher doses to control intracranial pressure) [14], as do those with inherited mitochondrial defects [15]. A more recent 2019 review of 108 publications documenting 168 cases of propofol infusion syndrome found lipidemia, fever and hepatomegaly to be more frequent in children, with rhabdomyolyses and hyperkalemia more common in adults. Mortality in children was associated with fever and hepatomegaly, and in adults with ECG changes, hypotension, hyperkalemia, traumatic brain injury and higher dosing [16].

The Society of Critical Care Medicine recently published a pediatric clinical practice guideline that included propofol, however it was conditional and a low-quality recommendation, limiting propofol to <4mgk/kg/hr (< 67mcg/kg/min) for <48 hours. Included in the article is good practice statement of < 48hr continuous propofol sedation to allow for weaning of other analgesic and sedative medications to facilitate endotracheal extubation but details are lacking [17]. European literature includes consideration of propofol for "difficult to sedate patients" but includes no dosing or monitoring guidance [18].

Propofol decreases mitochondrial function through uncoupling oxidative phosphorylation which may make children with mitochondrial diseases more vulnerable to its adverse effects [19]. Whether increased availability and lower cost of genetic testing will allow for diagnosis of metabolic and genetic disorders that might identify patients susceptible to propofol infusion syndrome is an interesting question. The limited lifespan of children with these diseases may explain the reduced incidence of propofol infusion syndrome in the adult ICU population.

Taken as a whole, patients receiving propofol infusions warrant routine monitoring for lactic acidosis, triglyceride levels, pancreatic enzymes, liver transaminases, creatinine kinase and renal function, in addition to continuous cardiopulmonary monitoring and telemetry. Many adult ICUs have established laboratory and monitoring schedules for screening when propofol infusions are utilized [20]. However, there is little in the literature to guide interpretation of laboratory results; and cutoffs for monitored values are lacking.

We present two cases of complex chronically ill infants whose clinical management in the ICU led to massive doses of continuous sedating infusions, additional CNS-acting agents, and frequent use of neuromuscular blockade. These infants also suffered from opioid induced hyperalgesia (OIH). OIH is defined as a state of enhanced pain sensitization in patients who are on chronic opioid therapy. Clinically the condition is characterized by a paradoxical response whereby a patient becomes more sensitive to painful stimuli when receiving opioids [21]. Severe chronic lung disease and pulmonary hypertension in these infants lead to neither patient being able to tolerate wakefulness while continuing to oxygenate and ventilate. Previous efforts to wean continuous benzodiazepines and narcotics had been unsuccessful, and ongoing severe desaturation events would lead to administration of further sedation and

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neuromuscular blockade. The high doses additionally caused hypotension and bradycardia, triggering volume administration, and preventing diuretic therapy and achievement of optimal fluid balance. After careful consideration of the risks (including sudden death) and limited remaining options, informed consent was obtained from family to undergo a Propofol Wash-Out. Utilization of propofol in these cases allowed for safe discontinuation of the other CNS-acting infusions and prevented the impact of withdrawal symptoms on patients' cardiopulmonary status. Close monitoring of both cases demonstrated no complications, including no obvious signs or symptoms suggesting propofol infusion syndrome.

Conclusion

The use of propofol infusion for pediatric procedural sedation has been widely adopted and is generally believed to be safe, as has its use in the operating room for total intravenous anesthesia [22]. In contrast, propofol use is greatly limited in pediatric ICUs for concern for propofol infusion syndrome. Some PICUs will utilize propofol for children >16 years of age (particularly as extension from the operating room and for procedural recovery), restricting administration to < 48 hours and doses < 5mg/kg/hr [23], while many avoid its use entirely [24]. In the absence of clinical trials or other published work, there will be no data to support reversal of the contraindication for propofol infusion in a pediatric ICU. Despite the risk and contraindication, in the cases described above, our team felt propofol infusion to be the safest option and created a pediatric Propofol Wash-Out Protocol to minimize risk. Education was provided to all clinicians and the family to identify signs and symptoms consistent with propofol infusion syndrome, and a management plan created should this syndrome be recognized. We believe this case report provides some guidance for practitioners caring for a small subset of children where longer propofol infusions at higher doses might be considered to mitigate the risks of ongoing polypharmacy with sedating, narcotic and CNS-acting medications after exhaustion of other options.

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