

Class: General anaesthetic.

Indications: †Refractory agitated delirium or intolerable distress in the imminently dying, intractable nausea and vomiting.¹

Contra-indications: Children ≤16. When used for sedation in children in intensive care, the death rate was increased 2–3 times.² Allergy to eggs or soya (the available preparation contains purified egg phosphatide as an emulsifying agent and soya bean oil).³

Pharmacology

Propofol is an ultrafast-acting IV anaesthetic agent. It is rapidly metabolized, mainly in the liver, to inactive compounds which are excreted in the urine. The incidence of untoward haemodynamic changes is low. Propofol reduces cerebral blood flow, cerebral metabolism and, less consistently, intracranial pressure.⁴ The reduction in intracranial pressure is greater if the baseline pressure is raised. On discontinuation patients rapidly regain consciousness (10–30min) without a hangover effect.

Propofol is used to relieve refractory agitated delirium or intolerable distress in the imminently dying. 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

Propofol also has an anti-emetic effect resulting in less postoperative vomiting compared with other anaesthetic agents.⁵⁻⁷ Specific postoperative anti-emetic regimens have been designed.⁸⁻¹⁰ Chemotherapy-related nausea and vomiting is also helped by adjunctive propofol.¹¹ In patients receiving non-platinum regimens who were refractory to a combination of **dexamethasone** and a 5HT₃-receptor antagonist, propofol was of benefit in ≥80%.¹² Propofol has also been used to relieve refractory nausea and vomiting in dying patients.¹ It was more effective in relieving nausea than vomiting, although most of the patients probably had bowel obstruction.

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 5HT₃-receptors in the area postrema/chemoreceptor trigger zone.¹³

Propofol also has antipruritic, anxiolytic, bronchodilatory, muscle relaxant and anti-epileptic properties. 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 centres but not excitatory centres have been depressed.^{4,14}

Onset of action 0.5min.

Time to peak effect 5min.

Plasma half-life 2–4min initial distribution phase; 30–60min slow distribution and initial elimination phase; 3–12h terminal elimination phase.

Duration of action 3–10min after single IV bolus.^{15,16}

Cautions

Risk of cardiorespiratory depression. Involuntary movements and seizures have been reported, particularly in epileptics, during induction or recovery.^{14,17} With prolonged use in acute intensive care, metabolic acidosis, hyperlipidaemia and hepatomegaly have been reported.² However, whereas it is good practice to check plasma lipid

levels in patients receiving propofol for ≥ 3 days in this setting, it is not necessary in patients whose expected prognosis is only days.

Undesirable effects

For full list, see manufacturer's SPC.

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

Common ($<10\%$, $>1\%$): headache, hypotension, bradycardia, transient apnoea.

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

Dose and use

Propofol is an emulsion of oil-in-water. This gives it a white appearance and makes it a potential growth medium. Strict aseptic technique must be employed to prevent microbial contamination *and the container and IV line renewed every 6h.*

Undiluted propofol requires a computer-controlled volumetric infusion pump or IV syringe pump. If these are not available, undiluted propofol must *not* be used.

Undiluted propofol is given IV as a 1% (10mg/ml) or 2% (20mg/ml) solution. Pain at the IV injection site can be minimized by:

- co-administration of the first dose with **lidocaine**: mix 20 parts propofol injection 1% with 1 part **lidocaine** injection 0.5% or 1% immediately before administration
- using a large vein in the fore-arm.

Diluted propofol injection 1% using 5% glucose can be administered through a less sensitive infusion control device, e.g. an in-line burette (see manufacturer's SPC for full details)

Propofol injection 2% should not be diluted or mixed with other drugs.

Compatibility: propofol injection 1% is compatible with **alfentanil** and **lidocaine**, and can be diluted with 5% glucose before use (see manufacturer's SPC for details).

Propofol injection 2% should not be diluted or mixed with any other drugs. Both 1% and 2% propofol can be added through a Y connector to a running infusion of 5% glucose, 0.9% saline or 4% glucose + 0.18% saline; 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 (Figure 1)^{1,18-20}. Generally, **phenobarbital** should be used in preference to propofol because it is less complicated for clinical staff to titrate and monitor (see p.000)

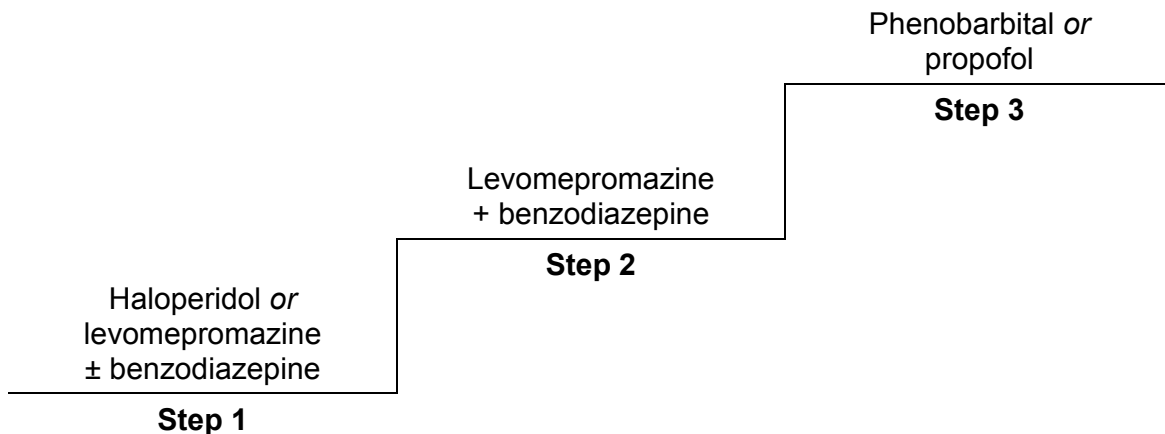


Figure 1 Drug treatment for irreversible agitated delirium in the last days of life.

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):

- generally start with propofol 1mg/kg/h IV
- if necessary, increase by 0.5mg/kg/h every 5–10min until a satisfactory level of sedation is achieved; smaller dose steps can be used to fine-tune the treatment; most patients respond well to 1–2mg/kg/h
- to increase the level of sedation quickly, a bolus dose can be given by increasing the rate to 1mg/kg/min for 2–5min
- 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 12h
- 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 2–3min and restarted at a lower rate; occasionally this leads to 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 7 days
- long-term use of doses >4mg/kg/h is not recommended because of increasing risk of undesirable effects
- if the patient does not respond to propofol 4mg/kg/h alone, supplement with **midazolam** by CSCI
- it is important to replenish the infusion quickly when a container empties, because the effect of propofol wears off after 10–30min
- *because propofol has no analgesic properties, analgesics should be continued.*

Intractable nausea and vomiting

*Consider propofol only if standard treatments have failed.*¹ Thus, when optimized treatment with standard anti-emetics (see p.000) such as **haloperidol**, **metoclopramide**, **cyclizine**, a 5HT₃-receptor antagonist and/or **dexamethasone**,

and also **levomepromazine** (see p.000) or **olanzapine** (see p.000), have failed (Figure 2).

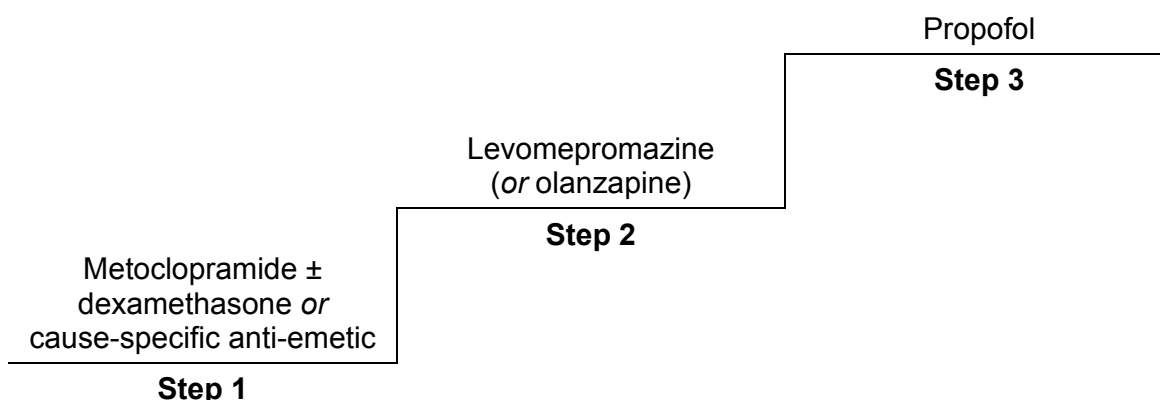


Figure 2 Drug treatment for intractable nausea and vomiting.

Dose titration is generally slower for intractable nausea and vomiting than for terminal agitation:

- generally start with propofol 0.5mg/kg/h
- if necessary, increase by 0.25–0.5mg/kg/h every 30–60min until a satisfactory response is obtained; smaller dose steps can be used to fine-tune the treatment
- most patients respond well to 0.5–1mg/kg/h; doses >1mg/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 12h
- continue to monitor the effect of propofol at least twice daily
- if the patient is too sedated, the infusion should be turned off for 2–3min and then restarted at a lower rate
- if the patient responds well, reduce the infusion rate on a trial basis after 18–24h
- tolerance can develop, necessitating a dose increase, but generally not within 7 days
- it is important to replenish the infusion quickly when a container empties, because the effect of propofol wears off after 10–30min
- when used solely for its anti-emetic effect in the last days of life, some centres reduce the dose of, or even discontinue, propofol when the patient becomes unconscious.

Supply

Propofol (non-proprietary)

Injection (emulsion) 10mg/ml (1%), 20ml amp = £2.50, 50ml infusion bottle = £6, 100ml infusion bottle = £12.

Injection (emulsion) 20mg/ml (2%), 50ml vial = £12.

Diprivan® (AstraZeneca)

Injection (emulsion) 10mg/ml (1%), 20ml amp = £4 50ml vial = £10, 100ml vial = £19.

Injection (emulsion) 20mg/ml (2%), 50ml vial = £19.

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