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AN UPDATE ON CLINICAL CONCEPTS OF PROPOFOL

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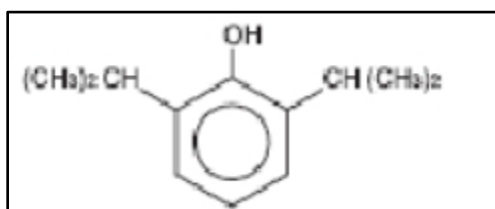
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ABSTRACT: Propofol is an intravenous anaesthetic agent. Used as an induction agent it has replaced sodium thiopentone to a large extent. Apart from induction Propofol is used for maintenance of anaesthesia, intravenous sedation and as infusion in mechanically ventilated patients. Its faster and clear recovery has made it a drug of choice in day care cases. Propofol is cardiorespiratory depressant drug. It also lowers intracranial pressure and the laryngeal-pharyngeal reflexes. The properties of Propofol has made it a widely accepted anaesthetic agent. Wide application and easy availability has put the person using it at the risk of drug abuse. This article has focused on the clinical pharmacology, use, abuse and the future prospects of Propofol.

KEYWORDS: Propofol, milk of amnesia, clinical pharmacology, drug abuse.

INTRODUCTION: 2, 6-diisopropylphenol commonly known as propofol is a short-acting, intravenously administered hypnotic agent. It has largely replaced sodium thiopentone for induction of anesthesia because recovery from propofol is more rapid and "clear" than thiopentone. Originally it was developed in the UK. Initial trials used a form solubilised in cremophor EL. Anaphylactic reactions reported in this trial led to the reformulation of this drug as an emulsion of a Soya oil/propofol mixture. The tiny droplets of the size of approximately 150 nm scatters light. This results in a opaque-white fluid which resembles milk in appearance giving it a nickname-milk of amnesia.^[1] Its molecular formula is C₁₂H₁₈O and molecular weight is 178.27g/mol.



A water-soluble prodrug, fospropofol is also available. Enzyme alkaline phosphatase breaks it to form Propofol in the body.^[2] The US Food and Drug Administration approved the product in 2008.

Propofol-Injectable Emulsion is a sterile, non-pyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. It is slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion.

The pKa is 11 and the octanol/water partition coefficient for propofol is 6761:1 at a pH of 6 to 8.5. It is isotonic and has a pH of 7 to 8.5.

Each mL of propofol- Injectable Emulsion contains;

Propofol 10 mg/ mL

Soyabean oil, 100 mg/mL

Glycerol, 22.5 mg/mL

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Egg lecithin, 12 mg/mL
Benzyl alcohol, 1 mg/mL
Sodium hydroxide; to adjust pH

CLINICAL PHARMACOLOGY: Propofol is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of propofol induces hypnosis, with minimal excitation, usually within one arm-brain circulation time. As with other rapidly acting intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately 1 to 3 minutes, accounting for the rate of induction of anesthesia.

Mechanism of Action: It has several mechanisms of action.^[3] It acts through potentiation of GABA-A receptor activity, thereby slowing the channel closing time.^[4,5 and 6] Also it acts as a sodium channel blocker. To add further endocannabinoid system may contribute significantly to propofol's anesthetic action and to its unique properties.^[7] When analysed electroencephalographically propofol reduces the capacity of the brain's information integration capacity at gamma wave band frequencies^[8] which may contribute to its effect upon the loss of consciousness.

CNS Effects: With adequate dose, propofol produces rapid loss of consciousness in 15-30 seconds. Onset of hypnosis with dose 2-2.5 mg/kg is rapid. Therapeutic plasma propofol concentration for sedation is 1-1.5 microgram/ml, the dose for total intravenous anesthesia with opioids is 2-4 microgram/ml and that without opioids is 6-9 microgram/ml. BIS monitoring can be used to monitor depth of anaesthesia^[9] and to assess the level of hypnosis. Though there is no significant difference in the induction dose of propofol when assessed either clinically (loss of verbal response) or by BIS monitoring.

Propofol lowers intracranial pressure (ICP) especially in patients with higher baseline ICP. Since propofol decreases mean arterial pressure (MAP), cerebral perfusion pressure (CPP) is also decreased. Cerebral auto-regulation is maintained during propofol administration. Cerebro-vascular responsiveness to CO₂ and increased BP is preserved after propofol administration. Propofol anesthesia is associated with varying changes in electrical activity recorded on EEG. In animal models it was shown to have pre-convulsive action but other studies showed that propofol possesses anticonvulsant properties.^[10] Propofol has neuroprotective action. It has cellular protective effect under oxidative stress.^[11]

CVS Effects: Propofol is cardiovascular depressant. Induction of anesthesia with propofol decreases arterial BP by 25%. This fall in BP is associated with decreases in cardiac output by 15%; stroke volume by 20% and systemic vascular resistance by 15-25%.^[12] Myocardial blood flow decreases by 26%.^[13] Hypotension is seen commonly with old age, poor physical status, concomitant use of opioids and benzodiazepines. These CVS effects are due to reduction of sympathetic tone manifesting as increased parasympathetic responses. Peripheral vasodilatation produced by Propofol leads to reduction in ventricular preload which in turn causes reduction in sympathetic activity thereby reducing myocardial activity. Propofol either resists or inhibits baroreceptor reflex thus reducing tachycardia in response to hypotension.

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Propofol effectively blunts the hypertensive response to laryngoscopy and intubations, LMA insertion or bronchoscopy. The effect appears to be more marked with concomitant use of opioids. An infusion of propofol results in significant reduction in myocardial blood flow and myocardial oxygen consumption which suggests that global myocardial oxygen supply/demand ratio is preserved.

RS Effects: Propofol is respiratory depressant. It causes reduction in tidal volume, respiratory rate and therefore in minute volume also. Induction dosages of propofol can cause apnea in 25-30% of patients.^[12] The ventilatory response to CO₂ is also decreased during maintenance infusion of propofol along with decreased ventilatory response to hypoxia.

Also it induces broncho-dilatation in COPD patients.

Other Effects: Propofol does not potentiate neuromuscular blockade produced by non-polarizing and depolarizing neuromuscular blocking agents.^[14] Propofol has been shown to decrease the intraocular pressure (31-50%). Effect occurs immediately after induction and sustained during intubations. Propofol also possesses significant anti-emetic property.^[15]

Propofol has significant chronobiotic effect (i.e phase resetting of circadian clock) as it causes disturbance in melatonin secretion which is the marker of circadian rhythm.⁽¹⁶⁾ It is secreted from suprachiasmatic nuclei. Propofol has protective role in free radical mediated cell injury. Free radicals may play an important role in the pathogenesis of myocardium and lung injury. Antioxidants within cell membranes protect the phospholipids from free radical mediated lipid peroxidation. The best characterized of these is radical mediated lipid peroxidation. Propofol contains a phenol group that donates hydrogen to free radicals, thus terminating lipid peroxidation.⁽¹⁷⁾

DOSAGE AND ADMINISTRATION:

Induction of Anesthesia:

- Adult (less than 55 yrs)—2-2.5 mg/kg
- ASA grade I & II---40 mg every 10 seconds until induction
- Elderly, debilitated, hypovolumic or ASA grade III and above—dose has to be reduced and given slowly.
- Children (Above 3 yrs of age)—2.5-3.2 mg/kg
- Propofol is not recommended before 3 yrs of age.

Maintenance Infusion:

- In adult (55 yrs)—6-12 mg/kg/hr.
- Elderly, ASA grade III and above -dose has to be reduced.
- Children (above 3 yrs of age)—7.5-18 mg/kg/hr.

Recovery: Recovery after propofol induction and maintenance is rapid and faster than any other IV anesthetic agent/ sedative.

Onset of Action: Propofol effectively and rapidly induces anesthesia. Induction is achieved in the mean time of 30.8 seconds after administration of induction dose. Time of induction is increased when same dose is given over a long period. But required induction dose is decreased after slow infusion.

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Metabolism: Propofol is highly (90%) protein-bound in vivo and is extensively metabolized by conjugation to glucuronides and sulfates in the liver and thereby producing water soluble compounds to be secreted finally through kidneys. Its rate of clearance exceeds hepatic blood flow, suggesting an extra hepatic site of elimination as well.

Pharmacokinetics: Both two and three compartmental models have been described. After a single bolus dose two distribution phases exist. Phase one is the phase of initial distribution with a half-life 3-9 minutes. The blood concentration of propofol falls rapidly due to redistribution of drug into the lipophilic compartment like brain and other fat tissues. Phase two is the phase of low distribution phase with half-life 30-70 minutes. Variety of factors like age, gender, weight, preexisting diseases and concomitant medications may alter the pharmacokinetics of propofol.

Female: Shows high volume of distribution and higher clearance rate.

Elderly: Decreased clearance rate and small central compartment volume.

Children: Show larger central compartment volume and rapid clearance.

Hepatic diseases related to larger steady state and central compartment volume with prolonged elimination half-life whereas in renal diseases the propofol kinetics are unaltered. The elimination half-life of propofol has been estimated to be between 2 and 24 hours. Volume of distribution; the duration of clinical effect of propofol is much shorter, because it is rapidly distributed into peripheral tissues. As required decrease in concentration for awakening anesthesia or sedation with propofol is less than 50%, when used for IV sedation, propofol typically wears off in minutes with rapid recovery. Propofol is versatile; the drug can be given for short or prolonged sedation as well as for general anesthesia. Its use is not associated with nausea as is often seen with opioid medications. These characteristics of rapid onset and recovery along with its amnestic effects^[15] have led to its widespread use for sedation and anesthesia. Propofol crosses placental barrier and is secreted in breast milk also.

Indications and Usage: Initiation and maintenance of Monitored Anesthesia Care in adults only
Combined sedation and regional anesthesia in adults only
Induction of General Anesthesia in patient ≥ 3 years of age
Maintenance of General Anesthesia in patient \geq years of age
Intensive Care Unit (ICU) sedation of intubated, mechanically ventilated patients in adults only
Propofol can be used for LMA without concomitant use of muscle relaxants.

Contraindications: Propofol injectable emulsion is contraindicated in patients with a known hypersensitivity to propofol or any of its components. Propofol injectable emulsion is contraindicated in patients with allergies to eggs, egg products, soybeans or soya products. Not recommended in pregnancy, lactation or in children below 3 years of age.

Interactions: The induction dose requirements of propofol may be reduced with IM or IV premedication, e.g., morphine, meperidine, and fentanyl, etc. and combinations of opioids and sedatives e.g., benzodiazepines, barbiturates, chloral hydrate, droperidol, etc. These agents may increase the anesthetic or sedative effects of propofol and may result in more pronounced decreases in hemodynamic parameters.

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During maintenance of anesthesia or sedation the rate of propofol administration may be reduced with supplemental analgesic agents e.g., nitrous oxide or opioids Propofol does not cause a clinically significant change in of action of the commonly used neuromuscular blocking agents e.g., succinylcholine and non-depolarizing muscle relaxants.

Adverse Reactions: Pain on injection; one of propofol's most frequent side effects is pain on injection, especially in smaller veins. This pain can be mitigated by pretreatment with lidocaine.^[18] Pretreatment with lidocaine along with venous occlusion for 60 sec significantly reduce propofol induced pain.^[19] Patients tend to show great variability in their response to propofol, at times showing profound sedation with small doses. Cardiovascular side effects; hypotension (mainly through vasodilatation), bradycardia, decreased Cardiac Output and transient apnea A more serious but rare side effect is dystonia and mild myoclonic. Propofol infusion syndrome; another recently described rare, but serious, side effect. This potentially lethal metabolic derangement has been reported in critically-ill patients after a prolonged infusion of high-dose propofol in combination with catecholamines and/or corticosteroids.^[20] Apnea and respiratory acidosis during weaning.

Drug abuse and Dependence: Abuse of propofol as a recreational drug has been reported, usually among medical staff such as anesthetists who have access to the drug. The steep dose response curve of the drug makes such abuse very dangerous without proper monitoring, and several deaths have been recorded.^{[21],[22]} The superstar Michael Jackson also succumbed to Propofol. Just three days prior to this sad demise, the American Association of Nurse Anesthetics called for the scheduling of this deadly milk as controlled substance.^[23] In 2010 Drug Enforcement Administration (DEA) proposed rules to include this in schedule drug list.^[24]

Elements Behavioral Health posted an article "Propofol Addiction" on January 28, 2013 which mentions that 33% death rate has been reported in professionals abusing Propofol.^[23]

E-mail surveys were sent to the 126 academic anaesthesiology training programs in the United States. The observed incidence of Propofol abuse was 10 per 10,000 anaesthesia providers per decade, it was seen that there was fivefold increase from previous surveys.^[25]

Drug over Dosage: There is no antidote of Propofol. If over dosage occurs, propofol administration should be discontinued immediately. Over dosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids, and administering pressor agents and/or anticholinergic agents.

Future Insight: Propofol when given at the rate of 6mg/kg/hr may emerge as first choice sedative in patients of acute liver failure presenting with raised intracranial pressure because it decreases CBF through metabolic suppression.^[26]

Further evaluation is also needed to understand mechanism and risk factors for Propofol related infusion syndrome.^[27]

Use of Propofol infusion in paediatrics patients has been a concern since long. Propofol 6% when used in <4mg/kg/hr dose for infusion can change the future of paediatric sedation practice.^[28]

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BIBLIOGRAPHY:

1. Euliano TY, Gravenstein JS. *Abrief pharmacology related to anesthesia. Essential anesthesia: from science to practice*, Cambridge, UK: Cambridge University Press. page 173.
2. Miner JR, Burton JH. *Clinical practice advisory. Emergency department procedural sedation with propofol*. *Ann Emerg Med*. 2007; 50 (2):182-7.
3. Trapani G, Altomare C, Liso G, Sanna E, Biggio G. *Propofol in anesthesia. Mechanism of action, structure-activity relationships, and drug delivery*. *Curr Med Chem*. 2000; 7 (2): 249-71.
4. Trapani G, Latrofa A, Franco M, Altomare C, Sanna E, Usala M, Biggio G, Liso G. *Propofol analogues. Synthesis, relationships between structure and affinity at GABAA receptor in rat brain, and differential electrophysiological profile at recombinant human GABAA receptors*. *J Med Chem*. 1998; 41 (11): 1846-54.
5. Krasowski MD, Jenkins A, Flood P, Kung AY, Hopfinger AJ, Harrison NL. *General anesthetic potencies of a series of propofol analogs correlate with potency for potentiation of gamma-aminobutyric acid (GABA) current at the GABA (A) receptor but not with lipid solubility*. *J Pharmacol Exp Ther*. 2001; 297 (1): 338-51.
6. Krasowski MD, Hong X, Hopfinger AJ, Harrison NL. *4D-QSAR analysis of a set of propofol analogues: mapping binding sites for an anesthetic phenol on the GABA (A) receptor*. *J Med Chem*. 2002; 45 (15): 3210-21.
7. Fowler CJ. *Possible involvement of the endocannabinoid system in the actions of three clinically used drugs*. *Trends Pharmacol Sci*. 2004; 25 (2): 59-61.
8. Haeseler G, Leuwer M. *High-affinity block of voltage-operated rat IIA neuronal sodium channels by 2, 6 di-tert-butylphenol, a propofol analogue*. *Eur J Anaesthesiol*. 2003; 20 (3): 220-4.
9. Arya S, Asthana V, Sharma JP. *Clinical vs. bispectral index-guided propofol induction of anesthesia: A comparative study*. *Saudi J Anaesth* 2013; 7: 75-9.
10. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. *The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties*. *CNS Neurosci Ther*. 2008; 14 (2): 95-106.
11. Xing-jun WU, Yong-jun ZHENG, Yong-yao CUI, Liang ZHU2, Yang LU, Hong-zhuan CHEN. *Propofol attenuates oxidative stress-induced PC12 cell injury via p38 MAP kinase dependent pathway*. *Acta Pharmacol Sin* 2007 Aug; 28 (8): 1123-1128.
12. J. Gerald Reves; Peter S. A. Glass; David A. Lubarsky: *Nonbarbiturate Intravenous Anesthetics*. churchill livingstone. Section 2; Part B; Chapter 9.
13. H. Stephan, H. Sonntac, HD. Schenk, D. Kettler, HJ. Khambatta. *Effects of Propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease*. *Br. J. Anaesthesia*.1986; 58 (9): 969.
14. Haeseler G, Karst M, Foadi N, Gudehus S, Roeder A, Hecker H, Dengler R, Leuwer M. *High-affinity blockade of voltage-operated skeletal muscle and neuronal sodium channels by halogenated propofol analogues*. *Br J Pharmacol*. 2008; 155 (2): 265-75.
15. Arslan M Demir ME. *Prevention of post-operative nausea and vomiting with a small dose of Propofol combined with Dexamethasone 4mg or Dexamethasone 8mg in patient undergoing middle ear surgery*. *Bratisl Lek Listy* 2011; 112 (6): 332-336.

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16. Etienne Challet, Sylviane Gourmelen, Paul Pevet, Philippe Oberling and Laure Pain: Reciprocal Relationships between General (Propofol) Anesthesia and Circadian Time in Rats.2007; 32: 728-735.
17. M. Aydin Ketani¹, Berna Ersöz Kanay, Sennur Ketani, Özkan Ünver and Mehmet Kiliç. Dose-dependent effects of propofol on expression ICAM-1 in rabbit aorta endothelial cells. African Journal of Biotechnology.2009 Vol. 8 (23), pp. 6688-6693.
18. Griner RL 2nd. AANA journal course: update for nurse anesthetists--the laryngeal mask airway: attributes and inadequacies. AANA J. 1996; 64 (5): 485-96.
19. Sedat Kaya MD, Selim Turhanoglu, Nihal Basak MD. Lidocaine for prevention of propofol injection induced pain: A prospective, randomized controlled study of effect of venous occlusion with tourniquet in adult. Current Therapeutic research.2008; 69 (1): 29-35.
20. Chari P, Ghai B. Comparison of butorphanol and thiopentone vs fentanyl and thiopentone for laryngeal mask airway insertion. J Clin Anesth. 2006; 18 (1): 8-11.
21. Kol IO, Egilmez H, Kaygusuz K, Gursoy S, Mimaroglu C. Open-label, prospective, randomized comparison of propofol and sevoflurane for laryngeal mask anesthesia for magnetic resonance imaging in pediatric patients. Clin Ther. 2008; 30 (1):175-81.
22. Smith CE, Lever JS, Sawkar S, Pinchak AC, Hagen JF. Sevoflurane-N₂O versus propofol/isoflurane-N₂O during elective surgery using the laryngeal mask airway in adults. J Clin Anesth. 2000; 12 (5): 392-6.
23. Elements Behavioral Health propofol Addiction.; 2013 Jan. Available from: <http://www.drugaddictiontreatment.com/types-of-addiction/priscription-drug-addiction/Propofol-addiction>.
24. M. Adams. DEA proposes placing Propofol into schedule IV of Controlled Substances Act. Gasroenterology and Endoscopy News. 2010; 61-11.
25. Wischmeyer PE, Johnson BR, Wilson JE, Dingmann C, Bachman HM, Roller E, ran ZV, Henthorn TK. A survey of propofol abuse in academic anaesthesia programs. Anesth Analg. 2007 Oct; 105 (4): 1066-71.
26. J. Rajiv. Acute liver failure: current management and future prospects; journal of Hepatology. 2005; 42 s115-12.
27. Roberts R.J etal. Incidence of Propofol related infusion syndrome in critically ill adults: a prospective, multicenter study; 2009critical care vol. 13 (5): R169. [PMC free article] [PubMed].
28. Prins S .A etal. Propofol 6% as sedative in children under 2 years of age following major craniofacial surgery. British Journal of Anaesthesia 94 (5): 630-5 (2005).

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