Propofol Infusion Syndrome: A Rare but Potentially Fatal Reaction

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PA-PSRS has received reports of patient death due to propofol infusion syndrome, a rare, adverse effect of propofol. PA-PSRS invited Patrick J. McDonnell, PharmD, to review this problem. Dr. McDonnell specializes in drug safety and adverse drug reactions and has lectured and written extensively on these issues.

—John R. Clarke, MD, Editor

Propofol is an intravenous anesthetic agent used in both inpatient and outpatient surgeries and as a sedative agent for the treatment of agitation in mechanically ventilated patients in the intensive care units (ICUs). Propofol has some advantages over other sedative agents in short-term use due to its favorable pharmacokinetic profile (i.e., quick induction of anesthesia with short recovery times); however, with long-term use, as seen when used for ICU sedation, more dose-related adverse effects can be seen. Propofol infusion syndrome (PRIS) is a rare, potentially fatal adverse effect of propofol that warrants attention to identify its mechanism, patients who are at risk for it, and how it may be prevented. PA-PSRS has received reports of events, such as the one above, in which patients have died due to PRIS.

PRIS is a complex syndrome involving the unwanted effects of propofol infusions, patient co-morbid conditions, concurrent drug therapies, and how these factors interact on a cellular level. The hallmark findings of PRIS are metabolic acidosis, rhabdomyolysis, renal failure, and cardiovascular collapse. PRIS is usually associated with high doses of propofol (greater than 5 mg/kg/hr) for prolonged periods of time (greater than 48 hours), particularly in certain patient types. Patients that appear to be most at risk for PRIS have certain priming and triggering factors in common.
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The common priming factor for PRIS is critical illness itself. Acute central nervous system disease, sepsis, burns, pancreatitis, trauma, and status asthmaticus have been identified as priming factor disease states. In these situations, inadequate stress hormonal responses lead to a systemic inflammatory response syndrome (SIRS). This results in a sustained imbalance of pro-inflammatory/anti-inflammatory cytokines and an imbalance of catabolic/anabolic hormone production. Under these disease states, pro-inflammatory cytokines produced at the site of tissue damage activate the body’s stress response system. Catecholamines and glucocorticosteroids are secreted, leading to anti-inflammation and immunosuppression. In SIRS, this persistent pro-inflammatory state can lead to a hypermetabolic state that can cause progressive end organ damage.

With the body now “hyper-primed,” high doses of propofol, usually with the administration of corticosteroids and/or catecholamines (phenylephrine, norepinephrine, and epinephrine), expedite end organ damage. These trigger factors of propofol infusions with infusions of corticosteroids and/or catecholamines have been identified in PRIS as leading to cardiac failure and muscle breakdown, followed by metabolic acidosis and renal failure. This appears to be the pathophysiologic mechanism of PRIS.2

Propofol is neither a catecholamine nor a corticosteroid, but molecularly contributes to PRIS by its several effects. Adverse cardiovascular effects of propofol include hypotension and bradycardia. These adverse effects undoubtedly contribute to deterioration of cardiac failure seen in PRIS.3 In addition, the formulation of propofol can contribute to PRIS. Propofol for intravenous infusion is dissolved in a mixture of long-chain triglycerides and soybean emulsion. Higher doses and longer durations of propofol infusions contribute to disruptions in fat and carbohydrate metabolism. Higher amounts of free fatty acids are produced, particularly in states of low carbohydrate intake and in children. Children are consequently more prone to the development of PRIS as a result of low glycogen storage and a higher dependence on fat metabolism.4 This increased production of free fatty acids has been identified as a cause of abnormal cardiac arrhythmias,5 again contributing to the cardiovascular collapse in PRIS. To suppress this fat metabolism, a carbohydrate intake of 6 to 8 mg/kg/min is needed.6

Post-marketing surveillance reports of PRIS have identified the following patients who are most at risk:

- Patients with severe head trauma receiving propofol at greater than or equal to 5 mg/kg/hr have double the risk of developing PRIS.7 For these patients, high-dose propofol is not recommended.8

- In patients with severe burns, trauma, sepsis, pancreatitis, and status asthmaticus, avoid use of prolonged infusions of high-dose propofol. Concurrent use of corticosteroids and catecholamines increases the risk of PRIS.8 If high-dose propofol is needed for these patients, particularly the aforementioned concurrent therapies, careful monitoring of serum levels of creatine phosphokinase, myoglobin, and troponin can detect early manifestations of muscle breakdown.9

If PRIS is suspected, discontinue propofol immediately. Treatment for PRIS is non-specific, with hemodynamic stabilization being the main priority. To suppress free fatty acid metabolism, which contributes to the cardiovascular instability in PRIS, a carbohydrate infusion equivalent to 6 to 8 mg/kg/min is recommended.3

Although rare, PRIS is a potentially fatal adverse drug reaction. With an insight to the complex biochemical mechanism of PRIS, identifying at-risk patients and weighing the risk versus benefit of therapy may reduce its incidence.

Notes

Self-Assessment Questions

The following questions about this article may be useful for internal education and assessment. You may use the following examples or come up with your own.

1. Hallmark findings of PRIS include all EXCEPT which one of the following?
   A. Metabolic acidosis
   B. Rhabdomyolysis
   C. Renal failure
   D. Liver failure
   E. Cardiovascular collapse

2. The formulation of propofol does not contribute to PRIS.
   A. True
   B. False

3. Factors common to patients that appear to be most at risk for PRIS include all EXCEPT which one of the following?
   A. Severe head trauma
   B. Concurrent use of corticosteroids and catecholamines
   C. Psychosis
   D. Sepsis
   E. Severe burns

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- “Bone Cement Implantation Syndrome” (December 2006)
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- “Who Administers Propofol in Your Organization?” (March 2006)
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