CLINICAL PHARMACOLOGY

Fospropofol: Clinical Pharmacology

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Sedation in clinical practice extends from minimal sedation to general anaesthesia. Most endoscopic procedures require sedation as it reduces the patient's memory of the events, makes them less anxious, more comfortable and improves the outcome of the procedure. In moderate sedation , patient responds purposefully to verbal or tactile stimulation, does not require airway intervention, has adequate spontaneous ventilation and cardiovascular function is maintained.[1] In colonoscopy and flexible bronchoscopy this type of sedation can be utilized

Currently intravenous benzodiazepines with opioids are used to provide moderate sedation (midazolam & fentanyl). But, benzodiazepines (BZDs) have several disadvantages like drug-drug interactions (with opioids- CNS depression), high inter-individual metabolic variability (and long recovery periods. Propofol may be used as an alternative to benzodiazepines because it has rapid onset of action, shorter recovery time, has antiemetic actions and produces better amnesia.[2] However the limitations of propofol when used for endoscopic procedures are, narrow therapeutic index, ability to induce general anaesthesia, cause haemodynamic and respiratory depression, lack of a pharmacological antagonist, contamination is easy and has to be avoided in patients with hyperlipidemia(because of its lipid formulation and contains omega 6 fatty acids).[3] As a result of these disadvantages, it is not used routinely in endoscopic procedures and hence alternative formulations of the drug were investigated, resulting in the development of fospropofol, a water-soluble prodrug of propofol.[1] Both propofol and fospropofol are indicated for use as monitored anaesthesia care (MAC) sedation in adults and fospropofol has been approved for use by US FDA in December 2008.

Chemistry

The chemical nature of propofol is diisopropyl phenol (Figure 1A). When a phosphate group is added to this molecule, it results in formation of water soluble propofol that does not contain lipids, egg products or preservatives, thereby eliminating the allergic, bacterial infections and hyperlipidemic concerns associated with propofol. The two phosphorylated propofol prodrugs so synthesized were named as propofol phosphate and phosphonooxymethyl propofol4 (Figure 1B, 1C).

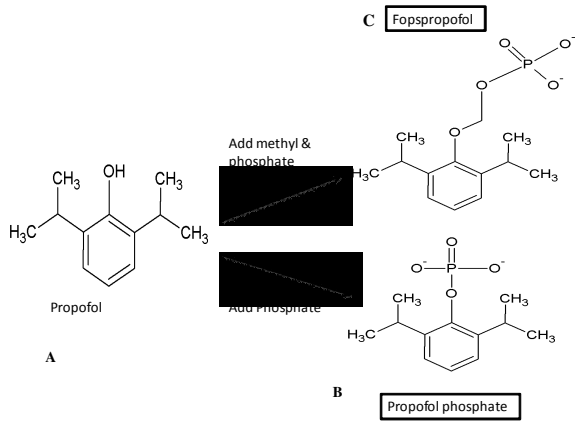

Figure 1

2,6 diisopropyl phenol molecule (propofol) and prodrug variations

A. Propofol molecule (2,6 -diisopropyl phenol).
B. Propofol phosphate.
C. Phosphonooxymethyl propofol (2,6 diisopropylphenoxymethyl phosphate).

Substitution of hydroxyl by charged phosphate group introduces electronegativity which allows fospropofol to dissolve readily in water, hence does not cross lipid membrane.[4] Sodium salt of fospropofol are commonly used.

Mechanism of Action

Fospropofol gets converted to propofol by endothelial alkaline phosphatases[5] Propofol is a agonist at GABAA receptor .It binds to a specific site on the a and ß subunits of the receptor complex, but not to the GABA binding site. Activation of the GABAA receptor results in increased Cl- conductance and hyperpolarization, thus inhibiting the postsynaptic neuron. It also inhibits the excitatory NMDA glutamate receptors thus decreasing Ca++ entry resulting in postsynaptic inhibition. Above mechanisms results in sedation.[6]

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Pharmacological actions

Fospropofol, once metabolized to propofol, is comparable to propofol lipid emulsion, however, the delayed liberation of propofol results in differences in the timing of the pharmacodynamic actions.[7] Only liberated drug and not fospropofol exert a CNS effect. The sedative effects are similar to those of propofol emulsion but not equipotent because inactive fospropofol must be converted to propofol. Hence equivalent doses of fospropofol and propofol emulsion will not have similar effects, infact fospropofol has a delayed onset and decreased clinical effect when compared to propofol for producing moderate sedation required for endoscopy procedures.

Pharmacokinetics

Onset of Action. Fospropofol is administered intravenously. Every 1.86 mg of fospropofol disodium administered results in the molar equivalent of 1 mg of propofol.[7] The time dependant enzymatic conversion releases the active drug slowly and thus creates a sedative profile which differs significantly from that of propofol emulsion.[4] The onset of sedation occurs after 4-8 min.[3] Phase I studies have shown that, 6 and 18 mg/kg intravenous bolus doses have achieved peak plasma concentration [Cmax] at 12 minutes and 8 minutes respectively indicating a dose dependant effect.[7]

Distribution

Fospropofol has a low volume of distribution of 0.33±0.069 L/kg as compared to liberated propofol of 5.8 L/kg. After 6.5mg/kg bolus dose, the mean terminal phase half-life (t1/2) of fospropofol was 48 and 52 minutes in healthy subjects and patients respectively.[3] The mean terminal phase half-life of liberated propofol was 2.06 ± 0.77 hours following 6mg/kg bolus, but it does not reflect the duration of sedation due to rapid redistribution.[3]

Both are 98% protein bound. Propofol readily crosses the placenta and is also found in breast milk but not established for fospropofol.[7]

Metabolism and Elimination

Fospropofol must first be converted to propofol to achieve sedative effects. Alkaline phosphatases present in endothelium and liver are responsible for the enzymatic conversion.[8] (Figure 2). Propofol is metabolized to propofol glucuronide and other metabolites in small quantities. The formaldehyde and phosphate plasma concentrations are comparable to endogenous levels.[7] Metabolism formaldehyde involves rapid oxidation to formic acid catalyzed by glutathione dependent and independent dehydrogenases in the liver and erythrocytes and therefore there is no increase in serum levels.[7] Oxidation to CO_2 is the primary means of eliminating excess formate through tetrahydrofolate pathway.[9] Serum phosphate levels not shown to reach the toxic concentration and gets excreted through kidney.10 Renal elimination of fospropofol is negligible(<0.02%).[7]

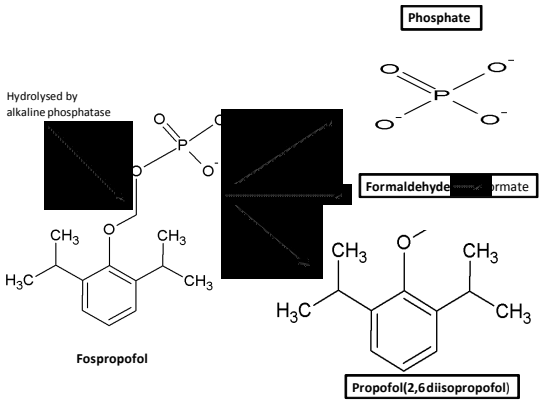

Figure 2

Metabolism of fospropofol into diisopropyl phenol (propofol), free phosphate, formaldehyde to formate

Uses

Fospropofol sodium is an intravenous sedative-hypnotic agent indicated for monitored anesthesia care (MAC) sedation in adult patients. The dosing regimen used in studies were based on the age and comorbid conditions as categorised by American Society of Anaesthesiologist.[7]

- Undergoing diagnostic procedures like bronchoscopy, colonoscopy[1,7]
- Minor surgical procedures(arthroscopy, bunionectomy, osteotomy and fasciotomy in carpal tunnel syndrome)[11]

Adverse reactions

Injection was less painful as compared to propofol emulsion. The most common adverse reactions were transient paresthesias (49-74%) and pruritus in 16-28%, mild to moderate in intensity and self limiting.[3] The other reported adverse effects were cough, nausea and vomiting. Paresthesia (burning, tingling, stinging) and pruritus in perineal region had occurred within 5 minutes of administration of the initial dose of fospropofol.[4,7] The pharmacologic basis of these sensory phenomena is unknown.[7] Paresthesia and pruritus may be because of the phosphate ester present in the drug formulations as seen with other phosphate-containing drugs such as dexamethasone phosphate, hydrocortisone phosphate sodium, prednisolone phosphate, fosphenytoin and estramustine phosphate.[3,4,12,13]

Sedation related adverse effects such as hypoxia, respiratory depression, apnea, loss of purposeful responsiveness and non sedative effects like hypotension were also reported.[7]

Respiratory adverse effects

Respiratory adverse effects are hypoxia, respiratory depression and apnea. Hypoxia was reported in 4% of 455 adult patients but more frequently among patients aged =75 years.[7] Use of supplemental oxygen was shown to reduce the risk of hypoxia. Apnea at standard or modified dosing regimen (>65 years) and higher dose of fospropofol was observed in < 1 % and 3 % respectively.[5] Airway assistance maneuvers(verbal stimulation, tactile stimulation, jaw thrust, chin lift, suction, and manual ventilation) may be required in the management of respiratory depression, hypoxemia, or apnea.

Loss of purposeful responsiveness to Vigorous Tactile or Painful Stimulation : Fospropofol has not been studied for use in general anaesthesia. Release of propofol from fospropofol may cause patients to become unresponsive or minimally responsive to vigorous tactile or painful stimulation indicating patients moving towards deep sedation or general anaesthesia (annexure 1). Their incidence during colonoscopy and bronchoscopy was 4% lasting for 2 to 16 minutes and 16% for 2 to 20 minutes respectively.[7] Hence, fospropofol is used for monitored anesthesia care (MAC) sedation in adults undergoing endoscopic procedures.

Hypotension

Hypotension was observed in 4 % and 6 % of patients with the standard or modified dosing regimen and greater than the recommended dose respectively. Patients with compromised myocardial function, reduced vascular tone or who have reduced intravascular volume may be at an increased risk for hypotension.[7]

Table 1
Advantages of fospropofol over propofol[3,9,14,15,16,17,18]

	Propofol emulsion	Fospropofol
Administration	Mainly infusion	Bolus injection
Formulation	Emulsion	Aqueous
Antimicrobial preservatives	Present	No preservatives
Aqueous solubility	Low	High
Dose	1- 2mg/kg	6.5mg/kg
Onset	40 seconds-1 min, fast onset	4 to 8 minutes delayed onset
Duration of action (single bolus dose)	3-10 min (dose dependant)	5-18 min
Distribution	Three compartments	Two compartments (prodrug), Three compartments for propofol
Half life	Short duration of action, terminal half life 1.5-11hrs	Sustained duration of action, terminal half-life o fospropofol is 48 min and liberated propofol is 2.06 ± 0.77 hours.
Elimination	>1% is excreted in urine	0.02% of the drug is excreted unchanged in urine
Indication	Induction and maintenance of general anaesthesia, short term procedural sedation, sedation of mechanically ventilated patients .	MAC sedation-Diagnostic (bronchoscopy, colonoscopy) or therapeutic procedures (minor surgical procedures)
Solubilizing agents-soybean oil and egg lecithin	Allergic reactions, bacterial growth, hyperlipidemia, pain on injection	No allergic reactions, bacterial growth, hyperlipidemia, but less pain on injection
Paresthesias and prutitus (perineal region)	Absent, but used as anti-pruritic agent	Present
Cardio-respiratory depression	More	Less
Apnea	12%	< 1%
Bradycardia, convulsion	Present	Absent
Contra indications-	Epilepsy	None

Table 2
Clinical studies

Author	Design	No.of pts	Dose	Indications	Outcome
Cohen 19	Randomized, Double-Blind, Dose-Response Study	127	Fospropofol 2,5, 6.5 and 8.0 mg/kg or midazolam 0.02 mg/kg , pretreatment with intravenous fentanyl 50 mcg.	Colonoscopy	Fospropofol 6.5 mg/kg was established as the ideal dose
Silvestri et.al20	Randomized, Double-Blind active control phase III	252	Fospropofol 6.5 mg/kg(n=150) compared dose of 2.0 mg/kg (n=102), pretreatment with intravenous fentanyl 50 mcg.	Bronchoscopy	Sedation success was 88.7% and 27.5% respectively
Cohen LB et. al.21	Double-blind,	314	Fospropofol 2 mg/kg, fospropofol 6.5- mg/kg, or midazolam 0.02 mg/kg, after pretreatment with intravenous fentanyl 50 mcg.	Colonoscopy	Sedation success was higher in the fospropofol 6.5 mg/kg versus 2 mg/kg group (87% vs. 26%; P<0.001) and was 69% in the midazolam group.
Gan TJ et.al11	Phase 3, open-label, single-arm study.	123	Pretreated with fentanyl 50 mcg, fospropofol 6.5 mg/kg.	Sedation in patients undergoing minor surgical procedures	Initial dose of iv fospropofol 6.5 mg/kg with supplemental doses was found to be safe

The above cardio-respiratory-CNS serious adverse effects during clinical trials were commonly seen in patients undergoing bronchoscopy, because 46% patients were ASA P3 or P4 (high risk) category as compared to colonoscopy (3%) and minor surgical procedures (19%).

Specific populations

There is no influence of race, gender, renal and concentrations on the pharmacokinetics of fospropofol or propofol. Fospropofol is not recommended for use in labor, caesarean section deliveries, nursing mothers and patients <18 years as its safety is not yet established.[7] There are no adequate and well-controlled studies in pregnant women (Pregnancy Category B.). No dosing adjustments are required for patients with creatinine clearance > 30ml/min5 but data for creatinine clearance < 30 mL/min is not available.

Overdose

Overdosage of fospropofol can lead to cardiorespiratory depression. Signs of formate toxicity would be similar to those of methanol toxicity and are associated with anion-gap metabolic acidosis because of formic acid, ketonemia, acetonuria, respiratory compromise and blindness. Phosphate could potentially cause hypocalcemia with paresthesia, muscle spasms, and seizures.[7]

Drug Interactions

Fospropofol may produce additive cardio-respiratory effects when administered with sedative-hypnotics and opioids but less as compared to propofol emulsion,[7] which may be due to the time taken for conversion of fospropofol to propofol, a rate-limiting process. The enzymatic conversion limits immediate release and rapid rise in the blood concentration of propofol, which results in delayed action on the CNS and respiratory depression.[4]

Precautions

Fospropofol should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the diagnostic or therapeutic procedure. Sedated patients should be continuously monitored during sedation and through the recovery process for early signs of hypotension, apnea, airway obstruction, and oxygen desaturation.[7] Small doses increased beyond 6mg/kg leads to exponential increase in risk for deep sedation making the 8mg/kg dose a poor choice for moderate sedation.[14] During fospropofol anaesthesia, facilities for maintenance of a patent airway, artificial ventilation, supplemental oxygen, and cardiovascular resuscitation must be immediately available.

Summary of clinical studies

In clinical trials, IV fentanyl was administered 5 min before giving bolus dose of 6.5mg/kg fospropofol with repeated doses of 25% of the original dose every 4 minutes to obtain adequate sedation. Most procedures were completed within half an hour.3 The primary endpoint in the clinical studies was the rate of "sedation success," defined as the proportion of patients who did not respond readily to their name spoken in a normal tone of voice (Sedation Scale score of 4 or less) on 3 consecutive measurements taken every 2 minutes, who completed the procedure without the use of alternative sedative medication and without the use of manual or mechanical ventilation.[7] (annexure 1)

Annexure 1

Modified Observer's Assessment of Alertness/ Sedation Scale

Responsiveness Score	
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

Future prospects

Clinical trials are in progress to assess the use of fospropofol for

- Procedural sedation with regional anesthesia block prior to orthopaedic surgery[22]
- For long-term sedation and intravenous anesthesia.[23]
- To sedate patients on ventilator in intensive care unit[24]
- To anesthetize patients during coronary artery catheterization surgery.[25]
- To provide adequate sedation in patients undergoing percutaneous coronary (PC) procedures.[26]

CONCLUSION

Fospropofol, a phosphate ester ater soluble prodrug of propofol has been found to be safe and effective alternative to propofol and midazolam for use in endoscopic and other procedures. The unique pharmacology of fospropofol provides scope for expansion to introduce new drug options for sedation.

REFERENCES

1. Garnock-Jones KP, Scott LJ. Fospropofol. Drugs 2010; 70 (4): 469-77.
2. Fanti L, Testoni PA. Sedation and analgesia in gastrointestinal endoscopy: What's new? World J Gastroenterol 2010; 16(20): 2451-57
3. Mueller SW, Moore GD, MacLaren R.Fospropofol Disodium for Procedural Sedation: Emerging Evidence

of its Value? Clinical Medicine Insights: Therapeutics 2010; 2: 513-22.
4. Welliver M, Rugari SM. New drug, fospropofol disodium: a propofol prodrug. AANA J. 2009;77(4): 301-8.
5. Fospropofol Disodium Injection NDA 22-244,MGI PHARMA, Inc. Briefing materials for the anaesthetic and life support drugs advisory committee to the division of anaesthesia, analgesia, and rheumatology products (DAARP)/CDER/FDA. May 7,2008 Available from URL:http: www.fda.gov/ ohrms/dockets/ ac/08 /briefing/ 2008-4354b1-02-MGI.pdf. [Accessed 2010 Aug 17].
6. Grasshoff C, Gilless T. Effects of propofol on N -methyl-D-aspartate receptor-mediated calcium increase in cultured rat cerebrocortical neurons. Eur J Anaesthesiol 2005; 22(6):467-70.
7. Eisai I. Lusedra_ (fospropofol disodium) US prescribing information [online]. Available from URL: http:// www.eisai.com/package_inserts/Lusedra%20PI.pdf [Accessed 2010 Aug 17]
8. Schywalsky M, Ihmsen H, Tzabazis A, Fechner J, Burak E, Vornov J, et al. Pharmacokinetics and pharmacodynamics of the new propofol prodrug GPI 15715 in rats. Eur J Anaesthesiol 2003;20(3):182-90.
9. Dharshwar SS, Stella VJ. Your prodrug releases formaldehyde: should you be concerned? No! J Pharm Sci 2008;97(10):4184-93.
10. Fechner J, Ihmsen H, Hatterschild D, Jeleazcov C, Schiessl C, Vornov JJ, et al. Comparative pharmacokinetics and pharmacodynamics of the new propofol prodrug GPI 15715 and propofol emulsion. Anesthesiology 2004; 101(3): 626-39.
11. Gan TJ, Berry BD, Ekman EF, Muckerman RC, Shore N, Hardi R. Safety evaluation of fospropofol for sedation during minor surgical procedures. J Clin Anesth 2010; 22(4): 260-7.
12. Neff SPW, Stapelberg GF, Warmington A. Excruciating perineal pain after intravenous dexamethasone. Anaesth Intensive Care 2002; 30(3): 370-71.
13. Hudes G, Haas N, Yeslow G, Gillon T , Gunnarsson PO, Ellmanet M. Phase I clinical and pharmacologic trial of intravenous estramustine phosphate. J Clin Oncol 2002; 20(4): 1115-1127.
14. Levitzky BE, Vargo JJ. Fospropofol disodium injection for the sedation of patients undergoing colonoscopy. Ther Clin Risk Manag 2008; 4 (4): 733-8.
15. Gibiansky E, Struys MMRF, Gibiansky L, Vanluchene AL, Vornov J, Mortier EP, et al. AQUAVAN injection, a water-soluble prodrug of propofol, as a bolus injection: a phase I dose-escalation comparison with DIPRIVAN, part 1: pharmacokinetics [published correction appears in Anesthesiology. 2008; 109(5): 940]. Anesthesiology 2005; 103(4): 718-29.
16. Sweetman SC. Martindale: The Complete Drug Reference. 36th ed, Pharmaceutical Press London; 2009: p1791-93.
17. Gan TJ. Pharmacokinetic and pharmacodynamic characteristics of medications used for moderate sedation. Clin Pharmacokinet 2006; 45 (9): 855-69.
18. Harris HA, Lubarsky DA, Candiotti KA. Monitored anesthesia care. Ther Clin Risk Manag 2009; 5: 949-59.
19. Cohen LB. Clinical trial: a dose-response study of fospropofol disodium for moderate sedation during colonoscopy. Aliment Pharmacol Ther 2008; 27 (7): 597-608.
20. Silvestri GA, Vincent BD, Wahidi MM, Robinette E, Hansbrough JR, Downie GH, et al. A phase 3, randomized, double-blind study to assess the efficacy and safety of fospropofol disodium injection for moderate sedation in patients undergoing flexible bronchoscopy. Chest 2009;135 (1): 41-7.
21. Cohen LB, Cattau E, Goetsch A, Shah A, Weber JR, Rex DK, et.al. A randomized, double-blind, phase 3 study of fospropofol disodium for sedation during colonoscopy. J Clin Gastroenterol 2010; 44(5): 345-53.
22. Lusedra (Fospropofol Disodium) for minimal to moderate sedation for regional anesthesia block prior to orthopedic surgery [ClinicalTrials.gov identifier NCT01195103]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL:http: www//clinicaltrials.gov/show/ NCT01195103 [Accessed 2010 Aug 17].
23. Fechner J, Ihmsen H, Jeleazcov C, Schüttler J. Fospropofol disodium, a water-soluble prodrug of the intravenous anesthetic propofol (2,6-diisopropylphenol). Expert Opin Investig Drugs 2009 18(10) :1565-71.
24. GPI 15715 For sedation in the Intensive Care Unit (ICU) setting [ClinicalTrials.gov identifier NCT00125398]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL:http:// clinicaltrials.gov / show/ NCT00125398 [Accessed 2010 Aug 17]
25. Comparison of AQUAVAN injection to DISOPRIVAN injectable emulsion for anesthesia during coronary artery surgery [ClinicalTrials.gov identifier NCT00209521]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL:http:// clinicaltrials.gov/show/ NCT00209521 [Accessed 2010 Aug 17]
26. Study to assess safety and efficacy of AQUAVAN injection for sedation during cardiac catheterization [ClinicalTrials.gov identifier NCT00209547]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL:http:// clinicaltrials.gov /show/ NCT00209547 [Accessed 2010 Aug 17]