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Frequently Asked Questions

Does fospropofol offer advantages over conventional propofol?

Background

Propofol is an oil-in-water emulsion sedative-hypnotic labeled for¹⁻⁴:

- initiation and maintenance of monitored anesthesia care sedation in adults
- combined sedation and regional anesthesia in adults
- sedation of intubated mechanically ventilated adults
- induction of general anesthesia for patients ≥ 3 years of age
- maintenance of general anesthesia for patients ≥ 2 months of age

Propofol's rapid onset (40 seconds) and short duration of action (10 to 15 minutes) make it an ideal sedative for conscious sedation and sedation in the intensive care unit (ICU) setting.¹⁻⁴ However, the lipid-based formulation also has some risks that may restrict its use. Common or serious adverse events due to propofol are bradycardia (1% to 3%), hypotension (17% to 26%), pain at the injection site (17.6%), hyperlipemia (3% to 10%), and apnea (3% to 10%).

In 1990, the Centers for Disease Control and Prevention (CDC) traced an outbreak of post-surgical infections to the then newly approved anesthetic, propofol.⁵ At the time it was preservative-free, which combined with a lack of proper aseptic technique and the fact that the lipid formulation fostered the growth of microorganisms rendered the product prone to contamination. Failure to use aseptic technique has led to fever, infection, sepsis, and/or death.¹⁻⁴ The manufacturers of propofol have added preservatives to help suppress the growth of microorganisms; however, a bag should not hang for more than 12 hours without being changed.

A water-soluble prodrug of propofol, fospropofol (Lusedra), has recently been approved by the Food and Drug Administration (FDA) for monitored anesthesia care sedation in adult patients undergoing diagnostic or therapeutic procedures.⁶ Fospropofol is hydrolyzed to propofol, formaldehyde, and phosphate. The formaldehyde and phosphate are comparable to endogenous levels and may only be of concern in cases of overdose. As fospropofol must first undergo metabolism to propofol, time to onset is prolonged. Table 1 provides a comparison of available propofol formulations to fospropofol.

Table 1. Preparation characteristics of propofol and fospropofol.^{1-4,6}

Medication	Manufacturer	Preservatives	Onset of action
Propofol	APP Pharmaceuticals	Disodium edetate	Onset: 40 seconds
Propofol	Baxter	Sodium metabisulfite	
Propofol	Hospira	Benzyl alcohol, sodium benzoate	
Propofol	Teva	Sodium metabisulfite	
Fospropofol	Eisai	Preservative-free	Onset: 4 to 13 minutes

The usual dose of fospropofol is a bolus of 6.5 mg/kg followed by 1.6 mg/kg (supplemental) as needed to obtain the desired level of sedation. The usual dose is given to patients aged 18 to <65 years of age who are healthy or have a mild systemic disease based on the American Society of Anesthesiologists (ASA) Physical Classification (see table 2).³ For patients > 65 years of age or who have severe systemic disease (ASA Physical Classification 3 or 4), 75% of the initial dose is given (bolus and supplemental). Patients whose actual body weight is less than 60 kg should be dosed as a 60 kg patient, and patients whose actual body weight is greater than 90 kg should be dosed as a 90 kg patient. Since fospropofol is preservative-free, each vial is intended for single use and should be discarded after the bolus injection is drawn up into a sterile syringe.

Table 2. Summary of ASA classification used to dose fospropofol.⁷

Healthy patient	P1
Mild disease	P2
Severe disease	P3
Severe, life-threatening disease	P4
Not expected to survive without the surgery	P5
Brain-dead patient undergoing organ removal for donation	P6

ASA=American Society of Anesthesiologists

Literature Summary

Cohen conducted a randomized, double-blind, multicenter, dose-ranging trial to assess the efficacy and safety of fospropofol in patients undergoing elective colonoscopy.⁸ A total of 127 patients with an ASA status ranging from P1 to P4 were randomized to receive an initial dose of fospropofol 2 mg/kg (n=25), 5 mg/kg (n=26), 6.5 mg/kg (n=26), 8 mg/kg (n=24), or midazolam 0.02 mg/kg (n=26). Dosing was adjusted for weight and age as described above, and all patients were given fentanyl 50 mcg prior to study treatment. Up to 2 additional supplemental (25% of the initial bolus dose) doses of fospropofol were permitted as at for patients assigned to the drug, whereas the midazolam group received up to 4 supplemental doses of 1 mg midazolam. The primary efficacy outcome measure was sedation success. Sedation was considered successful if:

- 3 consecutive Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) of ≤4 (0=does not respond to painful trapezius squeeze; 5=alert)
- no need for alternative sedatives during procedure
- no need for manual or mechanical ventilation

Key secondary endpoints included measures of sedation level and time to sedation, doses required (sedative and fentanyl), need for alternative sedative(s), patient and doctor satisfaction, and safety.⁸

Sedation success was dose-dependent across all groups: 2 mg/kg (24%), 5 mg/kg (35%), 6.5 mg/kg (69%), and 8 mg/kg (96%) vs. 81% with midazolam. The success rates were higher in the 6.5 and 8 mg/kg groups ($p < 0.001$, for both compared to lower doses).⁸ A greater number of patients in the 8 mg/kg treatment group (25%) had MOAA/S scores of 0 or 1, indicating the patient is at the most sedated state at any time after the first dose as compared to the 6.5 mg/kg dose (4%). No significant difference was found among the fospropofol dosing regimens in terms of need for alternative sedative(s), time to sedation, and number of supplemental doses (fospropofol or fentanyl); however, an inverse relationship between dose used and need for alternative sedatives was found. Patients in the 6.5 mg/kg group had the highest overall satisfaction scores; however, this did not reach statistical significance. Doctors' satisfaction scores were higher in the 6.5 mg/kg group (26.9% ranked scores 9 to 10) and 8 mg/kg group (50% ranked scores 9 to 10; $p = 0.0028$ for dose-response relationship). The most common adverse event reported with fospropofol was paresthesia in 49 (49%) of 101 patients, which generally occurred in the perineal area. The author concluded that fospropofol 6.5 mg/kg provided the desired balance of efficacy and safety.

Silvestri and colleagues conducted a randomized, double-blind, phase 3 study in 252 patients to determine the efficacy and safety of fospropofol in patients undergoing flexible bronchoscopy.⁹ Adult patients with ASA classifications of P1 to P4 were randomly assigned

(2:3) to receive a fospropofol bolus dose of 2 mg/kg (n=102) or 6.5 mg/kg (n=150) followed by up to 3 supplemental doses at 25% of the bolus dose. Initial doses were adjusted for age, ASA Physical Classification System status, and weight. For the maintenance phase, supplemental fospropofol doses could be administered at intervals > 4 minutes if the patient had a MOAA/S score of > 4 and demonstrated purposeful movement. Fentanyl 50 mcg was given prior to fospropofol, and an additional 25 mcg was allowed for pain during the maintenance phase. The endpoints mirrored those of the trial conducted by Cohen (see above).⁸

The primary efficacy endpoint of sedation success was significantly higher in the 6.5 mg/kg group vs. the 2 mg/kg group (88.7% vs. 27.5%, respectively, $p < 0.001$).⁹ Patients in the 6.5 mg/kg needed a mean of 1.7 supplemental doses compared to a mean of 2.9 in the 2 mg/kg group ($p < 0.001$). Eight percent of patients in the 6.5 mg/kg needed alternative sedation with midazolam vs. 58.8% in the 2 mg/kg group ($p = \text{not reported}$). The median time to sedation was shorter for the 6.5 mg/kg group (4 minutes) than for the 2 mg/kg group (18 minutes, $p = \text{not reported}$). Patient satisfaction and physician satisfaction were higher with the 6.5 mg/kg treatment group, but significance was only reached for 2 satisfaction measures (both assessed by patients); fewer patients reported being awake during the procedure in the higher dose group ($p < 0.01$), and more patients in the higher group would agree to use the agent again ($p < 0.01$). The most common adverse events reported were paresthesia (47.6%) and pruritus (14.7%). The most common cardiopulmonary adverse events were hypoxemia (14.3%) and hypotension (3.2%). Patients in the 6.5 mg/kg group accounted for all 8 patients with hypotension. The authors concluded that fospropofol is an effective sedative regimen that results in moderate sedation with an acceptable safety profile.

Conclusion/current status

Fospropofol has been assessed for the use in sedation for surgical procedures, sedation for cardiac catheterization, and sedation for the intensive care unit setting, but these studies have yet to be published.¹⁰ Although fospropofol is FDA approved (December 2008); it is not currently available as it is awaiting a scheduling decision from the Drug Enforcement Agency (DEA). The role of fospropofol for patients undergoing monitored anesthesia care sedation for diagnostic or therapeutic procedures has been evaluated in 2 published clinical studies; however, use of conventional propofol during colonoscopy and bronchoscopy procedures is generally not problematic since the procedures are of short duration. In addition, clinical experience with fospropofol is limited, including safety of prolonged infusions as compared to the available experience in the literature with propofol. Until further studies are published evaluating efficacy and adverse effects, benefit over propofol has not been established.

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