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Propofol-Related Infusion Syndrome



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Propofol-related infusion syndrome (PRIS) is a rare yet often fatal syndrome that has been observed in critically ill patients receiving propofol for sedation. PRIS is characterized by severe unexplained metabolic acidosis, arrhythmias, acute renal failure, rhabdomyolysis, hyperkalemia, and cardiovascular collapse. Although the exact pathophysiology of PRIS remains to be determined, impaired tissue metabolism caused by propofol infusion appears to be an important mechanism leading to complete cardiovascular collapse. Risk factors for developing PRIS include sepsis, severe cerebral injury, and high propofol doses. Early recognition of the manifestations is the key to managing PRIS. If PRIS is suspected, propofol should be discontinued and an alternative sedative agent initiated. General measures to support cardiac and renal function should be initiated promptly in patients with suspected PRIS.

INTRODUCTION

Propofol-related infusion syndrome (PRIS) is a rare yet often fatal syndrome. It is described as acute bradycardia progressing to asystole combined with lipemia, severe metabolic acidosis (often with base excess less than -10 mEq/L), rhabdomyolysis or myoglobinuria associated with the continuous infusion of propofol, regardless of the duration (1). The syndrome

was originally described in the literature in the early 1990s in children receiving propofol at high doses (>4 mg/kg/hour) for long-term sedation (>48 hours). Most of these patients developed severe metabolic acidosis, rhabdomyolysis, acute renal failure, progressive cardiac failure, with a high mortality rate (see Table 1). Based on these findings, the Food and Drug Administration (FDA) issued warnings against propofol's use in pediatric patients (2). Although originally thought to be a problem related to use in children, reports of deaths associated with propofol use in adults appeared in the literature beginning in the late 1990s (2). According to

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these case reports, the clinical presentation of PRIS in adults appeared very similar to those reported in the pediatric population.

FORMULATION AND CLINICAL PHARMACOLOGY OF PROPOFOL

Propofol is an intravenous short-acting sedative hypnotic agent that has been in use for over two decades (3). It has a rapid onset of action (within seconds) and a very short half-life. It was initially used as an inducing agent for general anesthesia. Because of its favorable pharmacokinetic and pharmacodynamic profiles, it later became widely used for sedation in intensive care units. The pharmacokinetic properties of propofol make it an attractive option for sedation of intubated, mechanically ventilated patients in intensive care units. Its short onset of action and half-life allows for rapid awakening once the infusion is discontinued. It can also be easily titrated to maintain the desired level of sedation in critically ill patients. In addition, propofol is rapidly deactivated via a conjugation reaction both hepatically and extra-hepatically. The non-renal, non-hepatic dependent metabolic clearance makes it a superior sedative agent over benzodiazepines or opioids for ICU patients with end organ failure, especially from a safety perspective. In addition to its sedative and amnesia effects, propofol also decreases cerebral oxygen consumption and reduces intracranial pressure. It also shows excellent antiepileptic activities with proven efficacy in treating patients with refractory seizures. These characteristics have further expanded the use of propofol beyond its initial approved indication as a sedative for induction and maintenance of anesthesia.

Propofol is a highly lipophilic compound and is essentially insoluble in water or other aqueous medium. Therefore, it is formulated as an intravenous emulsion with 10% lipid (1 mL contains 1.1 kcal; 0.1 g fat) containing soybean oil and egg lecithin so that the lipid component is used as a carrier for the drug. Because of this, infusion of propofol at a high rate or as a large bolus may lead to lipid intolerance. Similarly, the presence of lipid emulsion also causes concern for sterility and the risk of contamination by bacteria and fungi. Therefore, tubing and open vials of propofol should be replaced every twelve hours (3).

Table 1.
Clinical Features of Propofol-Related Infusion Syndrome

- Metabolic Acidosis
- Arrhythmias
- Lipemia
- Hepatomegaly
- Rhabdomyolysis
- Acute Renal Failure
- Hyperkalemia
- Progressive Myocardial Failure
- Cardiovascular Collapse

The common side effects of propofol include pain on injection, hypotension, bradycardia, decreased cardiac output, hyperlipemia, and hypertriglyceridemia.

INCIDENCE

Because the definition of PRIS has not been standardized, the exact incidence of propofol infusion syndrome is unclear. In addition, no longitudinal investigations or patient registry designed to determine the incidence of PRIS exists. Therefore, the information available is based solely on case reports published over the last two decades. The reported incidence varies depending on which symptoms were being considered and provided in each case report. For instance, using metabolic acidosis with no other apparent causes as the primary criterion, Cravens and colleagues reported that 24% of patients receiving propofol during radiofrequency ablation developed PRIS (4). Compared with other reports, the incidence is unusually high in this study because the investigators used base excess (-2 mEq/L or less) as the case definition. On the other hand, using unexplained acidosis, creatine kinase elevation unrelated to trauma, and electrocardiographic changes as criteria in patients with severe head trauma, Smith and colleagues reported a 6% incidence of PRIS (5). Using the FDA MED-WATCH Adverse Event Reporting System database between 1989 and 2005, and applying symptoms based on all the published case reports as clinical criteria,

Fong and his colleagues identified 1,139 cases of PRIS over a period of 17 years (6). Therefore, the actual incidence remains to be determined but appears to be very infrequent. Nevertheless, the mortality rate among these 1,139 cases was 30%. Iyer and colleagues recently reported their experience using propofol over an 11-year period to manage refractory status epilepticus. Of the patients receiving propofol in this series, there was a 6% mortality rate and a 10% frequency of cardiorespiratory arrest. Approximately 39% of patients receiving propofol developed features of PRIS (7).

RISK FACTORS

Major risk factors for the development of this syndrome include poor oxygen delivery, sepsis, severe cerebral injury, and high propofol dosage. For instance, 68% of the cases from the MEDWATCH database involved propofol infusion rate exceeding 83 mcg/kg/minute (5 mg/kg/hour) (6). Among the cases with reported duration of infusion, 54% of the cases received propofol for over 48 hours. This finding is consistent with many earlier published case reports.

Major triggering and predisposing factors for PRIS have been suggested by different researchers. Vasile and her colleagues describe a priming factor and triggering factors for the syndrome (8). The priming factor is critical illness—acute neurologic injury, trauma, sepsis, or pancreatitis. Triggering factors are concurrent use of catecholamines and corticosteroids. Other authors describe predisposing factors—age, cumulative dose of propofol, severe critical illness of CNS or respiratory origin, infusion of catecholamines, infusion of corticosteroids, inadequate delivery of carbohydrates, and subclinical mitochondrial disease (9). Based on these clinical observations, several mechanisms of PRIS have been proposed.

PROPOSED MECHANISMS/PATHOPHYSIOLOGY

The proposed pathophysiology of PRIS remains controversial and is likely multifactorial. One of the leading hypotheses involves impaired electron transport chain function caused by propofol which eventually causes metabolic collapse of the body (2). Animal

models suggest that propofol uncouples oxidative phosphorylation and inhibits electron flow along the electron transport chain in the mitochondrial membrane (9). Impaired electron transport chain function decreases the ability of the mitochondria to produce energy and may lead to a regional imbalance between energy demand and utilization. In the state of metabolic stress and decreased food intake, free fatty acids (FFA) derived from catecholamine-mediated lipolysis of adipose tissue are the most important fuel for myocardial and muscle cells. In order to generate acetyl-CoA to feed into the citric acid cycle to maintain ATP production, FFAs undergo beta oxidation in the mitochondria, where free electrons are generated through the biosynthetic process. At clinically relevant doses, propofol has been shown to inhibit the formation of ATP from its substrates (10) and interfere with electron transfer across the mitochondria membrane causing a decrease in the transmembrane electrical potential (11,12). Additionally, propofol has been shown to increase hepatocellular oxygen uptake while inhibiting gluconeogenesis, especially from the substrates lactate and alanine. Collectively, these processes disrupt FFA utilization, impair ATP synthesis, and alter cellular oxygen and substrate delivery and may result in cell death and necrosis. If the process takes place in cardiac tissue when increase cardiac output is needed, cardiac symptoms such as bradyarrhythmias, bradycardia, Brugada-like electrocardiogram pattern, myocardial failure, ventricular tachycardia/fibrillation, asystole, or cardiac arrest may develop. In the muscle, the metabolic imbalance can result in muscle necrosis, presenting as rhabdomyolysis.

Altered lipid metabolism in the absence of cardiac ischemia or tissue necrosis may also precipitate some of the cardiac symptoms as presented in the case reports. Under normal physiology, carnitine acts as the cofactor to transport long-chain acyl groups from fatty acids into the mitochondrial matrix so they can be broken down through beta-oxidation to release energy from the citric acid cycle. Inhibition of beta-oxidation by propofol would result in the intracellular accumulation of FFA and acyl-carnitine complexes. High plasma concentrations of unutilized FFAs have been shown to possess pro-arrhythmogenic properties (9).

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This may also partially explain some of the cardiac symptoms described in some of the case reports.

Since lipid emulsion is the solvent and excipient for propofol, questions arise on whether the impaired FFA metabolism is a result of propofol itself or the lipid emulsion. A study using rabbits was conducted to address this question (13). Two groups of animals were sedated for up to 48 hours with either propofol alone or inhaled anesthetic with equal doses of intravenous lipid emulsion. Both groups exhibited similarly elevated serum cholesterol concentrations, but the group receiving propofol showed higher triglyceride concentrations, suggesting that the propofol, rather than the lipid emulsion excipient, is the more likely cause of lipemia observed in PRIS cases. The marked increase in triglyceride concentration may independently (independent of what was discussed above) cause impaired beta-oxidation of FFAs.

It has been proposed that the rate of carbohydrate depletion also affects the significance and magnitude of impaired lipid metabolism (9). In the absence of carbohydrate, phosphorylated citrate levels fall and lipid metabolism slows. This suggests that if regulation of lipids is impaired, triglyceride accumulation will occur and reach lipemic levels within 2–5 days, depending on the rate of infusion. Carbohydrate reserves are depleted more rapidly in children than in adults and may explain the higher prevalence of PRIS in children.

There is also evidence suggesting an association between propofol infusion and catecholamine response as a cause of PRIS (9). In animal models, propofol impairs binding of catecholamine to adrenergic receptors. This finding may explain why higher doses of catecholamines are necessary in patients receiving propofol. Simultaneously, plasma propofol concentrations in animal models are decreased. Presumably, this reduction in propofol concentration is associated with an increased propofol clearance due to hyperdynamic states. Subsequently, this necessitates higher doses of propofol to achieve an adequate level of sedation and may accentuate the negative impact of propofol on electron transport chain function and FFA metabolism. A vicious cycle then ensues in which a decreased level of sedation prompts an increase in propofol infusion rate, resulting in

hypotension, which prompts an increase in rate of catecholamine infusion.

Steroids are commonly cited as a cause of muscle damage (8). In the setting of critical illness, steroids can promote proteolysis of the cardiac myofilaments and trigger acute muscle damage, which manifests as rhabdomyolysis.

PRIS is a relatively rare occurrence and, given the widespread use of propofol, suggests the existence of a genetic susceptibility (9). Further studies are needed to identify a genetic risk profile.

Despite the limited scientific research and bedside observations, some researchers remain skeptical about the clinical validity of PRIS. Ahlen and colleagues, representing AstraZeneca, one of the manufacturers of propofol, offer a dissenting opinion regarding the existence of PRIS (14). Their published counterargument refers to the “so-called propofol infusion syndrome.” Based on their review and interpretation of published clinical trials, case reports, and internal company data, they argue that most of the physiologic effects described with PRIS can be explained by alternate mechanisms (e.g. metabolic acidosis secondary to inadequate tissue oxygenation; rhabdomyolysis by inadequate delivery of oxygen to skeletal muscles, lipemia by impaired lipid regulation from carbohydrate depletion, hepatic impairment by any mechanism can exacerbate hyperlipemia such as sepsis, hypoperfusion, hypoxia, or hypermetabolic states). They argue that although they cannot exclude the possibility of the existence of PRIS, most events that occur with the syndrome can be explained by other physiologic processes not related to propofol. Their recommendations for safely using propofol include assessing and managing hemodynamic compromise and assuring adequate oxygen delivery, identifying and addressing underlying causes of lipemia, using propofol within or close to recommended range, and providing adequate carbohydrate to assist in the management of lipemia or when mitochondrial defects are present.

MARKERS

There is much interest in identification of early markers of PRIS. Unexplained metabolic acidosis, elevated serum lactate, creatine phosphokinase and myoglobin,

Table 2.
Predisposing Factors for Developing Propofol-Related Infusion Syndrome

- Critical Illness
 - Severe Cerebral Injury
 - Sepsis
 - Pancreatitis
 - Trauma
- Propofol dose >4 mg/kg/hour
- Propofol infusion >48 hours
- Presence of “triggering factor” (i.e. catecholamine infusion or corticosteroids)
- Inadequate delivery of carbohydrate

hyperlipidemia, and ECG changes (ST elevation in precordial leads V1 to V3) have all been described as early markers for PRIS (2). However, the utility and sensitivity of routine monitoring serum creatine kinase and myoglobin to predicting PRIS is, at this time, questionable.

PREVENTION AND MANAGEMENT OF PRIS

Depletion of carbohydrate stores can promote mobilization of fat stores and increase lipid metabolism. This, in turn, increases circulating fatty acid load and may predispose patients to PRIS. Theoretically, it is therefore possible that early adequate carbohydrate intake may prevent PRIS by preventing the switch to fat metabolism. There is some suggestion that providing a carbohydrate intake of 6–8 mg/kg/minute can suppress fat metabolism and thus prevent PRIS (8).

Because many cases of PRIS occur at high doses and prolonged duration of propofol infusion, most authors agree that it is prudent to minimize the dose (<5 mg/kg/hour) and duration (<48 hours) of propofol infusion in patients with risk factors for developing PRIS (see Table 2).

Successful management of PRIS relies on prompt recognition and discontinuation of propofol. Once a patient presents with symptoms compatible with PRIS, propofol infusion should be discontinued promptly and an alternative sedative agent should be initiated.

Table 3. Guarding Against Propofol-Related Infusion Syndrome

- Important clinical presentations that warrant further work-up for PRIS:
 - Unexplained metabolic acidosis
 - Rhabdomyolysis unrelated to trauma
 - Acute renal failure
 - Cardiac arrhythmias
- Abnormal laboratory results that may indicate the progression of PRIS:
 - Elevated serum lactate
 - Elevated creatine phosphokinase
 - Myoglobinuria
 - Hyperkalemia
 - Hypertriglyceridemia
- Avoid high propofol doses and minimize the duration of infusion in high risk patients
- Avoid lipid overload by assessing all sources of fat calories (e.g., parenteral nutrition, enteral nutrition)
- Assure adequate provision of carbohydrates
- Monitoring of serum triglycerides in any patient receiving propofol in doses >4 mg/kg/hour or >48 hours is highly recommended

Cardiovascular support may require a combination of vasopressors and inotropes. Cardiac pacing has been utilized in some case reports and should be considered (9). Hemodialysis or hemofiltration have been suggested to decrease the plasma concentrations of circulating metabolic acids and lipids, and have been used successfully in some case reports (9). Other cases have reported the successful use of extracorporeal membrane oxygenation (ECMO) for combined respiratory and circulatory support (1).

CONCLUSION

PRIS is a serious side effect of propofol infusion that appears to affect both adults and pediatric patients. Once it develops, PRIS can prove fatal. Although the pathophysiology of PRIS remains to be confirmed, impaired tissue metabolism caused by high dose and/or prolonged propofol infusion appears to be a

likely and important mechanism leading to complete cardiovascular collapse. Therefore, guarding against and recognizing the early signs and symptoms of PRIS, may have an important impact on the clinical outcomes of patients experiencing this syndrome (see Table 3). If PRIS is suspected, propofol should be discontinued and an alternative sedation agent initiated. Hemodynamic support and renal replacement therapy should be instituted promptly. Further research is necessary to establish the precise mechanism of the syndrome and to identify genetic predisposition. ■

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