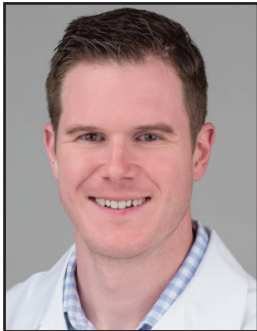


Carol Rees Parrish, MS, RDN, Series Editor

Propofol Related Infusion Syndrome: Implications for Nutrition in the Intensive Care Unit



Matthew Hulse

Propofol is an intravenous anesthetic agent widely used for a variety of indications in both the operative and critical care settings. Propofol's ability to produce rapid sedation with a short duration of action makes it an especially appealing agent within the critical care population. While propofol's beneficial properties have been widely exploited in the past several decades, the drug can also be associated with undesirable side effects such as hypotension, hypoventilation, bradycardia, and hyperlipidemia. Rarely, propofol is also linked to the development of severe lactic acidosis, bradycardia, rhabdomyolysis, renal failure, hepatomegaly, hyperlipidemia, cardiovascular collapse and ultimately death. These severe adverse events when combined are referred to under the umbrella of "propofol related infusion syndrome" (PRIS) which can occur in the setting of prolonged, high dose infusions. In this review, we will discuss the pharmacokinetics and pharmacodynamics of propofol and the potential mechanisms for the development of PRIS. Importantly, new evidence suggests that a thoughtful nutritional strategy focusing on carbohydrate administration may help avoid the development of this feared complication.

INTRODUCTION

Developed by James Baird Glen in 1980 and approved by FDA in 1989, propofol (Diprivan) is now the most commonly used anesthetic agent around the world. Due to its poor solubility in water, propofol is formulated at 1% in an oil/water emulsion containing 10% soybean oil, 2.25% glycerol and 1.2% egg lecithin (contains

long-chain triglycerides). Given the medium for preparation, bacterial contamination of propofol solution is possible and care should be taken to avoid long delay in administration when vials are open. Presence of EDTA in propofol formulation, a bacteriostatic agent, delays bacterial growth; other propofol formulations (generic) contain sodium metabisulfite as an antibacterial agent. Allergic reactions to propofol have been a cause for concern due to the egg and soy components. Original formulations contained cremophor but

(continued on page 32)

Matthew Hulse, MD Assistant Professor of Anesthesiology, Division of Critical Care Medicine, Medical Director, Thoracic and Cardiovascular ICU, University of Virginia, Charlottesville, VA

(continued from page 30)

were withdrawn because of high incidence of anaphylactic reactions observed in both animals and humans.¹ It was once assumed that patients with egg, soybean, or peanut allergy could not receive propofol, however this was subsequently disproven in both children and adults.^{2,3}

Propofol exerts its main activity through interaction with the γ -Aminobutyric acid type A (GABA_A) receptors in the central nervous system. GABA_A is the main inhibitory transmitter in the brain and when GABA_A receptors are activated, chloride conductance increases leading to hyperpolarization of post-synaptic cell membrane and subsequent neuronal inhibition.

Propofol is highly protein bound and is removed from the plasma via hepatic and non-hepatic pathways. Hepatically, propofol is metabolized via cytochrome P-450 to inactive sulfates and glucuronic acid metabolites which are subsequently eliminated by the kidneys. The half-life of propofol after a single injection is very short, with the initial half-time of approximately 2 minutes. A more important consideration is the context sensitive half-time (CST) of propofol, the time required for the drug plasma concentration to decrease by 50%, which is a major consideration in the critical care setting when prolonged infusions are more likely to be used. It is estimated the CST can approach 45 minutes after prolonged infusions.⁴

Propofol Related Infusion Syndrome

Propofol infusion syndrome is a rare and potentially fatal condition first reported in children in 1990 and more recently in adults receiving long-term (>48 h), high dose (>4/mg/kg/h) propofol infusions.⁵ The first pediatric patients described experiencing the syndrome were characterized by profound metabolic acidosis, bradycardia, and other dysrhythmias eventually leading to cardiac arrest.⁶ Since that time, PRIS is now characterized by a constellation of symptoms which involves nearly every organ system. Other commonly reported biochemical and clinical features include rhabdomyolysis, lactemia, and acute kidney injury (AKI). Table 1 summarizes the reported clinical features associated with PRIS.⁷

Despite initially being considered a syndrome associated only in the pediatric population, it is

now clearly evident that it can occur in adults as well. While difficult to estimate, the incidence of PRIS remains rare, likely less than 2% of those being treated with propofol, but continues to be associated with high mortality, up to 80%.⁸ The incidence of PRIS has been decreasing in recent years due to improved education surrounding the condition, as well as improvements in recognition of the clinical features of the disease process and predisposing conditions. A prolonged and relatively high dose propofol infusion remains a necessary, but not necessarily sufficient, mechanism to induce PRIS. For instance, 68% of the cases from the MEDWATCH database involved propofol infusion rate exceeding 83 mcg/kg/minute (5 mg/kg/hour); 54% of the cases received propofol for over 48 hours.⁹ Various predisposing factors for PRIS have been suggested by different researchers. Vasile et al. proposed the notion of “priming factors” and “triggering factors” for the syndrome. The priming factor is critical illness and the consequences that follow (systemic inflammation and endogenous catecholamine, glucocorticoid, and cytokine production).⁷ Triggering factors are the concurrent use of high dose propofol, exogenous catecholamines and corticosteroids.

Table 1. Clinical Features Associated with PRIS

| Organ System | Clinical Presentation |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Cardiovascular | Hypotension, acute systolic heart failure, pulmonary edema, RBBB, widening of the QRS, ventricular dysrhythmias (VT/VF), asystole |
| Renal/Urinary | Acute kidney injury, change in urine color |
| Musculoskeletal | Rhabdomyolysis |
| Metabolism/ Nutrition | Hyperkalemia, lipidemia, lactemia |
| Hepatobiliary | Hepatomegaly, elevated transaminases, hepatic failure |

RBBB: right bundle branch block, VT: ventricular tachycardia, VF: ventricular fibrillation

Other authors describe predisposing factors including age, cumulative dose of propofol, severe critical illness of the central nervous system (CNS) or respiratory origin, infusion of catecholamines, infusion of corticosteroids, inadequate delivery of carbohydrates, and subclinical mitochondrial disease.^{10,11} The pathogenesis of propofol related infusion syndrome is complex and beyond the scope of this article, however, several important mechanisms underlie the syndrome (Table 2).

While the pathologic cellular energetics which underlie the development of PRIS are complex, it is important to broadly review these topics in order to understand how nutritional therapies can be exploited to potentially prevent the syndrome. Early theories about the cause of acidosis in PRIS included impaired hepatic lactate metabolism caused by the lipid present in propofol leading to lactate accumulation and acidosis, accumulation of inactive propofol metabolites, and lipid microembolization. However, recent research has focused on impaired mitochondrial respiratory chain function being one of the primary mechanisms. Free fatty acids (FFA) are derived from catecholamine-mediated lipolysis of adipose tissues and are the most important fuel for the myocardium and

skeletal muscle tissues under fasting conditions or in critical illness. Any obstacle to FFA utilization determines various degrees of metabolic acidosis and resultant myocytolysis. Cray et al. supported the theory that a propofol metabolite caused a direct biochemical inhibition which disrupts the respiratory chain causing a failure of adenosine triphosphate (ATP) production, cellular hypoxia, and metabolic acidosis.¹² Mehta et al. demonstrated a reduced complex IV activity in the mitochondria,¹³ and Wolf et al. has implicated the disruption of mitochondrial fatty-acid oxidation.¹⁴ Long-term propofol infusion is associated with an increase in malonylcarnitine, which ultimately results in impairment of mitochondrial transport proteins (malonyl coenzyme A and carnitine palmitoyl transferase I). Consequently, the entry of long chain acylcarnitine esters in the muscle is impaired. Medium and short chain fatty acids diffuse into the mitochondria and inhibit and uncouple the respiratory chain (at complex II) causing a failure of ATP production in the mitochondria, leading to a further buildup of long chain, medium chain, and short chain fatty-acid metabolic by-products.¹⁴ Thus, the literature suggests at least two impairments in FFA metabolism level of the mitochondria necessary for the syndrome to occur. Firstly, long-chain FFA cannot enter the mitochondria due to inhibition of the active transport, and secondly, while the medium and short-chain FFA, that freely cross the mitochondrial membranes which do not require enzyme-mediated transfer, these cannot be used due to the mitochondrial uncoupling by propofol itself. These biochemical processes which increase FFA combined with the lipid formulation of the drug, drastically increases the medium and long chain triglyceride fat load. As a consequence of the impaired fatty-acid oxidation, a rapid buildup of toxic fatty-acid intermediates results and when coupled with cellular hypoxia, creates a cycle of worsening acidosis and patient decompensation. Excess serum fatty-acid concentrations have been shown to directly contribute to ventricular dysrhythmias, one of the hallmarks of the disease.¹⁵

Nutrition and the Role of Carbohydrates

Further attempts to prevent PRIS and optimize cellular energetics in critically ill patients have begun to focus on the role of nutrition and the

Table 2. Predisposing Factors for the Development of Propofol Related Infusion Syndrome

| |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Critical Illness |
| <ul style="list-style-type: none"> • Neurologic Injury (Traumatic Brain Injury, Status Epilepticus) • Sepsis • Pancreatitis • Trauma • Subclinical Mitochondrial Disease |
| Propofol Dose >4 mg/kg/hr |
| Duration of Infusion >48 hrs |
| “Triggering Factors” |
| <ul style="list-style-type: none"> • Exogenous catecholamines • Exogenous corticosteroids |
| Inadequate delivery of carbohydrate (NPO, inadequate or delays in enteral feeding, dextrose free IV fluids, etc.) |

provided macronutrient profile, especially focusing on dietary carbohydrates. Illustrative of the importance of carbohydrate administration, a case report published in 2004 speculated that PRIS was precipitated by the commencement of a ketogenic diet (high fat, low carbohydrate) as adjuvant therapy for refractory status epilepticus in a 10-year-old boy sedated with propofol.¹⁶ The premise of this case report suggests that the dietary fat load, coupled with the propofol-mediated impairment of mitochondrial fatty-acid oxygenation contributed to the metabolic acidosis and clinical decompensation. Furthermore, PRIS mimics the congenital mitochondrial DNA myopathies in which specific defects in the mitochondrial respiratory chain result from a disturbance in the lipid metabolism in cardiac and skeletal muscle. A typical case scenario is a pediatric patient who is well until stressed by infection or starvation, when fat metabolism is needed for energy production. Under such conditions, the patients develop severe rhabdomyolysis, cardiac, and hepatic insufficiency associated with hypoglycemia. Now various guidelines support avoiding propofol in patients known to have these inborn errors in metabolism due to this association.¹⁷ These biochemical foundations of altered mitochondrial fat oxidation in the PRIS disease process have lent importance to strategies that focus on nutritional alterations which may modulate the disease state and its predisposition. As evidenced by the above ketogenic diet example, both high lipid loads as well as low-carbohydrate intake have been implicated in the development of PRIS. A major concern with propofol is the lipid load owing to its formulation which increases solubility. A daily intravenous lipid load of 2-3 g/kg/day is regarded as adequate for children on total parenteral nutrition (TPN).¹⁸ This is equivalent to a fat load conferred by a 1% propofol infusion running at 4 mg/kg/h. Given that most of the case reports documenting PRIS were associated with infusion rates greater than 4 mg/kg/hr, it is postulated that the excessive

lipid load may be a significant contributory factor. Considering the lipid load and resultant hyperlipidemia noted in PRIS, the importance of carbohydrate substrates in the process of normal lipid metabolism in the liver cannot be understated. Ahlen et al. have postulated that as a result of the depletion of carbohydrate stores in the critically ill patient, lipid accumulation associated with the high propofol infusion rate is not a direct implication of the toxicity of propofol, rather a consequence of the exhaustion of carbohydrate stores.¹⁹ Carbohydrate depletion can, in turn, lead to a reduction in citric acid levels, which slows lipid metabolism.²⁰ Although further research is necessary, some evidence suggests early adequate intake of a source of carbohydrate may reduce the risk of developing PRIS by preventing the switch to fat metabolism. The larger carbohydrate stores in adults may partially explain the lower incidence of the syndrome in adults. Wolf et al. suggested that a carbohydrate intake of 6-8 mg/kg/min can suppress fat metabolism in critically ill children and thus prevent PRIS.¹⁴

Management Considerations

A high index for suspicion for development of disease-state and prompt discontinuation of propofol sedation remains the hallmark of both the diagnosis and treatment of PRIS. The disease commonly presents as unexplained high anion gap metabolic acidosis (HAGMA), rhabdomyolysis, hyperkalemia, AKI, elevated liver enzymes, and cardiac dysfunction (brady or tachydysrhythmias, cardiogenic shock, and asystole). There are no established guidelines for the treatment of propofol infusion syndrome nor is there a specific antidote. The successful management of PRIS relies on the awareness of the condition, the clinical features, and maintaining a high index of suspicion of the development of such symptoms in patients who are at elevated risk. The treatment of the condition must rely firstly on prompt discontinuation of the propofol infusion and selection of an alternative sedative agent, if necessary. Management of the metabolic acidosis in the literature includes volume optimization for optimal cardiac output and renal replacement therapy. Sodium bicarbonate in the management of lactic acidosis is

(continued on page 36)

Visit Our Website:
practicalgastro.com

(continued from page 34)

controversial, not universally accepted, and could paradoxically worsen acidemia.²¹ Hyperkalemia and rhabdomyolysis are strong indications to consider renal replacement therapy for patient with metabolic acidosis due to PRIS. Extrapolating from other guidelines for the treatment of rhabdomyolysis, patients should receive vigorous fluid resuscitation.²² However, euvolemia should be maintained in certain patient populations such as those with traumatic brain injuries or heart failure. Calcium administration, insulin with or without dextrose, beta-2 agonists, sodium bicarbonate, and potassium binding resins can be considered in the treatment of hyperkalemia. Despite these interventions and conventional circulatory support measures in modern critical care medicine, many case reports highlight the refractory nature of the condition to intravenous fluid volume loading and the use of escalating doses of vasopressors and inotropes. Limited success has been achieved with cardiac pacing for dysrhythmias, and there is

emerging literature of success with extracorporeal membrane oxygenation (ECMO).²³ Table 3 outlines the major management considerations for treatment of suspected PRIS.

CONCLUSION

PRIS is a rare but extremely dangerous complication of propofol administration with high mortality in both the pediatric and adult patient populations. Risk factors for the development of PRIS are described such as: large doses of propofol and prolonged duration of infusions, carbohydrate depletion, critical illness, and concomitant administration of catecholamines and glucocorticoids. The pathophysiology of the condition includes impairment of mitochondrial beta-oxidation of fatty acids, and the disruption of the electron transport chain resulting in metabolic disarray. The disease commonly presents as an otherwise unexplained metabolic acidosis, rhabdomyolysis, hyperkalemia, acute kidney injury, elevated liver enzymes, and cardiac dysfunction. Management of PRIS includes immediate discontinuation of the propofol infusion and problem-driven management which may include hemodialysis, hemodynamic support, optimization of glucose metabolism, nutritional supplementation to include adequate carbohydrate sources, and ECMO in refractory cases. Despite increased awareness of the clinical condition and improvements in the specialty of critical care medicine, mortality remains high. Clinicians should consider alternative sedation agents in patients who are receiving prolonged (>48 h) or high dose propofol infusions (>4/mg/kg/h) and be aware of the various strategies available to reduce the likelihood of developing the syndrome. ■

Table 3. Management of Propofol Related Infusion Syndrome

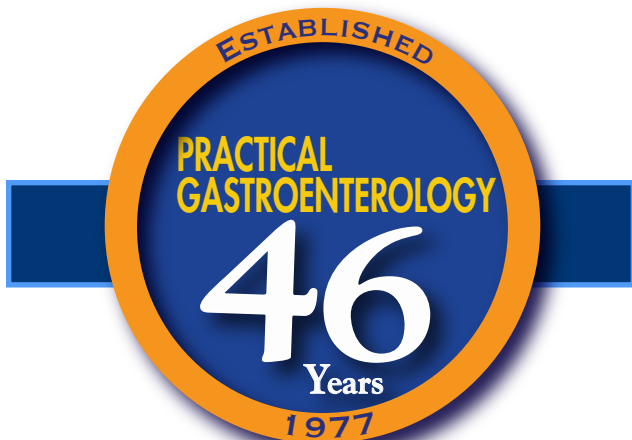
| |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Awareness and suspicion of the syndrome in clinical scenarios associated with the development of PRIS</p> <ul style="list-style-type: none"> • Consider monitoring triglyceride levels in patients receiving > 48 hours of propofol or > 4/mg/kg/hr |
| <p>Immediate discontinuation of propofol</p> |
| <p>Supportive Care</p> <ul style="list-style-type: none"> • Vasoactive and inotropic agents to support hemodynamics • Optimization of gas exchange • Cardiac pacing for bradycardia • Extracorporeal Membranous Oxygenation (ECMO) • Glucagon • Renal replacement therapy |

References

1. Briggs LP, Clarke RSJ, Watkins J. An adverse reaction to the administration of disopropofol (Diprivan). *Anaesthesia*. 1982;37:1099-1101.
2. Asserhøj LL, Mosbech H, Krøigaard M, et al. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. *Br J Anaesth*. 2016 Jan;116(1):77-82
3. Sommerfield DL, Lucas M, Schilling A, et al. Propofol use in children with allergies to egg, peanut, soybean or other legumes. *Anaesthesia*. 2019 Oct;74(10):1252-1259.

4. Hughes MA, Glass PS, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology*. 1992 Mar;76(3):334-41
5. Kam, P.C.A. and Cardone, D. Propofol infusion syndrome. *Anaesthesia*. 2007. 62: 690-701.
6. Hatch DJ. Propofol-infusion syndrome in children. *Lancet*. 1999 Apr 3;353(9159):1117-8.
7. Vasile B, Rasulo F, Candiani A, et al. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med*. 2003 Sep;29(9):1417-25.
8. Roberts RJ, Barletta JF, Fong JJ, et al. Incidence of propofol-related infusion syndrome in critically ill adults: a prospective, multicenter study. *Crit Care*. 2009;13(5):R169.
9. Fong JJ, Sylvia L, Ruthazer R, et al. Predictors of mortality in patients with suspected propofol infusion syndrome. *Crit Care Med* 2008;36:2281-7
10. Smith H, Sinson G, Varelas P. Vasopressors and propofol infusion syndrome in severe head trauma. *Neurocrit Care* 2009;10:166-72.
11. Otterspoor LC, Kalkman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. *Curr Opin Anaesthesiol* 2008;21:544-51
12. Cray SH, Robinson BH, Cox PN. Lactic acidemia and bradyarrhythmia in a child sedated with propofol. *Crit Care Med*. 1998 Dec;26(12):2087-92.
13. Mehta N, DeMunter C, Habibi P, et al. Short-term propofol infusions in children. *Lancet*. 1999 Sep 4;354(9181):866-7.
14. Wolf A, Weir P, Segar P, et al. Impaired fatty acid oxida-

- tion in propofol infusion syndrome. *Lancet*. 2001 Feb 24;357(9256):606-7.
15. Jorens PG, Van den Eynden GG. Propofol infusion syndrome with arrhythmia, myocardial fat accumulation and cardiac failure. *Am J Cardiol*. 2009 Oct 15;104(8):1160-2.
16. Baumeister FA, Oberhoffer R, Liebhaber GM, et al. Fatal propofol infusion syndrome in association with ketogenic diet. *Neuropediatrics*. 2004 Aug;35(4):250-2.
17. Hsieh VC, Krane EJ, Morgan PG. Mitochondrial Disease and Anesthesia. *Journal of Inborn Errors of Metabolism and Screening*. January 2017.
18. Goulet, O.J., Cai, W, Seo, J. Lipid Emulsion Use in Pediatric Patients Requiring Long-Term Parenteral Nutrition. *Journal of Parenteral and Enteral Nutrition*. 2020. 44: S55-S67.
19. Ahlen K, Buckley CJ, Goodale DB, et al. The ‘propofol infusion syndrome’: the facts, their interpretation and implications for patient care. *Eur J Anaesthesiol*. 2006 Dec;23(12):990-8.
20. Mirrakhimov AE, Voore P, Halytskyy O, et al. Propofol Infusion Syndrome in Adults: A Clinical Update. *Crit Care Res Pract*. 2015;2015:260385.
21. Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. *PLoS One*. 2013;8(6):e65283. Published 2013 Jun 5.
22. Vanholder R, Sever MS, Ereke E, et al. Rhabdomyolysis. *J Am Soc Nephrol*. 2000 Aug;11(8):1553-1561.
23. Mayette M, Gonda J, Hsu JL, et al. Propofol infusion syndrome resuscitation with extracorporeal life support: a case report and review of the literature. *Ann Intensive Care*. 2013;3(1):32. Published 2013 Sep 23.



Answers to this month's crossword puzzle:

| | | | | | | | | | | | | | | | | | | | |
|----|---|----|----|----|----|---|----|----|----|----|----|----|----|----|----|---|----|----|---|
| 1 | G | A | L | L | B | L | A | D | D | E | R | | 7 | K | I | T | 8 | | |
| | L | | A | | E | | P | | I | | A | | I | | O | | | | |
| 9 | U | N | G | 10 | U | E | 11 | N | T | | 12 | G | L | I | A | D | I | N | |
| | T | | | | S | | E | | | | N | | N | | O | | | | |
| 13 | E | N | T | 14 | E | R | O | P | A | T | H | Y | | 17 | E | L | M | | |
| | N | | E | | A | | | | E | | | | | Y | | E | | | |
| | | | 18 | A | N | G | I | O | 19 | G | R | A | P | H | Y | | 21 | C | T |
| 22 | C | U | E | | S | | U | | | E | | | | 23 | W | | E | | |
| | A | | 24 | S | T | E | A | T | 26 | R | | 27 | H | E | A | | R | | |
| 28 | T | 29 | U | M | | | R | | | E | | | E | | L | | | | |
| 30 | A | N | 31 | S | | | 32 | C | U | F | F | | 33 | P | O | L | Y | 34 | P |
| | L | | 35 | S | A | P | | | | L | | A | | | | | | | U |
| 37 | Y | 38 | E | | 39 | G | O | T | | 40 | G | U | T | T | 41 | U | R | A | L |
| 42 | S | A | 43 | C | | R | | 44 | G | | X | | | I | | A | | S | |
| 45 | T | R | O | P | I | C | A | L | | | | | | 46 | C | H | Y | M | E |