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REVIEW

Clinical Use of Fospropofol Disodium: Evaluation of Pharmacology, Safety, and Efficacy

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Abstract: Fospropofol disodium (FD) is a safe and effective alternative to propofol, as it avoids injection pain, severe hypotension, significant respiratory depression, and allergic reactions during intravenous anesthesia induction. FD, the water-soluble prodrug of propofol, was initially developed by Eisai in Japan and was approved by the FDA for marketing in the United States in 2008. However, due to formaldehyde accumulation, safety concerns in outpatient settings, and the requirement for administration by anesthesiologists, the product had poor sales and was withdrawn in 2012. Subsequently, short-term FD use was found resulting in limited formaldehyde accumulation, which is then metabolized to formate at levels comparable to endogenous concentrations, posing no significant health risk. Most adverse events, including respiratory depression and hypotension, were found to be transient, self-limiting, and predominantly mild to moderate in severity. On May 25, 2021, the National Medical Products Administration (NMPA) approved the injection of FD, with the approval number H20210017. As a new type Class I drug applied for market registration in China, it is indicated for general anesthesia induction in adults. The review covers the known and emerging characteristics of pharmacokinetic and pharmacodynamic properties of FD approved by the FDA and the new type Class I FD approved by China, emphasizing their non-inferior sedative efficacy and relatively mild adverse reactions compared to propofol and provides insights into their safer application in a broader population. Additionally, it highlights the necessity of structured personnel management during sedation and anesthesia procedures. In short, FD can be safely and effectively used for endoscopic examinations, minor surgeries and continuous sedation in the ICU. While FD demonstrates safety and efficacy as a sedative in specific clinical scenarios, larger and more rigorous clinical trials are essential to validate its long-term use, application in high-risk populations, and administration by non-anesthesiologist healthcare providers.

Keywords: fospropofol disodium, propofol, sedation, general anesthesia, induction, efficacy and safety

Introduction

Propofol is the most commonly used sedative agent for procedural sedation or anesthesia induction. Despite its success in clinical setting, it has been associated with side effects such as injection pain, hypotension, respiratory depression, proarrhythmic effects, the need for antibiotic drugs, potential hyperlipidemia, and propofol infusion syndrome.[1–6] Fospropofol disodium (FD) is a water-soluble prodrug of propofol that significantly addresses these side effects.[7,8] It was hydrolyzed by alkaline phosphatase on the surface of vascular endothelial cells in the body, releasing active propofol and initiating sedative or narcotic effects.[7,9] Compared to traditional agents like propofol, FD mainly differs due to its phosphate group.[7,10] Lacking a structural lipid chain, does not require fat emulsion as a carrier, thus effectively avoiding side effects such as allergies, bacterial contamination, and hyperlipidemia associated with fat emulsion.[8] Moreover, the slow-release pharmacokinetic characteristics of FD decreased the incidence of severe hypotension and obvious respiratory depression during intravenous administration for anesthesia.[7,8] Furthermore, FD does not activate the transient receptor potential vanilloid subtype 1 (TRPV1) receptor on nociceptors in rodent models, indicating that another advantage of FD over propofol is the absence of injection pain.[11] While FD demonstrates distinct advantages over propofol (eg, reduced injection pain and improved hemodynamic stability), several limitations warrant consideration: its delayed onset of action, insufficient long-term safety data, and relatively high incidence of transient paresthesia.

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Table 1 Comparison Between Two Kinds of Fospropofol Disodium

	Lusedra/Aquavan	$Fospropofol_{FD}$
Other name	GPI-15715	HX0507
Manufacturing country	USA	China
Manufacturer	Eisai Corporation/Guilford Pharmaceutical/ MGI Pharma	Yichang Humanwell
Marketing status	Marketed in 2008, discontinued since 2012	Marketed since 2021
Active ingredients	Fospropofol disodium	Fospropofol disodium
Properties	Liquid	Powder
Relative molecular weight	332.24	350.26
Excipient	Dihydroxypropyl thiol /aminobutyriol	Mannitol
Dose and strength	1050mg:30mL	500mg
Recommended bolus for GA	6.5 mg/kg	20 mg/kg

Abbreviations: USA, United States of America; GA, general anesthesia.

There present two types of fospropofol, as detailed in Table 1. Lusedra, produced by the Eisai Corporation of North America or Guilford Pharmaceutical, Baltimore, MD, and Aquavan injection, produced by MGI Pharma, INC, Bloomington, MN, USA, along with the experimental, GPI-15715 or chemically known as 2,6-diisopropylphenol, all pertain to the same liquid drug with a molecular weight of 332.24 g/mol containing 0.25% dihydroxypropyl thiol and 0.12% aminobutyriol as the excipients.[10] Lusedra was approved by the US Food and Drug Administration (FDA) in mid-December 2008 for use in monitored anesthesia care for diagnostic or therapeutic procedures in adults by trained personnel.[12] Several factors have limited FD's widespread adoption: (1) Insufficient clinical data tracking formaldehyde accumulation and its associated safety concerns, which prompted FDA restrictions; (2) The requirement for administration by trained anesthesiologists, rendering it unsuitable for many procedural sedation settings typically managed by non-specialists; and (3) A pharmacokinetic profile less favorable than established alternatives (eg, delayed onset compared to midazolam/propofol) for outpatient or minor surgical procedures. These limitations ultimately led to its market withdrawal in the U.S.[13] The newly developed fospropofol disodium for injection, also known as HX0507, or $Fospropofol_{FD}$, is produced by Yichang Humanwell pharmaceutical Co., Ltd., Hubei, P.R. China.[14] It is a phosphate ester that uses mannitol as an excipient and has a different molecular weight of 350.26 g/mol.[7] Each vial contains 500 mg of lyophilized powder, which, when reconstituted with normal saline or aquaporin for injection, yields a clear solution for intravenous injection.[14]

This narrative review aims to summarize the pharmacokinetic and pharmacodynamic characteristics, the efficacy and safety, as well as the prospects for widespread clinical application in the near future of both the old and new formulations of fospropofol.

Pharmacokinetics of Fospropofol Disodium

FD can only be administered intravenously. Following intravenous injection, each millimolar of FD is enzymatically converted into one millimolar of propofol. The primary metabolic process from prodrug to subsequent inactive propofol occurs in the liver. A dose-range trial involving 30 healthy participants demonstrated that following an intravenous injection in the dose range of 10–30 mg/kg, FD reached an average peak serum concentration at 4 to 5 minutes later, whereas the released propofol peaked at 9 to 15 minutes after injection. The average peak serum concentrations of FD and activated propofol were 138.4 ± 20.0 ug/mL and 3.4 ± 1.0 ug/mL, respectively.[7] Regarding the terminal elimination half-life, FD is 27 ± 6 minutes, activated propofol is 478 ± 287 minutes, which is different from propofol of 88 ± 48 minutes.[7] Their formaldehyde and phosphate metabolites remain at endogenous levels and do not reach toxic concentrations.[8]

Pharmacodynamics of Fospropofol Disodium

FD inhibited the neuronal excitatory activity mainly via two primary mechanisms: first, it augments the inhibitory action of GABA (Gamma-Aminobutyric Acid) by activating chloride channels, promoting the binding of inhibitory neurotransmitter GABA to the GABAA receptor complex or by directly acting on the GABAA receptor complex; second, it suppresses the glutamate release in the central nervous system, diminishes the influx of calcium ions and, exerts anesthetic effect on cerebral cortex, subcortical area, thalamus and midbrain.[7]

The relatively longer duration of action of FD is mainly due to its pharmacodynamic properties. Following intravenous injection, FD needs to be slowly converted into propofol within the body, which then exerts its sedative effect. As a single bolus dose, when administered at a dose range of 10 to 30 mg/kg, it has a shorter onset time and an extended duration of action.[14]

Clinical Use of FD

Moderate Sedation in Gastrointestinal Endoscopy

In a Phase III trial, it was found that FD demonstrated dose-dependent sedation success: 69.2% in the FD 6.5 mg/kg group and 95.8% in the FD 8.0 mg/kg group.[15] Sedation success was defined as achieving a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores are ≤4 consecutively three times after procedural sedation, and without the need for alternative sedation or mechanical/manual ventilation.[16] The average time to sedation success, depth of sedation, and the need supplemental medication all showed similar dose-dependent trend. It was reported that FD 6.5 mg/kg group is exhibited good tolerance and efficacy, providing sufficient sedation effects, indicating a single bolus of 6.5 mg/kg would be favored and is feasible for achieving adequate sedation, memory retention, and satisfaction from both physicians and patients.[15,17] Compared to traditional agents commonly used in colonoscopy, such as midazolam and opioids, FD and propofol demonstrate practical efficiency and economic benefits due to their rapid recovery properties and shorter time from admission to discharge.[9] An potential advantage of FD is the absence of concerns regarding lipid emulsion contamination, which alleviates the plight of patients with hyperlipidemia.

Slower onset, longer duration, and wider therapeutic window are the distinct advantages of FD.[18] However, sedation-related respiratory or circulatory depression frequently occurs when FD is administered during brief procedures, particularly for patients over 65 years old, with severe comorbidities, or weighing less than 60 kg or more than 90 kg.[17,19,20] This partly explains why the 2021 Korean Society of Gastrointestinal Endoscopy Clinical Practice Guidelines emphasize the need for more intensive monitoring by trained personnel in addition to anesthesiologists during FD injection.[21] Due to the pharmacokinetic and pharmacodynamic characteristics of FD, there is some controversy over whether non-anesthesiologists can use FD.[22,23] The FDA conservatively and firmly announced that "Lusedra should be administrated only by personnel trained in general anesthesia, and not involved in the operation of the diagnostic or therapeutic procedures".[24] A single bolus dose of FD, along with a low dose of narcotics, may provide safe and moderate sedation similar to propofol in endoscopic procedures.[22,25] This offers an attractive alternative with fewer respiratory depression or hypotension in both adults and the elderly. Therefore, Bergese et al initiated a clinical trial on FD dose adjustment for the high-risk population.[18] The trial concluded that a lower modified dose of FD did not demonstrate significant safety advantage due to its need for more additional rescue medication associated with a higher rate of treatment- and sedation-related side effects. As he suggested in the article, careful observation and conservation dosing of FD remain crucial. A prospective study from Rex et al showed that nurse-administered propofol sedation can be safe for endoscopic procedures.[25] This provides a possibility for the use of FD by non-anesthesiologists. Nonetheless, it remains crucial for non-anesthesiologists or trained registered nurses, to receive appropriate training programs and ensure the correct use of FD. This includes rapid identification of different levels of sedation, a comprehensive understanding of the pharmacokinetic and pharmacodynamic profiles of FD, and rescue skills such as advanced life support and airway management. The safety and efficacy of FD in advanced endoscopic procedures (including upper gastrointestinal endoscopy, ERCP, and endoscopic ultrasound) require further validation through multinational clinical studies.

The adverse events associated with FD differ significantly from those of propofol. Currently reported FD-related adverse events include paraesthesia, delayed-onset hypotension or delayed hypoxemia. These events are predominantly

transient, self-limited, most are of mild to moderate in severity, and often resolve without escalation to advanced management. It might be a chance that non-anesthesiologists equipped with PK and PD of both FD and propofol, experience of timely intervention such as increasing oxygen flow, raising blood pressure, adjusting drug doses, repositioning, suctioning, or verbal stimulation would be effective enough for taking care of mild-to-moderate sedation patient during examination procedure. Accordingly, more clinical studies are needed for the feasibility assessment and guideline draft of FD clinical use by those non-anesthesiologists.

Moderate Sedation in Flexible Bronchoscopy

During flexible bronchoscopy, the aim of sedation is to alleviate patient's anxiety, pain, cough, or dyspnea, thereby ensuring comfort throughout the entire examination process. It is very crucial for patients to willingly undergo healthcare examinations or treatments. A Phase III, randomized, double-blind study involved 252 patients undergoing flexible bronchoscopy.[19] After each patient received a pretreatment 50 μg of fentanyl, they were randomly assigned to two groups received 2 mg/kg and 6.5 mg/kg of fospropofol, respectively. The success rate of sedation and treatment, patient/physician satisfaction and drug safety are compared between the two groups.[19] The results showed that in the 6.5 mg/kg group, the sedation success rate was 88.7% (compared to 27.5% in 2 mg/kg group), the treatment success rate was 91.3% (compared to 41.2% in the 2 mg/kg group), the patient satisfaction was 94.6% (compared to 78.2% in the 2 mg/kg group) and the median time to sedation was 4 minutes (compared to 18.0 minutes in the 2 mg/kg group).[19] Additionally, the patients in the 6.5 mg/kg group required fewer analgesic supplemental drugs and alternative sedative medications.[19] Regarding adverse events (AEs), paresthesia (47.6%) and pruritus (14.7%) were the most common AEs.[19] Hypoxemia (14.3%) and hypotension (3.2%) were also observed in both groups, but few procedures were interrupted due to severe AEs. The study findings indicate that a dose of 6.5 mg/kg of fospropofol achieves a good balance of efficacy and safety for moderate sedation during flexible bronchoscopy. However, robust international clinical data are needed to establish FD's safety and efficacy profile for flexible bronchoscopy applications.

Anesthesia or Sedation in Minor Surgeries

FD provides appropriate sedation and can be safely used in minor procedures, but data on its application for moderate or major surgeries is currently lacking. A phase III study evaluated the safety of the sedative FD on patients scheduled for minor surgeries.[26] Eligible procedures included arthroscopy, arteriovenous shunt placement, bunionectomy, dilatation and curettage, esophagogastroduodenoscopy, lithotripsy, transesophageal echocardiography, and ureteroscopy.[26] A total of 123 patients aged ≥18 years with an ASA status ranging from I to IV were included in this study. A pretreatment of fentanyl 50 μg was administered 5 minutes prior to a single bolus dose of FD 6.5 mg/kg. Then, a supplemental dose of 1.63 mg/kg was intravenous injected to maintain the sedation, with a MOAA/S score of ≤4.[26] An additional 25 μg of Fentanyl was administered every 10 minutes based on the patients' pain.[26] The procedure duration ranged from 2 minutes to 110 minutes, with the majority (75%, 92 of 123 patients) lasting 26 minutes or less. Most patients (67.5%, 83 of 123 patients) only required the initial 50 μg of fentanyl for pain management. When it came to sedation, an average of 2.4 times additional doses of FD were frequently given during the procedure, although 2 or fewer additional doses of FD were sufficient to provide adequate sedation. Eighty-two percent of 123 patients were found to have AEs.[26] Paresthesia (62.6%, 77 of 123 patients) and pruritus (27.6%, 34 of 123 patients) were the two most common mild-to-moderate AEs. Three patients experienced hypotension during medication and recovery, which was resolved by using atropine or ephedrine with normal saline. Additionally, some patients experienced hypoxemia, which reminded us it is crucial to clean oral secretion when performing undertaking sedation procedures.

In 2013, FD was first proven to be an effective sedative for the patients undergoing elective coronary artery bypass graft surgery under general anesthesia.[27] In 2016 and in 2021, Liu et al and Wu et al reached the same conclusion in Phase II and phase III RCTs, respectively, using the newly developed water-soluble $Fospropofol_{FD}$ in China.[14,28] They both recommended that $Fospropofol_{FD}$ at a dose of 20 mg/kg can be safely used in induction of general anesthesia, and its sedative efficacy was non-inferior to propofol at a dose of 2 mg/kg.

Continuous Sedation of FD in the Intensive Care Unit (ICU)

FD is an acceptable continuous sedative agent in ICU patients with mechanical ventilation. The first pilot study in 2011 analyzed the safety and efficacy of FD or propofol in 60 patients with mechanical ventilation in the ICU.[29] A continuous infusion rate of 25 μg/kg/min of FD, adjusted every 5 minute for potential agitation, with either an infusion/bolus or an infusion-only regimen, is adequate to maintain sedation for up to 12-hours, achieving a Ramsay Sedation Score of 2 to 5. Additionally, adequate analgesia and antiemetic agents are necessary to reduce treatment-emergent adverse events (TEAEs). Thirteen years later, a large-scale multicenter clinical trial involving 60 patients on mechanical ventilation in the ICU over 24 hours concluded that Fospropofol$_{FD}$ can not only provide feasible, effective and safe sedative effects for short-term procedures but also for long-term sedation in invasive mechanical ventilation for ICU patients.[30]

Main Adverse Reactions of FD

No serious adverse events or deaths were reported during FD administration.[15] The currently reported AEs of FD are mainly transient, self-limited, and most are of mild to moderate in severity. However, most mild or moderate adverse events should not be overlooked. Paraesthesia, characterized by sensations of burning, itching, tingling, stinging, etc., is the most common adverse event, typically lasting 1 to 2 minutes. It usually begins in the genital or perineal area and spreads throughout the trunk.[14,31,32] Although it does not cause physical harm to the patients, it can lead to unpleasant sensations. Fospropofol$_{FD}$ has been found to have a 95% high incidence of paraesthesia or pruritus, with mild, moderate and severe rate of 25.9%, 50.9% and 23.2%, respectively.[14] Similarly, a high frequency of paresthesia and pruritic has been reported with the use of intravenous fosphenytoin (64%; 41 of 64 patients) or dexamethasone (46%; 12 of 26 women), but no clear mechanism has been established.[33,34] Despite the absence of a definitive mechanism, the common feature of fospropofol, dexamethasone, and fosphenytoin is the phosphate group, which is speculated to be the cause of these burning sensations.[14,34,35] Interestingly, experiencing a similar itching sensation when injecting formic acid from insect venom experiencing similar itching sensation, which suggests that the metabolism of formic acid may be a cause of paresthesia and itching.[36] Notably, these sensations can be mitigated by diluting the dose concentration or lowering the injection speed.[32,34]

As is well known, FD can be rapidly hydrolyzed by alkaline phosphatases, releasing propofol as well as phosphate and formaldehyde. Subsequently, formaldehyde is quickly converted into formate. A pilot study found that relatively short-term use of FD in ICU patients does not cause harm to their bodies, as the limited accumulation of formate or phosphorus is comparable to endogenous levels.[29]

Delayed-onset hypotension or hypoxemia is one of the most concerning issues during intravenous use with FD. It commonly occurred at a rate of 46% during bronchoscopy, 3% during colonoscopy, and 19% during minor surgical procedures.[17,23,26] In a phase III, randomized controlled trial, 15.4% of the patients in the 6.5 mg/kg fospropofol group required airway assistance, compared to 12.6% in the 2 mg/kg group.[19] In this experiment, two patients experienced severe hypoxemia with possible causes being their older age and severe cardiopulmonary comorbidity. Liu et al conducted a multicenter trial comparing the hemodynamic changes associated with Fospropofol$_{FD}$ and propofol in patients undergoing elective surgeries.[14] They found that from the 7th to the 11th minute, the systolic blood pressure and mean arterial pressure were lower in the Fospropofol$_{FD}$ group. However, there was no significant difference in the incidence of hypotension between the two groups (5.8% vs 3.3%, $p > 0.05$). Based on critical monitoring, timely intervention such as increasing oxygen flow, repositioning, suctioning, or verbal stimulation would be effective in addressing the hypoxemia.

The most common adverse events following up to 12 hours of sedation treatment with FD in ICU patients were completely different from those associated with short-term use. The most prevalent issues associated with long-term FD use were procedural pain (21.1%) and nausea (13.2%).[29] We speculated that the antiemetic effect of FD is weaker than that of propofol during continuous infusion. This observation highlights the necessity for adequate analgesic and additional antiemetic implementations in ICU sedation protocols.

Concerns have been raised regarding whether FD could also lead to propofol infusion syndrome. Nevertheless, the pilot study focusing on the mean triglyceride levels in ICU patients noted a slight decrease (−6.1 mg/dL) in FD group, whereas there was a modest increase (+31.4 mg/dL) in the propofol group, indicating a lower likelihood of FD-related propofol infusion syndrome.[29]

Other AEs include QT interval prolongation, ST-T abnormality, short RR interval and bradycardia.[14,37,38] These abnormal ECG results are unrelated to significant clinical symptoms or signs.

Future Prospects

To date, FD has been found to be a safe and effective lipid-free propofol formulation, which can be safely used for endoscopic examinations, minor procedures, or continuous sedation in the ICU.[8,29] So far, there still exist several limitations, such as high risk of paresthesia, lack of long-term safety data, delayed onset of hypotension or respiratory depression. There are no published studies on its use in advanced procedures such as endoscopic ultrasound or endoscopic retrograde cholangiopancreatography. These procedures typically require longer time to complete, and the safety and efficacy of FD in such settings might differ. FD has not been used in obstetrics or in lactating female yet,[39] nor can it be used in pediatrics.[40] Future research should prioritize large-scale, international multicenter trials to evaluate FD's suitability for: (1) long-term sedation, (2) major surgical procedures, and (3) obstetric, lactating, or pediatric populations. Additionally, pharmacoeconomic studies comparing FD with current standard sedatives may help clarify its clinical value. The new $Fospropofol_{FD}$ from China has been integrated into clinical practice for adult anesthesia induction. Its higher market price than propofol and midazolam, restricted use by non-anesthesiologists, as well as challenges including the FDA's safety concerns limited its widespread use across the world. It may finally be resolved when ongoing research and increasing clinical practice of FD are undertaking.

In the near future, it may be feasible to train non-anesthesiologists to administer FD combined analgesic agents to achieve the appropriate degree of sedation in outpatient treatments or diagnostic procedures. The confidence in this practice will be based on a comprehensive understanding of the FD pharmacology, advanced monitoring throughout the procedures, qualified emergency techniques, a combined approach to mitigate side effects of the drug, and an optimized personnel structure. As emerging evidence accumulates, FDA may reconsider FD's therapeutic potential, potentially leading to revised indications or reinstatement in certain markets.

Author Contributions

All authors made significant contributions to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; They participated in drafting, revising, or critically reviewing the manuscript; approved the version to be published, agreed on the journal to which the article was submitted, and agreed to be accountable for all aspects of the work.

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