The Use of Propofol in Anaesthesia and the Critically Ill

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Propofol is an alkylphenol or substituted phenol designated as 2,6-di-isopropylphenol (Figure 1). It was described in 1980 by James and Glenn and solubilised initially in Cremophor El. Because of the high incidence of pain on injection using this formulation, in 1984 Glenn and Hunter described a new formulation for propofol and subsequently it was approved for clinical use in the United Kingdom in 1986 and in the United States in 1988.

Propofol is highly lipid soluble and highly protein bound. It is formulated at present as an isotonic 1 % solution in an aqueous emulsion with 10 % soya bean oil, 2.25 % glycerol and 1.2 % purified egg phosphatide. It is also available as a 2 % solution for use as an infusion where there is a need to reduce the total fat load administered to a patient.

Dosage

The dose required to produce induction of anaesthesia varies between 1.5-2.5 mg kg⁻¹ and this dose is associated with both cardiovascular and respiratory depression. The end point to loss of consciousness using loss of eyelash reflex is not as well defined as with thiopentone. The dose required varies with age, pre-medication and rate of injection. Because of its short duration of action, it is ideally suited for day case anaesthesia. It may also be used by continuous infusion to maintain anaesthesia with a total intravenous technique and it has also been used in low dose to provide sedation during local anaesthetic procedures and as part of a sedative regimen in patients in the intensive care unit.

Pain on Intravenous Injection

Pain on intravenous administration of propofol in its current formulation is a serious problem as it may obviate what would otherwise be a relatively pleasant experience for most patients. Pain is a common occurrence affecting 30-90 % of patients (Helbo-Hanson et al 1988). Recently it has been clearly demonstrated that this side effect is a function of the drug itself and not the formulation. The pain induced was related to the aqueous
concentration of propofol as it was reduced by dilution of Diprivan with intralipid to a greater extent than dilution
with 5 % glucose (Klement and Arndt 1991). Various strategies have been proposed to reduce the pain on i.v.
administration including use of a large diameter vein (Scott et al 1988) and prior administration of aspirin or an
opioid (Bahar et al 1982).

The two commonest methods used for reducing pain on administration of propofol are cooling and the use of

In a prospective randomised double blind study, Gehan and colleagues (1991) showed that a dose of lignocaine
0.1 mg kg\(^{-1}\) significantly reduced the incidence of pain on injection and that there was no improvement when the
dosage was increased to 0.4 mg kg\(^{-1}\) when anaesthesia was induced with propofol 2.5 mg kg\(^{-1}\). The cause of pain
on injection is thought to be via a direct effect on the vein wall but in addition mediators such as kininogens are
also involved (Scott et al 1988, Stokes et al 1989). Overall, the effect of addition of lignocaine seems to reduce the
incidence of pain to the region of 5-15 %.

In a study designed to examine the effect of temperature on pain during injection Barker and colleagues
(1991) demonstrated that prior injection of cold saline reduced the incidence of pain and discomfort significantly
to 22 % compared with unmodified propofol (75 %) or similar to that after cold propofol (33 %) and propofol
with lignocaine 0.05 % (44 %).

Pharmacokinetics

Because of its high lipid solubility, propofol is distributed rapidly after i.v. administration and the blood
concentration declines rapidly with a short alpha half life of 2-4 minutes. It has a rapid elimination half life ; The
T\(_{1/2} \beta \) is 4-7 hours, the initial volume of distribution is 20-40 litres, and the volume of distribution at a steady state
is large, approximately 500 litres.

It is metabolised rapidly in the liver with a high hepatic extraction ratio and a clearance approaching that of
hepatic blood flow (1-2 litres/min\(^{-1}\)) which accounts for the rapid elimination half life. Propofol is highly bound
to plasma protein (exceeding 97 %).

Metabolism

Propofol is metabolised by the liver and excreted in the urine, approximately 40 % of a single i.v. bolus dose
undergoes glucuronidation before excretion and less than 1 % appears in the urine in unchanged form. 60 % of radio
labelled doses of propofol are conjugates of 2,6-di-isopropyl 1,4-quinol formed by hydroxylation of the phenol ring
(Kanto and Gepts 1989). It has been suggested that there may be interactions between propofol and alfentanil or
sufentanil involving the isoenzymes related to cytochrome P450. This suggestion followed the demonstration that
propofol in clinical concentrations was found to interfere with the oxidative metabolic degradation of alfentanil
and sufentanil in the microsomal fraction of human liver (Janicki et al 1992). This supports the suggestion that
when propofol and alfentanil are used in combination, there is mutual potentiation (Gepts et al 1988).

A recent investigation in patients undergoing orthotopic liver transplantation suggested that some degree of
extra hepatic metabolism of propofol occurred because of the presence of a propofol metabolite in urine when the
liver was excluded from circulation (Veroli et al 1992).

Interest in the potential hepatotoxicity of volatile anaesthetic agents led Murray and Trinnick (1992) to
examine the effect of induction of anaesthesia with propofol 2.0 mg kg\(^{-1}\) and maintenance with an infusion of
initially 10 mg kg\(^{-1}\) for 10 minutes followed by 8 and 6 mg per mg kg\(^{-1}\) hour\(^{-1}\) at 10 minute intervals followed by
adjustment to match the clinical response of the patient to surgery. In 13 patients in whom surgery lasted
approximately 10 hours, propofol anaesthesia was not associated with significant changes in glutathione-S-
transferase activity or plasma clearance of indocyanine green (Murray and Trinnick 1992).

Central Nervous System

In low doses propofol produces sedation followed by unconsciousness as the blood concentration increases. Increasing depths of anaesthesia lead to an increase in beta then delta waves (Newton 1991). Spontaneous movements occur frequently on induction of anaesthesia with propofol but these are not associated with the increase in EEG activity that take place during the delta wave phase.

Respiration and the Respiratory Tract

Propofol produces a dose related central respiratory depression leading to hypoventilation. The incidence of apnoea on induction of anaesthesia, for periods longer than 30 seconds, is about 80%. This is increased by increasing the dosage of propofol and by more rapid administration (Peacock et al 1990). When propofol infusions are used to maintain anaesthesia in spontaneously breathing patients hypoventilation is manifested by an increase in respiratory rate but a decrease in tidal volume. The CO₂ response to hypercapnia is depressed markedly, in common with all other anaesthetic agents, but the ventilatory response to hypoxia is also reduced even during conscious sedation (Blouin et al 1993).

A remarkable feature associated with induction of anaesthesia using propofol is the low incidence of hiccup, laryngeal spasm and bronchospasm which may occur with other intravenous anaesthetic agents. Examination of the vocal cords by fibre optic laryngoscopy revealed that after induction of anaesthesia the angle formed by the vocal cords decreased with thiopentone 4.4 mg per kg⁻¹ and propofol 2.5 mg kg⁻¹ but that the angle with the the latter was significantly larger. It was suggested that this was caused by the greater depressant effects of propofol on upper airway reflexes and that this would explain the low incidence of laryngeal spasm after induction of anaesthesia with propofol and the greater ability of patients to tolerate insertion of a laryngeal mask and Guedel airway than with thiopentone (Barker et al 1992).

It has been known for some time that it is possible to perform tracheal intubation with propofol alone. Recently there have been comparisons of various techniques using propofol on the ease of tracheal intubation. Several groups have assessed the effect of adding alfentanil to propofol 2.5 mg kg⁻¹. It was found that addition of alfentanil 20 μg kg⁻¹ caused acceptable intubating conditions in more than 70% of patients (Davidson and Gillespie 1993, Coghlan et al 1993) but that the further addition of lignocaine 1 mg kg⁻¹ led to acceptable intubating conditions in more than 90% of patients (Davidson et al 1993).

In a study on out-patients undergoing dental extraction, comparing propofol 2.5 mg kg⁻¹ and alfentanil 10 μg kg⁻¹ with propofol 2.5 mg kg⁻¹ and suxamethonium 1 mg kg⁻¹, successful intubation was achieved in more than 90% of the former but 100% of the latter group. However, there was significantly less sore throat in the propofol/alfentanil group and only 20% complained of myalgia compared with 74% in the suxamethonium group (Alcock et al 1993).

Cardiovascular Effects

It has been known for many years that induction of anaesthesia in healthy patients with propofol leads to a reduction in systolic arterial pressure of some 15-25% in. The degree of hypotension is greater with larger doses of propofol, with faster rates of administration, and is more marked in ASA 3 and 4 patients. It causes greater cardiovascular depression than equipotent doses of thiopentone.

Induction of anaesthesia with propofol using target controlled infusion is associated with a reduction in systolic
arterial pressure of 10–13% with little apnoea (Chaudri, White & Kenney 1992). Thus the extent of cardiovascular
depression is less than that associated with bolus administration (Coates et al 1987) or with continuous infusions
(Peacock et al 1990).

The cardiovascular effects of anaesthetic agents result from complex interactions between the effects of the
drug on systolic vascular resistance, myocardial contractility, baro-receptor activity and venous capacitance. Most
of the recent investigations of the effect of propofol on the circulation have been designed to examine the effect
of propofol on these separate components of the circulation.

There is little doubt that propofol depresses myocardial contractility. In chronically instrumented dogs,
propofol in a bolus of 5 mg kg⁻¹ followed by an infusion resulted in direct depression of myocardial contractility
as assessed by left ventricular dp/dt max together with a decrease in systolic vascular resistance (Pagel 1993).
However in an isolated rabbit heart model Mouren and colleagues (1994) could not demonstrate that propofol
depressed myocardial contractility whilst thiopentone did cause a substantial decrease in contractility and
myocardial oxygen consumption. This work supported an earlier observation of Riou (1992) on isolated rat left
ventricular papillary muscles indicating that propofol had only modest effects on intrinsic myocardial contractility.
Further support for these observations came from the work of Ismael and colleagues (1992) in open chested dogs
suggesting that therapeutic concentrations of propofol had little direct negative inotropic effects although higher
concentrations caused direct cardiac depression.

In a study on acutely instrumented dogs, graded infusion rates of propofol were found to reduce left ventricular
pre-load and myocardial contractility and high infusion rates impaired ventricular relaxation. There was no effect

These defferences in experimental findings may be explained by differences in species, methodology, and dose
and mode of administration of propofol.

In summary, whilst propofol may depress myocardial contractility directly, such effects are robably only
important with very high blood concentration and the negative inotropic effect of propofol is less than that of
equipotent doses of thiopentone. Thus the depression in cardiac state which occurs clinically on induction of
anaesthesia with propofol may occur partly because of direct negative inotropic effects but mostly secondary to
other haemodynamic changes.

A method used in humans to separate the confounding efffects of other cardiovascular variables is to
administer drugs to patients during cardiopulmonary bypass with constant pump flow. Using this technique, it was
found that after thiopentone 4 mg kg⁻¹ systemic vascular resistance decreased to 78% of control values, after
etomidate 0.3 mg kg⁻¹ to 72% of control and after propofol 2 mg kg⁻¹ to 68% of control, there being no
significant difference in these changes between the 3 groups (Boer et al 1991). The majority of other clinical
studies also demonstrate that systemic vascular resistance decreases after propofol.

Using echocardiography in ASA 1 and 2 patients, Gauss and colleagues compared induction of anaesthesia with
etomidate 0.2 mg kg⁻¹, thiopentone 4 mg kg⁻¹ and propofol 2 mg kg⁻¹. Whilst propofol was found to decrease after
load and also the inotropic state of the myocardium, the hypotensive effect of thiopentone was found to be
produced predominantly by a reduction in cardiac contractility (Gauss et al 1991). Other recent studies have also
demonstrated that propofol causes a marked reduction in systemic vascular resistance (Price et al 1992 and
Fairfield et al 1991). In most human studies it has been found that propofol has less effect on heart rate than
thiopentone and this has been explained on the basis of resetting of the baro-receptors by the former drug. In a
recent comparison between propofol and etomidate, Ebert and colleagues using measurements of RR intervals,
forearm vascular resistance and efferent muscle sympathetic nerve activity found there was a reduction in cardiac
and sympathetic baro-slopes with propofol but not with etomidate; these findings suggested that the hypotension
induced by propofol resulted from inhibition of the sympathetic nervous system and impairment of baro-reflex
regulatory mechanisms (Ebert and colleagues 1992).
The pattern of cardiovascular changes on induction of anaesthesia with propofol also persists with intubation. Thus in a comparison of the cardiovascular and sympathetic responses to induction and tracheal intubation in patients receiving either propofol 2.5 mg kg⁻¹ or thiopentone 5 mg kg⁻¹, after induction there was a reduction in arterial pressure in both groups followed by a significant increase with tracheal intubation although the extent of reduction in pressure was greater in the propofol group. On intubation there was a significant increase in plasma adrenaline concentration in the thiopentone but not the propofol group (Lingren et al 1993). Similar cardiovascular changes were reported for adults by Vohra and colleagues (1991) and for children by Aun and colleagues (1993). Because increases in plasma catecholamines may adversely effect the placental circulation, Gin and colleagues (1993) examined plasma catecholamines and neonatal conditions after induction of anaesthesia with propofol 2 mg kg⁻¹ or thiopentone 4 mg kg⁻¹ in Chinese patients undergoing Caesarean section. Although maximum noradrenaline concentrations were higher in the thiopentone group, there were no differences between the two groups in adrenaline concentrations or neonatal conditions despite the fact that propofol attenuated the hypertensive and catecholamine response associated with laryngoscopy and tracheal intubation (Gin et al 1993).

Recovery From Anaesthesia

Extensive clinical experience shows that recovery from anaesthesia with propofol is superior to that after induction of anaesthesia with thiopentone or etomidate (Heath et al 1988, Runcie et al 1993) and similar or slightly better to that with methohexitone (Doze et al 1986). However, there have been fewer investigations until recently comparing the recovery profile after propofol with that following volatile anaesthetic agents.

In 1994, Pollard and colleagues compared the recovery characteristics of day case patients undergoing oral surgery under anaesthesia comprising induction of anaesthesia with propofol 4 mg kg⁻¹ followed by suxamethonium 100 mg and spontaneous respiration of 67 % nitrous oxide in oxygen with halothane, enflurane or isoflurane. The fourth group underwent maintenance of anaesthesia with a propofol infusion 25 mg kg⁻¹ per hour for 5 minutes, 20 mg kg⁻¹ hour⁻¹ for 5 minutes and 10 mg kg⁻¹ hour⁻¹ thereafter with spontaneous respiration of nitrous oxide in oxygen but no volatile anaesthetic agent. Each patient was subjected to psychometric tests including anxiety scores, reaction times and eye divergence measurements using the Maddox wing. In all groups, there was impairment of reaction time after approximately 30 minutes of anaesthesia: reaction times returned to preoperative levels in the enflurane and propofol groups but not in the halothane or isoflurane groups. There was no significant difference in the Maddox wing tests which were impaired in the first hour after surgery but were restored to normal by 4 hours at the time of the discharge and there were no differences in anxiety and stress scores. In essence, although there was slightly better recovery in the propofol infusion and enflurane groups, by the time of discharge at 4 hours there was little difference between all 4 groups. It is interesting that, as reported elsewhere, psychomotor function improved between 24 and 48 hours postoperatively suggesting that even at 24 hours after anaesthesia for simple out-patient surgery (teeth extraction) subtle impairments of psychomotor skill were still present (Pollard et al 1994).

In this study, the dosage of propofol used for infusion was relatively high and no opioids were given for supplementation. In an analysis of phase 4 data obtained from more than 25,000 patients, White and colleagues suggested that in procedures lasting less than 60 minutes, time to awakening was faster in patients given propofol and nitrous oxide anaesthesia (propofol being given either by bolus or infusion) than those given isoflurane anaesthesia. This effect was not clinically important as the discharge times were similar for the 2 groups (White and colleagues 1993).

The use of propofol infusions for maintenance of anaesthesia has also been studied in children. The majority of studies have revealed that the recovery profile from an anaesthetic comprising induction and maintenance with propofol was superior to that comprising thiopentone induction and maintenance with halothane (Puttick and
Rosen 1988, Borgeat and colleagues 1990). Doyle and colleagues (1993) also found that recovery was superior following propofol induction and maintenance than after anaesthesia comprising propofol induction and maintenance with halothane. Surprisingly this was not confirmed by Aun and colleagues 1994, who observed delayed recovery after a propofol infusion given to Chinese children for minor surgery. The reasons for this difference are not clear but it may be that there is an ethnic difference in the pharmacodynamic profile of the drug in different populations. Where side effects were observed in these paediatric studies, it was a common finding that the incidence of involuntary movement was greater with propofol but that the incidences of emetic sequelae were less than with thiopentone or other anaesthetics.

**Nausea and Vomiting**

There are considerable data to suggest that the use of propofol is associated with a lower incidence of emetic sequelae compared with other standard techniques using volatile anaesthetic agents (Gunawardane and White 1988, Doze et al 1988). In a recent study in children undergoing strabismus surgery, (a group known to have a high incidence of emetic sequelae,) the incidence of emesis was significantly less in those given a propofol infusion compared with those given halothane, nitrous oxide and droperidol. However, there was no significant difference in emesis between children given propofol alone and children given propofol, nitrous oxide and droperidol (Watcha et al 1991). There are no data to suggest that propofol has specific anti-emetic properties ; and its use may be associated with a lower incidence of such problems because of the avoidance of other emetic agents and conditions.

The speed of recovery after propofol alone is faster than that after other volatile anaesthetic agents (with the possible exception of desflurane) and it may be that this property also is associated with a reduced incidence of nausea and vomiting postoperatively.

**Infection and Immunology**

It is well known that some anaesthetics inhibit the immune response (Stevenson et al 1990) but as the effects of agents used for induction are transient, these are usually of no clinical relevance in comparison with the effects of stress induced by surgery. In the intensive care unit, however, the immunological effects of anaesthetics used for sedation may assume some importance and this issue has been examined in respect of propofol.

O’Donnell and colleagues (1992) compared the effects of propofol, thiopentone and midazolam on one aspect of immune function, notably neutrophil polarisation which is a response induced by chemotactic stimuli such as bacteria. They found that when compared with equivalent concentrations of midazolam, propofol produced significantly greater inhibition and this was not caused by intralipid. Human serum albumin conferred some degree of protection against all but the highest concentrations of propofol. Interestingly, they found that intralipid augmented polarisation. In clinically relevant concentrations likely to be used for sedation (3 \( \mu \)g per ml) the percentage of inhibition of neutrophil polarisation was approximately 25 %. This study supported the results of another examination of the effect of propofol on both random and chemotactic locomotion of human neutrophils in vitro, this suggested that clinically relevant concentration of propofol depressed migration of human neutrophil granulocytes. These effects were produced by both propofol and intralipid and it was suggested that the mechanism was similar to that caused by inhalation anaesthetics which depress chemotactic locomotion by a degree proportional to lipid solubility (Jensen et al 1993).

These in vitro studies suggest that propofol may have a deleterious effect on the immune response thereby enhancing the development of infection. However, this is not supported by an in vivo study on the effect of a propofol infusion on immunological function during minor surgery. Pirttikangas et al (1994) compared an anaesthetic comprising propofol 2.5 \( \text{mg kg}^{-1} \) and an infusion of 12 \( \text{mg kg}^{-1} \text{ hour}^{-1} \) with a technique of thiopentone
4 mg kg\(^{-1}\) for induction and maintenance with 70% nitrous oxide in oxygen. The effects on immune responses were similar for both anaesthetic agents but the higher percentage of T-helper cells after propofol anaesthesia is theoretically beneficial. This study failed to confirm earlier studies suggesting that propofol depressed PWM induced lymphocyte proliferative responses in lymphocytes obtained from critically ill intensive care patients (Pirttikangas et al 1993).

Although propofol solution supports multiplication of bacteria this effect is limited and no greater than with midazolam. Thus provided that propofol infusions are made up under aseptic conditions in a controlled environment, there is no evidence to suggest that the solution is more likely to present a contamination risk than any other infusion solution. (Farrington et al 1994).

In summary therefore, there are conflicting data on the effect of propofol in sedative doses on immune responses. In anaesthetic doses, it seems that depression occurs but there are no clinical data to suggest that infusions of propofol in the intensive care unit are associated with a greater risk of infection than use of other sedative agents.

**Administration of Propofol by Infusion**

The pharmacokinetic profile of propofol makes it an ideal drug for total intravenous anaesthesia. It has gained widespread use for maintenance of anaesthesia by infusion either alone or as a supplement to nitrous oxide or in total intravenous anaesthesia with fentanyl or alfentanil.

Although it may be given for simple procedures by intermittent bolus administration, for example in short procedures such as maintenance of anaesthesia for dilatation and curettage or other procedures lasting 5–10 minutes, for longer durations of anaesthesia it is customary to administer propofol by infusion.

If propofol is infused at a constant rate, it takes some time before a steady state blood concentration ensues because of redistribution. Similarly, if anaesthesia is induced with a bolus followed immediately by a constant rate infusion, there is a prolonged dip in the blood concentration (Figure 2) caused by redistribution. In order to overcome this problem, it has been suggested that variable rates of infusion be administered in order to rapidly achieve a relatively constant blood concentration. A 3 stage infusion regimen was proposed by Roberts and colleagues 1988 (Figure 3). In order to achieve a blood concentration of 3 \(\mu g\) ml\(^{-1}\), they proposed that there should be an initial bolus of 1 mg kg\(^{-1}\) followed by an infusion of 10 mg kg\(^{-1}\) hour\(^{-1}\) for 10 minutes, 8 mg kg\(^{-1}\) hour\(^{-1}\) for 10 minutes and finally a constant infusion rate of 6 mg kg\(^{-1}\) hour\(^{-1}\) for the duration of the anaesthetic.

The objective of achieving a blood concentration of 3 \(\mu g\) per ml was based upon studies by Spelina and colleagues (1986) who determined that the EC 95 blood propofol concentration (concentration required to inhibit movement of 95% of the population to the initial incision during nitrous oxide/morphine anaesthesia) was 3.39 \(\mu g\) ml\(^{-1}\). However, as the clearance estimates during maintenance of anaesthesia with propofol varies between 1.3 and 2.09 litres per minute (Shafer et al 1988, Cockshott et al 1990, Morgan et al 1990), the estimated blood concentrations would be expected to vary considerably. In order to examine this question Sear and Glenn (1995) compared blood concentrations of propofol produced using an infusion regimen based on body weight and one based on an assumed body weight of 70 kg. They found that in patients weighing 60–90 kg a standard dose infusion regimen uncorrected for weight provided blood concentrations which did not differ significantly from those given a fixed regimen although patients of less than 60 kg in weight had higher blood concentrations than those given a weight corrected infusion. In clinical practice therefore, this infusion regimen (70 mg for induction, 700 mg per hour for the first 10 minutes, 560 mg per hour for the next 10 minutes and 420 mg per hour thereafter) provided satisfactory anaesthesia and this could be titrated to match patients' clinical responses (Sear and Glenn 1995).

A range of other dosage requirements is described in Table 1.
Target Controlled Devices

Although manual infusion regimens are simple and maintain a relatively constant blood concentration, a more sophisticated way of very rapidly altering blood concentrations is by the use of a computer to control administration of the drug. The computer is programmed with the mathematical solution to a pharmacokinetic model of a patient which includes the patient’s weight. Such a device has been described by White and Kenny (1990, 1994). Such target-controlled methods of infusion of propofol have been shown to induce anaesthesia in patients without serious haemodynamic or respiratory side effects and compared with bolus induction of anaesthesia the degree of
hypotension was less (Chaudri et al 1992).

**Sedation with Propofol**

Propofol has become increasingly popular as a means of sedating patients, either healthy patients undergoing procedures such as oocyte retrieval for treatment of infertility or as an alternative to neurolytic agents with or without combination with local analgesia for patients who may be regarded as unfit to undergo deep general anaesthesia.

In both instances, propofol may be given either as small intermittent bolus doses or as a continuous infusion at a dose rate much less than that required to maintain unconsciousness.

With the extensive use of patient controlled analgesia techniques, it is perhaps not surprising that the patient controlled technique has also been applied to the production of sedation and in a recent study Osborne and colleagues (1994) compared patient controlled sedation with propofol (bolus dose 18 mg over 5.4 seconds, lockout period 1 minute) with a continuous propofol infusion (3.6 mg kg⁻¹ hour⁻¹) in a randomised study in patients undergoing extraction of teeth under local anaesthesia. In the patient controlled group, the total dose of propofol administered was slightly but not significantly less than that in the infusion group. The level of sedation achieved was that of eyelid closure with ability to rouse to command. However, there was a significantly greater number of patients who preferred patient controlled sedation than those receiving a continuous infusion of propofol. It is clear that propofol is an appropriate drug for use with this technique as it has a short duration of action with rapid metabolism permitting rapid control of the level of sedation. In the critically ill patient, the dose of propofol should be reduced and perhaps the lockout interval increased.

<table>
<thead>
<tr>
<th>INFUSION RATE mg kg⁻¹ hour⁻¹ (95% confidence interval)</th>
<th>OTHER CNS DEPRESSANTS</th>
<th>SPONTANEOUS/IPPV</th>
<th>PATIENT GROUP</th>
<th>AUTHORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED50 6.0 ug/kg/hour ED95 8.6 (6.8 - 7.8)</td>
<td>Alfentanil - Load 85 ug/kg infusion 65 ug/kg Temazepam 0.3 mg/kg</td>
<td>IPPV</td>
<td>Children 3-12 years</td>
<td>Browne et al 1992</td>
</tr>
<tr>
<td>ED50 7.5 (8.0 - 9.8) ED95 10.5 (9.6 - 13.1)</td>
<td>Alfentanil load 65 ug/kg infusion 50 µg/kg</td>
<td>IPPV</td>
<td>Children 3-12 years</td>
<td>Browne et al 1992</td>
</tr>
<tr>
<td>3 stage infusion maintenance 6 mg/kg/hour</td>
<td>N₂O + fentanyl</td>
<td>IPPV</td>
<td>Morbidly obese</td>
<td>Servin et al 1993</td>
</tr>
<tr>
<td>ED50 3.21 ED95 6.73</td>
<td>Morphine premed 0.15 mg/kg + N₂O 67 %</td>
<td>Spont ventilation</td>
<td>Adults ASA1 mean age 41 years</td>
<td>Speilina et al 1986</td>
</tr>
<tr>
<td>ED50 7.8 (6.36 - 10.02) ED95 20.9 (13.9 - 77.7)</td>
<td>Premedication with lorazepam 2-3 mg 67 % N₂O</td>
<td>Spont ventilation</td>
<td>Adults ASA1 18-70 years</td>
<td>Turtle et al 1987</td>
</tr>
<tr>
<td>ED50 2.94 (2.35 - 3.37) ED95 4.98 (4.13 - 8.8)</td>
<td>Temazepam 20 or 30 mg</td>
<td>IPPV without relaxant</td>
<td>Adults ASA1 Aged 16-40</td>
<td>Richards et al 1990</td>
</tr>
<tr>
<td>Dose for loss of consciousness</td>
<td>Spont ventilation</td>
<td>Adults ASA1 Aged 16-40</td>
<td>Dunnet et al 1994</td>
<td></td>
</tr>
<tr>
<td>ED50 4.9 (4.7 - 5.1) ED95 7.9 (7.3 - 8.8)</td>
<td></td>
<td></td>
<td>Dunnet et al 1994</td>
<td></td>
</tr>
<tr>
<td>ED50 4.2 (4.0 - 4.4) ED95 5.8 (5.4 - 6.4)</td>
<td></td>
<td>Spont ventilation</td>
<td>Adults ASA1 Aged 41-65</td>
<td>Dunnet et al 1994</td>
</tr>
</tbody>
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**Table I** Infusion rate of propofol required to maintain unconsciousness
The USE of Propofol in ASA 4 and 5 Patients

1. Porphyria

The barbiturates are contra-indicated as induction agents in the porphyrias and animal tests suggest that etomidate also causes porphyrinogenicity (Harrison et al 1985). Although ketamine has not been shown to cause porphyrinogenicity in animal models, it has other disadvantages which inhibit its use as a routine induction agent for anaesthesia.

Propofol has not been demonstrated to possess porphyrinogenicity in the rat model (Parikh and Moore 1986). Recently Meissner and colleagues undertook a prospective trial in 13 patients with variegate porphyria to determine if propofol could be used safely as an anaesthetic induction agent. There were no significant differences in plasma or stool porphyrin concentrations before or 1-5 days after operation in either the 13 porphryric patients or 21 control subjects. The author suggested cautiously that this trial implied potential safety of propofol when used as an induction agent in this category of porphyria but that their conclusions could not be extrapolated to the use of propofol infusions for maintenance of anaesthesia until further clinical experience has been obtained (Meissner et al 1991).

2. Chronic Renal Failure

Propofol is metabolised in the liver and the resultant glucuronidated metabolites are excreted through the kidneys into the urine. It may be expected therefore that the pharmacokinetics of the parent compound, propofol, would not be changed in the presence of renal failure. This has been known for some time and confirmed recently by Kirvela et al (1992).

In the past, haemodynamic instability was common in patients in renal failure with all anaesthetic induction agents as a result of concomitant renal vascular disease, electrolyte abnormalities, and volume depletion as a result of lack of fine control during haemodialysis.

Nowadays patients in chronic renal failure presenting for surgery are usually in optimal condition with good cardiovascular control using appropriate anti-hypertensive therapy, and better volume status as a result of modern haemodialysis techniques.

In a recent study comparing 10 uraemic patients undergoing renal transplantation with 7 healthy matched control patients, haemodynamic changes and pharmacokinetic variables were measured (Kirvela et al 1992). Anaesthesia comprised premedication with diazepam, preloading with fluid to achieve a CVP of 4 mm of mercury followed by glycopyrronium, fentanyl, droperidol and an induction dose of propofol 2 mg kg⁻¹. Anaesthesia was maintained with isoflurane and nitrous oxide in oxygen. The pharmacokinetic parameters were similar in both groups with an elimination half life of 1638 (SD 340) minutes in the uraemic group and 1714 (842) minutes in the control group.

Propofol produced a significant similar decrease in systolic pressure in both groups on similar induction: whilst laryngoscopy and intubation caused a significant increase in systolic pressure in the control group, this increase was not significant in the uraemic group. Heart rate followed a similar pattern in both groups. In essence therefore the cardiovascular system remained as relatively constant in uraemic patients on induction with propofol as it did in control patients suggesting that uraemic patients tolerate the drug quite well and it is an appropriate agent for induction and probably maintenance of anaesthesia (Kirvela et al 1992).

3. Cardiac Disease

Propofol has been studied extensively since 1985 in patients undergoing cardiac surgery. In those patients with good left ventricular function, the haemodynamic changes produced are similar to those patients anaesthetised by
other anaesthetic techniques both for induction and also maintenance of anaesthesia.

More recent investigations have concentrated on the effect of total intravenous anaesthesia with propofol in patients undergoing cardiac surgery. In a study of 8 patients undergoing coronary artery bypass grafting with an ejection fraction greater than 0.5 and LVEDP less than 12 mm of mercury, Manara and colleagues found that the haemodynamic effects of total intravenous anaesthesia with a combination of propofol and alfentanil were similar to those reported for opioid based anaesthesia (Manara et al 1991). In this investigation, anaesthesia was induced with alfentanil 15 \( \mu \)g kg\(^{-1}\) followed by a continuous infusion of 50 \( \mu \)g kg\(^{-1}\) hour\(^{-1}\) and with propofol 0.5 mg kg\(^{-1}\) followed by a stepped infusion of 5 mg kg\(^{-1}\) hour\(^{-1}\) for 10 minutes, 4 mg kg\(^{-1}\) hour\(^{-1}\) for a further 10 minutes and 3 mg kg\(^{-1}\) hour\(^{-1}\) thereafter. Induction of anaesthesia was associated with a significant reduction in systolic pressure (−22%), mean arterial pressure, (−22%) diastolic arterial pressure (−18%) and LVSWI (−30%). There was no significant haemodynamic response to intubation or sternotomy with this regimen. No patient required inotropic support during weaning from cardiopulmonary bypass and none had new ischaemic changes on the postoperative ECG.

In a comparison of fentanyl and propofol with fentanyl and enflurane, Underwood and colleagues (1992) studied 20 patients with a left ventricular ejection fraction greater than 30% undergoing coronary bypass graft surgery. In one group of 10 patients anaesthesia comprised propofol 6 mg kg\(^{-1}\) hour\(^{-1}\) for 10 minutes reduced to 3 mg kg\(^{-1}\) hour\(^{-1}\) thereafter and in the second group anaesthesia was maintained with enflurane 0.8% for 10 minutes and then 0.6% thereafter. Both regimens were adjusted if necessary. There were no significant differences between the groups in haemodynamic variables during the study. After intubation, systolic vascular resistance decreased significantly in both groups then returned to base line during surgery whilst stroke index was unchanged after intubation but was reduced during surgery as systemic vascular resistance increased. Regional and global coronary blood flow were maintained in both groups as were myocardial oxygen consumption and lactic extraction (Underwood et al 1992).

Of more significance than these data, however, are investigations of the effect of propofol in patients with impaired left ventricular performance. In a recent study Philips and colleagues (1993) compared propofol, fentanyl anaesthesia in 24 patients with good left ventricular function (ejection fraction more than 45% and left ventricular end-diastolic pressure less than 16 mm of mercury) with 9 patients with impaired left ventricular function. Anaesthesia comprised fentanyl followed by a variable propofol infusion rate of 2.6 mg kg\(^{-1}\) hour\(^{-1}\) in the good group and 2.7 mg kg\(^{-1}\) hour\(^{-1}\) in the impaired function group with additional fentanyl as required. There were no significant differences in any haemodynamic measurement between groups before intubation, before or after sternotomy or before aortic cannulation. The autonomic responses to sternotomy were controlled in both groups. This suggests that total intravenous anaesthesia with appropriate doses of propofol and fentanyl maintain a similar haemodynamic status in patients with poor left ventricular function as in patients with good left ventricular function (Phillips et al 1993).

4. Intensive Care

Appropriate sedation is essential for critically ill patients in the intensive care unit. Currently the level of sedation produced is that of a patient who is sleepy but easily aroused and it is now relatively uncommon to sedate a patient deeply. The level of sedation required, however, varies from unit to unit but the aim is to provide relief from anxiety and analgesia. In general, morphine is the standard analgesic drug and midazolam, propofol or more recently isoflurane have been suggested for sedation.

Propofol is popular for sedation in intensive care units. It has the advantage that discontinuing the infusion permits rapid restoration of consciousness but unwanted effects include arrhythmias, hypotension and fat overload (Burns, Shelly and Park 1992).

The pharmacokinetics of propofol for long term infusion for sedation of patients in the intensive care unit have
been studied by several groups of workers (Bailie et al 1992, Albanese et al 1990). The former group of workers reported a terminal phase half life of 1411 minutes (SD586) whilst the latter a terminal phase of 1878 (SD 672) minutes. The terminal half life is longer than the values reported for short periods of infusion; however, total body clearance was high in both studies and the long terminal half life was very variable between different patients.

It has also been documented that stable sedation produced with a decreasing rate of propofol infusion had no significant effects (at a blood concentration of 1 µg ml⁻¹) on cardiac output, oxygen delivery, oxygen consumption or arterial blood lactate concentrations. Whilst there were small reductions in mean arterial pressure and heart rate, there was no significant reduction in oxygen delivery in these patients who were undergoing mechanical ventilation for treatment of septic shock and respiratory failure (Nimmo et al 1994). In this study, the propofol infusion rate was that which had been devised for patients in the intensive care unit and was based on the regimen described by Albanese and colleagues (1990); this comprised an infusion of 4 mg kg⁻¹ hour⁻¹ for 10 minutes, 3 mg kg⁻¹ hour⁻¹ for 50 minutes and then 2 mg kg⁻¹ hour⁻¹ subsequently (Nimmo and colleagues 1994).

Recently in a randomised crossover study it has been shown that equally satisfactory sedation could be achieved with either isoflurane or propofol in 24 patients undergoing artificial ventilation for 48 hours. There were no significant differences in the level of sedation achieved and no difference in the time from cessation of ventilation to ability to write the name (2-30 minutes for isoflurane, 1-300 minutes for propofol); there was also no difference in time to tracheal extubation or difference in heart rate, mean arterial pressure or CVP (Millane et al 1992).

In order to reduce the fat load presented to patients recently a 2 % solution of propofol in intralipid has been prepared. Comparison of the 2 % solution with 1 % propofol showed that the stronger solution gave satisfactory sedation in the intensive care unit with a lower fat load. (Ewart et al 1992).

Propofol is not recommended for use as an infusion in children following a report in 1992 of fatal myocardial failure in 5 children (Parke et al 1992). This study represented a retrospective analysis of the case reports of 5 children aged between 4 weeks and 6 years undergoing ventilation in the intensive care unit for tracheobronchitis in 4, and bronchiolitis in one. In all instances propofol was used for sedation and the patients developed a similar clinical course, manifest as an increase in metabolic acidosis proceeding to myocardial failure. Death resulted from refractory asystole. In all instances, lipaemic serum was present indicative of inadequate fat clearance. Ketone bodies resulting from metabolism of fatty acids and impairment of liver function, which may be caused by intralipid, may both have contributed to the development of metabolic acidosis. However, these mechanisms are speculative. Similar problems have not been reported in adults undergoing sedation with propofol but until further investigations are performed it seems sensible to avoid the use of propofol infusions in paediatric practice.

5. Neurosurgery and Neurological

Whilst the volatile anaesthetic agents and nitrous oxide are cerebral vasodilators and may increase cerebral blood flow and intracranial pressure, it is thought that propofol has little effect on cerebrovascular resistance but it may decrease cerebral blood flow as a result of systemic vasodilatation leading to a reduction in mean arterial pressure.

In order to compare the effect of propofol with isoflurane and nitrous oxide, Todd and colleagues recently undertook a prospective comparison in 121 adults undergoing removal of a supratentorial intracranial mass lesion (Todd et al 1993). In the 3 groups, anaesthesia was maintained with propofol infusion and fentanyl, with isoflurane and nitrous oxide or with nitrous oxide and a fentanyl infusion. The isoflurane group had a significantly lower mean arterial pressure and cerebral perfusion pressure with a slightly higher intracranial pressure. The isoflurane group also had a higher heart rate. However, there was little difference in emergence from anaesthesia or in postoperative neurological state. The authors concluded that despite the relatively different effects on cerebrovascular haemodynamics, all three anaesthetic regimens were equally satisfactory.
This study confirmed the fact that propofol has less effect on cerebrovascular resistance and intracranial pressure than the volatile anaesthetic agents. It is also known that it has no effect on cerebrovascular responses to changes in arterial CO₂ tension (Fox et al 1992).

It is commonly observed that there are more spontaneous movements on induction of anaesthesia with propofol than with thiopentone. However, there is no evidence to suggest that these effects are epileptic in nature as they occur in the absence of EEG abnormalities and this suggests a subcortical origin (Borgeat et al 1991).

Electro-physiological studies in cats have demonstrated that the effects of propofol and thiopentone on CNS electrical activity are similar (Tomoda et al 1993).

The depressant effect of propofol on CNS electrical activity suggest that it may be useful for the treatment of epilepsy and in experimental aminals (rabbits) it was confirmed that propofol was effective against convulsions induced by two epileptogenic chemicals applied to the brain. The authors of this study concluded that the drug may be used for therapeutic treatment of epilepsy where other standard measures have failed (De Riu et al 1992) despite the fact that the Committee on Safety of Medicines warned in 1987 of the possibility of seizures occurring after administration of propofol. It is likely however, that this phenomenon is similar to that present with the majority of anaesthetic agents: notably during recovery from anaesthesia, at subnarcotic plasma concentrations of the drug there may be intensification of EEG abnormalities in patients suffering from epilepsy.

Further evidence of the anti-epileptogenic effect of propofol in established fits was obtained by Heavner and colleagues (1993) who compared the effects of propofol with those of thiopentone on seizures induced in rats by an infusion of bupivacaine. Both drugs were equallly effective in preventing both seizures and EEG abnormalities; in fact the dose of bupivacaine that induced arrhythmias and a iso-electric EEG was significantly smaller in the thiopentone group compared with the propofol group (Heavner et al 1993).

Other experimental data in rats suggests that propofol may have beneficial effects on outcome after neurological damage caused by incomplete cerebral ischaemia (Kochs et al 1992) compared with fentanyl and nitrous oxide but not compared with halothane anaesthesia (Ridenour et al 1992). Thus further studies are required to resolve this conflict and determine if propofol has a protective effect against brain ischemia.

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