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Propofol

An Overview of its Pharmacology and a Review of its Clinical Efficacy in Intensive Care Sedation

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Synopsis

Propofol is a phenolic derivative that is structurally unrelated to other sedative hypnotic agents. It has been used extensively as an anaesthetic agent, particularly in procedures of short duration. More recently it has been investigated as a sedative in the intensive care unit (ICU) where it produces sedation and hypnosis in a dose-dependent manner. Propofol also provides control of stress responses and has anticonvulsant and amnesic properties. Importantly, its pharmacokinetic properties are characterised by a rapid onset and short duration of action.

Noncomparative and comparative trials have evaluated the use of propofol for the sedation of mechanically ventilated patients in the ICU (postsurgical, general medical, trauma). Overall, propofol provides satisfactory sedation and is associated with good haemodynamic stability. It produces results similar to or better than those seen with midazolam or other comparator agents when the quality of sedation and/or the amount of time that patients were at adequate levels of sedation are measured. Patients sedated with propofol also tend to have a faster recovery (time to spontaneous ventilation or extubation) than patients sedated with midazolam. Although most studies did not measure time to discharge from the ICU, propofol tended to be superior to midazolam in this respect. In a few small trials in patients with head trauma or following neurosurgery, propofol was associated with adequate sedation and control of cerebral haemodynamics.

The rapid recovery of patients after stopping propofol makes it an attractive option in the ICU, particularly for patients requiring only short term sedation. In short term sedation, propofol, despite its generally higher acquisition costs, has the potential to reduce overall medical costs if patients are able to be extubated and discharged from the ICU sooner. Because of the potential for hyperlipidaemia and the development of tolerance to its sedative effects, and because of the reduced need for rapid reversal of drug effects in long term sedation, the usefulness of propofol in long term situations is less well established.

While experience with propofol for the sedation of patients in the ICU is extensive, there are still areas requiring further investigation. These include studies in children, trials examining cerebral and haemodynamic outcomes following long term administration and in patients with head trauma and, importantly, pharmacoeconomic investigations to determine those situations where propofol is cost effective. In the meantime, propofol is a well established treatment alter-

native to benzodiazepines and/or other hypnotics or analgesics when sedation of patients in the ICU is required. In particular, propofol possesses unique advantages over these agents in patients requiring only short term sedation.

Pharmacodynamic Properties

Continuous infusions of propofol produce increasing levels of sedation in a dose-dependent fashion. There is a good correlation between plasma propofol concentrations and the level of sedation. Propofol also produces amnesia in a dose-dependent manner although to a lesser degree than midazolam.

Propofol has cardiac depressant effects including an infusion rate–dependent decrease in blood pressure. Heart rate is also generally decreased to a modest extent, and some but not all studies have reported a decrease in myocardial contractility. Reductions in systemic vascular resistance and heart rate help in the control of stress responses. In general, propofol is associated with adequate haemodynamic stability in patients requiring sedation in a variety of settings including those recovering from coronary bypass graft surgery.

Sedation with propofol following head injury is associated with either unchanged or slightly decreased intracranial pressure. While mean arterial pressure is also usually decreased, adequate cerebral perfusion pressure is usually maintained.

Both anticonvulsant and neuroexcitatory effects have been reported with propofol during anaesthesia. The neuroexcitatory effects are not thought to represent true cortical seizure activity.

Long term infusions of propofol tend to be associated with a progressive increase in lipid levels (particularly triglycerides), an effect related to the formulation of the drug. Cortisol levels are decreased when propofol is used in patients undergoing anaesthesia; however, these patients generally demonstrate an adequate response to exogenous adrenocorticotrophic hormone.

Pharmacokinetic Properties

The pharmacokinetics of propofol are characterised by fast distribution from the blood into the tissues, rapid metabolic clearance from the blood and slow return of the drug from deep peripheral compartments into the blood. Because of its high lipophilicity, propofol rapidly penetrates the blood-brain barrier, followed by swift redistribution to peripheral tissues; this results in a fast onset but short duration of action.

After initial doses, the clearance of propofol is dependent on both metabolism and on distribution to peripheral compartments. However, as peripheral compartments fill, the distributional component of clearance decreases. Total body clearance values for patients given continuous infusions for intensive care unit (ICU) sedation range from 94.2 to 126.6 L/h, similar to values reported after short term infusions for anaesthesia. These values generally exceed hepatic blood flow, indicating extrahepatic elimination. Propofol is extensively metabolised and excreted in the urine (≥88% of the administered dose) primarily as sulphate and/or glucuronide conjugates of the parent compound or its hydroxylated metabolite. Distribution, second phase and terminal elimination half-lives of 1.8 minutes, 70.9 minutes and 23.5 to 31.3 hours, respectively, have been reported after long term continuous infusions for ICU sedation. The presence of cirrhosis or renal dysfunction does not significantly affect the pharmacokinetics of propofol.

Therapeutic Efficacy

Propofol has been evaluated as a sedative agent during mechanical ventilation in the ICU in numerous patient populations including postsurgical patients (e.g. cardiac, abdominal, neurosurgery), patients with head trauma and general medical patients.

Of patients requiring sedation after cardiac surgery, the percentage who ob-

tained adequate sedation was similar for propofol and midazolam in most comparative studies. However, both the time to spontaneous ventilation and time to extubation were shorter in patients receiving propofol (13.6 to 52 minutes and 11.9 to 250 minutes, respectively) than in those receiving midazolam (66 to 197.8 minutes and 127.9 to 391 minutes, respectively). In comparative studies with midazolam involving mixed patient populations (medical, postsurgical, trauma), parameters measuring quality of sedation or rate of recovery were either similar between groups or favoured propofol.

Data from a limited number of studies assessing the efficacy of propofol for the sedation of patients following head trauma indicate that propofol provides adequate sedation and control of cerebral haemodynamics. Propofol was as effective as fentanyl, morphine plus midazolam or morphine plus pentobarbital in controlling intracranial pressure in patients with head trauma. Propofol also produced adequate sedation and cerebral haemodynamic stability in a few small trials measuring sedation in patients after neurosurgery.

Tolerability

Propofol has cardiovascular depressant effects which most commonly manifest as hypotension and bradycardia. The elderly, patients with hypotension or severe cardiac disease (ejection fraction <50%) and debilitated patients may be at greatest risk for hypotension. There have also been case reports of asystole, heart block and other arrhythmias occurring during propofol anaesthesia.

Neuroexcitatory effects such as convulsions, opisthotonos, myoclonus and choreoathetoid movements have been reported during propofol anaesthesia, although they are not believed to represent true cortical seizure activity.

Postsurgical infection caused by a variety of organisms has been associated with the failure to use aseptic technique in the preparation and administration of propofol. Other adverse effects include respiratory acidosis during weaning of ventilation (3 to 10% of patients), pain on injection when administered into peripheral veins, anaphylaxis/anaphylactoid reactions and green discoloration of the urine.

The use of propofol in paediatric patients has been associated with myocardial failure, often in children with respiratory tract infections and often associated with lipaemia and metabolic acidosis.

Dosage and Administration

In mechanically ventilated adult patients in the ICU, propofol should be initiated at an intravenous dosage of 0.3 mg/kg/h and adjusted upward as clinically required in increments of 0.3 to 0.6 mg/kg/h at intervals of at least 5 minutes. Most patients require maintenance infusion rates of 0.3 to 3 mg/kg/h, although higher dosages may be needed. Daily evaluations of CNS function and the level of sedation should be performed. The use of propofol in children as an ICU sedative is not currently recommended.

Propofol is a phenolic derivative that is chemically distinct from other intravenous sedative hypnotics (fig. 1). It is formulated as a 1% oil-in-water emulsion containing soybean oil, glycerol and egg lecithin. This review focuses on the clinical use of propofol as a sedative in the intensive care unit (ICU) and provides an overview of the clinical pharmacology of the drug relevant to its use in this setting. The use of propofol as an anaesthetic agent has been recently reviewed in *Drugs*.[1] Since most studies on the pharmacological properties of propofol were conducted in patients receiving the drug for indications other than ICU sedation, unless specified otherwise, the pharmacological proper-

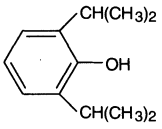

Fig. 1. Structural formula of propofol.

ties of propofol described in this review were not determined in patients in the ICU.

1. Pharmacodynamic Properties

1.1 Sedative/Amnesic/Analgesic Effects

In healthy volunteers[2] or in patients requiring sedation during urological procedures[3] or after cardiac surgery,[4,5] continuous infusions of propofol increased sedation in a dose-dependent manner. Lower plasma propofol concentrations are required for light and deep ICU sedation (0.5 to 1 mg/L and 1 to 1.5 mg/L, respectively) than for surgical anaesthesia (3 to 16 mg/L depending on the depth of anaesthesia and whether concomitant agents are used).[6] In mechanically ventilated patients in the ICU, a good correlation between plasma propofol concentrations and level of sedation has been reported.[7] In a comparative study, propofol 1.27 mg/kg/h and midazolam 0.035 mg/kg/h produced similar sedative effects in healthy volunteers.[8]

In patients in the ICU, recovery from sedation is rapid even after long term (≤7 days) infusions.[9,10] After stopping continuous infusions of propofol (mean dosage 2.85 mg/kg/h), recovery times were similar after 24, 48, 72 or 96 hours of infusion (fig. 2)[10]. The need to increase infusion rates of propofol to maintain the desired level of sedation has been reported in some patients in the ICU who have received propofol for more than 7 days, indicating that either tolerance or changes in drug elimination may develop during long term sedation with propofol.[11,12]

Combination of propofol with alfentanil,[13] thiopental,[14] midazolam[13,15] or midazolam plus alfentanil[13] produces a synergistic hypnotic effect while combination of propofol with fentanyl was found to produce an additive hypnotic effect.[16]

Patient-controlled administration or continuous infusions of propofol resulted in amnesia in 63 to 70% of patients undergoing surgical dental procedures.[17,18] Amnesia is reported to occur in a dose-dependent fashion.[3] However, at dosages that produced similar sedative effects, midazolam produced more amnesia than propofol in healthy volunteers.[8]

Data regarding the analgesic properties of propofol are inconclusive.[19] Pharmacodynamic studies have reported that hypnotic doses of propofol have analgesic effects[20,21] while subhypnotic doses are reported to have either analgesic[22] or hyperalgesic effects.[21] Some clinical trials in ICU sedation after coronary artery bypass graft surgery have indicated that propofol has a greater analgesic-sparing effect than midazolam.[23-25]

1.2 Haemodynamic Effects

Decreases in blood pressure in patients sedated with propofol may be marked and are generally dose- and infusion rate–dependent.[4,26,27] Other

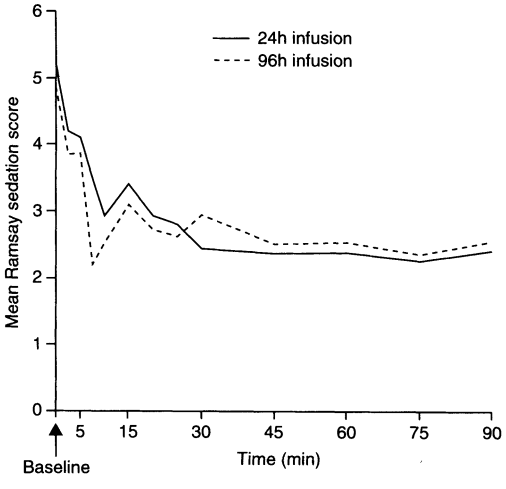

Fig. 2. Recovery after discontinuation of propofol. Recovery times (based on mean Ramsay scores) in 14 patients in the intensive care unit following the temporary discontinuation (90 min) of short (24h) or long term (96h) infusions of propofol at a mean dosage of 2.85 mg/kg/h.[10]

risk factors for hypotension include increased age, hypovolaemia or concomitant use of opioids or β-adrenoceptor antagonists.[28,29] The cause of the hypotensive effect ascribed to propofol is unknown but may include peripheral vasodilation, a reduction in ventricular preload and/or a reduction in myocardial contractility possibly mediated via a decrease in sympathetic activity.[28,30]

Propofol tends to cause a modest decrease in heart rate despite the reduction in arterial pressure. The effect was significantly greater than that seen with midazolam in sedated patients in the ICU.[31] Data regarding the effect of propofol on baroreceptor activity have been conflicting but most recent work indicates that propofol impairs baroreflex regulatory mechanisms.[30,32,33]

Results of studies of the effect of propofol on myocardial contractility (primarily from animal studies) have been equivocal, with studies reporting either decreased contractility or no significant effect.[28,34]

Haemodynamic stability is maintained in patients receiving continuous infusions of propofol for sedation after coronary bypass graft surgery. The haemodynamic effects of propofol in these patients were difficult to determine as haemodynamic parameters (mean arterial pressure, central venous pressure, heart rate, etc.) were usually maintained within predetermined values by the use of vasodilators, fluids and plasma expanders. However, as in other patient groups, propofol generally caused an initial transient decrease in mean arterial blood pressure (fig. 3). In comparative studies in patients requiring sedation following cardiac surgery, the hypotensive effect of propofol was similar to or greater than that seen with midazolam.[23-25,35-37] Systemic vascular resistance and heart rate tended to be reduced with propofol, generally beneficial effects in postcardiac surgery patients.[24,35,37] Propofol was also associated with a similar or lower requirement for concomitant vasodilators [sodium nitroprusside or nitroglycerin (glyceryl trinitrate)] to treat postoperative hypertension than midazolam in this patient group.[23-25,37] Additionally, cardiac output remained stable

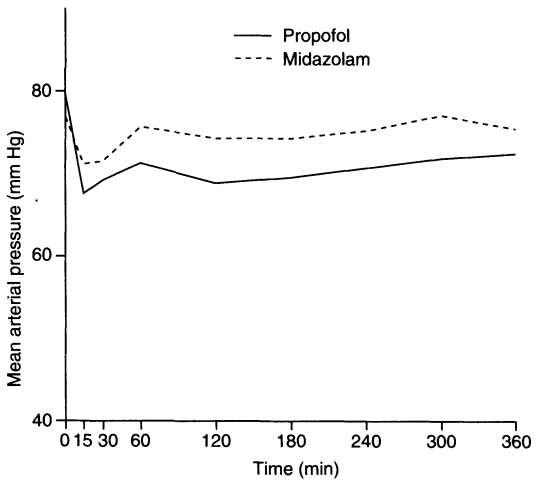

Fig. 3. The effects of propofol on mean arterial pressure. The effects of propofol (1 mg/kg loading dose followed by a mean infusion rate of 2.7 mg/kg/h) and midazolam (0.07 mg/kg loading dose followed by a mean infusion rate of 0.092 mg/kg/h) on mean arterial pressure in mechanically ventilated patients (n = 15 for each group) requiring sedation following coronary artery surgery.[35]

and there was no evidence of myocardial ischaemia.[23-25,37]

1.3 Respiratory Effects

The respiratory depressant effects of propofol have been previously reviewed.[38,39] Although respiratory depression is of no consequence during mechanical ventilation, it becomes important during the weaning process.[40]

The relative effects of propofol compared with midazolam on respiratory parameters following weaning from mechanical ventilation in postsurgical patients receiving sedation have been evaluated in a few studies.[24,25,37,41] With one exception, there was no significant difference between propofol and midazolam in arterial blood gas or respiratory measurements during weaning or after extubation. In 100 patients sedated with propofol 1.15 mg/kg/h or midazolam 0.034 mg/kg/h for a mean duration of approximately 17 hours, $PaCO_2$ (arterial partial pressure of carbon dioxide) was significantly higher in midazolam-treated patients

(6.4 kPa) than in propofol-treated patients (5.6 kPa), indicating alveolar hypoventilation in the midazolam group.[25] However, this may have been caused by the significantly greater amounts of morphine administered to midazolam recipients.

Bolus doses of propofol are reported to cause bronchodilation in patients with chronic obstructive pulmonary disease,[42] status asthmaticus[43] or hyperactive airways.[44]

1.4 Cerebral Effects

1.4.1 Cerebral Haemodynamics and Metabolism

In patients receiving anaesthetic dosages of propofol, cerebral vascular resistance tends to be increased, and this is accompanied by a decrease in cerebral blood flow.[45-47] At these dosages, cerebral metabolic rates (glucose or oxygen consumption) also tend to be decreased.[47,48] In patients receiving propofol for sedation after head trauma, propofol (mean dosage 232 mg/h) was associated with a transient decrease in global brain metabolism at 4 hours after the initiation of the infusion followed by a return to presedation rates.[49]

In mechanically hyperventilated patients with head injury, sedation with propofol has been associated with either unchanged or slightly decreased intracranial pressure (ICP).[50-53] In one of these studies, ICP was decreased in patients with baseline ICP >16mm Hg but not in patients with baseline ICP ≤16mm Hg.[53] Despite a decrease in mean arterial pressure (MAP) in some patients with head injury, cerebral perfusion pressure (CPP = MAP – ICP) above the target value of 60mm Hg was usually maintained.[50,51,54]

1.4.2 Effects on the Electroencephalogram

The effects of propofol on the electroencephalogram (EEG) are dose-related. Sedative dosages of propofol are typically associated with an increase in activation of the EEG, primarily in the β-frequency range.[55-58] Anaesthetic dosages of propofol produce a slowing of the EEG characterised by a progressive reduction of activity in the β-frequency range and an increase in the δ-range,[55] with high dosages being associated with EEG burst suppression.[59,60]

1.4.3 Anticonvulsant/Neuroexcitatory Effects

Propofol has been reported to have both anticonvulsant and neuroexcitatory properties. In animal models, propofol has been shown to inhibit seizures induced by a variety of stimuli (as reviewed by Bryson et al.[1]). It has also been reported to be effective in the treatment of anticonvulsant-refractory status epilepticus in mechanically ventilated patients.[61-66] In contrast, a variety of neuroexcitatory events including convulsions, myoclonus and opisthotonos (section 4.2) have also been reported to be associated with propofol anaesthesia, although most of these have not been evaluated by simultaneous EEG recordings. The reason for these conflicting reports is not known but it has been suggested that the neuroexcitatory manifestations are not representative of true cortical epileptic activity.[67,68]

1.5 Other Effects

1.5.1 Lipid Effects

Since propofol is formulated in a 1% lipid emulsion, there is concern about the potential for elevated serum lipid levels, particularly in patients receiving prolonged infusions. Although short term infusions (≤3 days) of propofol are generally not associated with such changes, long term infusions tend to be associated with a progressive increase in serum lipid levels (particularly triglycerides).[12,69-71] Infusions for 7 days or more resulted in serum triglyceride levels that were 3 to 4 times normal values.[69,71] After propofol cessation, serum lipid levels may take several days to return to normal values.[69] To minimise the potential for elevations in serum triglycerides, the caloric content of the propofol infusion should be included in calculations of lipid requirements in patients receiving enteral or parenteral nutrition.

An *in vitro* study found that, as with soya-oil-emulsion (Intralipid®), propofol agglutination occurs in serum from critically ill patients but not in serum from healthy volunteers.[72] Serum from patients with acute respiratory dysfunction agglutinated propofol and soya-oil-emulsion significantly more often than serum from patients with normal

respiratory function leading the authors to speculate that this effect might be related to some of the adverse effects reported with propofol in children (section 4.4).[72]

1.5.2 Effects on Cortisol and Catecholamine Levels

Propofol has been reported to be associated with significant decreases in plasma cortisol levels when used for anaesthesia[73-75] or ICU sedation.[24,27,31] This decrease has usually been attributed to the effects of anaesthesia or sedation on the stress response and is considered unlikely to be of clinical significance since these patients generally demonstrated an adequate response to exogenous corticotrophin (ACTH) administration.[27,31,76,77] However, 1 study reported decreased cortisol levels in the presence of normal corticotrophin levels, indicating a possible inhibition of cortisol production.[75]

Elevations in catecholamine levels are an indication of an activation of the stress response.[78] Propofol, titrated to deep sedation, was associated with significantly lower levels of adrenaline, noradrenaline and dopamine than the use of as needed boluses of morphine and midazolam in 88 patients following coronary artery bypass graft surgery.[79]

1.5.3 Antioxidant Effects

Propofol is chemically related to other phenol-based antioxidants such as butylated hydroxytoluene (BHT) and tocopherol (vitamin E).[80] *In vitro* experiments have shown that clinically relevant concentrations of propofol have little antioxidant activity in the aqueous compartments.[80,81] However, at concentrations achievable during anaesthesia, propofol has been found to inhibit lipid peroxidation.[82] The clinical significance of these antioxidant effects in lipid compartments require further study.

1.5.4 Immune System Effects

A number of anaesthetic agents are reported to have an inhibitory effect on the immune response.[83] While the clinical relevance of this effect after short term use of the drug for surgical procedures is probably minimal, the effect is likely to be more significant after long term use. *In vitro* and *in vivo* studies evaluating the immune system effects of propofol in healthy volunteers and patients in the ICU have yielded conflicting results. Some studies[84-86] have described propofol as having immunosuppressant effects while others[87,88] have not.

2. Pharmacokinetic Properties

The pharmacokinetics of propofol have most commonly been described using a 3-compartment model. The dominant pharmacokinetic characteristics of propofol are a rapid distribution from the blood into tissues, a similarly rapid metabolic clearance from the blood and the slow return of the drug from the deep peripheral compartments into the blood.[89] The rapid penetration of the blood-brain barrier, followed by a redistribution from the CNS to inactive tissue depots (muscle and fat), results in a fast onset of action along with a rapid rate of recovery.

The pharmacokinetic properties of propofol after bolus doses or short term continuous infusions when used for anaesthesia have been well described.[89] A few longer term pharmacokinetic studies have been conducted in patients receiving propofol for sedation in the ICU. Table I summarises the pharmacokinetic parameters of propofol after continuous infusions for anaesthesia or ICU sedation.

2.1 Blood Concentrations

Peak propofol blood concentrations after bolus doses are difficult to measure: propofol is rapidly distributed from the blood leading to swiftly decreasing drug concentrations during this period.[89] However, in 9 ICU patients given a 1 to 3 mg/kg bolus dose of propofol followed by a constant rate infusion of 3 mg/kg/h for 72 hours, peak blood propofol concentrations ranged from 0.77 to 15.3 mg/L. After 6 hours of the infusion the mean drug concentration was 1.3 mg/L.

After initiation of a constant rate infusion, there is an initial rapid, dose-dependent increase in blood concentration followed by a slow rate of in-

Table I. Pharmacokinetic parameters of propofol. Summary of propofol pharmacokinetic values after short term continuous infusions (≤9h) in anaesthesia regimens or long term continuous infusions (≥72h) in intensive care unit (ICU) sedation

Reference	V_c (L/kg)	V_{ss} (L/kg)	V_z (L/kg)	CL (L/h)	$t_{½\lambda_1}$ (min)	$t_{½\lambda_2}$ (min)	$t_{½\beta}$ (h)
Short term infusion in anaesthesia at 3-9 mg/kg/h							
90-97	0.21-0.28	1.8-5.3	9.7-16.4	91-156	2.8-9.5	30-37	2.4-44.7
Long term infusion in ICU sedation at 2.6-3 mg/kg/h							
98,99		25.5[a]		94.2-126.6	1.8	70.9	23.5-31.3

a Assuming 70kg patients.

Abbreviations: CL = total body clearance; h = hours; min = minutes; $t_{½\lambda_1}$ = distribution half-life; $t_{½\lambda_2}$ = second-phase half-life; $t_{½\beta}$ = terminal elimination half-life; V_c = volume of distribution of the central compartment; V_{ss} = volume of distribution at steady-state; V_z = volume of distribution during the elimination phase.

crease.[96] This slow increase is due to the high rate of clearance that occurs during distribution to the second and third compartments.

Plasma propofol concentrations have been positively correlated with sedative effects in mechanically ventilated patients in the ICU (section 1.1).[7] In 20 patients titrated to the desired level of sedation over a period of 1.5 to 351 hours, the IC_{50} (concentration at which 50% of patients reached the desired level of sedation) was 0.47 mg/L for sedation score (Ramsay scale, table II) greater than 2, and 1.1 mg/L for a sedation score greater than 4.[7]

2.2 Distribution and Protein Binding

Propofol is highly lipophilic; this results in a rapid distribution from the blood into the CNS and peripheral tissues. Propofol is initially distributed to well-perfused tissue, then to lean muscle tissue and finally to fat tissue. The distribution half-life ranges from 1.8 to 9.5 minutes after continuous infusions for anaesthesia or ICU sedation. The blood-brain equilibration half-life has been estimated by pharmacokinetic modelling to be 2.9 minutes.[100] Following long term infusion, the volume of distribution at steady-state was reported to be much higher than after short term infusion (table I). This probably reflects increased peripheral distribution after long term administration.

The binding of propofol to plasma proteins (including albumin and haemoglobin) ranges from 96 to 99%.[101-103]

2.3 Metabolism and Elimination

After initial doses of propofol, metabolism and distribution to peripheral compartments each account for about one-half of the clearance of propofol from the blood.[6] As drug concentrations in the peripheral compartments begin to equilibrate with the blood, the distributional component of clearance decreases causing plasma concentrations to fall more slowly upon discontinuation of the infusion.[6] Thus, titration of infusion rates to clinical response is important to avoid excess drug accumulation during long term administration.

After administration of [^{14}C]-propofol (mean dose 0.47 mg/kg) in healthy volunteers, less than 0.3% of the administered dose was excreted in the urine as the parent compound.[104] The drug was primarily (≥88%) eliminated in the urine as sulphate and/or glucuronide conjugates of propofol or its hydroxylated metabolite with less than 2% excreted in the faeces.[104]

Total body clearance in patients in the ICU (94.2 to 126.6 L/h) is of the same magnitude as that seen

Table II. Ramsay sedation scale[77]

Sedation score	Level of sedation
1	Patient awake, anxious, agitated or restless
2	Patient cooperative, orientated and tranquil
3	Patient responds to commands only
4	Patient asleep, has brisk response to stimulus
5	Patient asleep, has sluggish response to stimulus
6	Patient asleep, has no response to stimulus

in patients given short term infusions for anaesthesia [91 to 156 L/h (table I)]. These values generally exceed hepatic blood flow, indicating some form of extrahepatic elimination. Indeed, glucuronide and sulphate conjugates have been detected in the plasma of patients who were given propofol during liver transplantation at times their livers were not being perfused.[105] Conflicting results have been reported in studies examining the possibility of pulmonary extraction.[105-107]

Propofol undergoes triphasic elimination (table I, fig. 4). The first phase ($t_{1/2\lambda_1}$) corresponds to the fast distribution of propofol from the blood into tissue while the second phase ($t_{1/2\lambda_2}$) is characterised by rapid metabolic clearance. The terminal elimination half-life ($t_{1/2\beta}$) represents the slow return of a small amount of propofol from poorly perfused tissue (probably fat) to the blood.[89] The wide variation in values for $t_{1/2\beta}$ in anaesthesia studies (table I) is primarily due to differences in sampling times; prolonged sampling times generally result in higher $t_{1/2\beta}$ values.

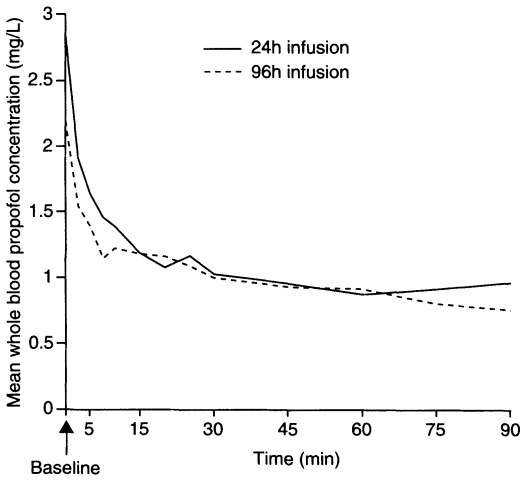

Fig. 4. Blood elimination curves of propofol. Decline of blood propofol concentrations in 14 patients in the intensive care unit following the temporary discontinuation (90 min) of short (24h) or long term (96h) infusions of propofol at a mean dosage of 2.85 mg/kg/h.[10]

2.4 Effects of Age, Bodyweight and Renal or Hepatic Dysfunction

The volume of distribution of the central compartment of propofol was significantly lower in patients aged 65 to 80 years (0.32 L/kg) than in patients aged 18 to 35 years (0.40 L/kg).[101] This probably reflects either a reduction in the volume of highly perfused tissues relative to body mass or a reduction in the perfusion of these tissues due to decreased cardiac output in the elderly. Total body clearance was also significantly lower in elderly (86.4 to 94.8 L/h) than in younger patients (107.4 to 131.4 L/h).[101,108] These differences mean the elderly may require lower dosages of propofol than younger patients.

Total body clearance and volume of distribution at steady-state were significantly greater in obese than nonobese patients during propofol anaesthesia.[108,109] The combined effect of these changes resulted in no difference in the $t_{1/2\beta}$ of propofol between obese and nonobese patients indicating that dosage adjustments may not be needed for these patients.[109]

The pharmacokinetics of propofol are not significantly affected by the presence of cirrhosis[110,111] or renal dysfunction.[112-115]

The pharmacokinetics of propofol in patients receiving the drug for postoperative sedation after orthotopic liver transplantation were similar to values reported in patients without hepatic disease.[116]

2.5 Pharmacokinetic Drug Interactions

Pharmacokinetic studies to date have reported the interactions of propofol with other anaesthetic agents or analgesics to be of only marginal clinical significance. Since volatile anaesthetics decrease hepatic blood flow[117] they have the potential to decrease propofol clearance. The $t_{1/2\beta}$[118] and serum concentration[119] of propofol have been reported to be increased by isoflurane and/or halothane.

Propofol pharmacokinetics are unaffected by alfentanil;[97] however, propofol is reported to either impair the elimination of alfentanil,[97,120] or

have no effect on alfentanil pharmacokinetics.[121] Conflicting reports have described fentanyl to either slightly decrease (27 to 32%) the clearance of propofol[118,122] or to have no effect on propofol pharmacokinetics.[123-125] *In vitro* studies have found that propofol inhibits cytochrome P450 and a variety of mono-oxygenases in human liver microsomes.[126]

The introduction of enteral nutrition in 8 patients in the ICU receiving long term (≥7 days) propofol infusions had no effect on blood propofol concentrations or total body clearance.[127]

3. Therapeutic Efficacy

The use of propofol for sedation in the intensive care unit has been the subject of a number of investigations in a variety of patient populations. This review primarily focuses on randomised comparative trials, with the use of Ramsay scores (table II) as the most common method to measure the level of sedation. Trials were not blinded; this is presumably due to the difficulty of doing so given the distinctive appearance of the propofol formulation. Recovery parameters such as the time to spontaneous ventilation and/or time to extubation were also often assessed. Other end-points that were measured, such as ICP and CPP in patients with head trauma or in patients undergoing neurosurgery, varied depending on the patient group being studied.

3.1 Sedation in Medical or General Surgery Contexts

3.1.1 Noncomparative Trials

In noncomparative trials, propofol (mean infusion rates of 1.93 to 4.9 mg/kg/h for up to 7 days) alone or in combination with opioid analgesics and/or peridural analgesia with local anaesthetics has been reported to be effective in providing adequate sedation (based on clinical assessments using Ramsay or modified Glasgow Coma scales) in mechanically ventilated patients.[9,10,27,69,128] Most patients recovered within 20 minutes after the end of the infusion. The use of propofol for long term sedation (up to 38 days) has been reported in a small number of patients.[11,129] However, some of these patients needed increased dosages to maintain a desired level of sedation, an observation that may indicate the development of tolerance to the sedative effects of propofol (section 1.1).[11]

3.1.2 Comparative Trials

A number of randomised, comparative trials have evaluated the use of propofol for the sedation of a mixed group of critically ill patients (table III). Continuous infusions of propofol resulted in patients having similar percentages of time (71 to 94%) under adequate sedation compared with those receiving midazolam (71 to 93%).[31,130,131] The overall quality of sedation and the patients' ability to tolerate the ICU environment (as assessed by nursing staff) was similar[133,134] or superior[41] in propofol-treated patients compared with those receiving other agents (table III).

Parameters evaluating the rate of patient recovery favoured propofol in some studies (table III). Aitkenhead et al.[31] reported that in a subgroup of patients whose ability to breathe spontaneously was assessed, the mean time to ventilator weaning was significantly shorter ($p < 0.001$) in patients receiving propofol (5 minutes) than in those receiving midazolam (148 minutes). Similarly, results from 2 studies[29,132] indicated that the mean time to recovery (defined either as being awake or having the ability to answer questions) was shorter in propofol-treated patients (13.8 and 14 minutes, respectively) than in midazolam-treated patients (35.3 and 85 minutes, respectively), although this difference was statistically significant in only 1 study.[29] In patients receiving either short term (<24 hours), medium term (24 hours to <7 days) or long term (>7 days) sedation, the time to extubation was significantly shorter in patients receiving propofol (0.3 to 0.8 hours) than in those receiving midazolam (2.5 to 36.6 hours) for all 3 subgroups.[131] In these same patients, the time to recovery and discharge from the ICU was also shorter in the propofol groups (1 to 1.8 hours) than the midazolam groups (3.6 to 54.7 hours), although statistical analyses were not provided for this parameter. A pharmacoeconomic analysis of these patients revealed that while drug acquisition costs were sig-

Table III. Efficacy of propofol for sedation of patients in the intensive care unit (ICU). Summary of randomised trials comparing propofol (P) with midazolam (M) or isoflurane (I) for the sedation of critically ill patients (medical, general surgery or trauma) requiring mechanical ventilation in the ICU

Reference	Patient type	No. of patients	Mean dosage (mg/kg/h)	Mean duration of infusion (h)	Results			
					time with adequate sedation (%)	mean time to ventilator weaning (min)	mean time to recovery (min)	quality of sedation
Comparison with midazolam								
Aitkenhead et al.[31]	Gen surg, med, trauma	P 53	1.77	20.2	94[a]	5**(n = 21)		
		M 47	0.10	21.3	93[a]	148 (n = 18)		
Beyer & Seyde[29]	Abd surg	P 20[b]	1.9	NR			14*[c]	
		M	0.11				85[c]	
Boyle et al.[130]	Gen surg, med	P 29	NR	67	71[a]			
		M 29		41	71[a]			
Carrasco et al.[131]	Gen surg, med, trauma	P 46	2.3	NR	93*[d]			
		M 42	0.17		82[d]			
Früh[132]	Med, gen surg, trauma	P 10	1.62	10			13.8[e]	
		M 10	0.20	10			35.3[e]	
Ronan et al.[41]	Abd surg, ortho surg	P 25	1.43	23.8				2.21*[f]
		M 25	0.028	33.2				2.48[f]
Wolfs et al.[133]	Abd surg	P 17	1.7	6		16.4		P ≡ M
		M 17	0.11	6		85.2		
Comparison with isoflurane								
Millane et al.[134]	Med, gen surg	P 24[g]	1.4	27	96			1.93[h]
		I 24[g]	0.35%	24	97			1.94[h]

a Ramsay score 2 to 4.

b Total number of patients; distribution not specified.

c Time to answering questions.

d Ramsay score 2 to 5.

e Time to being awake.

f Nurse rated scale: 1 = excellent; 2 = above average; 3 = average; 4 = below average; 5 = poor.

g Crossover study.

h Nurse rated scale: 1 = poor; 2 = optimal; 3 = too deep.

i Mean inspiratory concentration.

Abbreviations and symbols: abd surg = abdominal surgery; gen surg = general surgery; h = hours; med = medical; min = minutes; NR = not reported; ortho surg = orthopaedic surgery; ≡ indicates no significant difference between treatments but no values reported; * $p < 0.05$ *vs* comparator; ** $p < 0.001$ *vs* comparator.

nificantly higher in the propofol groups, this was offset by significantly lower postsedation care costs associated with propofol. Postsedation care costs were determined by the number of hours in which the patient required special care until their level of consciousness permitted transfer to a ward multiplied by the price charged to the patient per hour of stay. Total costs of sedation (drug acquisition costs plus postsedation care costs) were significantly higher for midazolam than propofol in the short term sedation group. There was no significant difference between propofol and midazolam in total costs of sedation for the medium or long term sedation groups.[131]

In the only comparative trial with isoflurane, the quality of sedation as assessed by nurses was similar between propofol and isoflurane.[134] In this crossover trial, the proportion of patients with suboptimal sedation was 3.6 and 3.4% for the propofol and isoflurane groups, respectively.

3.2 Sedation Following Cardiac Surgery

Sedation following cardiac surgery is important to facilitate mechanical ventilation and to minimise the haemodynamic responses to pain (which activates the sympathetic nervous system) that might damage an ischaemic myocardium.[40] Propofol has been evaluated as an intensive care sedative following cardiac surgery in a number of clinical trials. Exclusion criteria were not always described, but some studies excluded patients with left ventricular dysfunction (ejection fraction <35 to 40%)[24,35] or perioperative haemodynamic instability[37] because of the reported cardiovascular depressant effects of propofol (sections 1.2 and 4.1). Dose-finding studies evaluated propofol 0.24 to 4 mg/kg/h in patients following cardiac surgery.[4,5,26,135] In general, lower dosages tended to be associated with a greater need for supplemental sedatives or analgesics while higher dosages were associated with a more frequent need to temporarily discontinue propofol to prevent hypotension.[5,26]

Table IV summarises studies comparing propofol with midazolam or alfentanil in patients requiring ICU sedation following postcardiac surgery. The percentage of time that patients were at the desired level of sedation (based on Ramsay scores) was similar for all agents, with the exception of one study which reported propofol to be significantly superior to midazolam (86 *vs* 56%).[25] The mean time to spontaneous ventilation ranged from 13.6 to 52 minutes for propofol-treated patients, which was significantly shorter than the ranges observed in midazolam-treated patients (66 to 197.8 minutes).[23,35,37] Mean times to extubation ranged from 11.9 to 250 minutes and 127.9 to

Table IV. Efficacy of propofol for sedation of patients after coronary artery bypass graft surgery. Summary of randomised, comparative trials of propofol (P) *vs* midazolam (M) or alfentanil (A) in the sedation of mechanically ventilated patients following coronary artery bypass graft surgery

Reference	No. of evaluable patients	Mean dosage (mg/kg/h)	Mean duration of infusion (h)	Results		
				time with desired level of sedation (%)	mean time to spontaneous ventilation (min)	mean time to extubation (min)
Comparison with alfentanil						
Nollet & Verbeke[136]	P 12	2	13	87.5[a]	32.1	73.8
	A 13	0.038	14.2	82.5[a]	43.5	83.9
Comparisons with midazolam						
Higgins et al.[24]	P 42	0.7	9.2	73[b,c]		P ≡ M
	M 38	0.018	9.4	79[b,c]		
Grounds et al.[23]	P 30	0.79	8.3	91[d]	13.6**	24.9**
	M 30	0.016	10.3	81[d]	197.8	226.1
McMurray et al.[25]	P 50	1.15	16.7	86**[c]		11.9**
	M 50	0.034	16.2	56[c]		127.9
Roekaerts et al.[35]	P 15	2.7	9.5		52**[e]	250*
	M 15	0.092	9.7		195[e]	391
Snellen et al.[37]	P 20	0.91	10.5	59.6[b]	24*[e]	154
	M 20	0.038	10.6	53[b]	66[e]	243

a Ramsay score ≥3.

b Ramsay score 2 to 4.

c Derived from graph.

d Ramsay score 2 to 5.

e Time to initiation of ventilatory weaning.

Abbreviations and symbols: h = hours; min = minutes; ≡ indicates no significant difference between treatments but no values reported; * $p < 0.05$ *vs* comparator; ** $p < 0.001$ *vs* comparator.

391 minutes in propofol- and midazolam-treated patients, respectively.[23,25,35,37]

Propofol and midazolam generally produced similar haemodynamic effects. Both drugs tended to produce transient decreases in MAP although the effects were generally not clinically significant (fig. 3). The requirement for supplemental opioids for analgesia was significantly lower in patients sedated with propofol than in those receiving midazolam in some studies[23-25] but not in others.[35,37]

In one comparative trial with alfentanil, the degree of satisfactory sedation, the time to resumption of spontaneous respiration and time to extubation were similar between the 2 drugs.[136]

3.3 Sedation Following Head Injury or Neurosurgery

Sedation in patients with head trauma is important to facilitate smooth mechanical ventilation and to avoid increases in MAP and ICP. A major goal of therapy is to maintain CPP above 60mm Hg in order to prevent ischaemic damage. Limited data from small comparative or noncomparative trials suggest propofol may have a role in the sedation of patients with head trauma. In noncomparative studies involving 50 patients also receiving mechanical hyperventilation with or without mannitol and/or opioids, propofol 1.4 to 4.97 mg/kg/h provided adequate sedation and maintained CPP above 60mm Hg in all patients except one.[50-52] ICP was either unchanged or slightly decreased in these patients.

Results from comparative studies showed that propofol was as effective as morphine plus midazolam,[54] fentanyl[137] or morphine plus pentobarbital[138] in controlling ICP in patients with head injury.

In the postoperative period following neurosurgery, sedation is important to minimise the physiological stresses that may compromise cerebral function. Noncomparative trials in such patients found that propofol provided adequate sedation and allowed acceptable control of cerebral haemodynamics.[139-141] When compared with midazolam (mean dosage 0.075 mg/kg/h), propofol (mean dosage 2.67 mg/kg/h) showed no significant difference in cardiovascular or intracranial pressure measurements.[142] There also were no significant differences between the groups in the quality of recovery as assessed by the medical staff. However, for patients extubated before discharge from the ICU, the median time after discontinuation of the infusion to discharge was significantly shorter in the propofol group (6.25 hours) than in the midazolam group (9.79 hours).[142]

3.4 Sedation in Special Patient Populations

3.4.1 Patients with Chronic Obstructive Pulmonary Disease

The use of propofol in patients with chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation because of acute respiratory failure has been evaluated in one comparative[143] and one noncomparative[144] study. In 10 patients with COPD, propofol provided adequate sedation (as measured by Ramsay scale) in dosages of 1 to 3 mg/kg/h.[144] In the comparative trial, those receiving propofol (n = 5) had a superior overall quality of sedation (as assessed by nursing staff) than those receiving midazolam (n = 6) after mean dosages of 1.73 and 0.14 mg/kg/h, respectively.[143]

3.4.2 Paediatric Patients

The use of propofol for the sedation of paediatric patients in the ICU has not been well studied and there is significant concern regarding its use in this population. Only a few case reports or small studies involving mechanically ventilated children receiving propofol have been published to date.[145-148] These reports describe the successful use of propofol in children, although the dosages used varied considerably. Despite the lack of adequate information, propofol is reported to be commonly used for this purpose.[149] However, a number of adverse events (including fatalities) have been reported in children after propofol use in the paediatric ICU (section 4.4) and the use of propofol for intensive care sedation in paediatric patients is not recommended by the manufacturer.[6] Therefore, the unrestricted use of propofol in chil-

dren should not be undertaken outside of controlled clinical trials.

3.4.3 Other Patient Groups

Institution of venovenous haemodiafiltration in 10 mechanically ventilated patients with oliguric renal failure did not substantially influence the requirement of propofol for sedation.[150] Propofol has also been used for sedation of patients with tetanus[151,152] and delirium tremens[153] in a few cases.

4. Tolerability

Determining the causality and incidence of specific adverse effects of propofol when used in ICU sedation is complicated by the fact that patients receiving the drug are generally very ill and are often receiving multiple medications. Thus, it is often difficult to determine whether adverse events are related to propofol, the underlying disease state or other medications.

4.1 Cardiovascular Events

Propofol has well described cardiovascular depressant effects which are most commonly manifested as hypotension and to a lesser extent bradycardia (section 1.2). Hypotension was reported in 26% of patients receiving propofol for ICU sedation.[6] Some evidence suggests that the elderly, patients with hypotension, debilitated patients, patients with severe cardiac disease (ejection fraction <50%) or other American Society of Anesthesiologists (ASA) class III/IV patients may be at increased risk for adverse cardiovascular effects.[6] Additionally, reversible asystole has been reported after induction of anaesthesia with combinations of propofol and fentanyl[154,155] and propofol, fentanyl and suxamethonium chloride (succinylcholine chloride).[156] Heart block[157] and supraventricular and ventricular tachycardia[158] have also been reported during propofol anaesthesia.

4.2 Neurological Events

Although propofol has been used to treat status epilepticus in patients refractory to standard treatment (section 1.4.3), there have also been reports of neuroexcitatory events associated with the drug during use for anaesthesia. These include convulsions,[159-165] opisthotonos,[166-171] myoclonus[172,173] and choreoathetoid movements.[174] These effects are most commonly seen during emergence from anaesthesia and have usually been transient in nature,[159,175] although at least one case of permanent brain damage (probably related to hypoxia) has been reported.[175] It has been suggested that these abnormal movements are subcortical in nature rather than true cortical seizure activity and that the effect is more likely to be seen with low dosages of propofol.[68,176] The relevance of these effects in the ICU setting is unknown.

Withdrawal phenomena which include restlessness, movement disorders, convulsions, mental status changes and hallucinations have been reported in adults receiving propofol for ICU sedation for ≥5 days.[177,178]

4.3 Infection

Propofol is supplied in an oil-in-water emulsion and contains no preservative. *In vitro* studies have found propofol to be an excellent medium for the growth of a variety of organisms.[179-183]

A number of outbreaks of postsurgical Gram-positive, Gram-negative and fungal (*Candida albicans*) infections have been documented in patients receiving contaminated propofol.[184-187] However, in all cases the contamination was probably related to a failure to use aseptic technique in the preparation and administration of the drug.[187]

4.4 Events in Paediatric Patients

Case reports of fatal myocardial failure with[188,189] or without[190] lipaemia and metabolic acidosis have been reported in children sedated with propofol in the ICU. Many of these children had concurrent respiratory tract infections. However, the FDA's Anesthetic and Life Support Drugs Advisory Committee was unable to find an identifiable link between propofol and these adverse cardiac events.[191]

Withdrawal effects including restlessness, jitteriness, myoclonus and convulsions have been reported in children after discontinuation of prolonged (4 days to 2 weeks) propofol infusions.[192-194]

4.5 Other Events

Pain on injection is commonly reported when propofol is administered via a peripheral vein;[195] however, this is rarely a problem in ICU patients since they usually receive the drug via a central line. Long term infusions of propofol are associated with a progressive increase in serum lipid levels (section 1.5.1). Respiratory acidosis during weaning of ventilation has been reported in 3 to 10% of patients sedated in the ICU.[6] Anaphylaxis or anaphylactoid reactions to propofol, confirmed by skin tests, have been occasionally reported after either initial administration or re-exposure.[196-198] Green discoloration of the urine may be seen, particularly after long term administration.[199-202] The effect is transient and does not adversely affect renal function.[199] Tolerance to the sedative effects of the drug, necessitating increased dosages, has been reported in patients receiving the drug for more than 7 days (section 1.1).

5. Dosage and Administration

To minimise the risk of hypotension, continuous infusions of propofol in mechanically ventilated adult patients in the ICU should be initiated at a low rate [0.3 mg/kg/h (5 μg/kg/min)] and adjusted according to clinical requirements. Upward adjustments in increments of 0.3 to 0.6 mg/kg/h (5 to 10 μg/kg/min) at intervals of at least 5 minutes may be made. Most patients require a maintenance infusion rate ranging from 0.3 to 3 mg/kg/h (5 to 50 μg/kg/min) although higher rates may be necessary. Patients who have received large doses of opioids should be given reduced propofol dosages. Bolus doses of propofol 10 to 20mg to rapidly increase the level of sedation should be used only in patients in whom the risk of hypotension is low. A daily evaluation of the degree of sedation and CNS function should be carried out to determine the minimum dosage required.[6] For patients receiving enteral or parenteral nutrition, calculations of the dosage of intravenous lipids should be adjusted to include the lipid content of the propofol infusion. The use of propofol for children in ICU sedation is not currently recommended.[6]

6. Place of Propofol in Intensive Care Sedation

The ICU is an extremely stressful environment in which patients often experience anxiety, pain and inability to sleep. Sedation for patients in the ICU is used primarily to increase patient comfort through the provision of anxiolysis, analgesia and sedation and to minimise resistance to mechanical ventilation without causing autonomic or cardiopulmonary adverse effects.[203,204] Inhibition of stress- and pain-induced sympathetic responses is also important.[40] There is no single depth of sedation that is appropriate for all patients; clinicians need to take into account the underlying medical condition of the patient and the expected duration of sedation.[203] In general, nonparalysed patients should be sedated but easily arousable, whereas paralysed patients require sedation to unconsciousness.[203,204]

Agents used for ICU sedation can be divided into those which are principally analgesic (e.g. opioids) and those which are principally hypnotic (e.g. benzodiazepines, propofol). These groups of drugs are often used in combination in order to maximise clinical benefits at the lowest possible dosages. Benzodiazepines such as diazepam, lorazepam and midazolam are commonly used sedative agents in the ICU. They are effective sedatives and also have significant anxiolytic, amnesic and anticonvulsant effects.[204] Benzodiazepines have minimal cardiovascular effects and usually cause only mild respiratory depression.[205] However, drug accumulation after their prolonged administration can result in delayed recovery. Additionally, withdrawal syndromes, especially after high dose long term use, have been reported after discontinuation of benzodiazepines.[204]

Propofol has many qualities that make it an attractive alternative for the sedation of mechani-

cally ventilated patients in the ICU. It has a rapid onset and short duration of action, and its metabolism does not appear to be affected by renal or hepatic dysfunction. Recovery from sedation is rapid even after prolonged infusions. The reductions in systemic vascular resistance and heart rate associated with propofol mitigate pain- and stress-induced sympathetic responses. Additionally, propofol has anticonvulsant properties, is usually associated with good haemodynamic stability and does not have clinically significant adrenocortical suppressant effects.

Propofol has been shown to be an effective agent for the sedation of mechanically ventilated patients in the ICU including postsurgical (e.g. cardiac, abdominal, orthopaedic surgery) and general medical patients and patients with head trauma. It may be especially useful in postcardiac surgery where rapid extubation following a period of ventilation is desirable. In short term (<3 days) studies in general medical or postsurgical patients, propofol provided a quality of sedation at least as good as that provided by midazolam and tended to produce a faster recovery (time to spontaneous ventilation, time to extubation) than midazolam after discontinuation of administration.

In a few trials in patients with head trauma, propofol provided adequate sedation and maintenance of CPP. However, the tendency of propofol to decrease MAP (and thus the potential to decrease CPP) is of concern in these patients, although this has not been a problem in studies to date. Whether propofol has any advantages over barbiturates or opioids in patients with head trauma remains to be determined in future comparative trials.

The short duration of action of propofol allows easy titration of the level of sedation. This is a useful property when monitoring neurological function, performing procedures (e.g. physiotherapy) that require changes in the levels of sedation and in maintaining a day-night sleep pattern. The rapid recovery seen with propofol could also potentially reduce overall medical costs if this would allow patients to be discharged from the ICU sooner, although time to discharge has been measured in only 2 studies to date. Indeed, in 1 pharmacoeconomic evaluation, even though drug acquisition costs were higher for propofol than midazolam, total medical costs for patients sedated for less than 24 hours were lower in propofol-treated patients because of higher postsedation care costs than in patients receiving midazolam.

The benefits of the rapid recovery profile from propofol are less clear in patients requiring sedation long term; rapid reversal is rarely necessary in these patients.[204] Additionally, there is less likely to be an economic advantage for long term propofol sedation use since the increased total drug acquisition costs associated with longer term use would be more likely to exceed the savings obtained by a fast recovery. Other potential drawbacks to the use of propofol for long term sedation include the potential for hyperlipidaemia and the development of tolerance to the sedative effects of the drug. Moreover, there is a need to prepare propofol immediately prior to administration and to discard unused portions after 12 hours. This has the potential to increase drug wastage and thus to raise drug costs.

While the usefulness of propofol for ICU sedation is well established, some areas require further investigation. Additional studies in paediatric patients are required to establish the relative safety of propofol in this age group. More data on the postweaning pulmonary effects of propofol, particularly in patients with adult respiratory distress syndrome, are needed. Additional experience with the long term use of propofol and in patients with head trauma (both with emphasis on haemodynamic and cerebral outcomes) is also required. Importantly, pharmacoeconomic evaluations are needed to determine those situations where propofol is cost effective.

In summary, although some aspects regarding its optimum use from clinical and pharmacoeconomic perspectives need further clarification, there is considerable evidence to establish that propofol is a useful alternative to benzodiazepines and/or other hypnotics or analgesics for ICU sedation. The rapid recovery of patients after discontinuation of

the drug gives propofol an advantage over existing sedative agents, particularly in patients requiring short term sedation.

References

1. Bryson HM, Fulton B, Faulds D. Propofol: an update of its use in anaesthesia and conscious sedation. Drugs 1995 Sep; 50 (3): 513-59
2. Whitehead C, Sanders LD, Oldroyd G, et al. The subjective effects of low-dose propofol: a double-blind study to evaluate dimensions of sedation and consciousness with low-dose propofol. Anaesthesia 1994 Jun; 49: 490-6
3. Smith I, Monk TG, White PF, et al. Propofol infusion during regional anesthesia: sedative amnestic, and anxiolytic properties. Anesth Analg 1994; 79: 313-9
4. Karski JM, Teasdale SJ, Boylan J, et al. Propofol for continuous intravenous sedation after aortocoronary bypass graft surgery. Dose finding study [abstract]. Can J Anaesth 1994 May; 41 (Pt 2): A17
5. O'Connor M, Stow P, Mortimer A, et al. Propofol to provide sedation after coronary artery bypass surgery. A comparison of two fixed rate infusion regimens. Acta Anaesthesiol Belg 1992; 43: 235-41
6. Zeneca Inc. Propofol prescribing information. Wilmington, DE, USA, 1995.
7. Barr J, Egan T, Feeley T, et al. Depth of sedation vs propofol concentration in mechanically ventilated ICU patients [abstract]. Anesthesiology 1992 Sep; 77 Suppl. (3A): A313
8. Polster MR, Gray PA, O'Sullivan G, et al. Comparison of the sedative and amnesic effects of midazolam and propofol. Br J Anaesth 1993 Jun; 70: 612-6
9. D'Athis F, Chardon P, Mathieu-Daudé JC, et al. Propofol for sedation in the intensive care unit. J Drug Dev 1989 Aug; 2 Suppl. 2: 61-4
10. Beller JP, Pottecher T, Lugnier A, et al. Prolonged sedation with propofol in ICU patients: recovery and blood concentration changes during periodic interruptions in infusion. Br J Anaesth 1988; 61: 583-8
11. Foster SJ, Buckley PM. A retrospective review of two years' experience with propofol in one intensive care unit. J Drug Dev 1989 Aug; 2 Suppl. 2: 73-4
12. Boyle WA, Shear JM, White PF, et al. Tolerance and hyperlipemia during long-term sedation with propofol [abstract]. Anesthesiology 1990 Sep; 73 Suppl. (3A): A245
13. Vinik HR, Bradley Jr EL, Kissin I. Triple anesthetic combination: propofol-midazolam-alfentanil. Anesth Analg 1994 Feb; 78: 354-8
14. Naguib M, Sari-Kouzel A. Thiopentone-propofol hypnotic synergism in patients. Br J Anaesth 1991 Jul; 67: 4-6
15. Short TG, Chui PT. Propofol and midazolam act synergistically in combination. Br J Anaesth 1991 Nov; 67: 539-45
16. Ben-Shlomo I, Finger J, Bar-Av E, et al. Propofol and fentanyl act additively for induction of anaesthesia. Anaesthesia 1993 Feb; 48: 111-3
17. Rudkin GE, Osborne GA, Curtis NJ. Intra-operative patient-controlled sedation. Anaesthesia 1991 Feb; 46: 90-2
18. Osborne GA, Rudkin GE, Jarvis DA, et al. Intra-operative patient-controlled sedation and patient attitude to control: a crossover comparison of patient preference for patient-controlled propofol and propofol by continuous infusion. Anaesthesia 1994 Apr; 49: 287-92
19. Borgeat A, Wilder-Smith OHG, Suter PM. The nonhypnotic therapeutic applications of propofol. Anesthesiology 1994 Mar; 80 (3): 642-56
20. Dyar O, Jhaveri R, Glass PSA, et al. Does propofol have analgesic properties? [abstract]. Anesth Analg 1992 Feb; 74: S78
21. Wilder-Smith O, Borgeat A. Analgesia with subhypnotic doses of thiopentone and propofol [letter]. Br J Anaesth 1991 Aug; 67: 226-7
22. Anker-Møller E, Spangsberg N, Arendt-Nielsen L, et al. Subhypnotic doses of thiopentone and propofol cause analgesia to experimentally induced acute pain. Br J Anaesth 1991 Feb; 66: 185-8
23. Grounds RM, Lalor JM, Lumley J, et al. Propofol infusion for sedation in the intensive care unit: preliminary report. BMJ 1987 Feb 14; 294: 397-400
24. Higgins TL, Yared J-P, Estafanous FG, et al. Propofol versus midazolam for intensive care unit sedation after coronary artery bypass grafting. Crit Care Med 1994 Sep; 22 (9): 1415-23
25. McMurray TJ, Collier PS, Carson IW, et al. Propofol sedation after open heart surgery: a clinical and pharmacokinetic study. Anaesthesia 1990 Apr; 45: 322-6
26. O'Connor MO, Stow P, Mortimer A, et al. Propofol to provide sedation after coronary artery by-pass surgery – a comparison of three fixed-rate infusion regimens. J Drug Dev 1989 Aug; 2 Suppl. 2: 135-7
27. Newman LH, McDonald JC, Wallace PGM, et al. Propofol infusion for sedation in intensive care. Anaesthesia 1987; 42: 929-37
28. Foëx P, Diedericks J, Sear JW. Cardiovascular effects of propofol. J Drug Dev 1991 Oct; 4 Suppl. 3: 3-9
29. Beyer R, Seyde WC. Long-term sedation (24h) in the intensive care unit: a comparison of propofol and midazolam. J Drug Dev 1991 Oct; 4 Suppl. 3: 67-8
30. Ebert TJ, Muzi M, Berens R, et al. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology 1992 May; 76: 725-33
31. Aitkenhead AR, Pepperman ML, Willatts SM, et al. Comparison of propofol and midazolam for sedation in critically ill patients. Lancet 1989 Sep 23; 2: 704-9
32. Abdel Barr TM, Lemmens HJM, Zwijsen JHMJ, et al. Baroreflex effects of propofol plus vecuronium or pancuronium [abstract no. A93]. Anesthesiology 1992 Sep; 77 (3A)
33. Sellgren J, Ejnell H, Elam M, et al. Sympathetic muscle nerve activity, peripheral blood flows, and baroreceptor reflexes in humans during propofol anesthesia and surgery. Anesthesiology 1994; 80: 534-44
34. Searle NR, Sahab P. Propofol in patients with cardiac disease. Can J Anaesth 1993 Aug; 40: 730-47
35. Roekaerts PMHJ, Huygen FJ, de-Lange S. Infusion of propofol versus midazolam for sedation in the intensive care unit following coronary artery surgery. J Cardiothorac Vasc Anesth 1993 Apr; 7: 142-7
36. Chaudhri S, Kenny GNC. Sedation after cardiac bypass surgery: comparison of propofol and midazolam in the presence of a computerized closed loop arterial pressure controller. Br J Anaesth 1992 Jan; 68: 98-9
37. Snellen F, Lauwers P, Demeyere R, et al. The use of midazolam versus propofol for short-term sedation following coronary artery bypass grafting. Intensive Care Med 1990; 16 (5): 312-6
38. Langley MS, Heel RC. Propofol: a review of its pharmacodynamic and pharmacokinetic properties and use an intravenous anaesthetic. Drugs 1988; 35: 334-72
39. Sebel PS, Lowdon JD. Propofol: a new intravenous anaesthetic. Anesthesiology 1989; 71: 260-77

40. McMurray TC. Propofol for sedation following cardiac surgery. J Drug Dev 1991 Oct; 4 Suppl. 3: 51-8
41. Ronan KP, Gallagher TJ, George B, et al. Comparison of propofol and midazolam for sedation in intensive care unit patients. Crit Care Med 1995 Feb; 23 (2): 286-93
42. Conti G, Dell'Utri D, Vilardi V, et al. Propofol induces bronchodilation in mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. Acta Anaesthesiol Scand 1993 Jan; 37: 105-9
43. Conti G, Ferretti A, Tellan G, et al. Propofol induces bronchodilation in a patient mechanically ventilated for status asthmaticus [letter]. Intensive Care Med 1993 Jul; 19: 305
44. Pedersen CM. The effect of sedation with propofol on postoperative bronchoconstriction in patients with hyperreactive airway disease. Intensive Care Med 1992 Mar; 18: 45-6
45. Vandesteene A, Trempont V, Engelman E, et al. Effect of propofol on cerebral blood flow and metabolism in man. Anaesthesia 1988; 43 Suppl.: 42-3
46. Pinaud M, Lelausque J-N, Chetanneau A, et al. Effects of propofol on cerebral hemodynamics and metabolism in patients with brain trauma. Anesthesiology 1990 Sep; 73: 404-9
47. Stephan S, Sonntag H, Schenk HD, et al. Effects of Disoprivan on cerebral blood flow, cerebral oxygen consumption, and cerebral vascular reactivity [in German]. Anesthetist 1987; 36: 60-5
48. Alkire MT, Haier RJ, Barker SJ, et al. Cerebral metabolism during propofol anesthesia in humans studied with positron emission tomography. Anesthesiology 1995 Feb; 82 (2): 393-403
49. Stewart L, Bullock R, Rafferty C, et al. Propofol sedation in severe head injury fails to control high ICP but reduces brain metabolism. Acta Neurochir 1994; 60 Suppl: 544-6
50. Farling PA, Johnston JR, Coppel DL. Propofol infusion for sedation of patients with head injury in intensive care: a prelimilary report. Anaesthesia 1989; 44: 222-6
51. Todaro C, Iacopino D, Gambardella G, et al. Il propofol nella sedazione del traumatizzato cranico grave ricoverato in rianimazione monitoraggio con doppler transcranico. In: Montanini S, Fodale V, editors. Anestesia Endovenosa in Particolari Situazioni Cliniche e Sedazione in Terapia Intensiva; Apr 12-14, Taormina, 1991; 1: 295-9
52. Vezzani A, Barbagallo M, Furlan A, et al. Neurological assessment and ICP control in severe head injury: use of propofol as a short-acting sedative agent. J Drug Dev 1991 Oct; 4 Suppl. 3: 114-5
53. Mergaert C, Herregods L, Rolly G, et al. The effect of a 24-h propofol or fentanyl sedation on intracranial pressure. Eur J Anaesthesiol 1991 Jul; 8: 324-5
54. Farling PA, Johnston JR, Coppel DL. Propofol infusion compared with morphine and midazolam bolus doses for sedation of patients with severe head injuries in the intensive care unit. J Drug Dev 1989 Aug; 2 Suppl. 2: 97-8
55. Seifert HA, Blouin RT, Conard PF, et al. Sedative doses of propofol increase beta activity of the processed electroencephalogram. Anesth Analg 1993 May; 76: 976-8
56. Reddy RV, Moorthy SS, Mattice T, et al. An electroencephalographic comparison of effects of propofol and methohexital. Electroencephalogr Clin Neurophysiol 1992 Aug; 83: 162-8
57. Veselis RA, Reinsel RA, Wronski M, et al. EEG and memory effects of low-dose infusions of propofol. Br J Anaesth 1992 Sep; 69: 246-54
58. Sneyd RJ, Samra SK, Davidson B, et al. Electrophysiologic effects of propofol sedation. Anesth Analg 1994; 79: 1151-8
59. Van HJ, Tempelhoff R, Jellish WS, et al. Use of EEG for determining propofol requirement during neuroanesthesia [abstract]. Anesthesiology 1990 Sep; 73 Suppl. 3A: A202
60. Illievich UM, Petricek W, Schramm W, et al. Electroencephalographic burst suppression by propofol infusion in humans: hemodynamic consequences. Anesth Analg 1993 Jul; 77: 155-60
61. McBurney JW, Teiken PJ, Moon MR. Propofol for treating status epilepticus. J Epilepsy 1994; 7 (1): 21-2
62. MacKenzie SJ, Kapadia F, Grant IS. Propofol infusion for control of status epilepticus. Anaesthesia 1990 Dec; 45: 1043-5
63. Alia G, Natale E, Mattaliano A. On two cases of status epilepticus treated with propofol. Epilepsia 1991; 32 Suppl. 1: 77
64. Pitt-Miller PL, Elcock BJ, Maharaj M. The management of status epilepticus with a continuous propofol infusion. Anesth Analg 1994 Jun; 78: 1193-4
65. Wood PR, Browne GPR, Pugh S. Propofol infusion for the treatment of status epilepticus. Lancet 1988 Feb 27; 1: 480-1
66. Yanny HF, Christmas D. Propofol infusions for status epilepticus [letter]. Anaesthesia 1988; 43: 514
67. Borgeat A, Wilder-Smith OHG, Despland PA, et al. Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation. Br J Anaesth 1993 Apr; 70: 459-61
68. Bevan JC. Propofol-related convulsions. Can J Anaesth 1993 Sep; 40: 805-9
69. Cook S, Palma O. Propofol as a sole agent for prolonged infusion in intensive care. J Drug Dev 1989 Aug; 2 Suppl. 2: 65-7
70. Gottardis M, Khünl-Brady KS, Koller W, et al. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. Br J Anaesth 1989; 62: 393-6
71. Peduto VA, Angioi M, Sitzia A, et al. Caratteristiche cliniche ed implicazioni metaboliche della sedazione con propofolo in infusione continue di lunga durata nel paziente critico. In: Montanini S, Fodale V, editors. Anestesia endovenosa in particolari situazioni cliniche e sedazione in terapia intensiva; 12-14 Apr, Taormina, 1991; 1: 103-8
72. Gempeler F, Elston AC, Thompson SP, et al. Propofol and intralipid cause creaming of serum from critically ill patients. Anaesthesia 1994 Jan; 49: 17-20
73. Launo C, Riverso P, Bonilauri M, et al. General anaesthesia and protection from surgical stress: comparsion of three techniques [in Italian]. Acta Anaesthesiol Ital 1992; 43 (4): 533-8
74. Adams HA, Schmitz CS, Baltes-Götz B. Propofol vs. isoflurane: endocrine stress response, haemodynamic reaction, and recovery after total intravenous and inhalation anaesthesia [in German]. Anaesthesist 1994; 43: 730-7
75. O'Flaherty D, Catania A, Krishnan S, et al. Total intravenous anesthesia with propofol profoundly inhibits cortisol response to stress [abstract]. Anesth Analg 1992 Feb; 74: S223
76. Harris CE, Grounds RM, Murray AM, et al. Propofol for long-term sedation in the intensive care unit. A comparison with midazolam. Anaesthesia 1990 May; 45: 366-72
77. Ramsay MAE, Savege TM, Simpson BRJ, et al. Controlled sedation with alphaxalone-alphadolone. BMJ 1974 Jun 22; 2: 656-9
78. Mangano DT, Siliciano D, Hollenberg M, et al. Postoperative myocardial ischemia: therapeutic trials using intensive analgesia following surgery. Anesthesiology 1992 Mar; 76 (3): 342-53
79. Plunkett JJ, Reeves JD, Ramsay JG, et al. Postoperative response to stress: propofol versus standard care for sedation after coronary artery bypass graft surgery [abstract]. Anesthesiology 1994 Sep; 81 (3A): A143

80. Murphy PG, Myers D, Webster NR, et al. The anti-oxident potential of propofol. Br J Anaesth 1991 Aug; 67: 209P-10P
81. Green TR, Bennett SR, Nelson VM. Specificity and properties of propofol as an antioxidant free radical scavenger. Toxicol Appl Pharmacol 1994; 129: 163-9
82. Aarts L, van der Hee R, Dekker I, et al. The widely used anesthetic agent propofol can replace α-tocopherol as an antioxidant. FEBS Lett 1995 Jan 2; 357 (1): 83-5
83. Stevenson GW, Hall SC, Rudnick S, et al. The effect of anesthetic agents on the human immune response. Anesthesiology 1990 Mar; 72: 542-52
84. Pirttikangas C-O, Perttilä J, Salo M. Propofol emulsion reduces proliferative responses of lymphocytes from intensive care patients. Intensive Care Med 1993 Jul; 19: 299-302
85. O'Donnell NG, McSharry CP, Wilkinson PC, et al. Comparison of the inhibitory effect of propofol, thiopentone and midazolam on neutrophil polarization *in vitro* in the presence or absence of human serum albumin. Br J Anaesth 1992 Jul; 69: 70-4
86. Krumholz W, Endrass J, Hempelmann G. Propofol inhibits phagocytosis and killing of *Staphylococcus aureus* and *Escherichia coli* by polymorphonuclear leukocytes in vitro. Can J Anaesth 1994 May; 41 (Pt 1): 446-9
87. Davidson JAH, Boom SJ, Pearsall FJ, et al. Comparison of the effects of four i.v. anaesthetic agents on polymorphonuclear leucocyte function. Br J Anaesth 1995; 74: 315-8
88. Pirttikangas C-O, Salo M, Riutta A, et al. Effects of propofol and intralipid on immune response and prostaglandin E_2 production. Anaesthesia 1995 Apr; 50: 317-21
89. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. Clin Pharmacokinet 1989 Nov; 17: 308-26
90. Cockshott ID, Douglas EJ, Prys-Roberts C, et al. The pharmacokinetics of propofol during and after intravenous infusion in man. Eur J Anaesthesiol 1990 Jul; 7: 265-75
91. Gin T, Yau G, Chan K, et al. Disposition of propofol infusions for Caesarean section. Can J Anaesth 1991 Jan; 38: 31-6
92. Massey NJA, Sherry KM, Oldroyd S, et al. Pharmacokinetics of an infusion of propofol during cardiac surgery. Br J Anaesth 1990 Oct; 65: 475-9
93. Morgan DJ, Campbell GA, Crankshaw DP. Pharmacokinetics of propofol when given by intravenous infusion. Br J Clin Pharmacol 1990 Jul; 30: 144-8
94. Wessén A, Persson PM, Nilsson A, et al. Clinical pharmacokinetics of propofol given as a constant-rate infusion and in combination with epidural blockade. J Clin Anesth 1994 May-Jun; 6: 193-8
95. Cockshott ID, Douglas EJ, Prys-Roberts C, et al. Pharmacokinetics of propofol during and after i.v. infusion in man. Br J Anaesth 1987; 59: 941P-2P
96. Gepts E, Camu F, Cockshott D, et al. Disposition of propofol administered as constant rate intravenous infusions in humans. Anesth Analg 1987; 66: 1256-63
97. Gepts E, Jonckheer K, Maes V, et al. Disposition kinetics of propofol during alfentanil anaesthesia. Anaesthesia 1988; 43 Suppl.: 8-13
98. Bailie GR, Cockshott ID, Douglas EJ, et al. Pharmacokinetics of propofol during and after long term continuous infusion for maintenance of sedation in ICU patients. Br J Anaesth 1992 May; 68: 486-91
99. Albanese J, Martin C, Lacarelle B, et al. Pharmacokinetics of long-term propofol infusion used for sedation in ICU patients. Anesthesiology 1990 Aug; 73: 214-7
100. Schüttler J, Schwilden H, Stoeckel H. Pharmacokinetic-dynamic modeling of diprivan. Anesthesiology 1986; 65 (3A): A549
101. Kirkpatrick T, Cockshott ID, Douglas EJ, et al. Pharmacokinetics of propofol (Diprivan) in elderly patients. Br J Anaesth 1988; 60: 146-50
102. Altmayer P, Büch U, Larsen R, et al. Binding of propofol to native human serum, human serum albumin and human hemoglobin. Int J Clin Pharmacol Ther Toxicol 1992 Aug; 30: 296
103. Altmayer P, Büch U, Büch HP, et al. Propofol binding in human blood [abstract]. Br J Anaesth 1994 Feb; 72 Suppl. 1: 86
104. Simmons PJ, Cockshott ID, Douglas EJ, et al. Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of ^{14}C-propofol. Xenobiotica 1988; 18 (4): 429-40
105. Gray PA, Park GR, Cockshott ID, et al. Propofol metabolism in man during the anhepatic and reperfusion phases of liver transplantation. Xenobiotica 1992 Jan; 22: 105-14
106. Dogra S, Isaac PA, Cockshott ID, et al. Pulmonary extraction of propofol in post-cardiopulmonary by-pass patients. J Drug Dev 1989 Aug; 2 Suppl. 2: 133
107. Lange H, Stephan H, Rieke H, et al. Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery. Br J Anaesth 1990 May; 64: 563-70
108. Shafer A, Doze VA, Shafer SL, et al. Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. Anesthesiology 1988 Sep; 69: 348-56
109. Servin F, Farinotti R, Haberer J-P, et al. Propofol infusion for maintenance of anesthesia in morbidly obesity patients receiving nitrous oxide. Anesthesiology 1993 Apr; 78: 657-65
110. Servin F, Cockshott ID, Farinotti R, et al. Pharmacokinetics of propofol infusions in patients with cirrhosis. Br J Anaesth 1990 Aug; 65: 177-83
111. Van Obbergh LJ, Raoof AA, Verbeeck RK. Pharmacokinetics of propofol in children with end stage liver cirrhosis and billiary atresia (BA) [abstract]. Anesth Analg 1994; 78 Suppl. 1: S503
112. Nathan N, Debord J, Narcisse F, et al. Pharmacokinetics of propofol and its conjugates after continuous infusion in normal and renal failure patients [abstract]. Br J Anaesth 1993 May; 70 Suppl. 1: 78
113. Kirvelä M, Olkkola KT, Rosenberg PH, et al. Pharmacokinetics of propofol and haemodynamic changes during induction of anaesthesia in uraemic patients. Br J Anaesth 1992 Feb; 68: 178-82
114. Cazalaa JB, Trouvin JH, Nguyen HN, et al. The pharmacokinetics of propofol infusion in children with end-stage renal disease undergoing renal transplantation. In: Focus on infusion: intravenous anaesthesia. Proceedings of Intravenous Anasthesia Sessions, Cannes, 28-29 Apr, 1991; 1: 208-9
115. Morcos WE, Payne JP. The induction of anaesthesia with propofol ('Diprivan') compared in normal and renal failure patients. Postgrad Med J 1985; 61 Suppl. 3: 62-3
116. Debruyne D, Tartiere J, Albessard F, et al. Clinical pharmacokinetics of propofol in postoperative sedation after orthotopic liver transplantation. Clinical Drug Investigation 1995; 9 (1): 8-15
117. Nies AS, Shand DG, Wilkinson GR. Altered hepatic blood flow and drug disposition. Clin Pharmacokinet 1976; 1: 135-55
118. Cockshott ID, Briggs LP, Douglas EJ, et al. Pharmacokinetics of propofol in female patients. Br J Anaesth 1987; 59: 1103-10
119. Grundmann U, Ziehmer M, Kreienmeyer J, et al. Propofol and volatile anaesthetics. Br J Anaesth 1994 Feb; 72 Suppl. 1: 88

120. Miller DR, Martineau RJ, Greenway D, et al. Alfentanil pharmacokinetics during total intravenous anaesthesia with propofol in patients undergoing peripheral vascular surgery [abstract]. Can J Anaesth 1992 May; 39: A15
121. Avram MJ, Sanghvi R, Henthorn TK, et al. The pharmacokinetics of alfentanil administered by multiple bolus and continuous infusion in the presence of either nitrous oxide or propofol [abstract]. Anesthesiology 1991 Sep; 75 Suppl. (3A): A320
122. Benoni G, Cuzzolin L, Gilli E, et al. Pharmacokinetics of propofol: influence of fentanyl administration [abstract]. Eur J Pharmacol 1990 Jul; 183: 1457-8
123. Gill SS, Wright EM, Reilly CS. Pharmacokinetic interaction of propofol and fentanyl: single bolus injection study. Br J Anaesth 1990 Dec; 65: 760-5
124. Dixon J, Roberts FL, Tackley RM, et al. Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol. Br J Anaesth 1990 Feb; 64: 142-7
125. De Gasperi A, Cristalli A, Noé L, et al. Fentanyl pre-treatment does not affect the pharmacokinetic profile of an induction dose of propofol in adults. Eur J Anaesthesiol 1994 Mar; 11: 89-93
126. Chen TL, Ueng TH, Chen SH, et al. Human cytochrome P450 mono-oxygenase system is suppressed by propofol. Br J Anaesth 1995; 74: 558-62
127. Van Brandt N, Hantson P, Horsmans Y, et al. Absence of influence of enteral nutrition on propofol long-term pharmacokinetics [abstract]. Br J Anaesth 1995; 74 Suppl. 1: 60-1
128. Wolfs C. Propofol combined with peridural analgesia for sedation in post-abdominal surgery patients. J Drug Dev 1989 Aug; 2 Suppl. 2: 49-51
129. Maitan S, Garelli A, Lega P, et al. Sedazione in rianimazione: infusione prolungata di propofol in un paziente critico. Ruolo attuale degli anestetici endovenosi in anestesia, rianimazione e terapia intensiva; 1990 27-29 Apr; Padova, 413-419.
130. Boyle WA, Shear JM, White PF, et al. Long-term sedative infusion in the intensive care unit: propofol versus midazolam. J Drug Dev 1991 Oct; 4 Suppl. 3: 43-5
131. Carrasco G, Molina R, Costa J, et al. Propofol vs midazolam in short-, medium-, and long-term sedation of critically ill patients: a cost-benefit analysis. Chest 1993 Feb; 103: 557-64
132. Früh B. A comparison of propofol and midazolam for long-term sedation of ventilated patients: a cross-over study. J Drug Dev 1989 Aug; 2 Suppl. 2: 45-7
133. Wolfs C, Kimbimbi P, Colin L, et al. A comparison of propofol/fentanyl and midazolam/fentanyl for ICU sedation after abdominal surgery. J Drug Dev 1991 Oct; 4 Suppl. 3: 69-71
134. Millane TA, Bennett ED, Grounds RM. Isoflurane and propofol for long-term sedation in the intensive care unit. A crossover study. Anaesthesia 1992 Sep; 47: 768-74
135. Vandenberghe J, Rucquoi M, Camu F. Propofol sedation for controlled ventilation of post-operative aortic surgery patients: an evaluation of haemodynamics and sedation. J Drug Dev 1991 Oct; 4 Suppl. 3: 65-6
136. Nollet G, Verbeke J. Comparison of propofol and alfentanil as sedative agents after coronary artery by-pass graft. J Drug Dev 1991 Oct; 4 Suppl. 3: 62-4
137. Herregods L, Mergaert C, Rolly G, et al. Comparison of the effects of 24-hour propofol or fentanyl infusions on intracranial pressure. J Drug Dev 1989 Aug; 2 Suppl. 2: 99-100
138. Pearson K, Kruse G, Demetrion E. Sedation of patients with severe head injury: a randomized prospective comparison of propofol versus morphine and barbiturates [abstract]. Anesthesiology 1991 Sep; 75 Suppl.: A248
139. Plainer B, Weinstabl C, Spiss CK, et al. Propofol vs. midazolam in combination with sufentanil for continuous sedation in the neurosurgical unit. J Drug Dev 1989 Aug; 2 Suppl. 2: 101-3
140. Escarment J, Donne X, Palmier B, et al. Quality of sedation and neurologic evaluation following surgery of the posterior cranial fossa: the importance of propofol [in French]. Cah Anesthesiol 1992; 40: 29-35
141. Dewandre J, Van Bos R, Van Hemelrijck J, et al. A comparison of the 2% and 1% formulations of propofol during anaesthesia for craniotomy. Anaesthesia 1994 Jan; 49: 8-12
142. Clarke TNS. Propofol compared with midazolam for sedation following prolonged neurosurgery. J Drug Dev 1991 Oct; 4 Suppl. 3: 108-9
143. Degauque C, Dupuis A. A study to compare the use of propofol and midazolam for the sedation of patients with acute respiratory failure. J Drug Dev 1991 Oct; 4 Suppl. 3: 95-7
144. Santamaria LB, Praticò C, Venuti FS, et al. Sedation with propofol in COPD patients in the ICU [in Italian]. Minerva Anestesiol 1991 Jul-Aug; 57: 417-22
145. Macrae D, James I. Propofol infusion in children [letter]. BMJ 1992 Oct 17; 305: 953
146. Marx CM, Lebovitz DG, Blumer JL, et al. Preliminary evaluation of propofol monotherapy for sedation of mechanically ventilated children [abstract]. Pharmacotherapy 1992; 12 (3): 262
147. Nørreslet J, Wahlgreen C. Propofol infusion for sedation of children. Crit Care Med 1990 Aug; 18 (8): 890-2
148. Steur R. Use of propofol for sedation in young children. Intensive Care Med 1992; 18 Suppl. 2: S87
149. Matthews AJ. Sedation, muscle relaxation and analgesia in PICU. Care of the Critically Ill 1991 Jan/Feb; 8 (1): 34
150. Eddleston JM, Pollard BJ, Blades JF, et al. The use of propofol for sedation of critically ill patients undergoing haemodiafiltration. Intensive Care Med 1995; 21 (4): 342-7
151. Borgeat A, Dessibourg C, Rochani M, et al. Sedation by propofol in tetanus – is it a muscular relaxant? Intensive Care Med 1991; 17 (7): 427-9
152. Borgeat A, Popovic V, Schwander D. Efficiency of a continuous infusion of propofol in a patient with tetanus. Crit Care Med 1991 Feb; 19: 295-7
153. Ermakov JS, Hoyt J, Crippen D, et al. Conscious sedation with propofol in patients with delirium tremens [abstract]. Crit Care Med 1995; 23 (1) Suppl: A68
154. Guise PA. Asystole following propofol and fentanyl in an anxious patient. Anaesth Intensive Care 1991 Feb; 19: 116-8
155. Dandoy M, Poisson F, Lampl E. Cardiac arrest during propofol and fentanyl anaesthesia [in French]. Ann Franc Anesth Rean 1990; 9 (5): 465
156. Egan TD, Brock-Utne JG. Asystole after anesthesia induction with a fentanyl, propofol, and succinylcholine sequence. Anesth Analg 1991 Dec; 73: 818-20
157. James MFM, Reyneke CJ, Whiffler K. Heart block following propofol: a case report. Br J Anaesth 1989; 62: 213-5
158. Munoz R, Goldberg ME, Cantillo J, et al. Perioperative arrhythmias with a propofol-based anesthetic. J Clin Anesth 1991 Mar-Apr; 3: 149-52
159. Collier C, Kelly K. Propofol and convulsions – the evidence mounts. Anaesth Intensive Care 1991 Nov; 19: 573-5
160. Finley GA, MacManus B, Sampson SE, et al. Delayed seizures following sedation with propofol. Can J Anaesth 1993 Sep; 40: 863-5
161. Mäkelä JP, Iivanainen M, Pieninkeroinen IP, et al. Seizures associated with propofol anesthesia. Epilepsia 1993 Sep-Oct; 34: 832-5

162. Russell D, Kenny GNC. Convulsion following day case anaesthesia [letter]. Anaesthesia 1993 May; 48: 444
163. Herrema IH. A 10-second convulsion during propofol injection? Anaesthesia 1989 Aug; 44: 700
164. Thomas JS, Boheimer NO. An isolated grand mal seizure 5 days after propofol anaesthesia. Anaesthesia 1991 Jun; 46: 508
165. Jones GW, Boykett MH, Klok M. Propofol, opisthotonus and epilepsy [letter]. Anaesthesia 1988; 43: 905
166. DeFriez CB, Wong HC. Seizures and opisthotonos after propofol and anesthesia. Anesth Analg 1992 Oct; 75: 630-2
167. Ries CR, Scoates PJ, Puil E. Opisthotonos following propofol: a nonepileptic perspective and treatment strategy. Can J Anaesth 1994 May; 41 (Pt 1): 414-9
168. Gildar J. Another case report of opisthotonos and propofol. Anesth Analg 1993 May; 76: 1171
169. Haynes SR, Best CJ. Opisthotonus and propofol [letter]. Anaesthesia 1992 May; 47: 442
170. Laycock GJA. Opisthotonos and propofol: a possible association [letter]. Anaesthesia 1988; 43: 257
171. Victory RAP, Magee D. A case of convulsion after propofol anaesthesia [letter]. Anaesthesia 1988; 43: 904
172. Reynolds LM, Koh JL. Prolonged spontaneous movement following emergence from propofol/nitrous oxide anesthesia. Anesth Analg 1993 Jan; 76: 192-3
173. Patel P, Knights DT. Abnormal movements following recovery from propofol, alfentanil and nitrous oxide anaesthesia [letter]. Anaesthesia 1992 May; 47: 442-3
174. McHugh P. Acute choreoathetoid reaction to propofol [letter]. Anaesthesia 1991 May; 46: 425
175. Propofol: adverse neurological events. WHO Drug Info 1993; 7 (3): 127
176. Borgeat A, Wilder-Smith OHG, Tassonyi E, et al. Propofol and epilepsy: time to clarify. Anesth Analg 1994 Jan; 78: 198-9
177. Au J, Walker WS, Scott DHT. Withdrawal syndrome after propofol infusion. Anaesthesia 1990 Sep; 45: 741-2
178. Valente JF, Anderson GL, Branson RD, et al. Disadvantages of prolonged propofol sedation in the critical care unit. Crit Care Med 1994 Apr; 22: 710-2
179. Arduino MJ, Bland LA, McAllister SK, et al. Microbial growth and endotoxin production in the intravenous anesthetic propofol. Infect Control Hosp Epidemiol 1991 Sep; 12: 535-9
180. Tessler M, Dascal A, Gioseffini S, et al. Growth curves of Staphylococcus aureus, Candida albicans, and Moraxella osloensis in propofol and other media. Can J Anaesth 1992 May; 39 (5 Pt 1): 509-11
181. Berry CB, Gillespie T, Hood J, et al. Growth of micro-organisms in solutions of intravenous anaesthetic agents. Anaesthesia 1993 Jan; 48: 30-2
182. Sosis MB, Braverman B. Growth of *Staphylococcus aureus* in four intravenous anesthetics. Anesth Analg 1993 Oct; 77: 766-8
183. Thomas DV. Propofol supports bacterial growth [letter]. Br J Anaesth 1991 Feb; 66: 274
184. Postsurgical infections associated with an extrinsically contaminated intravenous anesthetic agent – California, Illinois, Maine, and Michigan, 1990. MMWR Morb Mortal Wkly Rep 1990 Jun 29; 39: 426-7, 433
185. Veber B, Gachot B, Bedos JP, et al. Severe sepsis after intravenous injection of contaminated propofol [letter]. Anesthesiology 1994 Mar; 80: 712
186. Daily MJ, Dickey JB, Packo KH. Endogenous *Candida* endophthalmitis after intravenous anesthesia with propofol. Arch Ophthalmol 1991 Aug; 109: 1081-4
187. Bennett SN, McNeil MM, Bland LA, et al. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. N Engl J Med 1995 Jul 20; 333 (3): 147-54
188. Parke TJ, Stevens JE, Rice ASC, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. BMJ 1992 Sep 12; 305: 613-6
189. Strickland RA, Murray MJ. Fatal metabolic acidosis in a pediatric patient receiving an infusion of propofol in the intensive care unit: is there a relationship? Crit Care Med 1995; 23 (2): 405-9
190. Bray RJ. Fatal myocardial failure associated with a propofol infusion in a child [letter]. Anaesthesia 1995; 50: 94
191. ICI's Diprivan (propofol) anesthetic has no direct link to pediatric deaths in ICUs, FDA advisory committee finds; FDA asks ICI to pursue pediatric indication. FDC Rep Pink Sheet 1992 Sep 7; 54: 14
192. Imray JM, Hay A. Withdrawal syndrome after propofol [letter]. Anaesthesia 1991 Aug; 46: 704
193. Lanigan C, Sury M, Bingham R, et al. Neurological sequelae in children after prolonged propofol infusion [letter]. Anaesthesia 1992 Sep; 47: 810-1
194. Trotter C, Serpell MG. Neurological sequelae in children after prolonged propofol infusion. Anaesthesia 1992 Apr; 47: 340-2
195. Stark RD, Binks SM, Dutka VN, et al. A review of the safety and tolerance of propofol ('Diprivan'). Postgrad Med J 1985; 61 Suppl. 3: 152-6
196. McHale SP, Konieczko K. Anaphylactoid reaction to propofol. Anaesthesia 1992 Oct; 47: 864-5
197. de-Leon-Casasola OA, Weiss A, Lema MJ. Anaphylaxis due to propofol. Anesthesiology 1992 Aug; 77: 384-6
198. Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, et al. Life-threatening anaphylactoid reactions to propofol (Diprivan). Anesthesiology 1992 Aug; 77: 275-80
199. Bodenham A, Culank LS, Parak GR. Propofol infusion and green urine [letter]. Lancet 1987 Sep 26; 2: 740
200. Ananthanarayan C, Fisher JA. Why was the urine green? [letter]. Can J Anaesth 1995; 42: 87-8
201. Hughes KR, Armstrong RF. Continuous infusion of propofol [letter]. Anaesthesia 1988; 43: 331
202. Motsch J, Schmidt H, Bach A, et al. Long-term sedation with propofol and green discolouration of the liver. Eur J Anaesthesiol 1994; 11: 499-502
203. Burns AM, Shelly MP, Park GR. The use of sedative agents in critically ill patients. Drugs 1992 Apr; 43: 507-15
204. Wheeler AP. Sedation, analgesia, and paralysis in the intensive care unit. Chest 1993 Aug; 104: 566-77
205. Durbin CG. Neuromuscular blocking agents and sedative drugs: clinical uses and toxic effects in the critical care unit. Crit Care Clin 1991 Jul; 7: 489-506

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