

# Propofol: Review of Potential Risks During Administration

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*Propofol is one of the most commonly used agents by anesthesia providers. Despite its excellent safety profile, numerous drawbacks and patient safety issues remain. This article is a focused review of the common issues surrounding propofol administration as they*

*relate to infection, pediatric sedation, and the propofol infusion syndrome.*

**Keywords:** Contamination, pediatric sedation, propofol infection, propofol infusion syndrome.

**P**ropofol is the most widely used hypnotic agent for induction of anesthesia and is a mainstay in sedation for adult patients in the intensive care unit (ICU). Propofol achieved Food and Drug Administration (FDA) approval in 1989.<sup>1</sup> This was met with widespread acceptance because of its excellent safety profile. In anesthetic practice, propofol's rapid onset of hypnosis, short duration of action, titratability, and minimal effects on evoked potentials make it ideal for general anesthesia, monitored anesthesia care, and total intravenous (IV) anesthesia. The application of propofol for prolonged sedation in the critical care patient was also readily apparent. The active ingredient, 2,6-diisopropylphenol, is a nonpyrogenic hydrophobic emulsion that requires a lipid base for suspension using soybean oil (100 mg/mL), glycerol (22.5 mg/mL), and egg yolk phospholipid (12 mg/mL).<sup>2</sup> Although its lipid base is required for production, it unfortunately has numerous drawbacks.<sup>3</sup>

## Propofol and Infectious Risks

Shortly following the introduction of propofol, the Centers for Disease Control and Prevention (CDC) was informed of numerous bloodstream, postoperative, and surgical site infections occurring in patients having received the drug between 1990 and 1993.<sup>4-7</sup> Thorough investigation by the CDC identified the culprit as extrinsic contamination due to lapses in aseptic technique occurring during handling and administration, particularly in patients receiving propofol by continuous infusion.<sup>1,4,8,9</sup> Despite handling recommendations from manufacturers and professional societies such as the American Society of Anesthesiologists and the American Association of Nurse Anesthetists, reports of propofol-associated infections continued to be reported.<sup>4,9-11</sup> Haddad et al<sup>12</sup> demonstrated that despite proper aseptic handling of propofol according to guidelines, the absence of microbial inhibitors itself was a risk factor for septic shock in the ICU.

In 1996, the FDA required microbial growth inhibitors, specifically edetate disodium, to be added to pro-

propofol.<sup>6,8</sup> Although the addition of edetate disodium significantly decreased the number of reported infections, the problem was not eliminated.<sup>6,8,10,13</sup> With edetate disodium, strict aseptic techniques must still be observed in handling, including adherence to the expiration date from the opening of the vial (Figure 1).<sup>3,13</sup> Additionally, adoption of edetate disodium-containing propofol has not been standard practice in all countries.<sup>12</sup>

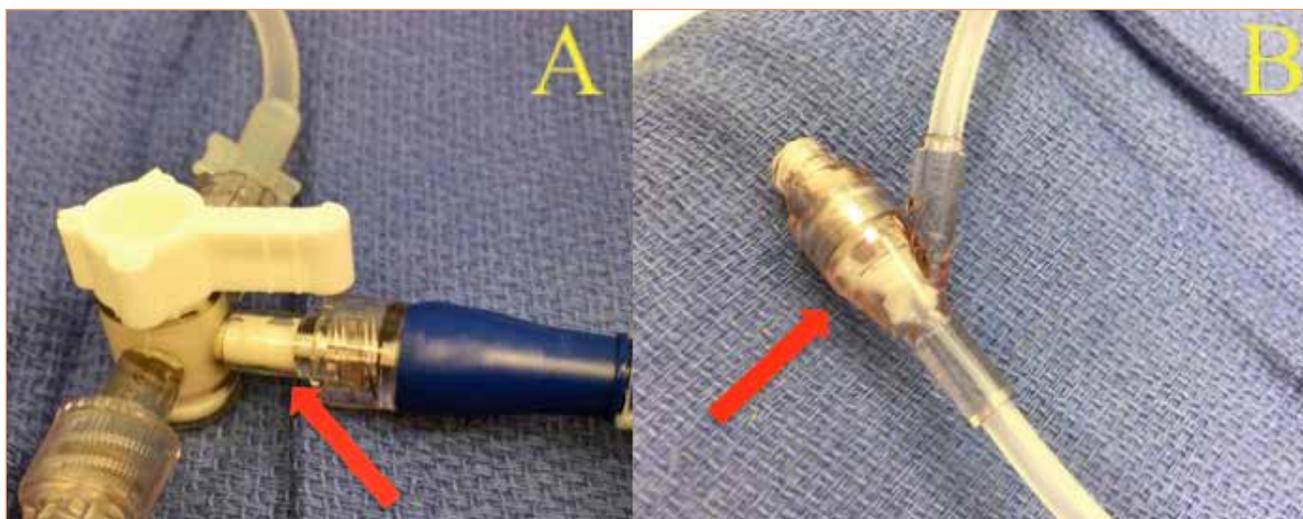
Identification of medication contamination as the vector for nosocomial infection generally proves difficult.<sup>4</sup> Thus, the burden of propofol contamination-caused nosocomial infection rates and ultimately on healthcare costs may still be wholly underestimated. The cost of a single healthcare-acquired bloodstream infection is estimated to exceed US \$23,000; thus, a shift toward identification of infectious vector transmission and prevention is under way.<sup>14,15</sup>

## Focus on Clinical Safety With Infection Prevention

Contamination of the anesthesia work environment and its contribution to the burden of hospital-acquired infection is now under investigation.<sup>16</sup> Highly infectious



**Figure 1.** Expiration Date Must Be Adhered to After Opening of Propofol Vial



**Figure 2.** Stopcock (A) and Inline Injection Port (B) Containing Residual Propofol (red arrow)

pathogens have been traced to the anesthesia work environment as well as the hands of anesthesia providers.<sup>17-19</sup> Many of the pathogens occurring in the anesthesia work environment are compatible with organisms linked to previously reported propofol infectious outbreaks.<sup>16,17</sup>

Syringes may become contaminated after a single use and may serve as a reservoir for bacterial overgrowth when filled with propofol.<sup>5,16,20</sup> In one study, transmission of bacteria to IV stopcock sets was identified in 32% of operating rooms.<sup>4</sup> Stopcock contamination has been associated with increased patient morbidity and mortality.<sup>17</sup> The IV tubing and stopcock contains dead spaces that can serve as a reservoir for small amounts of propofol supporting bacterial overgrowth, even in the absence of visible propofol (Figure 2).<sup>4</sup> Despite the Scrub the Hub campaign (disinfection of injection ports), which is effective at removing bacteria on the external surface of the stopcock port provided adequate decontamination time, the internal surface cannot effectively be disinfected.<sup>21</sup> Cole et al<sup>5</sup> identified positive results of bacterial cultures in 16% to 20% of IV stopcocks as well as a significantly greater bacterial density in the stopcocks following propofol anesthesia compared with nonpropofol techniques. This study identified a 48% incidence of IV bacterial contamination when there was visible propofol remaining in the stopcock dead space.<sup>5</sup> The importance of this finding is obvious because contaminated IV tubing is in direct contact with the patient's bloodstream. Recommendations for the handling and administration of propofol are suggested in the Table.

### Propofol in the Egg/Soy-Allergic Patient

The administration of propofol to the severely egg- or soy-allergic patient always leaves a hint of hesitation during injection. These allergies generally result from intolerance to the egg or soy proteins. In the preparation of propofol, proteins and therefore the allergens are

- Use of strict aseptic technique
- Hand hygiene before handling
- Scrubbing of vial's rubber top with isopropyl alcohol before each withdrawal
- Use of a new, sterile syringe for each administration
- Flushing of intravenous (IV) tubing and stopcocks at the end of an anesthetic administration or changing IV tubing every 12 hours during long cases
- Drawing up propofol immediately before administration and capping all remaining syringes
- Discarding propofol after 12 hours at any signs of contamination

**Table.** Recommendations for Handling and Administration of Propofol

separated from the desired carbohydrate, and thus, the risk of severe reactions are not substantiated.<sup>22</sup> However, the exact purification of protein in egg- and soy-based propofol remains unknown. Despite this, administration of propofol to the egg- or soy-allergic patient remains a manufacturer-listed contraindication.

### Propofol Infusion Syndrome

Propofol infusion syndrome (PRIS) is a rare and complex pathophysiologic occurrence with a substantial morbidity and mortality burden on those affected.<sup>23,24</sup> Although PRIS generally occurs in the ICU after prolonged administration, the anesthesia provider should understand the major systemic effects because these patients may require preoperative evaluation and operative interventions. The exact mechanism of PRIS is multifactorial and may include the disruption of free fatty acid metabolism by mitochondria in association with the large lipid load experienced during long-duration, high-concentration propofol infusion.<sup>25</sup> A high incidence of lipemia, hypertriglyceridemia, and fatty liver changes have also been noted after prolonged propofol infusion.<sup>23,26</sup> Risk factors

for the development of PRIS include duration of infusion longer than 48 hours, rate of infusion greater than 67 µg/kg/min, severe illness states, subclinical mitochondrial disease, carbohydrate depletion, and coadministration of catecholamines and glucocorticoids.<sup>25</sup>

### Drawbacks of Propofol in the Pediatric Population

In pediatric patients, use of propofol, while generally safe in anesthetic practice, comes with major limitations in critical care sedation.<sup>27</sup> Although propofol is heavily relied on for long-term sedation in adult intensive care settings, the FDA issued a warning regarding the safety of propofol sedation in pediatrics.<sup>2,28</sup> This was the direct result of numerous reported deaths in pediatric ICUs attributed to sedation using propofol.<sup>29</sup> This entity, known as propofol syndrome, includes anion gap metabolic acidosis, bradyarrhythmia, liver dysfunction and rhabdomyolysis of cardiac and skeletal muscle leading to multiorgan failure, hyperkalemia, acute kidney injury, and cardiac dysfunction.<sup>25,29</sup>

Because of its high lipophilicity, propofol enters the mitochondria, accepting electrons and disrupting the electron transport chain at the level of coenzyme Q.<sup>30</sup> As a potent inhibitor of the electron transport chain in mitochondria, propofol leads to a failure of adenosine triphosphate production inhibiting mitochondrial fatty acid metabolism, causing a buildup of fatty acids.<sup>25,30-32</sup> With prolonged administration at high concentrations, propofol tends to accumulate in the liver.<sup>25</sup> In patients with clinical and subclinical mitochondrial disorders (disorders related to fatty acid metabolism), as frequently encountered in pediatric centers, the use of propofol, especially for continuous infusion can be detrimental. These patients already lack the ability to metabolize fatty acids, and combined with the long-chain fatty acids in propofol, can predispose them to fatty acid accumulation and PRIS. Additionally, carbohydrate deficiency is a risk factor because energy supply relies on lipolysis. Thus, children are more prone to developing PRIS due to lower glycogen stores and greater dependence on fat metabolism.

### Discussion

The main issues with propofol, contamination, and propofol syndrome may hinge on the requirement of lipid additions to facilitate the formation of an aqueous solution. Additionally, strict adherence to aseptic guidelines in the preparation and administration of propofol are cumbersome and prone to lapses. Although there is a focus on improving asepsis in the anesthesia work environment, propofol contamination remains a concern. Inability to provide long-term propofol sedation in the pediatric ICU without undue risk is also suboptimal. Despite these issues, propofol remains one of the most

important anesthetic medications, and generally the benefits exceed the risks; however, it may be time for a “fat-free” water-soluble alternative.

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#### DISCLOSURES

The author has no financial relationships with any commercial interest related to the content of this article. The author did not discuss off-label use within the article.