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Propofol Related Infusion Syndrome: A Subtle Adversary

Brandon Harris, MD[1], Elizabeth C. Taylor, PharmD, BCCCP[1], John W. Plckstone, BS[1], Errington C. Thompson, MD, FACS, FCCM[1]

ABSTRACT

Propofol Related Infusion Syndrome (PRIS) was first described in 1998. It has a strange collection of symptoms, including marked bradycardia, persistent, recalcitrant metabolic acidosis, liver enlargement, rhabdomyolysis, and lipemic blood. We present 2 recent patients who appeared to have had PRIS. Creatinine kinase seems to be an early detector of PRIS. If PRIS is recognized early, this complex metabolic process seems to be completely reversible. Propofol (2,6-di-isopropylphenol) is a sedative that has been used in the intensive care unit (ICU) since at least the early 1990s.[1] It is an ideal drug for patients on mechanical ventilation. It reduces anxiety and discomfort. Propofol can be given by continuous intravenous infusion. The level of sedation correlates with the amount of drug infused. Because the drug is rapidly metabolized, the patient can be easily awakened and ready to participate in spontaneous breathing trials and extubation when the intravenous infusion is stopped. Critical care physicians have widely adopted propofol because it is a better intensive care unit sedative than midazolam or lorazepam. Early reports of the use of propofol in the ICU revealed minimal side effects.[2,3] Propofol related infusion syndrome (PRIS) was first truly documented by Bray in 1998.4 He described the sudden onset of marked bradycardia, which was resistant to treatment, lipemic plasma, clinically enlarged liver, metabolic acidosis, rhabdomyolysis, and myoglobinuria. In his original report of 15 children, 12 died from the syndrome. Three patients did survive. We report 2 patients who developed propofol related infusion syndrome and present a discussion of this syndrome.

Author affiliations are listed at the end of this article.

Corresponding Author:
Errington Thompson, MD
Marshall University
Joan C. Edwards
School of Medicine
thompsoner@marshall.edu

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CASE 1

A 52-year-old gentleman with a history of alcoholic cirrhosis presented after falling down a flight of steps. The patient was intubated at the scene by emergency medical service for a Glasgow Coma Scale of 5. The patient was transported to our trauma center. The patient was found to have a large intracranial hemorrhage which extended into the left basal ganglia, left temporal and parietal lobes. Neurosurgery did not believe that neurosurgical intervention would be beneficial. The patient was admitted to the ICU. The patient was on mechanical ventilation, and propofol was started. The patient developed a metabolic acidosis which was not amenable to fluid resuscitation. He also had elevated creatinine kinase. The patient became hypotensive, requiring pressors. Propofol infusion syndrome was suspected. The propofol was stopped. The patient progressed to cardiac failure and expired.

This patient was on propofol for a total of 56 hours. His maximum dose of propofol was 50 mcg/kg/min. The average dose for day 1 was 25 mcg/kg/min, day 2 was 50 mcg/kg/min, and day 3 was 20 mcg/kg/min.

CASE 2

A 17-year-old female was involved in a severe motor

vehicle crash. The patient was intubated at the scene. She presented to our trauma center with sluggish pupils and decerebrate posturing. CT scan of the head revealed an acute subarachnoid hemorrhage. The patient was admitted to the ICU and started on propofol. Within the first 12 hours, the patient developed diabetes insipidus. The patient's urine output was controlled with vasopressin and fluid resuscitation. The patient developed metabolic acidosis. This was not responsive to fluids. The patient's lipids were normal. The propofol was stopped, and the patient's metabolic acidosis resolved over the next 12 hours. The patient had a prolonged hospitalization secondary to a severe head injury. The patient required a tracheostomy as well as a percutaneous endoscopically placed gastrostomy tube. The patient was discharged to a cognitive rehabilitation center 36 days after admission.

This patient was on propofol for just under 24 hours. She was on 99.4 mcg/kg/min during that time.

DISCUSSION

Propofol is an amnestic/sedative that has been rapidly accepted in the ICU. It was approved for use in the United States in 1989.[5] The drug primarily works as a GABA receptor antagonist.[6] Propofol is mixed in a lipid emulsion (soybean, glycerol, and egg lecithin).[3] Cardiovascular effects are somewhat dose-dependent. A bolus of propofol can cause hypotension. Hypotension can be the most significant in patients with preexisting heart disease or hypovolemic patients. Some studies suggest that propofol causes bradycardia.[7]

A bolus of propofol can be associated with bronchodilatation. This has been reported in chronic obstructive pulmonary disease and status asthmaticus. Propofol can decrease intracranial pressure. It can also be used to control status asthmaticus.[7]

When compared to benzodiazepines (midazolam or lorazepam), patients on propofol have been shown to get off the ventilator sooner. This is a function of propofol's titratability.[3]

PRIS is a complicated subcellular process in which propofol is believed to impair free fatty acid utilization and mitochondrial activity.[8] Free fatty acids (FFAs) are created from catecholamine-mediated lipolysis of adipose tissue and are an essential fuel for the body's skeletal muscle and myocardium during states of critical illness. Prolonged exposure and elevated doses of propofol prevent long-chain FFA from entering the mitochondria by inhibiting carnitine palmitoyl transferase and uncoupling beta-spiral oxidation and the respiratory chain.[9] This failure of mitochondrial function leads to low energy production by preventing short and medium-chain FFA from crossing into the mitochondria membrane and ultimately results in cardiac and other muscle necrosis.[9]

Both of our patients were on relatively high doses of propofol. They are both critically ill and on pressors. Nurses and physicians need to be aware of the association between PRIS and high doses of propofol. In both cases, one can argue that PRIS was not proven beyond a doubt. We agree. Unfortunately, these are the types of complex patients that the average critical care physician and ICU nurse face daily. These are the patients who develop PRIS. Both patients likely had PRIS.

Vasile et al. postulated that priming factors and triggering factors could lead to PRIS.[8] (Figure 1) These priming factors can be catecholamines, cytokines, glucocorticoids, and/or systemic inflammation in extremely ill patients. High-dose propofol and intravenous catecholamines plus or minus steroids can act as triggering factors for PRIS.

Fong compiled over 1100 patients with PRIS in his 2008 article.[10] He found several factors associated with mortality, including age (< 18), male gender, and vasopressor therapy. The presence of cardiac failure, metabolic acidosis, renal failure, hypotension, rhabdomyolysis, or dyslipidemia were all associated with an increased incidence of death. Head injury was not found to be an associated factor in contrast to several other studies, which showed it to be a contributing factor. This may be a flaw in the design study. This study was based on the MedWatch database, which is maintained by the United States

Food and Drug Administration (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program). This database does not capture some relevant clinical information, including head injury data and cumulative propofol dose. The mortality rate in this study was 30%.

Some of the most pertinent questions with PRIS are to determine the very early warning signs and what test or marker should be measured in the ICU. Currently, the standard of care dictates that we order and monitor triglycerides while the patient is on propofol. It does not appear that lipemia is an early marker of PRIS.[11] It has been suggested that we should monitor lactic acid. Many patients who develop PRIS develop recalcitrant lactic acidosis, as reported in several papers.[10,12,13] Again, this does not appear to be an early marker of disease. A relatively recent study out of Memphis investigated a protocol in which creatinine kinase was measured daily in patients started on a propofol infusion.[14] Patients who had an elevated creatinine kinase had the propofol stopped. They noticed a significant drop in their mortality in patients on propofol once this protocol was implemented. From the current literature, creatinine kinase would be something simple that we can all measure, and elevations in creatinine kinase should cause the propofol to be stopped. It should be mentioned that this Memphis study was exclusively comprised of adults. Therefore, it is still being determined whether the bedside physician can use an elevated creatinine kinase in children as an early indicator of PRIS.

CONCLUSION

Propofol is probably the most popular sedative used in the ICU and the operating room today. For the most part, the drug is safe to use and behaves in a predictable, dose-dependent fashion. Unfortunately, for patients and practitioners, PRIS is a difficult

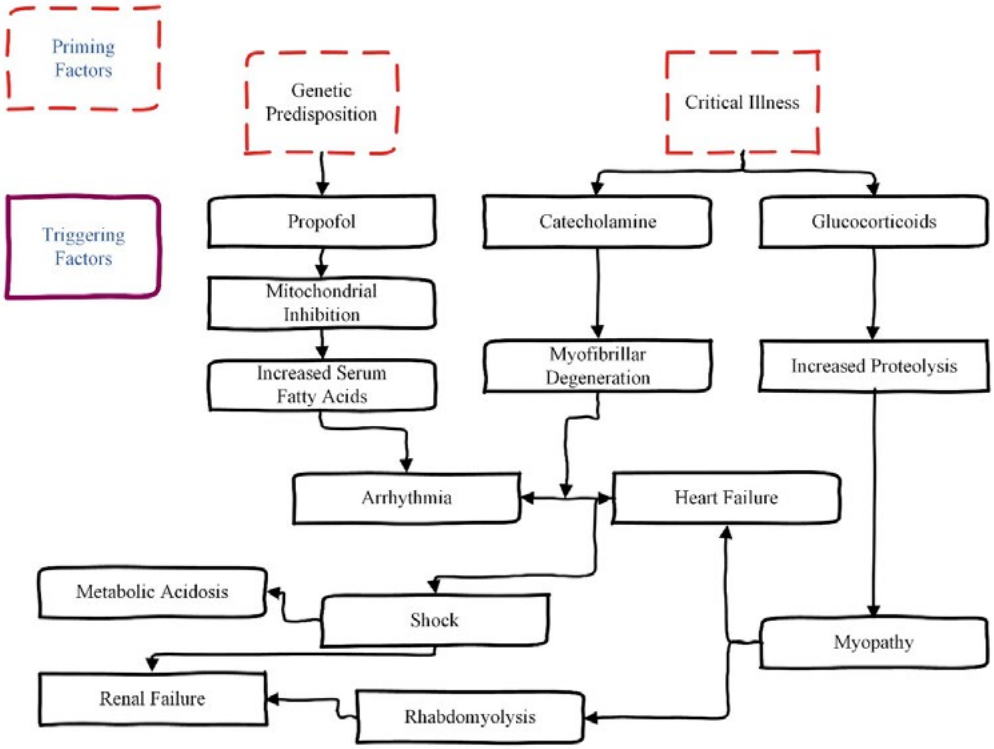

FIGURE 1 – Factor contributing to PRIS. Adapted from Vasile B, et al. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. *Intensive Care Med*, 2003;29(9):1417-25. DOI: 10.1007/s00134-003-1905-x. with permission.

diagnosis. It occurs in critically ill patients who are already on pressors (a risk factor for PRIS) and may already have a head injury (another possible risk factor for PRIS) who may then develop a combination of symptoms that can be seen with multiple organ dysfunction syndrome, sepsis, and other commonly seen complications in the ICU. It appears that measuring creatinine kinase daily while the patient is on propofol may be an early warning sign of PRIS. Elevated creatinine kinase should prompt the physician to stop the propofol. Thankfully, when diagnosed early, PRIS appears to be completely reversible. The physician must remain wary of the diagnosis of PRIS. If PRIS is not recognized early, mortality rates can be greater than 70%.

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1. Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia

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