Sulfite-induced propofol oxidation: A cause for radical concern*

Propofol (2,6-diisopropylphenol) is one of the most common sedatives used in the care of critically ill patients. It is an ultrashort-acting intravenous sedative that allows for rapid tapering of its effects. Propofol is a global central nervous system depressant. It binds to different γ aminobutyric acid receptor sites than the benzodiazepines, where it directly activates the γ-aminobutyric acid receptor. Propofol also inhibits *N*-methyl-D-aspartate glutamate receptors, modulates calcium influx through slow calcium ion channels, and scavenges free oxygen radicals. In addition to sedating properties, propofol possesses bronchodilating and antiseizure properties. Propofol is metabolized systemically and its half-life is marginally affected by renal and hepatic failure.

Propofol possesses anti-inflammatory properties (1). Taniguchi et al. (2, 3) reported that propofol attenuated cytokine responses, neutrophil activation, acidosis, and mortality after endotoxin administration in rats. Crozier (4) et al. reported that propofol blunted the interleukin-6 response to abdominal surgery. Propofol inhibits neutrophil activation and production of oxygen free radicals (1, 5). Propofol also scavenges free radicals and inhibits lipid peroxidation (1, 5–7). In the isolated heart, propofol attenuates ischemia-reperfusion injury (8). Propofol may also mediate some of its actions by inhibiting inducible nitric oxide synthase (1, 9). Thus, due to its beneficial effects, propofol is commonly used to sedate patients with multiple organ failure and those at risk for multiple organ failure.

Propofol is insoluble in water. Thus, it is administered as a lipid formulation. Shortly after widespread use of propofol-lipid formulations in the United States, there were reports of infections in patients linked to bacterial contamination of the propofol formulation during clini-

*See also p. 787.

Key Words: sulfite; propofol; metabisulfite; propofol oxidation; free radicals; EDTA; propofol dimer; propofol dimer quinone

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cal use of the drug. In an attempt to prevent or minimize such contamination, propofol is formulated with an antibacterial substance. In the United States, propofol is formulated with either edetate disodium (EDTA) or sodium metabisulfite. Thus, propofol represents a triple-agent combination (i.e., propofol, lipid emulsion, preservative) (10). Each component of the formulation has biological activity. Although the Food and Drug Administration considers propofol formulations containing EDTA and sulfites to be equivalent, numerous studies suggest the contrary. Chelators (similar to EDTA) decrease mortality rates during experimental sepsis (11) and in surgical intensive care unit patients (12). Chelation of calcium or zinc has been implicated to explain the beneficial effects of EDTA in models of systemic inflammation (12). On the other hand, a beneficial effect of sulfites on inflammation, organ injury, or outcome has never been demonstrated.

Propofol containing EDTA has a pH of 7.0–8.5, whereas sulfite containing propofol (P-sulfite) has a pH of 4.5–6.4. The lower pH of P-sulfite is required to maintain the antibacterial properties of sodium metabisulfite. Importantly, the pH of the formulation affects its stability because negative charges on the phosphates in the lipid emulsion are required to maintain repulsive forces between lipid globules and to keep the globules from coalescing. The P-sulfite preparation is less stable than the propofol containing EDTA formulation (13). There has also been concern regarding the allergic potential of sulfites in drug formulations (14).

In this issue of *Critical Care Medicine*, Dr. Baker and colleagues (15) add additional information on the effects of sulfites and EDTA in lipid formulations. Sulfite is known to support oxidation processes and may react with propofol. Thus, the investigators evaluated propofol degradation, dimer formation, and free radical generation in P-sulfite and propofol containing EDTA formulations during a simulated 12-hr hang time (i.e., dripped from spiked 50-mL vials). Propofol dimer is the product of oxidation of propofol to form propofol radicals that couple to form the dimer. A yellow discoloration has been noted clinically when air is introduced into P-sulfite lipid formulations during spiking of the bottles. The investigators demonstrate that the color is one manifestation of propofol dimerization (i.e., formation of propofol dimer quinone). The investigators report that dimerization of propofol to form both propofol dimers and propofol dimer quinones in lipid emulsions is induced by sulfites but not EDTA. Formation of propofol dimers was greatest between 6 and 12 hrs of hang time. Importantly, the cellular effects of the dimers are unknown. The investigators also evaluated the formation of free radicals using electron paramagnetic resonance. Free radicals were significantly elevated in the P-sulfite formulation but absent in the propofol containing EDTA formulation.

In addition, the investigators report that a comparative analysis of propofol containing EDTA with propofol containing sulfites demonstrates that sulfites induce the formation of the lipid peroxidation product, malondialdehyde. Malondialdehyde increased over time after air exposure in the P-sulfite formulation. Lipid peroxidation is a free radical–mediated process.

This study demonstrates that P-sulfite, but not propofol containing EDTA, undergoes chemical change during a simulated intravenous infusion. The results clearly demonstrate that sulfites in propofol-lipid emulsions promote oxidation of propofol and lipids after exposure to air during spiking of the vials. Sulfites induce the formation of propofol dimer, propofol dimer quinone, free radicals, and lipid peroxidation products. It seems that metabisulfite creates an oxidative environment when air is introduced during spiking of the propofol vials. Although sulfite usually functions as an antioxidant, it may also induce oxidation in certain environments, which include lipid emulsions (16, 17). Oxidation is believed to occur via formation of sulfite radicals in the presence of oxygen that subsequently react with lipids to form lipid radicals. The sulfite radicals also interact with propofol to induce the formation of propofol oxidation products (i.e., propofol dimer and propofol dimer quinone).

Multiple organ failure is linked to free radical formation and cellular oxidation (18, 19). Numerous studies have attempted to prevent or minimize organ failure via the use of antioxidants. Infusion of compounds, such as sulfites, with can generate free radicals and result in oxidation of cellular components, raises concern because such substances may induce or aggravate organ failure. The sulfite radical is a chemically reactive intermediate that has been shown to alter lipids, proteins, and nucleic acids. Sulfite radicals have been implicated as a cause of lung and neuronal injury (20, 21). The effect of sulfites on inflammation is unclear. However, sulfites have been reported to stimulate neutrophils to release oxygen free radicals (20) and to augment the free radical response to other neutrophil activators such as zymosan, phorbol myristate acetate, and *N*-formyl-methionine-leucine-phenylalanine (20). Long-term exposure of airways to sulfur dioxide and sulfites causes airway inflammation (20).

Although the authors did not perform the study during actual propofol administration to patients, the results of the simulated hang time are likely representative of changes that occur during actual administration. The study did not evaluate cellular, physiologic, or outcome effects of the two formulations. Clearly, it is important to determine the clinical consequences of the changes reported by Dr. Baker and colleagues (15). Nevertheless, the results of this investigation raise concern regarding the safety of P-sulfite preparations. They also clearly indicate that the two formulations are not biochemically equivalent.

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