Fospropofol, A New Sedative Anesthetic, and Its Utility in the Perioperative Period

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**Abstract:** Fospropofol is an intravenous sedative-anesthetic agent that is FDA-approved for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures. As a prodrug of propofol, fospropofol’s pharmacologic activity results from its breakdown by alkaline phosphatase and release of propofol, which is the active molecule. It exhibits a longer time to peak clinical effect and a more prolonged action compared to propofol. Thus patients may exhibit smoother hemodynamic and respiratory depression compared to propofol lipid emulsion bolus. Another advantage over propofol is that it does not induce a burning sensation on IV administration. Side effects include perineal paresthesia and itching, respiratory depression, hypoxemia, hypotension, loss of consciousness, and apnea with higher IV boluses. Therefore, current recommendations call for it to be administered only by clinicians trained in general anesthesia, who are thus skilled in advanced airway management.

Fospropofol has a unique dosing regimen, with a standard dose for adults 18-65 years of age, and a modified dose (75% of the standard dose) for patients > 65 years of age and for sicker adult patients whose American Society of Anesthesiologists physical status score is ≥ 3. Also, the minimum and maximum IV bolus doses are body-weight adjusted to 60 and 90 kg respectively.

Available evidence demonstrates that fospropofol in MAC sedation is successful in patients undergoing esophagogastroscopy, colonoscopy and flexible bronchoscopy. The use of fospropofol is also now being explored in many other perioperative settings. In light of current shortages of many anesthetic drugs, whether fospropofol can take the place of propofol in ICUs and operating rooms remains to be determined.

**Keywords:** Fospropofol, anesthetic management, perioperative care, side effects, anesthesia, conscious sedation, MAC anesthesia.

**INTRODUCTION**

Fospropofol is a new IV sedative/anesthetic drug. It is a water-soluble prodrug of propofol with pharmacokinetic attributes different from those of propofol. We discuss its unique structural and pharmacologic properties and dosing schedule. We also discuss the differences between propofol and fospropofol in chemical structure, pharmacodynamic and pharmacokinetic properties, clinical properties, and side effects. Moreover, we present an overview of the available clinical trials data on the clinical utility of fospropofol in sedation and anesthesia of adults undergoing diagnostic and/or therapeutic procedures. Finally, we provide an overview of future directions for investigators interested in further exploring the clinical utility of this unique sedative/anesthetic agent.

**FOSPROPOFOL VS PROPOFOL**

The decade 1996-2006 saw a substantial (~ 300%) increase in ambulatory anesthesia services in freestanding ambulatory centers [1]. This increase led to a greater need for varying degrees of sedation (MAC anesthetics) as well as general anesthetics in such outpatient settings. The ideal pharmacologic agent for ambulatory surgery would have a quick onset and offset, the ability to maintain a steady state of anesthesia intraoperatively without adverse side effects, stable hemodynamics, and preferably anti-emetic properties. In 1977 Kay and Rolly introduced propofol or 2,6-diisopropylphenol [2]. Since its introduction into clinical practice in 1986 by AstraZeneca under the trade name Diprivan®, it gradually became the so-called “wonder drug” with many characteristics of the conceptually ideal drug for ambulatory anesthesia.

Introduction of propofol in the market was welcomed by the medical community. It shortened recovery time as well as time to discharge from the PACU, and it increased the satisfaction of patients and physicians alike [3].

Close to 30% of patients experience some pain on intravenous injection of propofol [2,4,5,6]. Recently, the transient receptor potential (TRP) receptors, TRPA1 and TRPV1 have been found to play a role in this pain pathway via excitation of nociceptive neurons during propofol injection [6]. In addition, with propofol the transition from moderate sedation to general anesthesia may be sudden owing to the steep dose response curve, more so in volume-depleted or cardiovascularly compromised patients; and it has a narrow therapeutic window when used for sedation. Propofol also lacks a specific pharmacologic antagonist [6]. In addition, the propofol lipid emulsion formula introduces another set of concerns, including the need for absolute sterility when handling the drug, the relatively short window of usage (6 h) when the vial is opened and the hypertriglyceridemia seen in patients receiving prolonged duration propofol infusion in the ICU setting [8-11].

Propofol injectable emulsion is available in a single-use vial parenteral product which contains 0.005% disodium edetate to retard the rate of growth of microorganisms in the event of accidental extrinsic contamination. However, the lipid emulsion can still support the growth of microorganisms such as Escherichia coli or Candida albicans and is not an antimicrobially preserved product under USP standards. Propofol has been implicated in many infectious processes in the clinical setting including sepsis and other life-threatening illnesses [12-18].

Another concern involves propofol infusion syndrome, a rare condition that includes severe metabolic acidosis, rhabdomyolysis, renal failure, and hemodynamic instability. Impairment of the mitochondrial enzyme carnitine palmityl transferase I (CPT I)
uncoupling of oxidation and respiratory chain is the putative mechanism of this injury at the cellular and subcellular level. Fatty acid transport across the mitochondrial membrane is dependent on these enzymes and their underutilization leads to cell death and resultant myonecrosis [8]. This condition is more commonly seen with prolonged propofol infusion in critically ill patients, and the concurrent administration of catecholamines and steroids [8].

The search for alternatives to serve as carriers for propofol was initiated through the use of solvents such as β-cyclodextrins or microemulsion formulations [19-22]. Though investigators had demonstrated that addition of a large hydrophilic group, typically a phosphate monoester or a hemisuccinate, to a hydrophobic drug could convert it into a hydrophilic prodrug, such attempts at creating phosphoester prodrugs from propofol were unsuccessful.

It was determined that linking propofol with a methylphosphate group at C-1 (replacing a noncharged hydroxyl group with a charged phosphate group) increases electronegativity and lends polarity to the molecule, which leads to water solubility of this propofol prodrug. This finding led to the development of Aquavan® (Guilford Pharmaceuticals, Baltimore, MD), initially referred to as GPI 15715 and now as fospropofol.

GPI 15715, or fospropofol, is a N-phosphono-O-methyl prodrug of propofol. Chemically it is described as C13H19O5PNa2 and 2,6-diisopropylphenol methoxyphosphonic acid (or 2,6-diisopropylphenoxyethyl phosphate disodium salt). The comparative structure of propofol and fospropofol is illustrated in Fig. (1). Fospropofol has a higher molecular weight (332.24 gram/mole) than propofol (178.27 gram/mole).

Fospropofol is metabolized in vivo and releases propofol, phosphate, and formaldehyde by action of the enzyme alkaline phosphatase [23,24]. In vivo, 1 mg of fospropofol releases 0.54 mg of propofol. (See section under accumulation of metabolites.) Because the prodrug is converted to propofol, the time to peak of propofol concentration after a bolus of fospropofol and the elimination of propofol after infusion are longer than for propofol lipid emulsion. The released propofol increases activity of gamma-aminobutyric acid (GABA), the chief inhibitory neurotransmitter of the central nervous system (CNS), potentiating GABA-inhibitory

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Fig. (1). Metabolism of fospropofol and accumulation of end-products. Reprinted with permission from Cleveland Clinic Center for Medical Art and Photography © 2011 all rights reserved.
synaptic currents and forming the basis for its sedative-hypnotic action observed in vivo.

Fospropofol also has a distinct advantage over the traditional propofol preparation because it is less painful under IV injection, and lacks the lipid load when prolonged infusion is required.

INDICATIONS

As of the time of writing, the only FDA-approved indication for fospropofol injection is as an intravenous sedative-hypnotic agent for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures [24].

DOSEAGE AND ADMINISTRATION

Current usage guidelines for fospropofol recommend administration as a bolus injection [24]. Two dosing regimens are at present used for fospropofol, specifically the Standard Dosing Regimen and the Modified Dosing Regimen.

A. STANDARD DOZING REGIMEN FOR SEDATION

For adults aged 18 to 65 years who are healthy or who have only mild systemic disease (American Society of Anesthesiologists physical status [ASA PS] 1 or 2), the standard dosing regimen of fospropofol is an initial intravenous bolus of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg intravenously (25% of initial dosage), no more than every 4 min as needed to achieve the desired level of sedation.

B. MODIFIED DOZING REGIMEN

Adults ≥65 years of age or those with severe systemic disease (ASA PS ≥3) should receive initial and supplemental intravenous dosages of 75% of the standard dosing regimen [24]. Supplemental doses and individualization of dosing regimens to the patient’s level of sedation may be needed depending on the type of procedure the patient is undergoing. Assessment of the level of sedation will be contingent on the patient’s response to verbal or light tactile stimulation. In any event the recommendations for additional IV boluses (25% of the initial bolus) are that they should not be given more frequently than every 4 minutes.

Dosing of fospropofol is limited by lower and upper weight bounds of 60 kg and 90 kg. Adults who weigh ≥90 kg should be dosed as if they weighed 90 kg. No initial dose should exceed 16.5 ml (Lusedran™ is 35 mg/ml); no supplemental dose should exceed 4 ml. Adults who weigh ≤60 kg should be dosed as if they weighed 60 kg. Dosages lower than those specified for the lower weight limit may be used to achieve lighter levels of sedation [24].

ONSET OF ACTION—CLINICAL CORRELATIONS

Propofol is the “gold standard” for brief sedation because of rapid onset and rapid resolution. These features have made it a suitable agent in outpatient procedural sedation/anaesthesia. The fast-on, fast-off action leads to rapid emergence and patient satisfaction because of a clearheaded awakening.

Fospropofol has a slower onset of action than propofol because it is a prodrug which undergoes metabolism to break down into its active molecule. The onset of action is typically 4 to 13 min. Additionally the relatively slow breakdown process results in more or less sustained levels of propofol and hence the longer duration of action compared to propofol. Thus the use of fospropofol is characterized by fewer peaks and troughs in the released propofol bloodstream levels and requires fewer frequent boluses compared to propofol lipid emulsion [24]. These qualities make it an attractive option for very brief outpatient procedures where a single loading dose may be enough for an entire procedure. It is important for the clinician who administers the drug to recognize that a time lag will occur between drug injection and the onset of clinical effects. During this time, the clinician should therefore not give additional boluses, because these could lead to a deeper level of sedation than intended, which in turn could result in cardiorespiratory compromise.

CONTRAINDICATIONS

Allergy to the drug is the only absolute contraindication for fospropofol [24]. However, as we mention elsewhere in this review, several clinical situations call for cautious use of the drug.

PREPARATION

Fospropofol is formulated as a clear to slightly yellow aqueous solution. The commercially available formulation contains 3.5% of fospropofol per milliliter in water. Each 30 ml single use vial of Lusedra™ contains 35 mg of fospropofol disodium per ml (a total of 1,050 mg of fospropofol disodium in a 30 ml vial), monothioglycerol (0.25% w/v), and tromethamine (0.12% w/v); and it has a pH of 8.2 – 9.0 [23].

As with all intravenous medications, sterile syringes should be used and strict aseptic techniques should be followed. Fospropofol syrings should be prepared immediately after vials are opened. It is also prudent to look for evidence of particulate matter or discoloration immediately prior to use.

Fospropofol has been shown to be compatible with most of the commonly used perioperative intravenous (IV) fluids including normal saline (NS), and lactated ringer’s solution. It is physically incompatible with midazolam or meperidine; there is insufficient data on its compatibility with other agents. It is therefore recommended that the IV line be flushed with saline before and after administration. The drug does not appear to be photosensitive and does not require a filter for administration [24].

CLINICAL PHARMACOLOGY

The reader is to be reminded that as the topic of the pharmacokinetics and pharmacodynamics of fospropofol is explored here, we have addressed the issue of the retracted studies on the topic as explained below. However in this section we relied on data from the US prescribing information, which was based on a crossover study in healthy volunteers (n = 68) receiving a single intravenous bolus dose of fospropofol 6 and 18 mg/kg (unpublished data)[24]. This study used a newer assay method for the amount of propofol derived from fospropofol. Additional data are drawn from clinical trials in patients undergoing therapeutic and diagnostic procedures and receiving fospropofol 6.5mg/kg (n=667 [fospropofol data] and N=400 [released propofol data]). These data have been supplemented by an extensive review of published literature and abstracts from recent national meetings [24-29].

MECHANISM OF ACTION

Following intravenous injection, fospropofol is metabolized by alkaline phosphatase to release propofol (the active molecule), phosphate, and formaldehyde. Since for every molecule of fospropofol administered one molecule of propofol is produced this means that (based on their respective molecular weights) 1.86 mg of fospropofol will produce 1mg of propofol. It is important to remember in this regard that 1.86 mg of fospropofol is the molar equivalent of 1 mg propofol and thus for every millimole of fospropofol administered, one millimole of propofol is produced [24].

PHARMACOKINETICS AND PHARMACODYNAMICS

Early studies of the pharmacokinetic and pharmacodynamic properties of fospropofol have now been retracted [30] in a series of six studies which were all either phase I or phase II FDA trials and all of which were inaccurate in the analytical assay for the released propofol [31-36]. This analytical assay error rendered the results of these studies unreliable. The studies were sponsored by Guilford Pharma (Baltimore, MD), which was later acquired by MGI Pharma (Baltimore, MD). These were conducted by academic and industry
eral anesthesia, it has a peak onset of action of about 40 sec from the start of an injection (the time for one arm-brain circulation). As with other rapidly acting intravenous anesthetic agents, propofol has a half-time of the blood-brain equilibration of approximately 1 to 3 min, and this accounts for the rapid induction of anesthesia [16,43]. With fospropofol the recommended maximum dose is 12.5 mg/kg, which should lead to loss of consciousness (general anesthesia) in about 4 min (the recommended effective sedation dose is 6.5 mg/kg) [44].

The pharmacokinetic and pharmacodynamic profile of fospropofol has been evaluated in randomized, blinded, dose-controlled studies for sedation in patients undergoing colonoscopy and flexible bronchoscopy. Using the standard and modified dosing regimens, Cohen et al. studied fospropofol-induced sedation in patients undergoing colonoscopy. Their results showed that the median (range) time to sedation (time from first dose of sedative to the first of 2 consecutive MOAA/S scores of ≤4) was 8.0 (2-28) minutes and the median time to a fully alert state (3 consecutive responses to their name spoken in a normal voice) was 5.0 (0-47) minutes [24,45].
Silvestri et al. studied fospropofol-induced sedation in patients undergoing flexible bronchoscopy. They found that patients who received the standard and modified fospropofol dosing regimens, had a median time to sedation of 4 (2-22) min and a median time to a fully alert state of 5.5 (0-61) min [24,47].

Pharmacokinetic parameters from a crossover study of 68 healthy subjects, 18 to 45 years of age, who received 6- and 18-mg/kg intravenous bolus doses of fospropofol showed that the maximum concentration (Cmax) and area under curve (AUC)\(0\rightarrow\infty\) values of fospropofol and the released propofol were dose-proportional, and inter-individual variability was low. Propofol was rapidly released, reaching plasma Cmax at a median Tmax of 12 min for fospropofol 6 mg/kg and 8 min for fospropofol 18 mg/kg [24]. These results are similar to those reported by Shah et al. which showed that maximum released propofol concentration (Cmax) was achieved at 8 min with about 85% of Cmax being achieved by 4 min [27]. Concentration-time profiles in all these cases showed a bi-exponential decline.

**DISTRIBUTION**

Fospropofol has a much smaller volume of distribution (5.8 L/kg) as compared to the propofol released by fospropofol breakdown (0.33±0.069 L/kg). An important clinical implication for the perioperative physician to keep in mind is that both fospropofol and its active metabolite propofol are highly protein-bound (approximately 98%), primarily to albumin [24]. Therefore, free drug levels could be altered in malnourished or hypoprotenemic patients.
METABOLISM

Fospropofol is completely metabolized by the enzyme alkaline phosphatase to propofol, formaldehyde, and phosphate. Formaldehyde is further metabolized to formate by several enzyme systems, most importantly formaldehyde dehydrogenase, present in various tissues, particularly the red blood cells. The formate produced is rapidly eliminated by oxidation to carbon dioxide [24]. (See section under accumulation of metabolites.)

Propofol released from fospropofol is further metabolized (approximately 60%) in the liver to major metabolites propofol glucuronide (34.8%), quinol-4-sulfate (4.6%), quinol-1- glucuronide (11.1%), and quinol-4-glucuronide (5.1%). The rest of metabolism (approximately 40%) entails largely extra-hepatic clearance by the kidney, intestine and lungs (minor role). Fospropofol is not a substrate of CYP450 enzymes; therefore no interaction is expected with drugs that are enzyme-inducers or enzyme-inhibitors [24, 48].

ELIMINATION

After a single 400-mg IV dose of labeled fospropofol disodium in humans, total body clearance (CLp) was determined to be 0.280±0.053 L/h/kg. The terminal phase elimination half-life (t1/2) of fospropofol in healthy subjects was comparable to that in patients in whom it was used for MAC sedation and/or minor surgical procedures. After labeled drug administration, 70% of radioactivity was recovered in the urine within 8 days and the total body clearance had only a minor component of renal elimination (<0.02% of dose). An important clinical correlate that may be derived from these data is that fospropofol can be used in patients who have varying degrees of kidney failure since its clearance is not significantly renal dependent [24].

SIDE EFFECTS’ PROFILE

The side effect profile of fospropofol is very different from propofol. Table 2 shows pooled data of adverse reactions from various studies examining the use of fospropofol during colonoscopy, bronchoscopy and minor surgical procedures. Although fospropofol does not cause pain on intravenous injection, clinicians should be aware of the following reported side effects:

- Paresthesia (incidence 52–73%), including perineal discomfort or burning sensation [24].
Table 2. Pooled data of adverse reactions from a phase II dose response study and a phase III randomized control trial in patients undergoing colonoscopy (n=183) compared with an open-label trial in patients undergoing minor procedures (n=123) and a randomized, double-blind, controlled phase III study in patients undergoing flexible bronchoscopy (n=149) [44,45,48,52]. (Adopted from Eisai Inc. Package Insert Lusedra™ US prescribing information).

<table>
<thead>
<tr>
<th>Reaction Term</th>
<th>Colonoscopy (N=183) n (%)</th>
<th>Minor Procedure (N=123) n (%)</th>
<th>Bronchoscopy (N=149) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>5 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Procedural Pain</td>
<td>0</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Nervous system disorders Paresthesia Headache</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>135 (74)</td>
<td>77 (63)</td>
<td>78 (52)</td>
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<tr>
<td></td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>16 (11)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
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<tr>
<td>Pruritusb</td>
<td>30 (16)</td>
<td>34 (28)</td>
<td>24 (16)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (2)</td>
<td>4 (3)</td>
<td>10 (7)</td>
</tr>
</tbody>
</table>

bParesthesia includes the following terms: Paresthesia genital male; Burning sensation; Genital burning; Burning sensation; Genital pain (reported as burning); Perineal pain (reported as burning); Anal discomfort (reported as burning); Chest pain (reported as burning); Ear discomfort (reported as burning); Nasal discomfort (reported as burning); Buttock pain (reported as stinging); Groin pain (reported as stinging); Pain (reported as stinging); Sensory disturbance (reported as non-specific sensation in pubic area).

Pruritus includes the following terms: Genital pruritus female; Genital pruritus male; Pruritus genital; Pruritus ani; Pruritus generalized.

Pruritus (incidence 16-21%), including genital, perineal, and generalized pruritus [24].

Both pruritus and paresthesias are self-limiting, start within 5 min after drug administration, last about 1-2 min and are of a mild degree [46]. Premedication with other agents does not prevent them and at present there is no treatment for them. They were reported most frequently in the perineal region, and are not dose-dependent side effects [45]. The reason for these neural phenomena remains unknown [24].

Hypoxemia (4% incidence with standard or modified dosing regimen; 27% with greater than recommended dose). It may be present also in patients who retain purposeful responsiveness, and may go unrecognized. Hypoxia occurred more often during bronchoscopy (10% of patients), whereas in minor surgery or colonoscopy it was rare (0.8 – 1.6%) [24]. While such risk was dose-dependent, it was not associated with preoperative variables such as age, weight, and ASA status [47].

Unresponsiveness to vigorous tactile or painful stimulation (a state of general anesthesia) following doses intended for induction of sedation (4% during colonoscopy; 16% during bronchoscopy) [24].

Hypotension (4% incidence with standard or modified dosing regimen; 6% with greater than recommended dose) [24]. It is suggested that maintaining adequate intravascular volume, cautious use in patients who are volume-depleted or who have a perioperative myocardial dysfunction may ameliorate this complication.

Respiratory depression (<1% incidence with standard or modified dosing regimen; 3% with greater than recommended dose). This complication highlights the importance of continual assessment of adequate ventilation during sedation [24].

Due consideration should also be given to co-administration of narcotics and other sedative hypnotic drugs due to the potential for synergistic effects.

ACCUMULATION OF METABOLITES

Fospropofol’s metabolism creates propofol, phosphate and formaldehyde. Alkaline dehydrogenase and formaldehyde dehydrogenase (glutathione-dependent reaction) break down the formaldehyde to formate, which further liberates carbon dioxide and water. This latter reaction is catalyzed by 10-formyltetrahydrofolate dehydrogenase with tetrahydrofolate as coenzyme.

Formate is an end-metabolite of fospropofol and is also produced by endogenous metabolism of mammalian and human cells. However, in higher than normal concentrations (13 ± 7 μg/ml), as seen in cases of methanol intoxication (7 – 11 mg/ml), formate can have deleterious effects, including metabolic acidosis and retinal toxicity leading to blindness. These toxic concentrations are about 350 times higher than those that are reached with usual metabolism during standard or modified fospropofol dosing regimens. As long as tetrahydrofolate (the co-enzyme, catalyzing the breakdown of formate to CO₂ and H₂O) concentrations are normal and maximum dosing rates are not exceeded, there is a negligible chance of toxicity related to formaldehyde liberation via fospropofol [49-52]. Fig. (I) shows the breakdown of fospropofol into its constituent compounds after metabolism and the effect of the accumulation of breakdown products.
The most common reasons for discontinuation of fospropofol use were paresthesias and cough. The incidence of reported discontinuation has been low (<1%) in various studies [45,46].

Although QT prolongation is a concern with many of the currently used sedatives and anesthetics, fospropofol did not prolong corrected QT intervals. The effect of fospropofol on the corrected QT interval was measured in a crossover study in healthy volunteers (n = 68). In this study the subjects received the following treatments: 6 mg/kg intravenous fospropofol; 18 mg/kg intravenous fospropofol; moxifloxacin 400 mg orally (positive control); and normal saline IV. When given in doses of 6 or 18mg/kg the responses of the corrected QT interval did not differ significantly from those reported for placebo recipients [24,26].

FOSPROPOFOL INFUSION

Few studies have examined the efficacy and safety of a potential fospropofol infusion regimen and its clinical applicability. A study to characterize pharmacokinetics and pharmacodynamics of fospropofol administered as continuous infusion or bolus compared with continuous infusion of propofol injectable emulsion is presently recruiting (ClinicalTrials.gov identifier NCT01308541). Meanwhile, Candioti et al. conducted a single-center, randomized, open-label pilot study of the safety and tolerability of fospropofol for patients needing intubation and mechanical ventilation in the ICU [54]. In this study, 60 patients were randomized to receive 1 of 3 regimens with the goal of maintaining a Ramsay Sedation Score of 2 to 5: (1) fospropofol IV infusion at 25ug/kg/min with a 100mg bolus and increased infusion rate (25ug/kg/min every 5 min) for agitation events (infusion/bolus); (2) fospropofol IV infusion at 25 ug/kg/min with an increased infusion rate (25ug/kg/min every 5 min) for agitation events (infusion only); or (3) propofol IV infusion at 25ug/kg/min with an increased infusion rate(5-10 ug/kg/min every 5 min) for agitation events. Incidence rates for adverse events were similar between fospropofol groups. In the fospropofol groups, 28 of 38 patients (74%) experienced adverse events compared to 14 of 22 patients (64%) in the propofol group. The frequency of adverse events was similar between the two fospropofol dosing groups, with the exception of procedural pain (33.3% vs 5.0%; infusion/bolus and infusion only respectively). In the two fospropofol dosing groups, the most common adverse events with fospropofol were procedural pain (21.1%) and nausea (13.2%). Two patients (1 each in the fospropofol infusion/bolus group and the propofol group) experienced hypotension during the study as a potential sedation-related adverse event. Mean plasma formate levels were not significantly different among groups. Patients in all three treatment groups maintained Ramsay Sedation Scores of 2 to 5 for >90% of the time they were sedated. This pilot study suggests that fospropofol, administered in either an infusion/bolus or infusion-only regimen, is well tolerated and effective for short-term induction and maintenance of sedation in mechanically ventilated intensive care unit patients [54]. Additional details are available at the US National Institutes of Health website clinicaltrials.gov under the identifier NCT00125398.

A recent editorial has proposed a mathematical model for a possible fospropofol infusion regimen [55]. The authors have highlighted the possible advantages of such an infusion technique, in terms of more stable propofol levels that would result in a steady plain of sedation, avoidance of the possibility of excessive fospropofol administration and the convenience of use with syringe pumps eliminating the inconvenience of repetitive boluses. They proposed the need for derivation of a “propofol equivalent” regimen of fospropofol dosing [24,56]. To calculate the target fospropofol infusion, the first step would be to determine the propofol infusion rate needed for a particular infusion dosage in ug/kg/min of propofol. The second step would be to use that in the chemical equivalence that states that 1.86 mg of fospropofol disodium is the molar equivalent of 1 mg propofol. Mathematically this would mean that 186 ug/kg/min of fospropofol is equal to 100 ug/kg/min of propofol. Based on the fact that fospropofol is formulated as 35mg/ml compared to 10mg/ml of propofol and the molar equivalents, a flow rate of fospropofol can be derived. However, whether these cited advantages hold true remains to be seen when such a regimen is tried in actual clinical scenarios. It is worth remembering that fospropofol was never designed as an infusion drug. It was meant to be a single bolus dose that would serve as a possible “sustained release propofol” delivery agent and allow short procedures such as bronchoscopy, colonoscopy, and some other outpatient invasive procedures. It is obvious that this is a mathematical derivation and more research is required before the potential infusion of fospropofol, targeting propofol dosage rates, could be confidently applied to clinical use.

Side Effects’ Profile During Prolonged Exposure in Adult Patients

Few reports have been published on the use of this agent for prolonged sedation, as in the intensive care unit in intubated and mechanically ventilated patients [54,57]. As of this writing, FDA approval has not been granted for the use of fospropofol to maintain sedation during prolonged mechanical ventilation in the intensive care unit.

Candioti et al. in their study on intubated and mechanically ventilated patients observed a single episode of nonsustained ventricular tachycardia lasting 5-10 seconds. The patient in question had low-normal potassium and magnesium levels and the episode did not recur after adequate replacement of the deficiencies. Another patient in this study showed a significant increase in blood formate level on fospropofol infusion. However, this was attributable to co-existing renal and hepatic failure with ongoing acute myeloid leukemia and lack of dialysis. Importantly, there were no adverse effects seen in this case related to the elevated formate [24,54]. In an open-label, single-center, randomized study (unpublished data- ClinicalTrials.gov identifier NCT00209521) investigators compared fospropofol to propofol infusion in patients undergoing coronary artery surgery. This study examined the safety and tolerability of fospropofol when used perioperatively to sedate, induce, and maintain general anesthesia and to postoperatively sedate in the intensive care unit. Propofol and fospropofol infusions were run via a target-controlled infusion (TCI) system to target desired plasma concentrations. Infusions were started immediately preoperatively and continued into the post-operative period in the ICU. A given infusion was titrated to specific desired ranges of bispectral index (BIS) (Coviden, Berlin, Ireland) scores during induction, maintenance and emergence from general anesthesia. In addition, an alfentanil infusion was run with the TCI technique. Patients studied were between the ages of 20 and 70, and were scheduled for first-time elective coronary artery bypass graft (CABG) surgery, with 1 to 4 grafts. The patients had ASA PS 2 or 3 and good left ventricular function (LVEF ≥50%); if females, they were either surgically sterile or post-menopausal. Efficacy endpoints included adequate sedation/hypnotic events (as measured by the BIS index), hemodynamic instability, anesthesiologist’s assessment of overall quality of induction, maintenance and ease of control of anesthesia, and sedation. The results showed no significant difference between fospropofol and propofol treatment groups in mean MAP, heart rate, and BIS index; and adequate sedation was maintained in all patients.

Adverse events related to the CABG (reactionary pleural effusion and post-procedural pain) were similar (75% vs 50%) in type and frequency in both groups, with the exception of burning and pruritis, experienced only by the fospropofol group. Serious adverse events were experienced by one patient in each group and were not considered a consequence of drug administration. There were no visible patterns of increase in plasma formate concentrations above baseline levels and comparable formate levels; 52% vs 64% con-
centrations were below the limit of quantification after fospropofol and propofol administration, respectively. There were no deaths or treatment withdrawals during the study period. These results, yet unpublished, suggest that fospropofol infusion used for induction and maintenance of general anesthesia and postoperative sedation was well tolerated and was as effective as propofol infusion, both delivered via a TCI system.

DRUG INTERACTIONS

Co-administration of other opioids and/or sedative hypnotic drugs may produce additive cardiovascular and respiratory depression. However, the plasma pharmacokinetics of fospropofol are not affected by analgesic premedication such as fentanyl (1 mcg/kg); meperidine (0.75 mg/kg); midazolam (0.01 mg/kg) or morphine (0.1 mg/kg) [24].

Interestingly, an in-vitro protein-binding study has shown no significant interaction between fospropofol and propofol at concentrations up to 200 mcg/ml and 5 mcg/ml, respectively. Though both fospropofol and its metabolite, propofol, are highly protein bound their interaction with other highly protein-bound drugs given concomitantly has not been studied [24]. The potential of fospropofol or its major metabolite, propofol, to inhibit or induce major cytochrome P450 enzymes, are not known.

DRUG ABUSE AND DEPENDENCE POTENTIAL

While fospropofol is labeled as a schedule IV controlled drug substance, to date there is no adequate data on its abuse or potential for dependence.

OVERDOSE AND TOXICITY

Fospropofol overdosage will usually manifest as hemodynamic deterioration along with respiratory depression and apnea [24]. Management would entail IV fluids and/or pharmacologic vasopressor support. Depression of respiration may require elective intubation and mechanical ventilation until the drug is metabolized. Formate and phosphate are metabolites of fospropofol and may contribute to signs of toxicity following overdosage. This may be especially true in patients with altered metabolic pathways for metabolizing formaldehyde and formate. As mentioned previously under side effects, formate toxicity is a possibility but has not been reported with usual clinical doses in patients with normal metabolic pathways. Signs of formate toxicity are similar to those of methanol toxicity and are associated with anion-gap metabolic acidosis. Intravenous exposure to a large amount of phosphate could potentially cause hypocalcemia with paresthesia, muscle spasms, and seizures.

FOSPROPOFOL USE IN PATIENTS WITH HEPATIC AND RENAL IMPAIRMENT

There are no studies on pregnant human females to describe the safety and efficacy of fospropofol during labor, delivery, cesarean section, or its teratogenic effects on a human fetus in development and its use in nursing mothers. Animal studies (in pregnant rats and rabbits) have shown neither significant teratogenic nor non-teratogenic effects. Though propofol has been reported to be excreted in breast milk and transported across the placenta, there is no data on fospropofol in this regard. Hence, there are no recommendations supporting use of fospropofol in pregnant females and nursing mothers [24].

As for fospropofol use at both ends of the age spectrum, there is insufficient evidence to demonstrate its safe use in pediatric patients. However, it has been used effectively in patients > 65 years of age, although they received the modified dosing regimen as detailed above. It should be noted, however, that there was an increase in the incidence of hypoxemic events with increasing age comparing patients younger and older than 65 yrs of age [58].

FOSPROPOFOL USE IN EXTREMES OF AGE AND IN PREGNANCY

There are no studies on pregnant human females to describe the safety and efficacy of fospropofol during labor, delivery, cesarean section, or its teratogenic effects on a human fetus in development and its use in nursing mothers. Animal studies (in pregnant rats and rabbits) have shown neither significant teratogenic nor non-teratogenic effects. Though propofol has been reported to be excreted in breast milk and transported across the placenta, there is no data on fospropofol in this regard. Hence, there are no recommendations supporting use of fospropofol in pregnant females and nursing mothers [24].

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FOSPROPOFOL USE IN PATIENTS WITH HEPATIC AND RENAL IMPAIRMENT

There is also insufficient evidence to support its use in patients with liver impairment. Similarly, in patients with renal disease, though safety has been demonstrated in patients with creatinine clearance of >30ml/min (mild to moderate renal impairment), there are few data on the behavior of this drug at a creatinine clearance of <30ml/min (severe renal impairment and end-stage renal disease) [24].

CLINICAL INDICATIONS IN THE PERIOPERATIVE PERIOD

Fospropofol has great potential as a useful agent for sedation. Since it is a prodrug, the blood levels of propofol after a single IV bolus of fospropofol reach lower peak levels and are more sustained than after administration of intravenous bolus of propofol as a sole induction agent. Such unique properties would eliminate the need to deliver the drug by infusion as well as the need for frequent bolusing in short procedures.

A. Use in Colonoscopy

Use of fospropofol as a sedative for colonoscopy was one of the earliest investigatied uses of the drug [23]. In 2008 Cohen et al. published the results of their randomized, double-blinded, multicenter trial in 127 ASA 1 adults undergoing colonoscopy [46]. Patients in this trial were randomized to receive one of the following regimens: fospropofol 2, 5, 6.5, or 8 mg/kg or midazolam 0.02 mg/kg following pre-treatment with fentanyl 50 ug [46]. Fospropofol produced a significant dose-dependent increase in sedation success from 24% (2 mg/kg), 35% (5 mg/kg), and 69% (6.5 mg/kg) to 96% (8 mg/kg); P < 0.001). In the 6.5 mg/kg group, there were no recorded episodes of deep sedation, whereas 25% of patients experienced deep sedation in the 8mg/kg group, which was not a statistically significant difference, however, one can make the case for its clinical significance. Time to sedation, requirements for alternative sedative medication, supplemental doses of sedative and fentanyl, time to readiness for discharge and endoscopist-rated satisfaction scores were shown to be dose-dependent as well. The 8 mg/kg fospropofol group had the highest physician satisfaction ratings. Though the 8mg/kg dose had the maximum sedation success rates of 96%, time to readiness for discharge was also the longest with this dose. Overall, 6.5mg/kg was judged to be the best tolerated dose. While few patients receiving fospropofol experienced mild to moderate adverse events (including hypotension and paresthesia), there were no serious adverse events or deaths. An important limitation of this study is that it was not designed to compare the efficacy of fospropofol to midazolam. However, both the fospro-pofol (6.5 mg/kg) and midazolam treatment arms achieved high sedation success rates and overall patient satisfaction. The investigators concluded that the 6.5 mg/kg dose produced an optimal balance of safety and efficacy in this patient population. Such dose was then selected to be used in the subsequent phase III trial as described below.

The phase III trial by the same group of investigators was published in 2010. It was a multicenter, double-blind, randomized trial aiming to evaluate the safety and efficacy of two intravenous fospropofol bolus doses for moderate sedation in patients undergoing colonoscopy [45]. They compared fospropofol 6.5 mg/kg with a subtherapeutic dose of fospropofol (2 mg/kg) for patients undergoing colonoscopy. A third treatment group, serving as a control group, received 0.02 mg/kg of midazolam. The drugs were given in a 2:3:1 ratio, respectively. Supplemental doses of study medication (maximum of 3 doses > 4 min apart, 25% of initial dose) or 1 mg midazolam, were permitted to achieve a Modified Observer's Assessment of Alertness/Sedation score ≤4 to enable the proceduralist to begin the scheduled procedure. The investigators showed that sedation success was higher in the fospropofol group (6.5
mg/kg) than in the 2 mg/kg group (87.7% vs. 26%; p < 0.001) and was 69% in the midazolam group. Patients in the 6.5-mg/kg group were significantly less likely to remember being awake during the procedure (51% vs. 100% in the 2-mg/kg group, p = 0.001; 60% for the midazolam group). Mean physician satisfaction scores were higher in the fospropofol group (6.5-mg/kg) (7.7) than the 2-mg/kg group (4.5), p < 0.001. Most adverse events were mild to moderate; the most common treatment-related adverse events were paresthesia (68% vs. 60%) and pruritus (16% vs. 26%) in the fospropofol 6.5 and 2 mg/kg groups, respectively. Sedation-related adverse events were comparable in the three groups. The investigators concluded that the fospropofol 6.5-mg/kg dosing regimen for sedation during colonoscopy, was well tolerated, and associated with higher rates of sedation success and higher rates of physician satisfaction than with the fospropofol 2-mg/kg dose. The main limitations of this study included the lack of a formal comparison with the midazolam group (in the previous study) and the confounding effect of premedication with an opioid (in this case, fentanyl 50 mcg). Cumulatively, these results suggest that sedation success and physician satisfaction were dose-dependent.

B. Use in Bronchoscopy

Fospropofol was also investigated in several studies for sedation during flexible bronchoscopy [47,58]. Silvestri et al., in a randomized, double-blinded, multicenter study, evaluated the use of fospropofol in patients > 18 years of age and undergoing flexible bronchoscopy [47]. Patients were randomized to either fospropofol 6.5mg/kg (N = 150) or 2.0mg/kg (N = 102) [47]. Of the 150 patients who were randomized to fospropofol 6.5 mg/kg, 61 were at least 65 years of age and comprised the subgroup of elderly patients, who were used for post-hoc subgroup analysis, as discussed below.

All patients were pretreated with fentanyl, 50 mcg. Supplemental doses of fospropofol were given per protocol. Sedation success rates were significantly greater in the 6.5 vs. 2.5 mg/kg groups (88.7% and 27.5%, respectively [p < 0.0001]). In addition, treatment success (91.3% vs. 41.2%) respectively; (p < 0.001), willingness to be treated again (94.6% vs. 78.2%, respectively; p < 0.001), and absence of procedural recall (83.3% vs. 55.4%, respectively; p < 0.001) were significantly better with the administration of 6.5 mg/kg fospropofol. The proportion of patients requiring supplemental therapy with analgesics (16.7% vs. 37.4%, respectively) and the use of alternative sedative medications (8.0% vs. 58.8%, respectively) was lower for patients in the 6.5 mg/kg dose group (all comparisons, p < 0.001). The most frequent adverse events were transient and self-limited paresthesias and pruritus of mild-to-moderate severity. Hypoxemia (predominantly mild-to-moderate) was the most common sedation-related adverse event, and was comparable in both groups. The investigators therefore concluded that fospropofol at 6.5mg/kg provided safe and effective sedation for patients undergoing flexible bronchoscopy.

In a recent subset analysis by Silvestri et al., elderly patients aged > 65 years were compared with those <65 years enrolled in a phase III, randomized, double-blind, dose-controlled study, and undergoing flexible bronchoscopy [58]. Patients >65 years of age received the modified dosing regimen initially as well as the supplemental doses (reduced by 25%). Results of this analysis showed that sedation success and treatment success rates exceeded 85% in all groups and were higher in the elderly patients subgroup (92%). More patients in the younger group than in the elderly group required at least one alternative sedative medication during the procedure (10 [11.2%] vs 2 [3.3%]). Physician and patient satisfaction scores were comparable in both groups. The most common treatment-related adverse events were paresthesia, pruritus, hypotension, and hypoxia, but hypoxia was not significantly different between the two groups. Hypoxemia occurred in 26% of the elderly and 18% of the younger patients group, but escalation of care was not required. Airway assistance was required in 16 patients in each subgroup. In the elderly patients subgroup, airway assistance consisted of administering oxygen to all 16 patients; 4 of the 16 patients in the younger subgroup also required additional maneuvers including suction, chin lift, bag-mask ventilation, or tactile and verbal stimulation. Considering comorbidities and a high incidence of underlying chronic lung disease in this subgroup of patients, these adverse events were expected. It is noteworthy that the impact of age on the outcomes of flexible bronchoscopy is controversial. While some claim that adverse events are increased in elderly patients, others claim that outcomes after bronchoscopy are not attributable to age alone [60-65]. Thus, the reports of fospropofol being able to provide adequate sedation for bronchoscopy mixed with the reported adverse events that can be serious, sparked the debate regarding the FDA recommendation concerning the training and skills of the clinicians administering fospropofol that were obviously patients’ safety motivated [59].

MONITORED ANESTHESIA CARE (MAC) IN MINOR SURGICAL PROCEDURES

Gan et al., in an open label, multi-center, uncontrolled-single arm trial looked at 123 patients undergoing minor surgical procedures using fospropofol for MAC sedation. They included patients of ASA physical status I-IV and ≥ 18 years of age scheduled to undergo various minor surgical procedures which included arthroscopy, arteriovenous shunt placement, bunionectomy, dilatation and curettage (D & C), esophagogastroduodenoscopy (EGD), lithotripsy and transesophageal echocardiography (TEE) [53]. All patients received IV fospropofol 6.5 mg/kg followed by up to 5 supplemental doses of 1.63 mg/kg if needed. The initial dose of fospropofol was preceded by a prior dose of 50 mcg of fentanyl. Alternative sedative was administered to 4.9% of patients due to inadequate sedation; 5.7% of patients had a MOAA/S score of 0 or 1 and these patients required at least one type of airway assistance. Treatment-related adverse events were reported in 82.1% of patients. As might be expected, paresthesia (62.6%) and pruritus (27.6%) were the two most common adverse events and were mild to moderate. Other adverse events included hypoxemia (0.8%), hypotension (3.3%), and bradycardia (0.8%). This study, however, included only the use of one dose of fospropofol. The investigators concluded that an initial dose of IV fospropofol 6.5 mg/kg with supplemental doses was safe and well tolerated for the purpose of moderate sedation for use in minor surgical procedures [53].

FOSPROPOFOL: UNEXPLORED AVENUES AND AREAS OF INTEREST

Future studies are needed in a larger number of patients to further quantify its safety and efficacy not only in the most commonly studied applications like colonoscopy and bronchoscopy, but also in procedures performed at electrophysiology laboratories, interventional radiology, MRI, and awake intubation, to name a few. More importantly it should be compared with other commonly used sedation regimens (midazolam with or without narcotics) as well as other emerging sedatives like dexmedetomidine in a randomized controlled trial [66,67].

As an agent for induction and maintenance of general anesthesia, fospropofol has yet to be explored. The impact of its pharmacokinetic profile on patient flow and operating room efficiency and economics should also be determined.

ICU sedation in mechanically ventilated and intubated patients is another important area that deserves more attention. Fospropofol has in theory eliminated or at least lessened some of the issues with prolonged usage of propofol in the ICU; for example, bacterial contamination and lipid load. Prolonged administration of fospropofol could theoretically result in increased concentrations of formaldehyde and phosphate. However, as the available data suggest, much work remains to be done to determine its safety and efficacy when...
used for short-term and long-term infusions, in patients with clinical indications for the same [54]. Moreover, specific populations such as pediatric and obstetric patients and patients with end-stage liver disease deserve further study to determine its usefulness in such populations. Finally, because of the recent shortages of various anesthetic induction agents including propofol, an alternative agent (if fospropofol is indeed shown to be one) is certainly a desirable aim [68].

SUMMARY

Fospropofol is an intravenous sedative-hypnotic agent that is FDA-approved for monitored anesthesia care (MAC) sedation in adult patients undergoing diagnostic or therapeutic procedures. As a prodrug of propofol, its pharmacologic activity results from breakdown by alkaline phosphatases and liberation of propofol, which is the active agent. It exhibits a longer time to peak effect than propofol and a more prolonged action. Providers must be informed of this more gradual onset of sedative effect, in order to avoid unnecessary supplemental doses of fospropofol.

The standard dosing regimen consists of administration of an initial IV bolus dose of 6.5 mg/kg followed by supplemental doses of 1.6 mg/kg IV provided as needed, but no more frequent than at 4 min intervals, to achieve and maintain mild to moderate sedation. Patients ≥65 years of age or who have severe systemic disease (ASA P3/P4) should follow a modified dosing regimen of 75% of the standard dosing regimen. The FDA-approved package insert of fospropofol states that this drug should be administered only by persons who are trained in administering general anesthesia and who are not conducting the diagnostic or therapeutic procedure. Patients who receive fospropofol should be monitored for potential loss of spontaneous respiration, as well as for hypoxemia, unresponsiveness or minimal responsiveness to vigorous tactile or painful stimulation, and hypotension.

Recent studies have shown the safety of fospropofol as an agent for MAC sedation in patients undergoing colonoscopy and flexible bronchoscopy. However, whether it can be considered another agent like propofol in the ICU and in the operating room remains to be determined.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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