Therapeutic Reviews

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Therapeutic Reviews aim to provide essential independent information for health professionals about drugs used in palliative and hospice care. The content is also available on www.palliativedrugs.com and will feature in future editions of the Hospice and Palliative Care Formulary USA and its British and Canadian counterparts. The series editors welcome feedback on the articles (hq@palliativedrugs.com).

Propofol *AHFS 28:04*

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Class: General anesthetic.

Indications: Induction and maintenance of general anesthesia, monitored anesthesia care (MAC) sedation or continuous conscious sedation (surgical or diagnostic procedures, intubated and mechanically ventilated patients on intensive care units), †refractory agitated delirium or intolerable distress in the imminently dying, †intractable nausea and vomiting.[1]

Contraindications: MAC or continuous conscious sedation in children ≤16 years (≤18 years in Canada). When used for sedation in children in intensive care, the death rate increased 2–3 times.[2] However, propofol is used at some centers to enable radiation therapy in children.[3]

Allergy to eggs, soya or peanuts (the available products contain purified egg lecithin as an emulsifying agent and soya bean oil).[4]

Pharmacology

Propofol is an ultra fast-acting IV anesthetic agent. It is rapidly metabolized, mainly in the liver, to inactive compounds which are excreted in the urine. The incidence of untoward hemodynamic changes is low. Propofol reduces cerebral blood flow, cerebral metabolism and, less consistently, intracranial pressure.[5] The reduction in intracranial pressure is greater if the baseline pressure is raised. On discontinuation patients rapidly regain consciousness (10–30 min) without residual drowsiness.

In palliative care, propofol is occasionally used, when other approaches have failed, to relieve agitated delirium or intolerable distress in the imminently dying.[6] Careful titration generally permits 'conscious sedation,' i.e., patients open their eyes on verbal command, possess intact autonomic reflexes, and tolerate mild noxious stimuli.[1] Such use also has been described in children at the end of life.[7]

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Propofol also has an anti-emetic effect resulting in less postoperative vomiting compared with other anesthetic agents.[8–10] Specific postoperative anti-emetic regimens have been designed.[11–13] Chemotherapy-related nausea and vomiting is also helped by adjunctive propofol.[14] In patients receiving non-platinum regimens who were refractory to a combination of dexamethasone and a $5HT_3$-receptor antagonist, propofol was of benefit in ≥80%.[15] In palliative care, propofol also has been used to relieve refractory nausea and vomiting in dying patients.[1] Most of the patients probably had bowel obstruction, and it was more effective in relieving nausea than vomiting.

Animal studies suggest that the mechanism of action of propofol as an anti-emetic is by inhibition of serotonin release by enhancing GABA activity, possibly by direct GABA-mediated action on $5HT_3$-receptors in the area postrema/chemoreceptor trigger zone.[16]

Propofol also has antipruritic, anxiolytic, bronchodilatory, muscle relaxant and anti-epileptic properties. A possible role in refractory status epilepticus requires further clarification.[17,18] Transient excitatory phenomena are seen occasionally (e.g., myoclonus, opisthotonus, tonic-clonic activity), during induction or recovery when blood levels are low, and presumably at a time when inhibitory centers but not excitatory centers have been depressed.[5,19,20]

Onset of action: 30 sec.

Time to peak effect: 5 min.

Plasma half-life: 2–4 min initial distribution phase; 30–60 min slow distribution and initial elimination phase; 3–12 h terminal elimination phase. The terminal elimination half-life may increase with prolonged use.

Duration of action: 3–10 min after single IV bolus.[21,22]

Cautions

Risk of cardiorespiratory depression. Involuntary movements and seizures have been reported, particularly in epileptics, during induction or recovery.[19,23] With prolonged use in acute intensive care, metabolic acidosis, hyperlipidemia and hepatomegaly have been reported.[2] Although in this setting it is good practice to check plasma lipid levels in patients receiving propofol for ≥3 days, it is unnecessary in patients whose expected prognosis is only days.

Diprivan® contains disodium edetate (EDTA), a chelating agent that can reduce circulating concentrations and increase urinary losses of trace metals, e.g., zinc. Supplements should be considered for patients who are not imminently dying and who are likely to receive prolonged propofol treatment, particularly those at particular risk of deficiency, e.g., from fluid loss, catabolic states or infection.

Undesirable Effects

For full list, see manufacturer's Package Insert.

Very common (>10%): local pain at the injection site.

Common (<10%, >1%): headache, hypotension, bradycardia, transient apnea.

Uncommon (<1%, >0.1%): thrombosis, phlebitis.

Rare: misuse resulting in addiction and/or death. Concerns over a growing incidence among medical staff with access to propofol, e.g., anesthesiologists, has prompted moves to designate propofol a controlled substance.[24,25]

Dose and Use

Propofol is an emulsion of oil-in-water. This gives it a white appearance and makes it a potential growth medium. Diprivan® contains EDTA, a chelating agent that binds to divalent metal ions and reduces their availability for bacterial growth, replication and cell wall integrity. However, the concentration (0.005%) is sufficient only to *retard* microbial growth for up to 12 h in the event of accidental contamination.[26] The generic propofol product made by TEVA in the USA contains sodium metabisulfite as a preservative, whereas the generic products available in the UK and Canada contain no preservatives. Thus, with all propofol products, strict aseptic technique must be employed to prevent microbial contamination *and the container and IV line renewed every 6–12 h, in accordance with the individual manufacturer's instructions.* Propofol should be infused through a microbiological filter only if considered clinically necessary. The filter should have a pore size of ≥5 micrometers, otherwise it can restrict the flow of the emulsion or cause the emulsion to break down.

The use of propofol in palliative care should be restricted to units with access to the necessary expertise and equipment. It is generally given by CIVI as an undiluted 1% (10 mg/mL) solution through a computer-controlled volumetric infusion pump or IV syringe pump. Pain at the injection site can be minimized by using a large vein in the forearm and by co-administering the first dose with lidocaine:

- give 1 mL of lidocaine 1% IV before starting propofol *or*
- mix lidocaine with propofol immediately before starting the infusion; do not exceed a concentration of 20 mg lidocaine/200 mg propofol because this can cause the emulsion to separate.

If necessary, the injection can be diluted with 5% dextrose (glucose) immediately before administration. In some countries, dilution is advised if propofol is given through a less sensitive infusion control device, e.g., a drop-counter or in-line burette, because the weaker concentration reduces the risk of severe overdose if the infusion runs fast. The concentration of propofol in the diluted solution must not be less than 2 mg/mL as this can disrupt the emulsion. Diluted propofol should be used within 6 h.

Compatibility: Propofol injection 1% is compatible with alfentanil and lidocaine, and can be diluted with 5% dextrose (glucose) before use (see manufacturer's Package Insert for details). Propofol can be added through a Y-connector to a running infusion of 5% dextrose, 5% dextrose + 0.45% saline, 5% dextrose + 0.2% saline, lactated Ringer's solution or lactated Ringer's solution + 5% dextrose; the Y-connector should be placed as close to the injection site as possible.

Refractory agitated delirium or intolerable distress in the imminently dying

Consider propofol only if standard treatments have failed, i.e., a sedative antipsychotic + a benzodiazepine (Fig. 1).[1,27–29] However, generally, phenobarbital should be used in preference to propofol because it is less complicated for clinical staff to titrate and monitor.

Aim to titrate the dose until *conscious sedation* is achieved, i.e., patients open their eyes on verbal command but are not distressed by nursing interventions (e.g., mouth care, turning):

- remain with the patient throughout the initial titration process to ensure an effective and safe dose is found
- generally start with propofol 1 mg/kg/h IV
- if necessary, increase by 0.5 mg/kg/h every 5–10 min until a satisfactory level of sedation is achieved; smaller dose steps can be used to fine-tune the treatment; most patients respond well to 1–2 mg/kg/h
- to increase the level of sedation quickly, a bolus dose can be given by increasing the rate to 1 mg/kg/*min* for 2–5 min
- monitor the patient closely during the first hour of treatment with respect to symptom relief and/or level of sedation, and then after 2, 6, and 12 h
- continue to monitor the effect of propofol and the level of sedation at least twice daily
- if the patient is too sedated (i.e., does not respond to a verbal command to open their eyes, shows no response to noxious stimuli) and/or there is evidence of drug-induced respiratory depression, the infusion should be turned off for 2–3 min and restarted at a lower rate; occasionally this leads to

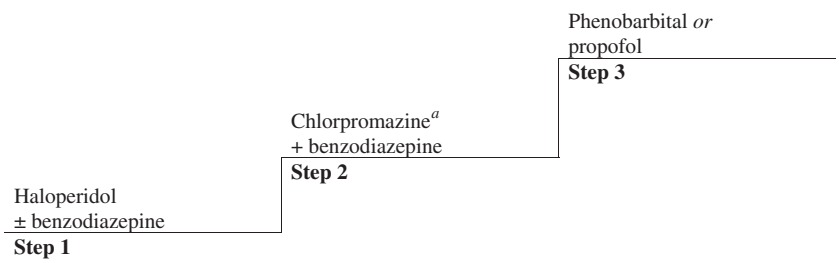

Fig. 1. Drug treatment used in some centers for irreversible agitated delirium or intolerable distress in the imminently dying. [a]In countries where it is available, levomepromazine (methotrimeprazine) is used instead of chlorpromazine.

a progressive reduction in dose because the patient has become unconscious as a result of their disease
- tolerance can develop, necessitating a dose increase, but generally not within one week
- long-term use of doses >4 mg/kg/h is not recommended because of increasing risk of undesirable effects
- if the patient does not respond to propofol 4 mg/kg/h alone, supplement with midazolam by CSCI
- it is important to replenish the infusion quickly when a container empties, because the effect of an infusion of propofol wears off after 10–30 min
- *because propofol has no analgesic properties, analgesics should be continued*

Intractable nausea and vomiting

The use of propofol as an anti-emetic should be considered only if all other treatments have failed.[1] Dose titration is generally slower for intractable nausea and vomiting than for terminal agitation:
- remain with the patient for at least 10 min following any dose change to ensure that excessive sedation does not occur
- generally start with propofol 0.5 mg/kg/h
- if necessary, increase by 0.25–0.5 mg/kg/h every 30–60 min until a satisfactory response is obtained; smaller dose steps can be used to fine-tune the treatment
- most patients respond well to 0.5–1 mg/kg/h; doses >1 mg/kg/h may result in sedation
- monitor the patient closely during the first hour of treatment with respect to symptom relief and/or level of sedation and then after 2, 6, and 12 h
- continue to monitor the effect of propofol and level of sedation at least twice daily
- if the patient is too sedated, the infusion should be turned off for 2–3 min and then restarted at a lower rate
- if the patient responds well, reduce the infusion rate on a trial basis after 18–24 h
- tolerance can develop, necessitating a dose increase, but generally not within one week
- it is important to replenish the infusion quickly when a container empties, because the effect of an infusion of propofol wears off after 10–30 min
- when used solely for its anti-emetic effect in the last days of life, some centers reduce the dose of, or even discontinue, propofol when the patient becomes unconscious

Supply

Propofol (generic)

Injection (emulsion) 10 mg/mL (1%), 20 mL amp = $5; 50 mL vial = $10; 100 mL vial = $20.

Diprivan® (AstraZeneca)

Injection (emulsion) 10 mg/mL (1%), 20 mL vial = $8, 50 mL vial = $18, 100 mL vial = $36.

The US manufacturer's Product Information is available from: http://www1.astrazeneca-us.com/pi/diprivan.pdf.

In the UK, generic propofol and Diprivan® are also available in a 20 mg/mL (2%) strength; this must not be diluted or mixed with any other drugs. The UK manufacturer's product information for Diprivan® is available from: http://www.medicines.org.uk/EMC/searchresults.aspx?term=propofol&searchtype=QuickSearch.

Abbreviations/Key

†	Off-label indication
5HT	5-hydroxytryptamine, serotonin
CIVI	Continuous intravenous infusion
EDTA	Disodium edetate
GABA	Gamma-aminobutyric acid
IV	Intravenous
MAC	Monitored anesthesia care

References

1. Lundström S, Zachrisson U, Fürst CJ. When nothing helps: propofol as sedative and antiemetic in palliative cancer care. J Pain Symptom Manage 2005;30:570–577.

2. Anonymous. Propofol (Diprivan) infusion: sedation in children aged 16 years or younger contraindicated. Curr Probl Pharmacovigilance 2001;27:10.

3. Harris EA. Sedation and anesthesia options for pediatric patients in the radiation oncology suite. Int J Pediatr 2010. Epub 2010 May 13, article ID 870921.

4. Hofer KN, McCarthy MW, Buck ML, Hendrick AE. Possible anaphylaxis after propofol in a child with food allergy. Ann Pharmacother 2003;37:398–401.

5. Mirenda J, Broyles G. Propofol as used for sedation in the ICU. Chest 1995;108:539–548.

6. McWilliams K, Keeley PW, Waterhouse ET. Propofol for terminal sedation in palliative care: a systematic review. J Palliat Medicine 2010;13:73–76.

7. Hooke MC, Grund E, Quammen H, et al. Propofol use in pediatric patients with severe cancer pain at the end of life. J Pediatr Oncol Nurs 2007;24:29–34.

8. Tramèr M, Moore A, McQuay H. Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia vs omitting nitrous oxide vs total i.v. anaesthesia with propofol. Br J Anaesth 1997;78:256–259.

9. Sneyd JR, Carr A, Byrom WD, Bilski AJ. A meta-analysis of nausea and vomiting following maintenance of anaesthesia with propofol or inhalational agents. Eur J Anaesthesiol 1998;15:433–445.

10. DeBalli P. The use of propofol as an antiemetic. Int Anesthesiol Clin 2003;41:67–77.

11. Gan TJ, Glass PS, Howell ST, et al. Determination of plasma concentrations of propofol associated with 50% reduction in postoperative nausea. Anesthesiology 1997;87:779–784.

12. Gan TJ, El-Molem H, Ray J, Glass PS. Patient-controlled antiemesis: a randomized, double-blind comparison of two doses of propofol versus placebo. Anesthesiology 1999;90:1564–1570.

13. Fujii Y, Tanaka H, Kobayashi N. Small doses of propofol, droperidol, and metoclopramide for the prevention of postoperative nausea and vomiting after thyroidectomy. Otolaryngol Head Neck Surg 2001;124: 266–269.

14. Scher CS, Amar D, McDowall RH, Barst SM. Use of propofol for the prevention of chemotherapy-induced nausea and emesis in oncology patients. Can J Anaesth 1992;39:170–172.

15. Borgeat A, Wilder-Smith O, Forni M, Suter PM. Adjuvant propofol enables better control of nausea and emesis secondary to chemotherapy for breast cancer. Can J Anaesth 1994;41:1117–1119.

16. Cechetto DF, Diab T, Gibson CJ, Gelb AW. The effects of propofol in the area postrema of rats. Anesth Analg 2001;92:934–942.

17. García Peñas JJ, Molins A, Salas Puig J. Status epilepticus: evidence and controversy. Neurologist 2007;13 (6 Suppl. 1):S62–S73.

18. Rossetti AO. Which anesthetic should be used in the treatment of refractory status epilepticus? Epilepsia 2007;48(Suppl 8):52–55.

19. Sneyd JR. Propofol and epilepsy. Br J Anaesth 1999; 82:168–169.

20. Meyer S, Grundmann U, Kegel B, Gortner L, Shamdeen G. Propofol: pro- or anticonvulsant drug? Anesth Analg 2009;108(6):1993–1994. author reply 1994.

21. Jungheinrich C, Scharpf R, Wargenau M, Dilger C, Bepperling F. Pharmacokinetics of the generic formulation propofol 1% fresenius in comparison with the original formulation (Disoprivan 1%). Clin Drug Investig 2002;22(7):417–427.

22. Fechner J, Ihmsen H, Hatterscheid D, et al. Comparative pharmacokinetics and pharmacodynamics of the new propofol prodrug GPI 15715 and propofol emulsion. Anesthesiology 2004;101:626–639.

23. AstraZeneca. Data on file. 2006.

24. Charatan F. Concerns mount over misuse of anaesthetic propofol among US health professionals. Br Med J 2009;339. b3673.

25. Wilson C, Canning P, Caravati EM. The abuse potential of propofol. Clin Toxicol 2010;48:165–170.

26. AstraZeneca. Personal communication. 2010.

27. Mercadante S, De Conno F, Ripamonti C. Propofol in terminal care. J Pain Symptom Manage 1995;10: 639–642.

28. Moyle J. The use of propofol in palliative medicine. J Pain Symptom Manage 1995;10:643–646.

29. Cheng C, Roemer-Becuwe C, Pereira J. When midazolam fails. J Pain Symptom Manage 2002;23:256–265.