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Propofol
A Review of its Pharmacodynamic and Pharmacokinetic Properties and Use as an Intravenous Anaesthetic

Mark S. Langley and *Rennie C. Heel*

ADIS Drug Information Services, Manchester and Auckland

Various sections of the manuscript reviewed by: ***D.P. Coates,*** Bristol Royal Infirmary, Bristol, England; ***J.W. Dundee,*** Department of Anaesthetics, Queen's University, Belfast, N. Ireland; ***N. Ellison,*** Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania, USA; ***N.W. Goodman,*** Department of Anaesthetics, University of Bristol, Bristol, England; ***I.S. Grant,*** Department of Anaesthesia, Ninewells Hospital, Dundee, Scotland; ***J. Kanto,*** Department of Anaesthesiology, Turku University Central Hospital, Turku, Finland; ***N. Mackenzie,*** Department of Anaesthesia, Ninewells Hospital, Dundee, Scotland; ***W. McCaughey,*** Department of Anaesthetics, Queen's University, Belfast, N. Ireland; ***K. McKeating,*** Department of Anaesthetics, Queen's University, Belfast, N. Ireland; ***M. Morgan,*** Royal Postgraduate Medical School, Hammersmith Hospital, London, England; ***G. Rolly,*** Department of Anesthesia, University Hospital, Ghent, Belgium; ***C. Siani,*** Anaesthesiology and Intensive Care Institute, University of Genova, Genova, Italy; ***H. Stephan,*** Zentrum Anaesthesiologie, Georg-August-Universität, Göttingen, Germany; ***H.R. Vinik,*** Department of Anesthesiology, University of Alabama, Birmingham, Alabama, USA; ***P.F. White,*** Stanford University Medical Center, Stanford, California, USA; ***J. Zattoni,*** Anaesthesiology and Intensive Care Institute, University of Genova, Genova, Italy; ***W.W.A. Zuurmond,*** Universiteit van Amsterdam, Amsterdam, Holland.

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Summary

Synopsis

Propofol is an intravenous anaesthetic which is chemically unrelated to other anaesthetics. Induction of anaesthesia with propofol is rapid, and maintenance can be achieved by either continuous infusion or intermittent bolus injections, with either nitrous oxide or opioids used to provide analgesia.

Comparative studies have shown propofol to be at least as effective as thiopentone, methohexitone or etomidate for anaesthesia during general surgery. The incidence of excitatory effects is lower with propofol than with methohexitone, but apnoea on induction occurs more frequently with propofol than with other anaesthetics. Additionally, a small number of studies of induction and maintenance of anaesthesia have found propofol to be a suitable alternative to induction with thiopentone and maintenance with halothane, isoflurane or enflurane. Propofol is particularly suitable for outpatient surgery since it provides superior operating conditions to methohexitone (particularly less movement), and rapid recovery in the postoperative period associated with a low incidence of nausea and vomiting. When used in combination with fentanyl or alfentanil, propofol is suitable for the provision of total intravenous anaesthesia, and comparative studies found it to be superior to methohexitone or etomidate in this setting.

Infusions of subanaesthetic doses of propofol have been used to sedate patients for surgery under regional anaesthesia, and also to provide sedation of patients in intensive care. In the latter situation it is particularly encouraging that propofol did not suppress adrenal responsiveness during short term studies. If this is confirmed during longer term administration this would offer an important advantage over etomidate.

Thus, propofol is clearly an effective addition to the limited range of intravenous anaesthetics. While certain areas of its use need further study, as would be expected at this stage of its development, propofol should find a useful role in anaesthetic practice.

Pharmacodynamic Properties

Single bolus doses of propofol 2 to 2.5 mg/kg produce unconsciousness within 1 minute in a majority of patients, although dose requirements are reduced in older patients and by premedication with opioids. Anaesthesia can be maintained with intermittent

bolus doses or continuous infusions: for example, an administration rate of 9 mg/kg/h fully anaesthetised 85% of patients and rates of less than 6 mg/kg/h produced sedation, but not unconsciousness, in most individuals.

Recovery from propofol anaesthesia is rapid. Psychomotor impairment following recovery is minimal – following maintenance of anaesthesia with propofol significant increases in reaction times are evident for up to 30 minutes after surgery and a degree of CNS sedation may be detectable for up to 3 hours. Comparative studies indicate that propofol produces slightly less residual impairment of performance than methohexitone. Propofol produces characteristic changes in EEG patterns which are correlated to blood concentrations of the drug. It does not have the antanalgesic properties associated with thiopentone, and has been shown to produce a low incidence of postoperative nausea.

Induction doses of propofol 2 mg/kg reduced systolic and diastolic blood pressures by 16 and 11%, respectively, in unpremedicated patients and 2.5 mg/kg reduced mean arterial blood pressure by up to 32% in patients premedicated with papaveretum. These actions of propofol are potentiated by the coadministration of fentanyl, and with this combination of drugs blood pressure increases in response to surgery and intubation are significantly reduced.

Induction with propofol is frequently accompanied by apnoea which may last more than 60 seconds, and maintenance of anaesthesia with propofol infusions produces dose-dependent decreases in respiratory rate, tidal volumes and minute volumes. This respiratory depression is increased by fentanyl, and when this is the case, the effect may persist into the postoperative period.

Propofol was found to be about 1,000 times less potent than etomidate at inhibiting ACTH-induced cortisol production *in vitro*. In clinical practice plasma cortisol concentrations were reduced in anaesthetised surgical patients and patients sedated using sub-anaesthetic infusions, but propofol did not inhibit adrenal responses to exogenous ACTH during short term administration.

Pharmacokinetic Properties

Following bolus injections of propofol, blood concentrations decline rapidly. Administration by infusion produces an initial rapid increase followed by a slower rise to a virtual steady-state, although blood propofol concentrations continue to increase asymptotically throughout the infusion. The final steady-state concentration resulting from an infusion of 9 mg/kg/h was estimated at 6 mg/L.

Propofol distributes rapidly and extensively from blood with a distribution half-life of approximately 2 to 4 minutes and a volume of distribution (Vd) of between 209 and 1008L. In several studies the pharmacokinetic data best fitted an open 3-compartment model, which indicates that propofol is probably distributed into 2 distinct tissue compartments.

Propofol is metabolised rapidly, with 88% of an administered dose appearing in the urine as a propofol conjugate (about 40% of urinary excretion products), conjugates of 4-hydroxy propofol (about 60%) and a small amount (< 0.3%) of unchanged propofol. Estimates of total body clearance of propofol vary from 94 to 139 L/h. In studies where a 2-compartment model was used, the elimination half-life ($t_{1/2}$) of propofol was usually about 100 minutes, whereas when a 3-compartment model was found more appropriate the elimination of propofol was considered biphasic, with a first-stage half-life ($t_{1/2\beta}$) of 25 to 56 minutes, and a terminal elimination half-life ($t_{1/2\gamma}$) of 184 to 309 minutes following single doses and 277 to 403 minutes following infusions.

Data from a small number of elderly patients show that the total clearance and initial volume of distribution of propofol are reduced in old age. Preliminary reports suggest that neither renal nor liver disease alter the pharmacokinetics of propofol. Other anaesthetic drugs may affect the disposition of propofol – in particular the concomitant use of fentanyl reduces its volume of distribution and elimination half-life, and also reduces propofol clearance by about one-third.

Clinical Studies

During general surgical procedures lasting up to 3 hours using propofol in combination with nitrous oxide and/or opioid analgesics, induction and maintenance of anaesthesia were rated 'good' or 'adequate/acceptable' in 84 to 100% of patients, with patients always waking within 15 minutes of the end of surgery. In comparative studies, propofol 2 to 2.5 mg/kg was at least as effective as thiopentone 4 to 5 mg/kg and methohexitone 1.5 mg/kg for induction of anaesthesia, with less spontaneous movement than with methohexitone and better recovery than after thiopentone, although propofol produced the highest incidence of apnoea. Propofol was also considered superior to both of these drugs for the maintenance of anaesthesia and usually produced more rapid recovery. Preliminary studies also reported propofol for both induction and maintenance to be a suitable alternative to induction with thiopentone and maintenance with halothane or isoflurane, although this requires further confirmation.

Favourable operating conditions and rapid recovery were noted when propofol was used as an anaesthetic for outpatient surgery. When compared with methohexitone in this setting, recovery of normal psychomotor function occurred more rapidly in patients anaesthetised with propofol and post operative nausea and vomiting occurred less frequently.

Although an infusion of propofol 12 mg/kg/h alone did not provide adequate anaesthesia, the additional use of alfentanil produced good operating conditions in total intravenous anaesthesia procedures. In comparative studies, propofol was superior to etomidate for maintenance of anaesthesia when used in combination with either alfentanil or fentanyl. The combination of propofol and alfentanil was also superior to methohexitone plus alfentanil in terms of induction and recovery from anaesthesia.

Infusions of subanaesthetic doses of propofol (between about 3 and 6 mg/kg/h) have been used to sedate patients for colonoscopy and for surgery using spinal analgesia. Similarly, critically ill patients under intensive care have been sedated with propofol infusions of less than 2 mg/kg/h, and in these circumstances propofol allowed good control of the depth of sedation and rapid recovery of spontaneous breathing when mechanical ventilation was withdrawn. Although plasma cortisol concentrations decreased during propofol infusions, the adrenal response to ACTH was not affected during these short term studies, in contrast to the depression of adrenal responsiveness seen with etomidate. If adrenal function is similarly unaffected during longer term administration of propofol, this will offer an important benefit in the intensive care setting.

Side Effects

The most frequent side effect of propofol is pain during injection. This is experienced by about 30% of patients when veins in the dorsum of the hand are used, but by only 6 to 8% of patients if administration is into the larger veins of the forearm or antecubital fossa. Apnoea is common during induction with propofol and may last for more than 60 seconds. Excitatory effects are seen in about 14% of cases.

Isolated instances of bradycardia have occurred in patients anaesthetised with propofol; these are usually associated with vagal stimulation and have not been clearly attributable to propofol itself. Epileptiform movements have also been reported in rare instances, but again these could not be directly related to propofol. The only other serious complications during surgery to which propofol may have contributed are a few reported cases of severe hypotension.

Dosage and Administration

Induction doses of propofol are best given as 40mg increments at 10-second intervals until full anaesthesia is achieved. The dose required in adults is normally 2 to 2.5 mg/kg, but older patients may require a lower dose. The rate of administration should be halved in infirm patients. Anaesthesia can be maintained either with a continuous infusion of propofol (approximately 6 to 12 mg/kg/h) or with bolus injections of propofol 20 to 50mg as required.

1. Pharmacodynamic Properties

Propofol (2,6-diisopropylphenol; fig. 1) represents a new class of intravenous anaesthetic agent, being chemically unrelated to the barbiturate, steroid or eugenol agents.

Since propofol is only very slightly soluble in water some form of solubilising agent is needed to prepare the drug in a form suitable for intravenous administration, and initially it was produced as a 1% solution in 16% 'Cremophor EL'. However an unexpectedly high occurrence of pain on injection was observed during early clinical studies with this preparation (Major et al. 1981). This, and the possible association between 'Cremophor EL' and anaphylactic reactions to intravenous anaesthetics (Clarke et al. 1975; Dye & Watkins 1980) necessitated the development of an alternative formulation for propofol, and it is now produced as a 1% w/v solution in an aqueous emulsion of 10% soya bean oil, 2.25% glycerol and 1.2% purified egg phosphatide.

Preliminary studies with this newer preparation suggested that it may differ slightly from the cremophor-based formulation in terms of its pharmacokinetic disposition (Kay et al. 1986) and that it may have a slightly reduced anaesthetic potency (Glen & Hunter 1984). Consequently this review will concentrate on the properties of the newer emulsion formulation – where results are referred to which were obtained with the cremophor-based preparation, this will be specifically stated.

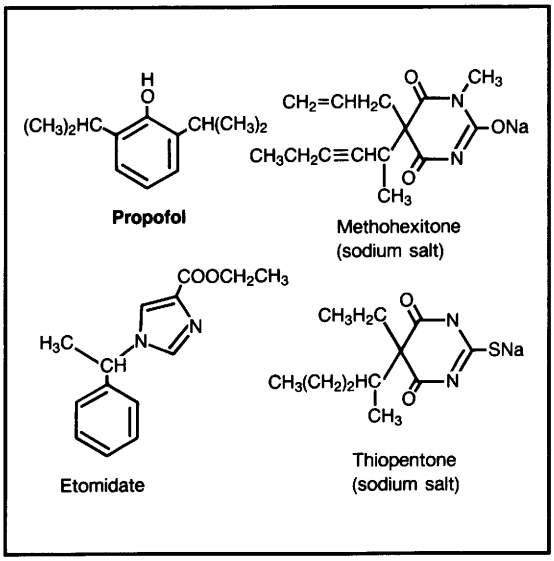

Fig. 1. The structural formulae of propofol, methohexitone, etomidate and thiopentone.

1.1 Anaesthetic Properties

1.1.1 Induction and Maintenance of Anaesthesia

When propofol is administered as a single bolus dose, induction of anaesthesia is dependent upon both the dose and the speed at which the injection is given. Rolly et al. (1985) found that the mean induction time (i.e. from the start of administration to the loss of verbal contact) in 20 surgical patients was 50.5 seconds when propofol 2 mg/kg was given over 60 seconds, but was significantly ($p < 0.001$) reduced to 21.5 seconds when the period of administration was reduced to 5 seconds (fig. 2). Similarly, induction was successful in 100% of patients with the 5-second period of administration, but in only 90% of patients with the 60-second period of administration (fig. 2).

Dose-ranging studies demonstrated that sensitivity to propofol is increased in the elderly (Dundee et al. 1986b). Figure 3 shows the mean induction times and percentage of successful inductions for groups of 20 patients aged between 16 and 59 years given bolus injections of propofol 1.5 to 3 mg/kg, and for groups of 10 patients aged 60 years and over given propofol 1.25 to 2.25 mg/kg. Whereas a dose of at least 2.25 mg/kg was necessary for successful anaesthesia in the younger patients, between 1.25 and 1.75 mg/kg appeared to be adequate in the older patients. Further, in another study of unpremedicated patients where the same age groupings were used, but where anaesthesia was induced with an initial bolus dose of propofol 1.25 mg/kg followed by 10mg increments at 15-second intervals until verbal contact was lost, the mean induction dose for the patients less than 60 years old ($n = 187$) was 2.01 mg/kg, whilst that for the patients over 60 years old ($n = 82$) was 1.64

mg/kg ($p < 0.001$) [Dundee et al. 1986b]. It is probable that these age-related changes in propofol sensitivity are a consequence of alterations in the disposition of propofol (primarily a reduction in the initial volume of distribution) which occur in the elderly (section 2.4.1). Similar increases in sensitivity have been observed with other intravenous anaesthetics in older patients, and these too have been associated with pharmacokinetic changes (Homer & Stanski 1985).

A number of groups have studied induction times and success rates for anaesthesia with bolus doses of propofol 2 and 2.5 mg/kg given to unpremedicated patients, and these are shown in table I. Whilst induction times were similar with both doses (approximately 30 seconds), 2.5 mg/kg was a more reliable dose in the younger patients for ensuring complete anaesthesia (McCollum & Dundee 1986; McCollum et al. 1985).

The duration of sleep following single doses of propofol has not been specifically studied, since this has little relevance to actual anaesthetic practice, although Kay and Stephenson (1981) demonstrated that sleep times increased proportionally with doses of propofol (cremophor preparation) of between 1 and 3 mg/kg. The mean duration of effect (from induction to correct recall of date of birth) of a single bolus dose of 3 mg/kg of the emulsion preparation of propofol given to 21 unpremedicated dental patients was 7.6 minutes (Logan et al. 1987).

Propofol anaesthesia can be maintained by either continuous infusion or repeated bolus injections, and whilst the infusion rate needed to maintain unconsciousness in 95% of cases (ED_{95}) was calculated to be 6.7 mg/kg/h for patients premedicated with morphine 0.15 mg/kg (Spelina et al. 1986), higher infusion rates have often been required in clinical studies (sections 3 and 4). Lower infusion rates produce continuous sedation without full anaesthesia. In a study of 60 patients premedicated with glycopyrrolate 0.4mg an infusion of propofol 3 mg/kg/h produced unconsciousness and heavy and light sedation in 15, 40 and 45% of patients, respectively; 6 mg/kg/h produced these states in 40, 35 and 25% of patients, respectively,

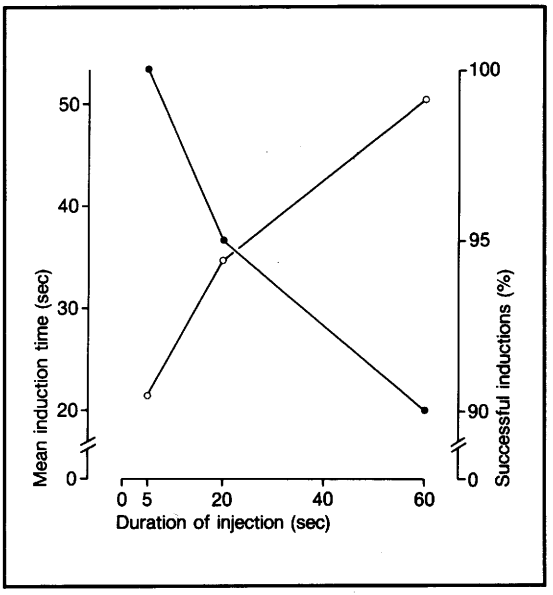

Fig. 2. The effect of speed of injection of a 2 mg/kg dose of propofol on induction time (○) and % of successful inductions (●) in unpremedicated patients; n = 20 for each point (after Rolly et al. 1985).

whilst an infusion of 9 mg/kg/h produced unconsciousness in 85% and light sedation in 15% of patients (Gepts et al. 1985b). Evidently there is wide variation in individual sensitivity to propofol.

1.1.2 Effect of Premedication on Propofol Anaesthesia

Premedication with either atropine 0.5mg or hydroxyzine 100mg given as an intramuscular injection 1 hour before surgery was found to have no effect on induction times or overall propofol requirements in a double-blind comparison with placebo in 90 patients who underwent surgery after induction with propofol 2 mg/kg, and in whom anaesthesia was maintained with incremental propofol and 70% nitrous oxide in oxygen (Bilaine & Desmonts 1985). Similarly, no changes in propofol anaesthesia were observed following premedication with oral diazepam 10mg or intramuscular pethidine (meperidine) 50 to 75 mg/kg with atropine 0.6mg (Briggs & White 1985), or oral midazolam 3mg with intramuscular atropine 0.5mg

(Schaer 1986) in open studies involving 120 and 20 patients, respectively.

McCollum et al. (1986) randomly allocated 320 patients to receive either no premedication, oral diazepam 10mg, or either pethidine 50mg with atropine 0.6mg or papaveretum 15 to 20mg with hyoscine 0.3 to 0.4mg by intramuscular injection. After 1 to 2 hours anaesthesia was induced with doses of propofol from 1.75 to 2.5 mg/kg, and whilst both diazepam and pethidine/atropine had some effect on propofol dose requirements, only the papaveretum/hyoscine combination produced a significant decrease in dose requirements compared to no premedication ($p < 0.01$). In the group pre-

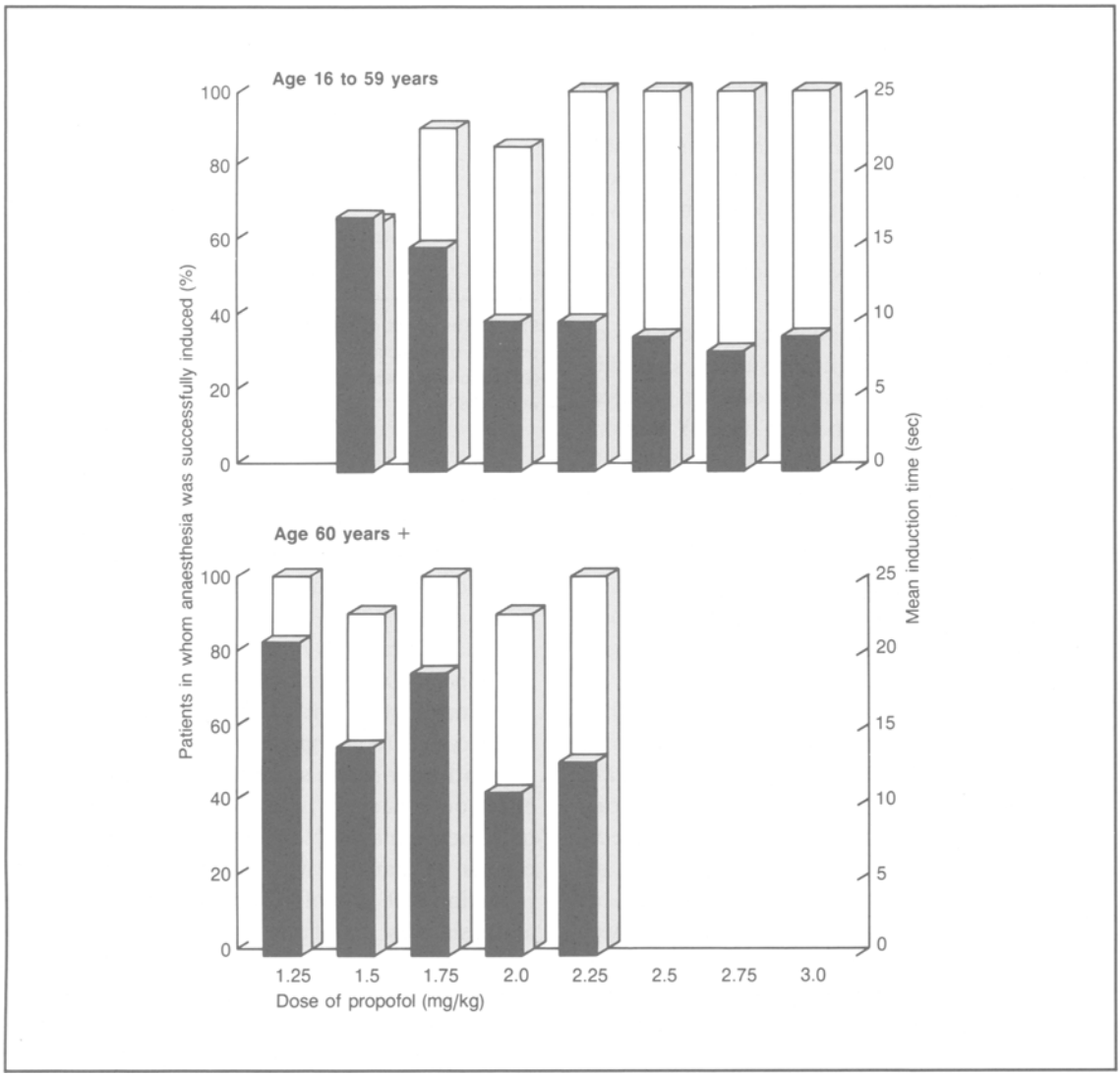

Fig. 3. Percentage of successful inductions (□) and mean induction times (■) in patients aged 16 to 59 years (n = 20 for each dose) and patients aged 60+ years (n = 10 for each dose) following single bolus injections of different doses of propofol (after McCollum et al. 1985).

Table I. Induction of anaesthesia in unpremedicated surgical patients with single bolus intravenous doses of propofol

Reference	Patients[a]		Dose[b] (mg/kg)	Mean induction[c] time (sec)	Successful inductions (%)
	age (y)	number			
Cummings et al. (1984)	18-65	31	2.0	29	87
		84	2.5	27	95
Fahy et al. (1985)	16-64	30	2.5	36	97
McCollum et al. (1985)	16-59	20	2.0	10	85
		20	2.5	9	100
	60+	10	2.0	11	90
McCollum & Dundee (1986)	33 ± 12[d]	50	2.0		90
	37 ± 12[d]	50	2.5		100
Rolly et al. (1985)	37 ± 14[d]	20	2.0	35	95

a All patients were class I or II using the American Society of Anesthesiologists Physical Status classification, i.e. they were either healthy persons or patients with mild systemic disease.
b In all cases the stated dose was injected over 20 seconds.
c Defined as the time from the start of the injection to loss of verbal contact.
d Mean ± SD.

medicated with papaveretum/hyoscine the lower dose of propofol (1.75 mg/kg) produced successful induction of anaesthesia in all patients.

Although these studies were neither extensive nor ideally designed, it seems clear that the commonly used premedications have little or no effect on propofol anaesthesia except that the use of the more potent opioids may reduce induction dose requirements.

1.1.3 Psychomotor Function Following Propofol Anaesthesia

Logan et al. (1987) measured psychomotor function in 21 patients who received single doses of propofol 3 mg/kg and 19 who received methohexitone 2 mg/kg for simple dental extractions. Critical Flicker Fusion Threshold (CFFT) values (a measure of CNS arousal) and Choice Reaction Times (CRT) were assessed before and 15 and 40 minutes after anaesthesia. Performance was impaired at 15 minutes with both drugs; CFFT was significantly reduced ($p < 0.02$) and the latency component of CRT was significantly increased ($p < 0.02$ for propofol, $p < 0.01$ for methohexitone), whilst the motor component of CRT was also increased in the methohexitone group ($p < 0.05$). By 40 minutes all psychomotor variables had virtually returned to pretreatment values with the exception that CFFT was still slightly reduced in the patients who received methohexitone ($p < 0.05$). Balance was also assessed by measurement of linear sway and whilst methohexitone produced a highly significant ($p < 0.01$) increase in sway (i.e. impairment of balance) at 15 minutes, that seen in the propofol group was not significantly different from pretreatment values.

Mackenzie and Grant (1985a) carried out an assessment of psychomotor function in patients who were anaesthetised with either propofol 2.5 mg/kg or methohexitone 1.5 mg/kg followed by incremental doses of the same drug sufficient to maintain light general anaesthesia in conjunction with spinal blockade. Propofol and methohexitone produced similar decreases in CRT, which were significant 30 minutes after awakening with both drugs ($p < 0.05$ and $p < 0.01$, respectively), but only significant after 60 minutes with methohexitone ($p < 0.001$). Some degree of impairment was detectable at 120 minutes with both drugs, but by 240 minutes the values had returned to pretreatment levels.

Propofol produced slightly greater decreases in CFFT than did methohexitone, with a significant effect still detectable at 240 minutes ($p < 0.01$), whereas the reductions in CFFT after methohexitone were only significant up to 120 minutes after surgery (Mackenzie & Grant 1985a).

In another study, digit-substitution test scores were significantly poorer ($p < 0.01$) for up to 180 minutes after surgery in 23 patients who received methohexitone (1.5 mg/kg followed by increments as required) when compared with 23 patients who received propofol 2 mg/kg followed by increments (Kay & Healy 1985). All patients were given alfentanil at induction (7 μg/kg) and during surgery when needed. In the propofol group digit – substitution scores returned to pretreatment values by 60 minutes after the end of surgery, whereas this degree of recovery did not occur in the methohexitone-treated group until after 180 minutes.

Other groups have examined psychomotor function following induction with propofol and maintenance with either isoflurane or propofol, given as increments (Milligan et al. 1987) or as an infusion (Zuurmond et al. 1987). Psychomotor function tests (CRT and p-deletion tests) revealed measurable effects with both anaesthetics for 20 to 30 minutes after surgery, and some reductions in CRT values were detected for up to 40 minutes in patients anaesthetised with isoflurane (Milligan et al. 1987).

Overall, these studies demonstrate that the use of propofol results in some degree of psychomotor impairment in the immediate postoperative period. Nevertheless, recovery of psychomotor function is rapid, and it is at least as good as methohexitone and isoflurane in this respect.

1.1.4 Effects of Propofol on EEG Patterns

Electroencephalographic (EEG) activity was monitored during induction and maintenance of anaesthesia with propofol in 16 patients premedicated with fentanyl 100μg, droperidol 5mg and atropine 0.5mg (Herregods et al. 1988). Induction was with a single dose of 2 mg/kg and maintenance was achieved by an infusion of propofol 9 mg/kg/h, reduced to 6 mg/kg/h after 30 minutes, and 67% nitrous oxide in oxygen. The mean EEG frequency decreased on induction, with a proportional increase in δ activity, but during the infusion the mean frequency returned to just below pretreatment levels over the first 15 minutes and subsequently remained stable. This increase in mean frequency corresponded to a proportional decrease in δ activity and increase in α activity. The mean amplitude of the EEG increased on induction and then fluctuated during the infusion period.

When the infusion of propofol was stopped the mean EEG frequency increased, with a proportional increase in β activity and the mean EEG amplitude was unchanged. Blood concentrations of propofol were found to be negatively correlated with mean EEG frequency ($r = -0.87$) and positively correlated with mean EEG amplitude ($r = 0.47$) and the authors proposed that EEG changes could be used to monitor anaesthetic depth, with an increase in mean frequency or the appearance of β activity indicating a lightening of anaesthesia.

Another characteristic effect of propofol on EEG patterns was described by Hazeaux et al. (1987) who found that high infusion rates (> 9 mg/kg/h) were associated with periods of burst-suppression lasting up to 15 seconds or longer.

1.1.5 Effects on Postoperative Pain, Nausea and Vomiting

Analgesia is an essential part of an anaesthetic procedure, and when a non-opioid intravenous drug is used to produce unconsciousness analgesia is obtained by the use of opioids or the inhalation of nitrous oxide. However, some intravenous anaesthetics, notably thiopentone, have the disadvantage of increasing sensitivity to somatic pain (Dundee & Moore 1960).

When subanaesthetic doses of the cremophor-based preparation of propofol (0.25 to 0.5 mg/kg) or thiopentone (0.5 to 1.5 mg/kg) were given to groups of 20 patients awaiting surgery, comparison of tibial pressure algesimetry readings taken before and after drug administration showed that propofol had an analgesic effect in 35%, an antanalgesic effect in 5%, and had no effect in 60% of patients

(Briggs et al. 1982). In contrast, thiopentone was antanalgesic in 60%, had no effect in 30%, and produced analgesia in only 10% of patients ($p < 0.001$ for all effects). In a second study, control algesimetry readings were taken prior to surgery and then full anaesthesia was induced with propofol 2 mg/kg or thiopentone 4 mg/kg and maintained with intermittent doses of the induction drug and inhaled nitrous oxide. When patients regained consciousness, readings were taken at 2- to 3-minute intervals until they had returned to within the preoperative range. In the majority of the 20 patients who received propofol residual analgesia was apparent, lasting for 40 to 50 minutes in some cases, whilst in most patients who received thiopentone sensitivity to pain was increased in the postoperative period and in a few instances this lasted for up to 5 hours (Briggs et al. 1982).

Therefore, although it has no analgesic properties as such, propofol does not produce antanalgesia and is clearly superior to thiopentone in this respect.

Gunawardene and White (1988) studied the occurrence of nausea and vomiting in 29 patients who received propofol for induction and maintenance, a further 29 patients who also breathed nitrous oxide (66% in oxygen) and a third group of 32 patients who were given enflurane (2 to 3%) and nitrous oxide (66%) following propofol for induction. The incidences of postoperative nausea in these 3 groups were 0, 3.4 and 9.4%, respectively, with an overall incidence of 4.4% for all patients. None vomited.

Retrospective analysis of data from 200 women anaesthetised with propofol for minor surgery also revealed a remarkably low incidence (1.5%) of nausea, and an absence of vomiting, in the postoperative period (McCollum et al. 1987). In a subsequent comparative study of women premedicated with opioids, the incidence of postoperative nausea and vomiting in patients who received morphine 7.5mg ($n = 40$) was significantly lower when propofol and nitrous oxide were used for anaesthesia (0% up to 1 hour postoperatively; 25% 1 to 6 hours postoperatively) than when methohexitone was used as the intravenous agent (40% up to 1 hour postoperatively, $p < 0.01$; 65% 1 to 6 hours postoperatively, $p < 0.05$). In addition, of 7 patients who were nauseated by the premedication and who were anaesthetised with propofol, none experienced nausea in the first postoperative hour and only 1 was nauseated during the following 5 hours. In contrast, 4 out of a total of 6 of the methohexitone-treated patients were still nauseated in the first hour after surgery, and for 2 this continued into the following 5-hour period.

These findings concur with the low incidence of nausea and vomiting reported in clinical studies with propofol (see section 5), and those of McCollum et al. (1987) in particular suggest that propofol may in fact have some antiemetic properties.

1.2 Haemodynamic Effects

1.2.1 Effects of Bolus Doses of Propofol for Induction of Anaesthesia

Animal studies demonstrated propofol to have cardiovascular effects which could be of importance in relation to its clinical use. Thus, Glen and Hunter (1984) reported that single intravenous doses of propofol 3.75 mg/kg administered to minipigs produced increases in heart rate (approximately 60%) and cardiac output (approximately 40%) and decreases in mean arterial blood pressure (approximately 16%) and total peripheral resistance (approximately 33%). Maximal effects occurred 2 minutes after administration and all parameters had returned to pretreatment levels after 15 to 20 minutes. More detailed investigations using dogs anaesthetised with ketamine and fentanyl showed that propofol 2.5 mg/kg reduced mean arterial blood pressure ($p < 0.05$) but that heart rate was unaffected and cardiac output decreased ($p < 0.05$). Left ventricular pressure was also reduced and a significant decrease was observed in the rate of change of left ventricular force (dF/dt) [Brüssel et al. 1986].

Similar haemodynamic effects have been observed in man. Administration of single doses of propofol 2 mg/kg to 20 unpremedicated surgical patients produced decreases of 11% and 16% in systolic and diastolic blood pressures, respectively, 2 minutes after injection, whilst after 5 minutes

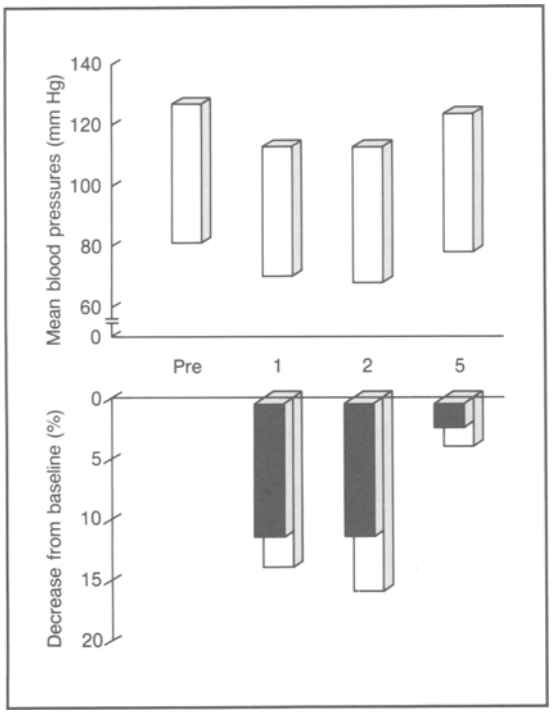

Fig. 4. Mean blood pressures with mean percentage decreases in systolic (■) and diastolic (□) pressures, before (Pre) and 1, 2 and 5 minutes after administration of propofol 2 mg/kg to 20 surgical patients who received no other drugs (after Rolly et al. 1985).

these values had returned almost to pretreatment values (fig. 4; Rolly et al. 1985). Similar decreases in systolic blood pressure were reported by McCollum and Dundee (1986) following a comparative study of propofol 2 and 2.5 mg/kg, thiopentone 4 and 5 mg/kg, etomidate 0.3 mg/kg and methohexitone 1.5 mg/kg, the results of which are shown in table II. Whilst propofol 2.5 mg/kg produced the greatest decrease in blood pressure ($p < 0.05$ when compared with thiopentone 5 mg/kg), heart rate was only modestly increased (5%) by both doses of propofol. In contrast, methohexitone 1.5 mg/kg increased heart rate by 24%.

In most clinical situations propofol has been used in combination with premedications, opioid analgesics or inhalation anaesthetics, some of which themselves have potent cardiovascular effects, and consequently the possibility of additive or synergistic effects on haemodynamic variables is of interest. In a randomised double-blind comparison with placebo neither atropine 0.5mg nor hydroxyzine 100mg given as intramuscular injections 1 hour before surgery significantly altered the hypotensive effects of propofol 2 mg/kg as measured in 90 patients (Bilaine & Desmonts 1985). In randomised non-blinded studies, premedication with oral benzodiazepines (diazepam 10mg, midazolam 3mg), or intramuscular opioids (pethidine 50 to 75mg, papaveretum 15 to 20mg) and anticholinergic drugs (atropine 0.5 to 0.6mg, hyoscine 0.3 to 0.4mg) did not significantly change reductions in blood pressures produced by propofol 1.75 to 2.5 mg/kg alone (Briggs & White 1985; McCollum et al. 1986; Schaer 1986).

When 20 premedicated patients (lormetazepam 1mg) were assigned randomly to receive propofol 2.5 mg/kg with or without a concomitant dose of fentanyl 3 μg/kg, it was found that the decrease in mean arterial blood pressure was significantly greater in patients who received fentanyl (24 *vs* 45mm Hg; $p < 0.05$), and that this was accompanied by a significant reduction in heart rate that did not occur with propofol alone (fig. 5; van Aken et al. 1986).

In patients premedicated with a combination of opioids and anticholinergic drugs propofol decreased mean arterial blood pressure to a much greater degree (by 22 to 32%) than did thiopentone 4 or 5mg (by < 10%), but had no significant effects on heart rate (table III). Propofol also produced significant reductions in stroke volume, cardiac index, systemic vascular resistance and left cardiac work indices. The mechanism whereby propofol produces these haemodynamic effects is not clear. Direct vasodilation and negative inotropy may be involved, but in most studies there may have been contributory effects from other drugs. Although hypotension during induction of anaesthesia can be minimised by titrating the dose to a suitable end-point, it would seem prudent to use propofol with caution in hypovolaemic patients and those with impaired left ventricular function.

Table II. Haemodynamic changes in unpremedicated surgical patients 2 minutes after administration of intravenous anaesthetics (after McCollum & Dundee 1986)

Induction agent	Dose[a] (mg/kg)	No. of patients	Mean decrease in systolic blood pressure (%)	Mean increase in heart rate (%)
Propofol	2.0	40	15	5
	2.5	50	17	5
Thiopentone	4.0	39	6	6
	5.0	45	10	9
Methohexitone	1.5	46	1	24
Etomidate	0.3	50	5	3

a Administered as a single bolus over 20 seconds.

1.2.2 Effects of Induction and Maintenance of Anaesthesia with Propofol

Coates et al. (1987) measured arterial blood pressures throughout surgery in patients premedicated with morphine 0.15 mg/kg who were anaesthetised with propofol 2 mg/kg followed by an infusion of propofol 3.2 mg/kg/h ($n = 9$) or 6.5 mg/kg/h ($n = 8$) with 67% nitrous oxide in oxygen. In both groups systolic blood pressure fell significantly from pretreatment levels (mean of 139mm Hg) during the 30-minute period of anaesthesia that preceded the start of surgery (mean decrease of 48mm Hg with the lower infusion rate, and 64mm Hg with the higher rate; $p < 0.05$ to $p < 0.001$). Although arterial blood pressures increased during surgery with the patients breathing spontaneously (mean systolic pressure during surgery of 98mm Hg with the lower infusion rate and 87mm Hg with the higher rate), systolic pressures remained significantly below pretreatment values ($p < 0.01$ and $p < 0.001$ for the low and high infusion rates, respectively). When ventilation was subsequently controlled mechanically, systolic blood pressures increased further. In patients receiving the lower infusion rate, the mean systolic pressure rose to 109mm Hg, which was not significantly different from the mean pretreatment value. However, with the higher infusion rate mean systolic pressure reached only 91mm Hg, which was still lower than the pretreatment value ($p < 0.001$).

1.2.3 Effects of Intubation on Blood Pressure Following Propofol Induction

General surgical manipulation and, in particular, tracheal intubation tend to produce increases in the arterial blood pressure of the anaesthetised patient and in such circumstances the hypotensive properties of propofol may be advantageous. Indeed, mean peak postintubation systolic blood pressure (124mm Hg) was less than the pretreatment value (142mm Hg) in 8 premedicated (morphine 0.15 mg/kg) patients who received propofol 2 mg/kg for induction followed by an infusion of 6.4 mg/kg/h (with 67% nitrous oxide in oxygen) for maintenance. This was not the case for 8 patients maintained with a lower infusion rate of propofol (3.2 mg/kg/h; postintubation mean systolic pressure of 142mm Hg *vs* 132 pretreatment) [Coates et al. 1986]. Further, in a group of 7 hypertensive patients included in this study who received an infusion of 3.2 to 3.9 mg/kg/h, the peak postintubation blood pressures were considerably lower than those measured before anaesthesia (141/65 *vs* 188/76mm Hg). Similar results were seen in a group of 8 elderly patients (aged 56 to 70 years), premedicated with morphine 0.15 mg/kg, who received an induction dose of propofol 2 mg/kg followed by an infusion of between 3.2 and 3.9 mg/kg/h with the addition of 67% nitrous oxide in oxygen (Monk et al. 1987). Significant decreases in systolic (29%; $p < 0.05$) and diastolic (22%; $p < 0.01$) blood pres-

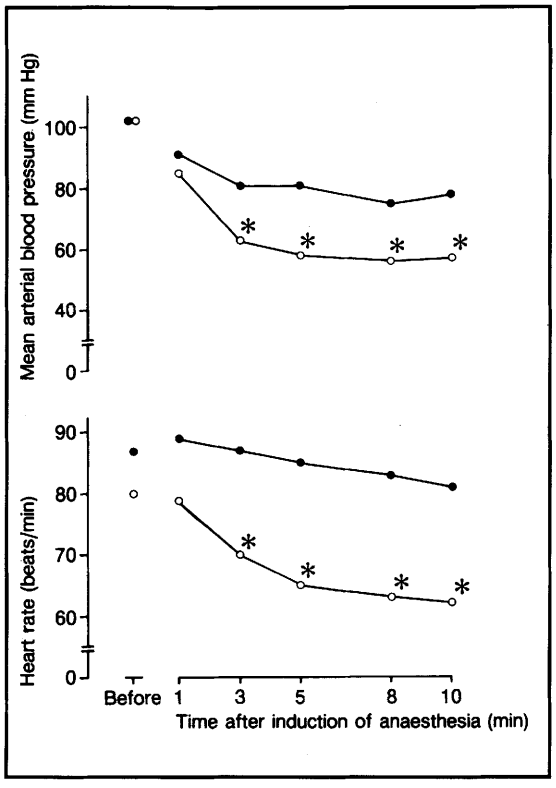

Fig. 5. Mean arterial blood pressures and mean heart rates of surgical patients anaesthetised with propofol 2.5 mg/kg, either with (○; n = 10) or without (●; n = 10) fentanyl 3 μg/kg. All patients received lormetazepam 1mg 2 hours before surgery and breathed 67% nitrous oxide once anaesthesia was induced; * = significantly lower than with propofol alone (after van Aken et al. 1986).

sures followed induction, and whilst both increased in response to laryngoscopy and tracheal intubation (53% for systolic and 47% for diastolic) these did not exceed preinduction values. In a comparative study of 51 unpremedicated patients a greater increase in blood pressure resulted from intubation following induction with thiopentone 5 mg/kg than with propofol 2.5 mg/kg (peak values of 169/119 and 148/110mm Hg, respectively, p value not given; Gauss et al. 1986).

1.3 Effects on Respiration

The first respiratory disturbance seen after administration of a bolus dose of propofol is a profound fall in tidal volume, leading to apnoea in many patients. This has been a consistent observation in clinical studies where propofol has been used to induce anaesthesia, and although the duration of apnoea is usually short (60 seconds or less) it may persist for up to 3 minutes (Goodman et al. 1987). Similarly, the incidence of apnoea varies considerably, occurring in between 50 and 84% of patients and this may be dependent upon a variety of factors, such as premedication, speed of administration, dose and presence of hyperventilation and hyperoxia. These last 2 effects can result from the common practice of allowing patients to breathe 100% oxygen before induction (Goodman et al. 1987).

Detailed respiratory measurements in 16 unpremedicated surgical patients who received an induction dose of propofol 2.5 mg/kg revealed that the apnoea was preceded by a rapid reduction in tidal volume (usually accompanied by tachypnoea) which was maximal about 30 seconds after injection and then progressed into full apnoea. Breathing then resumed spontaneously with small tidal volumes which increased over a period of about 1 minute to a steady rate (Goodman et al. 1987). The changes in tidal volume (Vt), respiratory frequency and minute volume (Vi) that occurred in 7 of these patients upon induction and subsequent infusions of 6 and 12 mg/kg/h are shown in figure 6. Both Vt and Vi were decreased during infusion at 6 mg/kg/h and showed a further reduction when the infusion rate was doubled, whilst the respiratory frequency increased to a maximum during the post-induction period then decreased slightly during the constant infusions (fig. 6). The inspiratory duty cycle (T_i/T_{tot}) was reduced during the lower rate infusion and further decreased when the rate was increased. In addition, analysis of the ventilatory response to rebreathed carbon dioxide in 8 of the patients indicated that an infusion of propofol 6 mg/kg/h reduced this response (determined as the gradient of the carbon dioxide rebreathing curve) to an average of 58%, within 95% confidence limits of 32 and 84% (Goodman et al. 1987).

Grounds et al. (1987b) compared the ventilatory effects of single induction doses of propofol (2.5 mg/kg) and thiopentone (4 mg/kg) in 12 fe-

Table III. Haemodynamic effects of propofol and thiopentone in premedicated surgical patients.

Reference	Premedication[a] drug [dose (mg)]	Induction drug [dose (mg/kg)]	No. of pts	Change in haemodynamic indices 2 minutes after induction (%)							
				MAP	HR	CVP	SV	CI	SVR	LCWI	LSWI
Grounds et al. (1985)	Papaveretum [15-20]	Propofol [2.5]	8	−32[b]	0	−9	−14[d]	−12	−21[d]		
	Hyoscine (scopolamine) [0.3-0.4]	Thiopentone [4]	8	−9[c]	+12	−17[d]	−16[c]	−6	−5		
Lippmann et al. (1986)	Pethidine (meperidine) [50-100]	Propofol [2.5]	21	−22[d]	−2	+26		−18[d]	−11	−35[d]	−35[d]
	Atropine [0.4] Pentobarbitone [50-75]	Thiopentone [5]	19	−5	+5	+29		−10	+12	−15	−21[d]

a Given as intramuscular injections 1.5 hours before surgery.
b $p < 0.001$ compared with preinduction values.
c $p < 0.01$ compared with preinduction values.
d $p < 0.05$ compared with preinduction values.

Abbreviations: MAP = mean arterial blood pressure; HR = heart rate; CVP = central venous pressure; SV = stroke volume; CI = cardiac index; SVR = systemic vascular resistance; LCWI = left cardiac work index; LSWI = left stroke work index.

male patients premedicated with papaveretum (10 to 20mg) and hyoscine (0.2 to 0.4mg). Significant decreases were observed in Vi ($p < 0.01$), Vt ($p < 0.001$) and the mean inspiratory flow rate (Vt/T_i; $p < 0.05$) following both drugs, with maximal effects occurring between 1 and 2 minutes after the start of induction. There were no significant differences between the drugs. Ventilatory frequency and T_i/T_{tot} were also decreased, but these changes were not statistically significant. The only difference found between propofol and thiopentone was that functional residual capacity fell following propofol, but increased following thiopentone ($p < 0.05$ between treatments).

Opioid analgesics are respiratory depressants, and their effects on respiration when combined with propofol are thus of interest. A few studies have specifically examined the combined action of propofol and opioids on ventilatory indices. Taylor et al. (1986) investigated the use of either atropine (0.6mg, n = 18) or papaveretum 10 to 20mg with hyoscine 0.2 to 0.4mg (n = 20) as an intramuscular premedication given 1 hour before induction of anaesthesia with propofol 2.5 mg/kg. The incidence of apnoea was significantly greater in the papaveretum/hyoscine group (80% *vs* 55%; $p < 0.05$) whilst maximum reductions in mean respiratory rate were 53% (after 2 minutes) in the patients treated with papaveretum/hyoscine and 34% (after 1 minute) in the atropine-treated patients ($p < 0.001$ and $p < 0.05$ from baseline values, respectively). Similarly, mean minute volumes were significantly reduced ($p < 0.05$ to $p < 0.01$ for both groups) for at least 4 minutes after induction; maximal reductions were 75% and 56% following papaveretum/hyoscine and atropine, respectively, occurring 2 minutes after induction.

Enhanced respiratory depression with propofol and an opioid has been shown to continue into the postoperative period. Thus, fentanyl 3.5 μg/kg or placebo were given 5 minutes before anaesthesia induction with propofol 2.5 mg/kg in 40 patients who underwent surgery, with subsequent maintenance of anaesthesia using isoflurane 0.5 to 1.5% with 60% nitrous oxide in oxygen (Streisand et al. 1987). Measurements taken 60 minutes after the end of surgery revealed that the ratio of expiratory volume to end-tidal pCO_2 ($V_E/P_{E'CO_2}$) was 30 to 60% less than baseline values in the patients who received fentanyl, but had returned to baseline val-

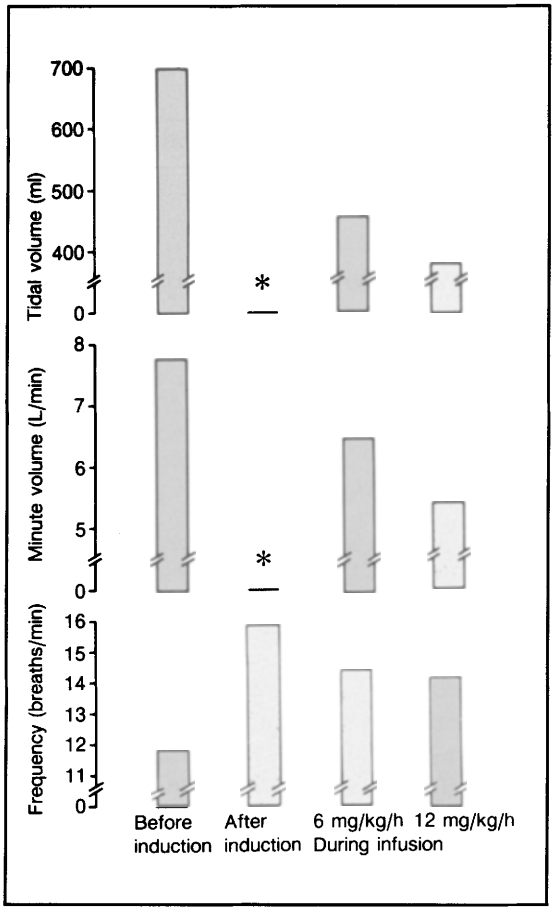

Fig. 6. Tidal volumes, minute volumes and respiratory frequency in 7 unpremedicated patients before and after induction with propofol 2.5 mg/kg and during infusions of propofol 6 and 12 mg/kg/h; * = not measurable (after Goodman et al. 1987).

ues in those who received placebo. This effect is not exclusive to propofol and fentanyl in combination, since similar results were observed when thiopentone 4 mg/kg was used instead of propofol for induction (Streisand et al. 1987).

In conclusion, although propofol clearly depresses respiratory function, this occurs to a degree which should not present the anaesthetist with any difficulties in management (Goodman et al. 1987; Taylor et al. 1986), at least in patients without preexisting respiratory dysfunction.

1.4 Effects on Adrenocortical Function

Intravenous anaesthesia using etomidate has been associated with marked suppression of adrenocortical function (Wagner et al. 1984), particularly when used for continuous sedation of patients in intensive care where it has been implicated with a possible increase in mortality (Ledingham & Watt 1983; Ledingham et al. 1983). Consequently the possible adrenocortical effects of a new intravenous anaesthetic are of considerable interest.

In isolated guinea-pig or bovine adrenal cell models propofol was about 1,000-fold less active than etomidate in inhibiting adrenocorticotrophic hormone (ACTH)-induced release of cortisol (Kenyon et al. 1985; Lambert et al. 1985), suggesting that propofol would be unlikely to have any important effects on adrenocortical function in clinical use (Robertson et al. 1985). *In vitro* experiments using different precursors revealed that propofol inhibits cortisol production at an early stage in the pathway, blocking the conversion of cholesterol to pregnenolone, whilst both etomidate and thiopentone act as inhibitors of 11β-hydroxylase, preventing the final conversion of 11-deoxycortisol to cortisol (Robertson et al. 1985).

Statistically significant changes in plasma cortisol concentrations have occurred in patients anaesthetised with propofol. Kay et al. (1985) measured plasma cortisol concentrations in two groups of 10 surgical patients (separated according to baseline concentrations) who were anaesthetised with propofol. Following an induction dose of 2.5 mg/kg anaesthesia was maintained with 67% nitrous oxide in oxygen and supplementary doses of propofol 10 to 20mg as required, for a mean time of 40 minutes in one group and 45 minutes in the second. After 30 minutes of anaesthesia, plasma cortisol concentrations in both groups were significantly lower than pretreatment levels (259 *vs* 270 nmol/L; $p < 0.05$ and 123 *vs* 207 nmol/L, $p < 0.01$), but by 3 hours after induction (approximately 140 minutes after anaesthesia was stopped) concentrations were at or above pretreatment levels in both groups (464 and 219 nmol/L, respectively). In a study by Herregods et al. (1987) 12

patients received propofol 2 mg/kg followed by an infusion of 9 mg/kg/h, reduced to 6 mg/kg/h after 30 minutes, with supplementary nitrous oxide (67% in oxygen). Plasma cortisol concentrations were reduced at 1 hour after the start of the infusion (mean of 0.47 *vs* 0.66 μmol/L pretreatment), but this was not statistically significant and 1 hour after the end of surgery plasma cortisol concentrations had essentially returned to pretreatment levels (mean of 0.61 μmol/L).

The effects of a bolus of propofol 2.5 mg/kg on adrenal function were compared with those of etomidate 0.3 mg/kg and thiopentone 4 mg/kg in groups of 10 patients each, who were subsequently maintained with 1 to 2% enflurane and 50% nitrous oxide in oxygen (Fragen et al. 1987). Plasma cortisol concentrations were significantly reduced ($p < 0.05$) in all groups 30 minutes after induction, by 29%, 33% and 37% for propofol, etomidate and thiopentone, respectively. In the group who received etomidate, plasma concentrations remained at this reduced level for up to 210 minutes after induction despite the administration of intravenous ACTH 0.25mg at 150 minutes. In contrast, plasma concentrations of cortisol in the propofol and thiopentone groups rose after the end of surgery (at about 80 minutes) and further increased to significantly above pretreatment concentrations ($p < 0.05$) following ACTH stimulation.

During subanaesthetic infusions of propofol given to a small number of patients in intensive care, plasma cortisol concentrations declined steadily over the infusion period of 8 hours (Newman et al. 1987; section 4.2.3) but adrenocortical responses to ACTH were not inhibited unless etomidate had been given prior to the infusion.

Clinical experience seems, therefore, to concur with *in vitro* studies, in that propofol does not inhibit adrenal responsiveness to ACTH. The decrease in basal cortisol production seen in patients receiving propofol may be a consequence of general anaesthesia rather than a direct effect of propofol itself (Fragen et al. 1987), and in intensive care patients cortisol levels may already be decreasing following the physiological effects of trauma or surgical stress (Newman et al. 1987). Nevertheless, in view of the critical condition of intensive care patients and the potential seriousness of any adverse effects in such patients, more studies should be carried out to confirm the suitability of propofol as an intravenous sedative in this setting.

1.5 Effects on Cerebral Physiology

The effects of an induction dose of propofol 2 mg/kg followed by an infusion of 12 mg/kg/h on cerebral metabolism and blood flow were investigated in 11 patients undergoing coronary bypass surgery (Stephan et al. 1987). Under normal ventilatory conditions (i.e. normocapnia) a 51% decrease in cerebral blood flow and a 55% increase in cerebral vascular resistance occurred as a consequence of a 36% decrease in cerebral oxygen consumption. These changes corresponded with decreases in EEG activity and so were considered to be the result of decreased neuronal activity during anaesthesia rather than a direct action of propofol on cerebral vasculature. In addition the normal cerebral vascular responses to increases and decreases in arterial pCO_2 (produced by hypo- and hyperventilation, respectively) were maintained during propofol anaesthesia.

Single doses of propofol 0.35, 0.8 and 2.5 mg/kg given to conscious spontaneously breathing patients ($n = 9$) undergoing minor neurosurgical procedures produced dose-dependent reductions in both intracranial pressure and cerebral perfusion pressure (fig. 7; Siani et al. 1986b), effects that have been confirmed with propofol 0.35 and 0.8 mg/kg in surgical patients under controlled ventilation (Zattoni et al. 1986) and using continuous infusions of propofol 6 and 12 mg/kg/h (Ravussin et al. 1988; Siani et al. 1986a). Hartung (1987) reported that an induction dose of propofol 1 mg/kg reduced intracranial pressure in 5 patients with head trauma, and whilst cranial perfusion pressure was decreased in 4 of 5 patients, this was to a degree where cerebral perfusion may have been compromised in only 1 patient. Continuous infusion of propofol 3 mg/kg for 8 hours to 10 patients with head injuries similarly reduced intracranial pres-

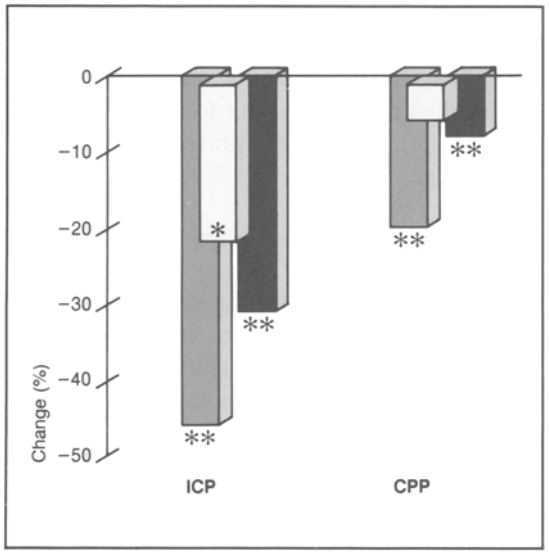

Fig. 7. Maximum percentage changes in cerebral perfusion pressure (CPP) and intracranial pressure (ICP) in 9 conscious, spontaneously breathing neurosurgical patients following bolus doses of propofol 0.35 mg/kg (□), 0.8 mg/kg (■) and 2.5 mg/kg (■); * = $p < 0.05$, ** = $p < 0.01$ (after Siani et al. 1986b).

sure, with a maximum decrease of 40% occurring after 4 hours (Mangez et al. 1987). The maximum reduction in mean cranial perfusion pressure was 12% and at no time did this fall enough to adversely affect cerebral perfusion.

On the basis of these preliminary findings, propofol seems to be a suitable anaesthetic for neurosurgical procedures, particularly in situations where intracranial pressure is raised, but more definitive studies in this area are clearly required.

1.6 Effects on Intraocular Pressure

Mirakhur and co-workers (1987) measured intraocular pressure (IOP) in patients anaesthetised with propofol 2 to 2.5 mg/kg or thiopentone 4.5 to 5 mg/kg ($n = 30$ in each group). Following induction, all patients received intravenous suxamethonium 1 mg/kg and tracheal intubation was performed 2 minutes later, but in half of the patients in each group an additional dose of induction agent (1 mg/kg propofol, 2 mg/kg thiopentone) was given immediately before intubation.

The induction doses of both drugs significantly reduced IOP by about one-third ($p < 0.0005$ compared with baseline), but the administration of suxamethonium subsequently increased IOP, to just below baseline levels in the propofol group and to just above baseline levels in the thiopentone group. In those patients who received a second dose of propofol, IOP again was reduced to significantly below baseline ($p < 0.0005$), and the pressure response to intubation was obtunded in that IOP did not exceed baseline values. In contrast, in those patients who did not receive supplementary propofol, and in all the patients treated with thiopentone, maximum postintubation IOP levels were significantly higher than baseline ($p < 0.05$ to $p < 0.001$). Similar results were reported for 25 patients to whom propofol was administered as a 2 mg/kg bolus followed by an infusion of 9 mg/kg/h (Vanacker et al. 1986). The induction dose produced a significant fall in IOP ($p < 0.001$) and a subsequent induction of vecuronium (0.1 mg/kg, 2 minutes before the start of the propofol infusion) produced a further slight decrease. Postintubation values never exceeded those recorded before induction.

Preliminary studies therefore indicate that propofol can be used in ophthalmic surgery, as it has advantageous effects on intraocular pressure which additionally offset the unwanted increase in pressure that results from the administration of depolarising muscle relaxants and from tracheal intubation. A recent study has also found propofol to be suitable for elderly patients undergoing ophthalmic surgery (Guedes et al. 1988).

2. Pharmacokinetic Properties

The pharmacokinetic properties of propofol were first assessed with the cremophor-based preparation (Adam et al. 1982a,b, 1983) which was never marketed. Re-evaluation of the newer emulsion-based formulation revealed some pharmacokinetic differences (Kay et al. 1986), and so the data presented below will relate to this preparation, unless the cremophor formulation is specifically identified.

In addition, since the pharmacokinetic dispo-

sition of intravenous anaesthetics may be affected by both premedication drugs and inhalation anaesthetics, many of the studies with propofol have been carried out in patients undergoing routine surgical procedures with standard anaesthetic regimens (Cockshott 1985), ensuring that the pharmacokinetic profile of propofol is relevant to the clinical setting. In these instances all patients were ASA class I or II (see section 3).

2.1 Blood Concentrations Following Intravenous Administration

Following a single bolus injection of propofol, blood concentrations of the drug decline rapidly due to extensive distribution (section 2.2). Consequently the blood concentration immediately following such administration cannot readily be measured since it would decrease during the mixing period. Indeed, such information would be of limited value since the onset of anaesthesia normally occurs within one arm-brain circulation time (section 1.1).

When propofol was administered as a continuous intravenous infusion of 9 mg/kg/h to 6 surgical patients an initial rapid increase in blood concentrations over 10 minutes was observed, followed by a slower rate of increase. Steady-state blood concentrations had almost been achieved after 45 minutes but levels continued to increase asymptotically over the whole infusion period. Using noncompartmental analysis it was calculated that a mean steady-state blood concentration of 6.2 mg/L would have been achieved in these patients (Gepts et al. 1985a).

Administration of repeated bolus injections is an alternative to continuous infusion for the maintenance of anaesthesia. This approach was used in patients undergoing surgery with a spinal anaesthetic block (Knell & McKean 1985), in whom anaesthesia was induced with propofol 2.5 mg/kg and then maintained with doses of 1 mg/kg after 3 minutes and subsequently at 6-minute intervals. This regimen produced peak and trough blood propofol concentrations of between 5 and 10 mg/L and 1 and 2.5 mg/L, respectively, in 2 individuals for whom data are available (Cockshott 1985). In 3 of 5 patients in whom propofol kinetics were assessed peak and trough concentrations increased slightly over the period of anaesthesia (mean duration = 75 minutes) [Knell & McKean 1985]. This is consistent with the continued increase in blood concentrations seen during constant infusions (Gepts et al. 1985a).

2.2 Distribution

Blood concentration-time curves obtained following single bolus injections show that propofol very rapidly distributes from the circulation into tissues (fig. 8). Estimations of the distribution half-life ($t_{1/2\alpha}$) have varied from 1.8 to 4.7 minutes (table IV). Autoradiographic studies in rats demonstrated that propofol appears in the brain within 30 seconds of intravenous administration (Rhodes & Longshaw 1977), whilst pharmacokinetic modelling of human data indicated a mean blood-brain equilibration half-life of 2.9 minutes (Schüttler et al. 1986), findings which concur with propofol's rapid onset of action (section 1.1).

The volumes of distribution of propofol in the central compartment (Vd_c), at steady-state (Vd_{ss}) and during elimination (Vd) are high (13 to 76L, 171 to 349L and 209 to 1008L, respectively; table IV), reflecting extensive tissue distribution of propofol related to its high lipophilicity (Cockshott 1985).

In most pharmacokinetic studies the data were best described by an open 3-compartment model (Gepts et al. 1987; Cockshott et al. 1987; Kay et al. 1986), and this would indicate that the tissues into which propofol distributes can be considered in 2 groups; one consisting of well-perfused organs and a second which has a more limited blood supply (e.g. fat deposits).

2.3 Elimination

2.3.1 Metabolism and Excretion

When a subanaesthetic dose of ^{14}C-labelled propofol was given intravenously to 6 male volunteers (mean dose 0.47 mg/kg), 88% of the administered

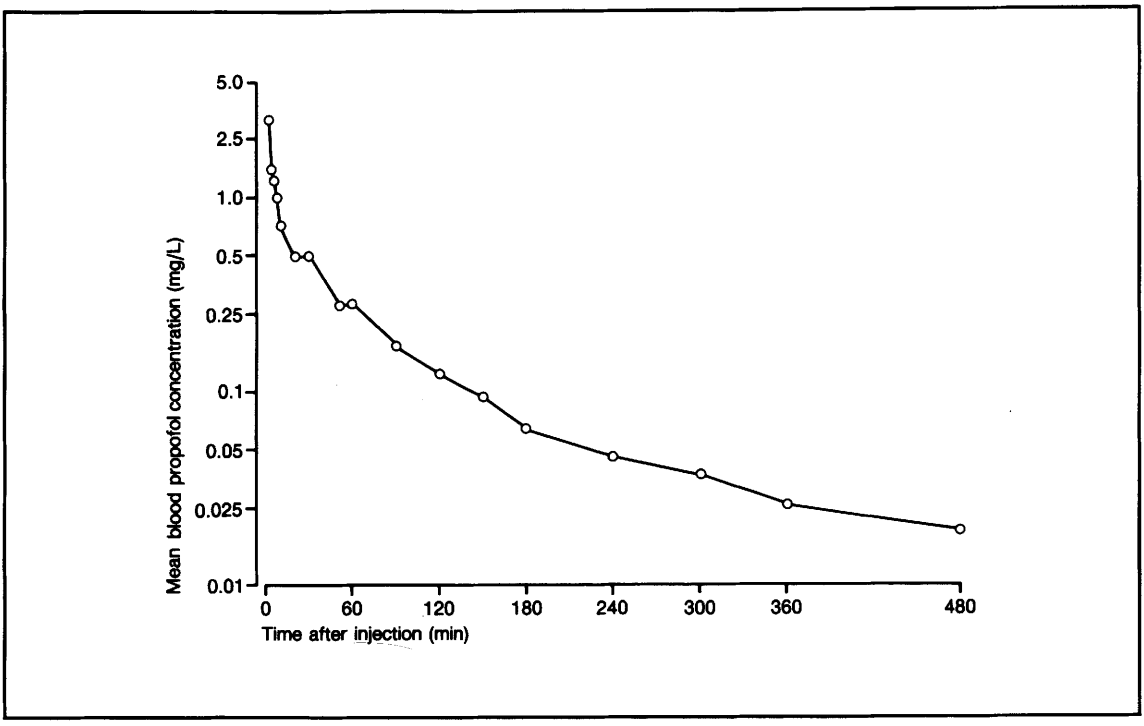

Fig. 8. Mean blood propofol concentrations in 6 female patients with normal hepatic and renal function following induction doses of propofol 2.5 mg/kg (after Cockshott 1985).

radioactivity was recovered in the urine, whilst less than 2% was excreted in the faeces (Simons et al. 1985, 1988). Analysis of the radioactive material excreted in urine revealed that less than 0.3% was unchanged propofol, whilst approximately 40% was propofol glucuronide and the remainder consisted of the 1- and 4-glucuronide and 4-sulphate conjugates of 2,6-diisopropyl 1,4-quinol (fig. 9). Metabolism of propofol is rapid; in the above study unchanged propofol accounted for 94% of the radioactive material in blood 2 minutes after injection, but after 30 minutes 81% of the radioactivity was in the form of metabolites.

The total clearance of propofol given either as a bolus injection or as an infusion to patients receiving no other anaesthetic agent was between 94 and 139 L/h (table IV). With the exception of those patients pretreated with fentanyl 100μg (Cockshott et al. 1987; see section 2.5), a similar range was observed when supplementary anaesthetics were given (108 to 136 L/h; table IV). Since normal hepatic blood flow in man has been estimated to be between 66 and 108 L/h (George 1979), these clearance values for propofol suggest that some extrahepatic metabolism occurs (Cockshott 1985), particularly as hepatic blood flow is reduced in anaesthetised patients (Nies et al. 1976).

2.3.2 Elimination Half-Life

The pharmacokinetics of propofol have been described using both open 2-compartment (Schüttler et al. 1985, 1986; Simons et al. 1988) and open 3-compartment models (Cockshott et al. 1987; Gepts et al. 1987; Kay et al. 1986). In those studies where a 2-compartment model was used the elimination half-life values ranged from 92 to 106 minutes (table IV).

In those studies where a 3-compartment model was utilised elimination of propofol was found to be biphasic. The first stage was rapid with a half-

Table IV. Pharmacokinetic data for propofol obtained in healthy volunteers and surgical patients

Reference	Number and type of patients	Dose	Other agents administered		Clearance (L/h)	Volumes of distribution (L)			Distribution half-life $t_{1/2\alpha}$ (min)	Elimination half-life[a]	
			premedication	inhalation agents		Vd_c	Vd_{ss}	Vd		$t_{1/2\beta}$ (min)	$t_{1/2\gamma}$ (min)
Gepts et al. (1987)	6 Surgical[b]	3 mg/kg/h infusion	Glycopyrronium bromide	None	113	21	349[c]	1008	3.1	32	403
	6 Surgical[b]	6 mg/kg/h infusion			112	16	348[c]	973	3.2	38	386
	6 Surgical[b]	9 mg/kg/h infusion			94	13	176[c]	598	2.3	25	277
Cockshott et al. (1987)	6 Surgical (F)	2.5 mg/kg bolus over 20 sec	None	N_2O[d]	115	41	305	722	2.9	45	284
	6 Surgical (F)		100μg Fentanyl	N_2O[d]	77	22	171	387	1.8	34	208
	6 Surgical (F)		None	N_2O[d] + 1.5% Halothane	107	35	229	460	4.1	34	184
Kay et al. (1986)	6 Surgical (M)	2.5 mg/kg	Diazepam 10mg	N_2O[d] + 1.5% Halothane	109	42	329	708	2.4	56	262
	6 Surgical (F)	bolus over 20 sec			108	36	313	801	2.2	45	309
Schüttler et al. (1985)	8 Volunteers (M+F)	200mg bolus over 30 sec	None	None	139	56		365			106
	8 Surgical (F)	160mg bolus	None	N_2O[e] + 1.5-2.0% Enflurane	136	37		298			92
Schüttler et al. (1986)	6 Volunteers[b]	Computer-controlled infusion[f]	None	None	113	26		209			
Simons et al. (1988)	6 Volunteers (M)	0.47 mg/kg bolus over 20 sec ^{14}C-propofol	None	None	132	76	239	322	4.7		97

a Two elimination half-life values ($t_{1/2\beta}$ and $t_{1/2\gamma}$) are given in studies where a triexponential blood concentration-time curve was observed, whereas a single value is given in studies where the curve was considered to be biexponential.

b Sex of patients not specified.

c Calculated using non-compartmental analysis.

d Nitrous oxide was administered as a 2 : 1 mixture with oxygen.

e Nitrous oxide was administered as a 3 : 2 mixture with oxygen.

f Infusion rate was controlled by computer to produce a constant increase in blood propofol concentrations of 0.45 mg/L/min.

Abbreviations: Vd_c = volume of distribution in central compartment; Vd_{ss} = volume of distribution at steady-state; Vd = volume of distribution during the elimination phase (alternatively called V_{area}, Vd_β and Vd_γ in some studies); M = male; F = female.

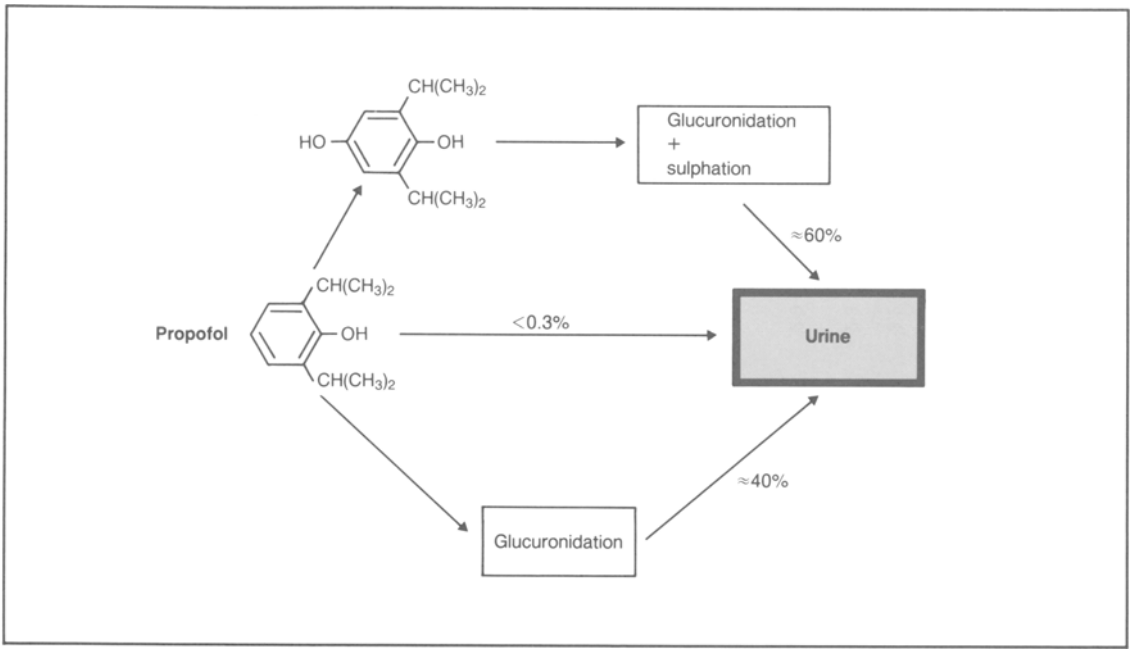

Fig. 9. The metabolism and urinary excretion of propofol (after Simons et al. 1988).

life ($t_{1/2\beta}$) of 25 to 56 minutes, whilst the terminal elimination phase occurred more slowly with a half-life ($t_{1/2\gamma}$) of 184 to 309 minutes following single bolus injections, and of 277 to 403 minutes following continuous infusions (table IV). Since this terminal elimination phase is probably a consequence of the slow return of propofol from a poorly perfused compartment, this apparent increase in $t_{1/2\gamma}$ following continuous infusion may be due to accumulation of propofol in this compartment.

2.4 The Effects of Age, Sex, and Renal and Hepatic Disease on the Pharmacokinetics of Propofol

2.4.1 Effects of Age

The pharmacokinetics of propofol have been assessed in only a small number of elderly patients (Kirkpatrick et al. 1988). Data were obtained for 12 elderly patients (65 to 80 years) who received single bolus injections of propofol 2 mg/kg and were compared with those obtained from a control group of 12 younger patients (18 to 35 years) who received doses of 2.5 mg/kg. In both groups papaveretum (10 to 20mg intramuscularly) was given 1 hour before surgery and anaesthesia was maintained with up to 1% halothane/67% nitrous oxide in oxygen. For both study groups the data were fitted to an open 3-compartment model. The terminal elimination half-life was similar for both the elderly (834 minutes) and younger patients (674 minutes), but propofol clearance was significantly reduced in the elderly 86 *vs* 107 L/h; $p < 0.05$). The initial volume of distribution (Vd_c) was significantly reduced in the elderly (19.6 *vs* 26.3L; $p < 0.05$).

The reduction in clearance suggests that metabolism of propofol is reduced in the elderly, possibly as a result of the reduction in hepatic blood flow that occurs with age (George 1979). Blood concentrations of propofol at 2 minutes after injection were significantly higher in the elderly patients (6.1 *vs* 4.2 mg/L; $p < 0.02$). This is a result of the decrease in Vd_c in these patients and probably explains why the elderly are more sensitive to propofol (Dundee et al. 1986b).

2.4.2 Effects of Sex

Kay and associates (1986) compared the pharmacokinetics of propofol in male and female surgical patients and found no significant differences in clearance, volumes of distribution and distribution and elimination half-lives (table IV). The ratio of volume of distribution at steady-state (Vd_{ss}) to volume of distribution during elimination (Vd) was relatively low in these patients (0.58 or less), again probably as a result of retention of propofol in poorly perfused fat deposits, but was significantly higher in men than in women ($p = 0.021$; Kay et al. 1986).

2.4.3 Effects of Renal and Hepatic Disease

Mean distribution and elimination half-lives were measured in 4 patients with renal insufficiency who were undergoing abdominal surgery and were found to be slightly lower than in a similar group of 6 patients with normal renal function, but the differences were not statistically significant. In addition, total propofol clearance values were similar in the 2 groups (renal insufficiency, 111 L/h; normal renal function, 100 L/h) [Morcos & Payne 1985], and on the basis of these limited findings it would seem that renal disease does not seriously alter propofol pharmacokinetics.

Servin et al. (1986) studied the pharmacokinetics of an induction dose of propofol 2.5 mg/kg in 10 patients with uncomplicated liver cirrhosis compared with a group of 10 patients with normal liver function. No significant pharmacokinetic differences were found between the groups, and the authors suggested that extrahepatic metabolism of propofol may compensate for reduced liver function.

2.5 Effects of Other Anaesthetic Drugs on Propofol Pharmacokinetics

Inhalation anaesthetics such as halothane reduce hepatic blood flow (Nies et al. 1976), and therefore have the potential to affect metabolism and clearance of many drugs. Similarly, fentanyl – frequently used as an analgesic during surgery – has been shown to alter the pharmacokinetic profile of etomidate. Cockshott et al. (1987) investigated the possible effects of both of these drugs on the disposition of a bolus dose of propofol 2.5 mg/kg in surgical patients who also received nitrous oxide (table IV).

The use of halothane to maintain anaesthesia resulted in a reduction of the volumes of distribution of propofol both in the central compartment (by 16%) and during the elimination phase (by 36%), whilst pretreatment with fentanyl produced even greater decreases in these volumes (by 47% and 46%, respectively). The rate of elimination of propofol was also affected by these drugs; the half-lives of the two elimination phases ($t_{1/2\beta}$ and $t_{1/2\gamma}$) were reduced by 24% and 35%, respectively, by halothane and 24% and 27% by fentanyl. In addition pretreatment with fentanyl reduced the clearance of propofol by 32% (table IV).

2.6 Blood Concentrations and Pharmacodynamic Effects

Whilst no data are available on the blood concentrations of propofol required to produce anaesthesia, a number of authors have measured concentrations at the time of awakening. In a study of 18 patients (pretreated with glycopyrronium bromide), in whom anaesthesia was induced and maintained with infusions of propofol 3, 6 and 9 mg/kg/h, the blood concentrations at awakening ranged from 0.74 to 1.66 mg/L (Gepts et al. 1987). Similarly, in 12 patients who were anaesthetised with a bolus injection of propofol 2.5 mg/kg and followed by repeated doses of 1 mg/kg at 3 minutes and then at 6-minute intervals, awakening occurred when the blood concentrations fell to between 0.9 and 1 mg/L, although in this study pretreatment with oral diazepam 10mg or lorazepam 2.5mg may have added to the hypnotic effect of propofol (Knell & McKean 1985). These findings in surgical patients agree with data obtained from 8 volunteers who received a single bolus dose of propofol 200mg – in this instance the mean blood concentration on awakening was 1.1 mg/L.

In some patients a small secondary peak in blood propofol concentration has been observed at the

Table V. Summary of non-comparative studies using propofol to induce and maintain anaesthesia during surgical procedures

Reference	Type of surgery	Premedication[a] (dose/mg)	Induction (dose, mg/kg)	Maintenance	No. of patients	Results				Comments
						mean duration of anaesthesia (min)	mean recovery time (min)	mean propofol consumption rate (mg/kg/h)	apnoea	
Danel et al. (1986)	Body surface	Diazepam (10 po)	P (2 or 3) F (0.05)	P bolus (1 mg/kg as required) + F (50 μg/20 min) + N_2O (60%)	82	39	15	9	> 60 sec in 70% of cases	
Herregods et al. (1987)	Ear surgery	F (0.1) Droperidol (5) Atropine (0.5)	P (2)	P inf (9 mg/kg/h, reduced to 6 after 30 min) N_2O (67%)	12	120 range 70-180	6			Anaesthesia 'acceptable' in 100% of cases
Hunter et al. (1985)	Minor general	Papaveretum + Hyoscine[b] or Benzodiazepine + Hyoscine[b]	P (2.5)	P bolus[b] N_2O[b]	30	33.2 range 14-65	13.9	9.5	Occurred in 20% of cases > 60 sec in 7%	Induction 'good' in 93%, 'adequate' in 7% of cases Maintenance 'good' in 73%, 'adequate' in 20%, 'poor' in 7% of cases Recovery 'good' in 97%, 'adequate' in 3% of cases
Martinelli et al. (1986)	Short gynaecological	Atropine (0.5)	P (2 or 2.5)	P bolus 0.5 mg/kg as required + N_2O[b]	45	6.4	2.4	33		
	Breast surgery or celioscopy	Atropine (0.5) Pethidine (50)	P (2.5)	P inf + N_2O[b] or F (0.05-0.1mg)[c] or Pethidine (10-80mg)[c]	47	32.8	8.5	16.7		Induction 'good' in 78%, 'insufficient' in 15% of cases Maintenance 'good' in 57%, 'insufficient' in 15% of cases

Melloni & Martinelli (1986)	Body surface surgery	Atropine (0.5) Pethidine (50)	P (2)	P inf N_2O[b] F, Pethidine (as required)[b]	61	8.4		Occurred in 84% of cases	Induction 'good' in 84% of cases Maintenance 'good' or 'adequate' in 87% of cases
Robinson (1985)	Body surface surgery	None	P (2.5)	P bolus (20-40mg as required) N_2O (67%)	37 range 11-72	12.2	11.3[d]	> 30 sec in 54% of cases	Induction 'good' in 86%, 'adequate' in 8% and 'poor' in 5% of cases Maintenance 'good' in 70%, 'adequate' in 24%, 'poor' in 5% of cases

a Administered between 30 and 120 minutes before surgery, as an intramuscular injection unless otherwise stated.
b Dose not stated.
c Dosing intervals not stated.
d Median value for 19 patients who underwent surgery lasting 40 or more minutes.
Abbreviations: po = oral administration; P = propofol; F = fentanyl; N_2O = nitrous oxide, at given percentage in oxygen; inf = infusion.

time of, or soon after, regaining consciousness (Cockshott et al. 1987; Kay et al. 1986; Schüttler et al. 1985). It is not known whether this peak is due to a local effect at the sample site, such as the return of propofol into the blood from adjacent tissues, or whether it is a true increase in systemic concentration (Cockshott et al. 1987).

3. *Use of Propofol in General Surgery*

The clinical performance of propofol as an anaesthetic has been studied in a number of trials involving a range of general surgical procedures (this section), and also in some more specific procedures or circumstances (section 4).

Propofol has mostly been compared with the other intravenous anaesthetics thiopentone, methohexitone and, to a lesser extent, etomidate, but a few studies have compared propofol with the inhalation anaesthetics halothane, isoflurane and enflurane. A problem of such comparative studies is that it is not realistically possible to give anaesthetics in a double-blind fashion. Events that occur during surgery – cough, apnoea, movement, etc. – can be recorded and quantified in an objective manner, but the final assessment by the anaesthetist of how the anaesthetic performed will be an overall impression of these factors and others, such as 'smoothness' of induction, which are not so easily defined or measured, and may therefore be influenced by investigator bias. However, postoperative assessment of the condition of the patient can be done under double-blind conditions, and in many of the studies with propofol this has been the case.

Surgical patients are classified according to the American Society of Anesthesiologists (ASA) physical status grading. Normal healthy persons are ASA class I, and patients with mild systemic disease are ASA class II, whilst ASA class III patients have serious systemic diseases which are not incapacitating. Class IV patients have an incapacitating disease which is a constant threat to life and those who are not expected to survive 24 hours without an operation are ASA class V. With the exception of the studies of propofol for sedation of patients

in intensive care (section 4.3.2), and undergoing cardiac surgery (section 4.4), all the clinical studies were carried out in ASA class I, II or III patients.

3.1 Non-Comparative Studies

Details of a number of non-comparative studies of propofol for both the induction and maintenance of anaesthesia are shown in table V. Induction doses ranged from 2 to 3 mg/kg, whilst maintenance of anaesthesia was managed by either intermittent bolus injections or a continuous infusion. Analgesia was provided with nitrous oxide, either alone or in combination with opioids (fentanyl and pethidine). Despite a varying duration of anaesthesia from 6 minutes to up to 3 hours, recovery was rapid in all studies (mean recovery time of 15 minutes or less), and the overall consumption rate of propofol was remarkably consistent between studies in spite of variations in premedications and supplementary analgesics. The exception to this is the high consumption rate reported by Martinelli et al. (1986) of 33 mg/kg/h, and in this case the procedures were so short that the induction dose disproportionately contributed to the overall consumption rate.

Subjective assessments by anaesthetists rated induction and maintenance of anaesthesia with propofol to be 'good' or 'adequate/acceptable' in 84 to 100% of patients (table V). Where recovery was assessed in 1 study only (Hunter et al. 1985) it was considered 'adequate' or 'good' in all patients.

Although propofol has been successfully used with only the addition of inhaled nitrous oxide for analgesia (table V), Dundee et al. (1986a) found that this was usually associated with some movement in response to skin incision when the propofol infusion rate was about 8 to 14 mg/kg/h and nitrous oxide was at 67%. However, they reported that this could be overcome in operations lasting up to 1 hour by the administration of a small dose of fentanyl (1 μg/kg) just before induction.

3.2 Comparative Studies

Propofol has been compared with other intravenous and inhalation anaesthetics for induction and maintenance of anaesthesia in a range of general surgical procedures (table VI).

Comparisons with methohexitone for both induction and maintenance (in combination with nitrous oxide) always found propofol to be at least as effective as methohexitone, irrespective of premedication and the use of additional analgesics. Recovery from propofol anaesthesia was often significantly faster, although Sampson et al. (1987) only found a significant difference for patients who were anaesthetised for at least 50 minutes, and Mackenzie and Grant (1985a) reported virtually identical recovery times after both drugs.

On the basis of the limited data available from these studies, propofol seems to produce a higher incidence of apnoea on induction than methohexitone, but there is less movement during the induction period with propofol. The latter was particularly apparent when no premedication or other drugs were given (analgesia being provided by regional blockade), when the incidence of movement was 75% with methohexitone but only 20% with propofol (Mackenzie & Grant 1985a). Similar incidences of movement occurred during maintenance (methohexitone 60%, propofol 15%; $p < 0.01$). The same authors reported that anaesthesia with methohexitone 1.5 mg/kg followed by an infusion of 12 mg/kg/h supplemented with 66% nitrous oxide in patients premedicated with papaveretum/hyoscine proved unacceptable because of an excessive level of excitatory effects and movement in response to surgery, whereas the use of propofol 2 mg/kg followed by an infusion of 18 mg/kg/h, reduced after 10 minutes to give a mean maintenance infusion rate of 13 mg/kg/h, in the same circumstances was found to be satisfactory when used in a group of 40 patients (Mackenzie & Grant 1985b).

Propofol has also been compared with thiopentone for induction and maintenance (table VI; Henriksson et al. 1987), and again propofol was associated with significantly shorter recovery times and was found to be superior by anaesthetists' overall assessments.

Use of propofol for both induction and maintenance of anaesthesia was also reported to be a suitable alternative to induction with thiopentone and maintenance with inhalation anaesthetics –

Table VI. Summary of randomised comparative studies of propofol for the induction and maintenance of anaesthesia

Reference	Surgical procedure	Premedication[a] [dose (mg)]	No. of patients	Anaesthetics		Clinical observations					
				induction [dose (mg/kg)]	maintenance	duration of anaesthesia or surgery (min)	recovery time (min)[b]		incidents during induction		comments
							eyes open	orientation[c]	excitation or spontaneous movement (% of patients)	apnoea	
Comparisons with thiopentone for induction and maintenance of anaesthesia											
Henriksson et al. (1987)	Short gynaecological	Atropine [0.2-0.5] (n = 77 only)	60	P [2.5]	P bolus [10-20mg] + N_2O [67%]	8.5	2.9**	3.9***	28	> 20 sec in 45% of patients	Patients' assessment; P ≡ T
			60	T [5]	T bolus [25-50mg] + N_2O [67%]	9.0	3.9	5.4	17	> 20 sec in 48% of patients	Anaesthetists' assessment P significantly better than T ($p < 0.05$)
Comparisons with methohexitone for induction and maintenance of anaesthesia											
Jessop et al. (1985)	Assorted surgery using light general anaesthesia and spinal analgesia	Papaveretum [10-20]	30	P [2.1][d]	P inf [6.2 mg/kg/h][e]	44	4.1***	(6.3***)[f]	17	43% of patients	Anaesthetists assessment; anaesthesia 'good' or 'adequate' in 97% of patients with both P and M
		Atropine [0.6]	30	M [1.5][d]	M inf [6.3 mg/kg/h][e]	47.3	9.6	(15.4)[f]	7	13% of patients	
Mackenzie & Grant (1985a)	Orthopaedic surgery under light general anaesthesia and spinal blockade	None	20	P [2.5]	P bolus [0.6 to 0.8 mg/kg]	51.6	9.3	(9.3)[f]	20	75%	P quality of induction; maintenance and recovery was 'good' or 'adequate' in 100% of cases. M quality of induction, maintenance and recovery was 'good' or 'adequate' in 90%, 95% and 100% of cases, respectively
			20	M [1.5]	M bolus [0.4 to 0.5 mg/kg]	58.7	8.8	(9.1)[f]	75	40%	

Table VI. Contd

Reference	Surgical procedure	Premedication[a] [dose (mg)]	No. of patients	Anaesthetics		Clinical observations					
				induction [dose (mg/kg)]	maintenance	duration of anaesthesia or surgery (min)	recovery time (min)[b]		incidents during induction		comments
							eyes open	orientation[c]	excitation or spontaneous movement (% of patients)	apnoea	
Sampson et al. (1987)	Orthopaedic or gynaecological surgery	Pethidine [1 mg/kg][g]	22	P [2]	P inf [7.2 mg/kg/h] + N_2O [70%]	81	9.5[h]	20.5[h]			In cases where infusion time > 50 min, recovery time after M = 19 min, P = 8 min, p < 0.05
			18	M [1.5]	M inf [6.6 mg/kg/h] + N_2O [70%]	65	11[h]	22.5[h]			
Comparisons with thiopentone for induction, and halothane and isoflurane for maintenance of anaesthesia											
Hartung & Freye (1988)	Abdominal surgery	Atropine [0.01 mg/kg] Pethidine [0.5 mg/kg]	15	P[2]	P inf [6 mg/kg/h] + N_2O [67%]	168		17			Anaesthetists' assessment; 'good' or 'adequate' in 15 patients with HX/EF, in 14 patients with P
		Promethazine [1 mg/kg]	15	HX[3]	EF [0.5-2.5%] + N_2O [67%]	201		34			
Ledderose et al. (1988)	ENT surgery with regional analgesia	Atropine [0.5] Pethidine [1 mg/kg] Promethazine [50]	25	P [2.2][d] + F [0.1-0.2mg]	P inf [12 mg/kg/h] reduced to 6 after 10 min] + F bolus	110	10*	(18)[f]*	3	100%	
			25	T [4.5][d] + F [0.1-0.2mg]	I [0.4-2%] + F bolus	122	15	(25)[f]*	3	100%	
Sear et al. (1988)	Body surface surgery	Papaveretum [10-20] Hyoscine [0.2-0.4]	25	P [2.5]	P inf [8.7 mg/kg/h][e] + N_2O [67%]	38	12*	(18.8)[f]*	16	> 30 sec in 40% of patients	
			25	T [4-5]	H [1-2%] + N_2O [67%]	37	17.8	(25.3)[f]	0	> 30 sec in 36% of patients	

Uppington et al. (1985)	Body surface surgery	Morphine [0.15 mg/kg] Atropine [0.6]	19	P [2.5]	P bolus [10-20mg] + N_2O [67%]	48.9 (mean for both groups)	2.3	(3.4)[f]	25%	> 30 sec in 42% of patients[i]	10 min after end of surgery 89% of P patients and 9% of T + H patients had recovered to give correct date of birth
			11	T [5]	H [1-1.5%] + N_2O [67%]				0%	> 30 sec in 0% of patients[i]	
Vinik et al. (1987)	Gynae-cological surgery	Pethidine [1 mg/kg][g]		P [2]	P inf [6-12 mg/kg/h] + N_2O [60%]	80	5***	18***			
				M [1.5]	M inf [6-18 mg/kg/h] + N_2O [60%]	36	21	34			
				T [4]	I [1-1.5%] + N_2O [60%]	51	10**	18***			
Youngberg et al. (1986)	Short surgical procedures	Atropine [0.4]	10	P [2.5] + F [1.5 μg/kg]	P bolus [0.63 mg/kg] + N_2O [60-70%]	65	(3.3*)[j]	9.0			
			10	T[5] + F [1.5 μg/kg]	I [0.2-2%] + N_2O [60-70%]	63	(9.0)[j]	24.9			

a Given 60 to 120 minutes before induction as an intramuscular injection, unless otherwise stated.
b From last bolus dose, discontinuation of infusion or withdrawal of N_2O, or end of operation, as appropriate.
c Defined as awareness of place and date.
d Mean or median dose required to induce anaesthesia.
e Mean infusion rate over period of anaesthesia.
f Time to giving correct date of birth.
g Given 5 minutes before induction.
h Figures taken from graphs.
i Data applies to both induction and maintenance stages.
j Time to first (verbal) response to questions.

Abbreviations: P = propofol; T = thiopentone; N_2O = nitrous oxide, at given percentage in oxygen; bolus = bolus injections given as required; M = methohexitone; HX = hexobarbitone; EF = enflurane; F = fentanyl; inf = constant intravenous infusion; I = isoflurane; H = halothane; po = oral administration; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.

halothane, isoflurane and enflurane – and recovery was often quicker after propofol anaesthesia (table VI).

Thus, propofol compares well with other intravenous and inhalation anaesthetics in a wide range of general surgical procedures, and results in more rapid recovery in most situations. Several authors have commented additionally on the good 'quality of recovery' after propofol, with regard to clear-headedness and alertness (Henriksson et al. 1987; Jessop et al. 1985; Mackenzie & Grant 1985a).

4. Clinical Use of Propofol in Specific Settings

4.1 Propofol for Outpatient Surgery

The need to make more efficient use of hospital resources has led to an increasing number of minor surgical procedures being carried out on an outpatient (day-case) basis. In such circumstances an important requirement is that recovery from anaesthesia should be rapid with minimal residual effect.

Non-comparative studies (table VII) showed that induction and maintenance using propofol with an additional small dose of fentanyl provided adequate anaesthesia for short gynaecological or urological procedures. Recovery was rapid and there was a very low incidence of postoperative nausea or vomiting. The fact that a number of patients reported feelings of hunger or asked for food indicates good recovery from the effects of the anaesthetic.

A number of studies have compared methohexitone with propofol for induction and maintenance, or for induction only followed by inhalation anaesthesia (table VII). Immediate recovery times were either equivalent for the two drugs or were shorter after propofol, with the exception of one study where single bolus injections were used to facilitate dental extractions (Logan et al. 1987).

Although recovery from anaesthesia with either propofol or methohexitone was sufficient to allow patients to be sent home on the same day as surgery was performed, psychomotor performance tests showed that functional impairment was less prolonged after propofol. Walking ability and correct balance also returned more quickly after propofol anaesthesia, whilst nausea and vomiting were more frequent in the patients who received methohexitone. Overall assessments of anaesthesia and recovery generally found propofol to be the superior drug (table VII). Results from take-home questionnaires which were used in one study indicated that patients generally felt better after propofol anaesthesia and that this difference persisted after discharge (Kay & Healy 1985).

Isoflurane has been compared with propofol for the maintenance of anaesthesia following induction with propofol in outpatient surgical procedures (table VII; Milligan et al. 1987; Zuurmond et al. 1987). Again, although both provided adequate anaesthesia and rapid recovery, psychomotor performance improved more rapidly after maintenance with propofol (Milligan et al. 1987).

4.2 Propofol for Total Intravenous Anaesthesia

In a non-comparative study intravenous anaesthesia using propofol alone was found to be inadequate in premedicated (fentanyl 50 to 100μg and droperidol 2.5 to 5mg) patients undergoing laryngeal microsurgery; 9 of 12 patients who received 2 mg/kg followed by an infusion of 12 mg/kg/h had periods of arrhythmia during surgery, indicating an insufficient depth of anaesthesia (Versichelen et al. 1986). The additional use of alfentanil (15 μg/kg at induction and 7 μg/kg increments as required) and a reduction of the propofol infusion rate to 9 mg/kg/h provided much greater control of anaesthesia in 41 patients who were subsequently studied, but did not increase recovery times or produce any unwanted effects. Similarly, the use of propofol (2 mg/kg then 9 mg/kg/h with increments as required) and lower doses of fentanyl (1.9 μg/kg then 7.5 μg/kg/h infusion with increments) provided 'good' or 'adequate' anaesthesia in 90% of 30 patients undergoing general surgical procedures lasting for up to 3 hours (de Grood et al. 1985).

Recovery was assessed as 'good' or 'adequate' for 76% of patients, with occasional transient epi-

sodes of euphoria and/or depression being reported and a few patients experiencing postoperative nausea or vomiting.

Other drugs used to provide hypnosis in total intravenous anaesthesia include methohexitone and, until its use was restricted to induction only, etomidate, both of which have been compared with propofol in the studies detailed in table VIII. When used in combination with alfentanil for anaesthesia during laryngeal surgery the induction properties of propofol and etomidate were found to be equivalent, but maintenance was superior under propofol, with a significantly lower incidence of cough ($p < 0.02$) and spontaneous movement ($p < 0.05$). Further, the stability and degree of control of anaesthesia was considered 'good' or 'adequate' in all of the operations where propofol was used, compared with 80% of those where etomidate was used ($p < 0.02$; de Grood et al. 1987b). In a similar study the use of either propofol or etomidate, both in combination with fentanyl, was investigated in 31 patients undergoing laparoscopy (de Grood et al. 1987a; table VIII). Again, operating conditions were superior with propofol (quality of maintenance rated 'good' or 'adequate' in 69 and 31% of operations, respectively, with propofol, and 'good', 'adequate' or 'poor' in 40, 20 and 40% of cases, respectively, with etomidate) and mean recovery time from the end of surgery to verbal contact was significantly shorter following propofol with fentanyl (8.6 *vs* 19.3 minutes; $p < 0.05$).

Alfentanil was also used in conjunction with propofol to provide total intravenous anaesthesia in patients undergoing major abdominal surgery in a comparative study with methohexitone (Kay 1986; table VIII). Both drugs provided satisfactory conditions for surgery with no unwanted effects during maintenance, but methohexitone produced a significantly greater incidence of spontaneous movement and hiccup during induction ($p < 0.05$). Recovery time to responding to commands was significantly shorter following propofol (12.4 *vs* 20.9 minutes; $p < 0.001$), and recovery was assessed as 'good' in 20 patients (95%) and 'adequate' in 1 patient (5%) for propofol, but was 'good' in 6 patients (29%), 'adequate' in 9 (43%) and 'poor' in 6 patients (29%) who had received methohexitone.

4.3 Propofol for Sedation

4.3.1 Sedation during Surgical and Other Procedures

A dose-ranging study in 60 patients undergoing colonoscopy utilised an induction dose of propofol 2 mg/kg followed by randomly allocated infusions of propofol 3, 6 or 9 mg/kg/h (Gepts et al. 1985b). The highest infusion rate produced unconsciousness in the majority of patients (85%), whilst at 3 mg/kg/h 40% of patients required supplementary bolus doses to maintain an adequate degree of sedation. A rate of 6 mg/kg/h produced heavy sedation in 35%, unconsciousness in 40% and light sedation in 25% of patients. This clear interindividual variation means that infusion rates will have to be determined for each patient and will have to be adjusted during surgery to ensure that sedation does not become too light or does not progress into full anaesthesia.

Propofol has similarly been used to sedate patients undergoing orthopaedic surgery with regional anaesthesia (Mackenzie & Grant 1987); 40 patients premedicated with oral benzodiazepines received propofol at an initial rate of 4 to 6 mg/kg/h, which was subsequently adjusted to maintain an appropriate level of sedation for a mean time of 98 minutes. Sedation was considered to be good throughout surgery in all cases, with transient episodes of movement in only 3 patients and no instances of cough, laryngospasm or apnoea. A particular benefit of this procedure was that when it was necessary to produce general anaesthesia in 3 patients, this was easily done by increasing the infusion rate to 10 mg/kg/h and giving nitrous oxide. The mean infusion rate for patients below 65 years of age was 4.1 mg/kg/h whilst those above this age required a mean of 3 mg/kg/h ($p < 0.005$).

4.3.2 Sedation in Intensive Care

Patients entering intensive care ($n = 60$) after cardiopulmonary surgery were randomly allocated to sedation by propofol infusion of 50 mg/h (adjusted as required) or intermittent injections of

Table VII. Summary of non-comparative and randomised comparative studies of propofol (P) for out-patient surgery in unpremedicated patients

Reference	Procedure	Anaesthetics		No. of pts in group	Events during induction		Recovery time[a]	Assessments of recovery
		induction (dose)	maintenance (dose)		apnoea (%) [duration (sec)]	excitation or spontaneous movement (%)		
Non-comparative studies								
McLeod & Boheimer (1985)	Termination of pregnancy	P (2.5 mg/kg) + F (1.5 μg/kg)	P inf (12.8 mg/kg/h)[b]	18	72 [>30]	0	(6 and 9 min)[c]	Nausea in 1 patient only, no vomiting. Global assessment of recovery was 'excellent' in all cases. All patients could stand unaided 30 min after surgery. 12 patients spontaneously requested food
Walmsley et al. (1986)	Gynaecological and urological surgery	P (2.5 mg/kg) + F (1.5 μg/kg)	P bolus (1 mg/kg)	30	57 (>30]	3	(7.3 and 9.3 min)[c]	Nausea with vomiting in 1 patient only. 14 patients reported feeling of hunger. All patients clear headed within 1 hour of surgery
Comparisons with methohexitone (M)								
Cundy & Arunasalam (1985)	Termination of pregnancy	P (2.5 mg/kg) + F (0.1mg)	P bolus (0.6-1.3 mg/kg) + N_2O (66%)	30	27 [>30]	0	M ≡ P	Vomiting in 23% of patients with M, 17% of patients with P. Overall assessment of anaesthetists P significantly better than M ($p < 0.001$). Patients significantly more drowsy on discharge with M ($p < 0.001$)
		M (2 mg/kg) + F (0.1mg)	M bolus (0.5-1 mg/kg) + N_2O (66%)	30	0 [>30]	67		
Doze et al. (1986)	Gynaecological surgery	P (2.5 mg/kg) Pt (1 mg/kg)[d]	P inf (6.9 mg/kg/h)[b] + N_2O (70%)	30	30 [>0]	0	M ≡ P	Nausea/vomiting significantly more frequent with M than P (43% *vs* 17%, $p < 0.05$)
		M (1.5 mg/kg) + Pt (1 mg/kg)[d]	M inf (5.8 mg/kg/h)[b] + N_2O (70%)	30	30 [> 0]	3		Headache more frequent with P, dizziness more frequent with M. Time to ambulation significantly shorter with P than M (67 *vs* 81 min, $p < 0.05$)
Kay & Healy (1985)	Cystoscopy	P (2 mg/kg) + A (7 μg/kg)	P bolus + A bolus[e]	31	29	0	M > P**	No nausea or vomiting in either group. Anaesthetists assessed recovery as good in significantly more P patients ($p < 0.01$). Later recovery assessed with take-home questionnaire; duration of drowsiness significantly greater with M ($p < 0.05$), time to eating significantly greater with M ($p < 0.05$), incidence of nausea greater with M (NS)
		M (1.5 mg/kg) + A (7 μg/kg)	M bolus + A bolus[e]	29	45	3		

Logan et al. (1987)	Dental surgery	P (3 mg/kg) M (2 mg/kg)	None None	21 19	14 [>20] 26 [>20]		P > M*	All patients could walk unaided at 15 min. Impairment of psychomotor performance[f] was same for both drugs. Performance fully recovered by 40 min
O'Toole et al. (1987)	Gynaecological surgery	P (2.5 mg/kg)	I (3-1%) + N_2O (66%)	25	60 [>30]	8	M > P*	Incidence of nausea/vomiting and headache greater in M group
		M (1.5 mg/kg)	I (3-1%) + N_2O (66%)	25	36 [>30]	24		Sedation was significantly greater in M group at 20 min after surgery ($p < 0.01$), but not at 40 or 60 min. Psychomotor performance[g] significantly worse at 20 min with M ($p < 0.05$) and ataxia more prolonged with M (difference between groups at 40 min $p < 0.01$)
Valanne & Korttila (1985)	Dental and oral surgery	P (2.5 mg/kg)	EF (1-3%) + N_2O (50%)	36		0	M ≡ P	Incidence of nausea and vomiting lower in P group up to 3h after surgery. Walking ability was similar in both groups at 30 and 60 min after surgery
		M (2 mg/kg)	EF (1-3%) + N_2O (50%)	37		16		
Comparisons with isoflurane (I)								
Milligan et al. (1987)	Gynaecological surgery	P (2.5 mg/kg)	P bolus (10mg) + N_2O (66%)	30			I > P*	Incidence of ataxia and nausea similar for both groups
			I (3-1%) + N_2O (66%)	30				Psychomotor function[h] recovered more quickly in P group
Zuurmond et al. (1987)	Arthroscopy	P (2 mg/kg)	P inf (10 mg/kg/h) + N_2O (66%)	20			I ≡ P	Ocular imbalance assessed using Maddox-Wing test – recovery was quick in both groups (85 *vs* 91 min, NS). Satisfactory recovery in all patients by 3 hours after surgery
			I (3-0.9%) + N_2O (66%)	20				

a In comparative studies assessment is of recovery times to opening of eyes, recall of correct date of birth, response to commands, or orientation to date and place.
b Mean infusion rate during surgery.
c Times to eye opening and recall of correct date of birth, respectively.
d Given as intravenous injection 5 minutes before induction.
e Dosages not given.
f Psychomotor function assessed using the Leeds Psychomotor Tester to measure Critical Flicker Fusion Threshold and Choice Reaction Times.
g Psychomotor function assessed by measurement of Choice Reaction Times.
h Psychomotor function assessed by p-deletion test and measurement of Choice Reaction Times.

Abbreviations: P = propofol; F = fentanyl; N_2O = nitrous oxide in oxygen at given percentage; MP = meperidine; A = alfentanil; I = isoflurane; EF = enflurane; inf = continuous intravenous infusion; bolus = intravenous bolus injections given as required; * = $p < 0.01$; ** = $p < 0.001$; NS = not statistically significant.

midazolam 2.5mg, with analgesia provided by injections of papaveretum 2.5mg (Grounds et al. 1987a). Sedation was continued until mechanical ventilation could be withdrawn. The total time attached to the ventilator was significantly shorter in the propofol group (median 6.5 *vs* 10 hours with midazolam; $p < 0.02$), and the median time from the withdrawal of mechanical ventilation to the return of satisfactory spontaneous ventilation was 9.5 minutes following propofol and 202 minutes after midazolam ($p < 0.001$). The depth of sedation varied with both regimens, but those patients who received propofol spent a greater proportion of time at the intended sedation level (45% *vs* 28% for midazolam group; $p < 0.025$) and both medical and nursing staff rated propofol the superior drug.

Ten critically ill patients were sedated for 8 hours in intensive care with a mean propofol infusion rate of 1.9 mg/kg/h subsequent to an initial bolus of 1 mg/kg (Newman et al. 1987). Cardiovascular monitoring showed that, in 8 patients who were normotensive at the start of the study, mean diastolic blood pressures were significantly reduced from baseline levels at 4, 7 and 8 hours of the infusion ($p < 0.05$). Mean arterial blood pressure fell to 60mm Hg or less in 6 of the patients during periods of deep sedation, requiring a reduction in the infusion rate or administration of plasma expanders, but these hypotensive episodes did not result in any signs of impaired peripheral perfusion.

Plasma cortisol concentrations were already significantly reduced in 4 patients who had received etomidate before entry into the study, and one other had been given intravenous corticosteroids, but samples taken from the remaining 5 patients showed that plasma cortisol concentrations decreased significantly during the infusion, although this may not have been a direct effect of propofol itself (see section 1.4) However, the adrenal response to intravenous ACTH was normal in these

Table VIII. Details of comparative trials of propofol (P) for total intravenous anaesthesia

Reference	Type of surgery	Premedication (dose)	Anaesthesia		Number of patients
			induction (dose)	maintenance (dose)	
de Grood et al. (1987a)	Laparoscopy	None	P (2.5 mg/kg) + F (0.1mg)	P inf (12 mg/kg/h)[a] + F bolus (0.05-0.1mg)	16
			E (0.3 mg/kg) + F (0.1mg)	E inf (1.8 mg/kg/h)[b] + F bolus (0.05-0.1mg)	15
de Grood et al. (1987b)	Laryngeal microsurgery	Atropine (0.5mg) Prednisolone (25mg)	P (2 mg/kg) + A (0.5-1mg)	P inf (12 mg/kg/h)[c] + A bolus (0.5-1mg)	15
			E (0.3 mg/kg) + A (0.5 to 1mg)	E inf (1.8 mg/kg/h)[d] + A bolus (0.5-1mg)	15
Kay (1986)	Major abdominal	None	P (2 mg/kg) + A (10 μg/kg)	P inf (12 mg/kg/h)[e] + A inf (60 μg/kg/h)[e]	21
			M (1.5 mg/kg) + A (10 μg/kg)	M inf (9 mg/kg/h)[e] + A inf (60 μg/kg/h)[e]	21

a Infusion rate reduced to 9 mg/kg/h after 15 minutes, then to 6 mg/kg/h after a further 25 minutes. Additional bolus injections of P given if necessary.

b Infusion rate reduced to 1.5 mg/kg/h after 15 minutes, then to 1 mg/kg/h after a further 25 minutes. Additional bolus injections of E (0.06 mg/kg) given if necessary.

c Infusion rate reduced to 9, then 6 mg/kg/h at 10-minute intervals.

d Infusion rate reduced to 1.5 then 1 mg/kg/h at 10-minute intervals.

e Infusion rate reduced by one-third after 20 to 30 minutes. Additional bolus injections of P and A given if necessary during surgery.

Abbreviations: P = propofol; A = alfentanil; E = etomidate; M = methohexitone; F = fentanyl; inf = continuous infusion; bolus = bolus injections given as necessary.

individuals, but was reduced in the patients who had received etomidate.

A further consideration with this use of propofol is the possibility of deleterious effects of the lipid emulsion on blood lipid concentrations and coagulation mechanisms. This has not been investigated adequately, although Newman et al. (1987) reported that lipaemia occurred only once in their study (see above), and this was in a patient also receiving a separate lipid infusion. The only haematological disturbance seen in this study was a slight increase in mean prothrombin time after 8 hours of infusion (19.4 *vs* 18 seconds before treatment; $p = 0.05$).

4.4 Propofol for Coronary Artery Surgery

Haemodynamic stability is obviously of particular importance during coronary artery surgery; endotracheal intubation, sternotomy and surgical manipulation can produce unwanted hypertension, whilst drug-induced hypotension might also precipitate ischaemia in patients with impaired myocardial blood flow. When used for the induction of anaesthesia in ASA class III or IV patients for coronary bypass operations propofol 2.5 mg/kg reduced systolic and diastolic blood pressures by 12 to 32% and central venous pressure by 16 to 29% (Williams et al. 1986). Corresponding decreases following thiopentone 4 mg/kg were 9 to 23% and 4 to 8%, respectively. Similar results were reported for propofol 1.5 mg/kg and thiopentone 2 mg/kg, and systemic vascular resistance was also reduced 16% by propofol, but only 1% by thiopentone ($p < 0.05$) [Patrick et al. 1985]. In contrast, mean arterial blood pressure increased after intubation to 36% above baseline values in thiopentone-treated patients, but only to 9% above baseline in those who received propofol ($p < 0.05$) [Patrick et al. 1985].

Stephan et al. (1986) used propofol 2 mg/kg followed by 12 mg/kg/h to anaesthetise 12 patients for coronary bypass surgery, with fentanyl 10 μg/kg given 30 minutes after the start of propofol administration, immediately before surgery was started. Significant reductions were observed in mean arterial blood pressure (by 15%), pulmonary capillary wedge pressure (by 20%), and central venous pressure (by 16%) at 30 minutes ($p < 0.05$ in each case), and heart rate was increased by 12% ($p < 0.05$). All of these returned to about baseline levels when surgery was started. Myocardial blood flow, oxygen consumption and glucose uptake were significantly reduced by 26, 31 and 54%, respectively ($p < 0.05$ in each case), during the initial propofol infusion, but as with blood pressure readings these variables increased during surgery, although myocardial blood flow did not return to pretreatment levels. Coronary vascular resistance significantly increased during surgery (by 21%, $p < 0.05$), and since myocardial lactate production was observed in 2 patients (once during the presurgical infusion and once during sternotomy) it is possible that myocardial ischaemia may have occurred in these patients. However, in a similar study of 15 patients undergoing coronary bypass surgery using propofol (1.5 mg/kg at induction, mean infusion rate of 5.15 mg/kg/h) and fentanyl (8 μg/kg at induction and 25 μg/kg before sternotomy) for anaesthesia, there was no indication of myocardial ischaemia either during or after surgery, based on an absence of S-T depression on the ECG and no increases in pulmonary capillary wedge pressure (Vermeyen et al. 1987).

Propofol has thus been used successfully in patients with good left ventricular function (above studies), and a preliminary report also found propofol to be suitable for induction in a group of more debilitated patients (Profeta et al. 1987). Even so, at this stage the suitability of propofol for cardiac surgery has to be carefully considered, since the benefits of reducing hypertensive episodes during surgery need to be balanced against the possible risk of myocardial ischaemia.

5. Side Effects

Attributing 'side effects' that occur during surgical procedures to the anaesthetics used for induction or maintenance is fraught with difficulties since, in most instances, several other drugs are used concomitantly. In addition, it can be difficult

to differentiate between drug-induced effects and those arising as a result of surgical manipulation, or which are generally associated with the anaesthetised state.

The most frequent side effect associated with the use of propofol has been pain on injection. Collation of data from a total of 1,465 patients found that injection of propofol into a vein in the dorsum of the hand (n = 428) was painful in 28.5% of cases (Stark et al. 1985); however, if the injection was into the large veins of the forearm or antecubital fossa (n = 821) this figure fell to 6%. Similar incidences were reported in a more recent comparative study of propofol as an induction agent in unpremedicated patients (McCollum & Dundee 1986). The incidences of pain on injection to the antecubital fossa and dorsum of the hand, respectively, were 8 and 31% for propofol (n = 100), 4 and 5% for thiopentone (n = 100), 14 and 29% for etomidate (n = 50) and 18 and 41% for methohexitone (n = 50).

Excitatory and respiratory effects that occur during induction are generally considered as side effects of the anaesthetic, although their incidence will to some extent be dependent upon other drugs that are used and the skill of the anaesthetist. In the studies reviewed by Stark et al. (1985) excitatory effects (movement, twitching, hiccup, tremor etc.) were seen in 14% of 1459 inductions with propofol. Apnoeic episodes are more frequently seen; McCollum and Dundee (1986) reported that apnoea of more than 30 seconds' duration occurred in 44% and 24% of unpremedicated patients who received propofol 2.5 and 2 mg/kg, respectively (n = 50 for each dose). In comparison, the figures for methohexitone 1.5 mg/kg, etomidate 0.3 mg/kg and thiopentone 5 mg/kg were 20, 0 and 38%, respectively. In some instances the duration of apnoea with propofol can exceed 60 seconds (Goodman et al. 1987); this will depend to some extent on the induction procedure (bolus dose or titrated increments), but, more importantly, it is likely to be exacerbated by the concomitant use of opioids.

A particular feature of propofol anaesthesia is the low occurrence of postoperative nausea and vomiting, with an overall incidence of about 2 to 3% (Stark et al. 1985). In the comparative studies included in this analysis 13% of patients who received thiopentone (n = 79) and 10% of patients who received methohexitone (n = 86) either vomited or became nauseous.

Isolated cases of bradycardia have been seen during propofol anaesthesia. These were often associated with surgical procedures that produce vagal stimulation (Henriksson et al. 1987) and were easily controlled by administration of atropine, although persistent bradycardia which was resistant to both atropine and isoprenaline (isoproterenol), and where heart rate recovered slowly only after propofol infusion was stopped has been reported in 1 patient (Thomson & Yate 1987). Epileptiform movements have also occurred rarely, but a causal relationship with propofol has not been established.

Since anaesthesia and surgery inevitably involve some degree of risk, serious complications are likely to be seen during trials of propofol. Of approximately 4,000 operations where propofol was used, 20 complications which were considered major were reported, including 3 deaths (Product Monograph 1986). These complications mostly had identifiable underlying causes unrelated to propofol, but 9 involved hypotension and, in view of its haemodynamic effects, it is possible that propofol contributed to this.

6. Dosage and Administration

Induction doses of propofol should be titrated to suit individual patient requirements by giving increments of about 40mg every 10 seconds until adequate anaesthesia is achieved. The total dose for adults aged 55 years or less is likely to be 2 to 2.5 mg/kg. Older or infirm patients often require a lower dose, and in ASA grade III or IV patients the induction dose should be given at a reduced rate of 20mg every 10 seconds.

Maintenance of anaesthesia can be achieved with either a continuous infusion of propofol or by giving bolus doses of 20 to 50mg when anaesthesia is considered to be lightening. Suitable infusion rates vary between individuals and will also depend upon

the use of muscle relaxants and analgesics, but between 6 and 12 mg/kg/h should prove satisfactory in most cases. Some investigators have found it useful to give a higher infusion rate (up to 18 mg/kg/h) for a short period at the start of surgery. In all cases the infusion rate will need to be adjusted during surgery according to the clinical response of the patient.

Lightening of anaesthesia can occur rapidly with propofol and the depth of anaesthesia should be closely watched during surgery. Changes in heart rate and blood pressure may not be reliable indicators, and some authors have found that an increase in respiratory rate is a more predictable sign of inadequate anaesthesia (McLeod & Boheimer 1985; Walmsley et al. 1986).

7. The Place of Propofol in Anaesthetic Practice

Propofol has proven to be a reliable anaesthetic that can be used for both induction and maintenance purposes in most common surgical procedures, either in 'standard' anaesthetic practice or as part of total intravenous anaesthesia. Comparative studies have shown that it is at least as effective as other intravenous anaesthetics in most respects, with both potential advantages and disadvantages in individual situations.

The greatest potential advantage for propofol is rapid recovery, even after long periods of anaesthesia. While this may not be particularly advantageous in some situations, in other settings such as outpatient surgery rapid return to normal psychomotor function is clearly important. Propofol also offers a particularly low incidence of postoperative nausea and vomiting, which is desirable in any setting, but again may be especially beneficial in outpatient surgery. The incidence of excitatory effects during surgery under propofol anaesthesia is also low, and propofol is superior to methohexitone in this regard. Finally, although plasma cortisol concentrations have been found to decrease during propofol infusions, it does not depress adrenal responsiveness to ACTH during short term administration, as occurs with etomidate. If this also holds true with longer term administration, this will offer an important benefit in the setting of sedation of intensive care patients.

Disadvantages of propofol include a relatively high incidence of apnoea, and blood pressure reductions that may occasionally be marked. However, in studies to date the magnitude of these effects was such that their management during anaesthesia was straightforward in most patients.

In conclusion, propofol is an effective addition to the limited range of intravenous anaesthetics which are currently available. While selection of the most appropriate anaesthetic for a particular patient depends on a wide range of factors, it is clear that propofol merits consideration by the anaesthetist in many situations.

References

Adam HK, Briggs LP, Bahar M, Douglas EJ, Dundee JW. ICI 35868 Pharmacokinetics in humans: single dose studies. British Journal of Anaesthesia 54: 1138-1139, 1982a

Adam HK, Briggs LP, Bahar M, Douglas EJ, Dundee JW. Pharmacokinetic evaluation of ICI 35868 in man. British Journal of Anaesthesia 55: 97-103, 1983

Adam HK, Kay B, Douglas EJ. Blood disoprofol levels in anaesthetised patients. Anaesthesia 37: 536-540, 1982b

Bilaine J, Desmonts JM. Effect of premedication with atropine or hydroxyzine on induction and maintenance of anaesthesia with propofol. Postgraduate Medical Journal 61: 38-39, 1985

Briggs LP, Dundee JW, Bahar M, Clarke RSJ. Comparison of the effect of disopropyl phenol (ICI 35868) and thiopentone on response to somatic pain. British Journal of Anaesthesia 54: 307-311, 1982

Briggs LP, White M. The effects of premedication on anaesthesia with propofol ('Diprivan'). Postgraduate Medical Journal 61: 35-37, 1985

Brüssel T, Vigfusson G, Luukenheimer P, Theissen J, Lawin P. Influence of diprivan and etomidate on cardiodynamic parameters in the dog. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986

Clarke RSJ, Dundee JW, Garrett RT, McArdle GK, Sutton JA. Adverse reactions to intravenous anaesthetics. A survey of 100 reports. British Journal of Anaesthesia 47: 575-585, 1975

Coates DP, Monk CR, Prys-Roberts C, Turtle M. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anaesthesia in humans. Anesthesia and Analgesia 66: 64-70, 1987

Coates DP, Monk CR, Prys-Roberts C, Turtle M, Norley I, et al. Haemodynamic responses to induction and endotracheal intubation with propofol/nitrous oxide anaesthesia. European Journal of Anaesthesiology 3: 65, 1986

Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism – an overview. Postgraduate Medical Journal 61 (Suppl. 3): 45-50, 1985

Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. British Journal of Anaesthesia 59: 1103-1110, 1987

Cummings GC, Dixon J, Kay NH, Windsor PW, Major E, et al.

Dose requirements of ICI 35868 (Propofol, 'Diprivan') in a new formulation for induction of anaesthesia. Anaesthesia 39: 1168-1171, 1984

Cundy JM, Arunasalam K. Use of an emulsion formulation of propofol ('Diprivan') in intravenous anaesthesia for termination of pregnancy: a comparison with methohexitone. Postgraduate Medical Journal 61: 129-131, 1985

Danel O, Duvaldestin P, Renard C, Normand S. Induction and maintenance of anaesthesia with propofol. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986

Doze VA, Westphal LM, White PF. Comparison of propofol with methohexitol for outpatient anesthesia. Anesthesia and Analgesia 65: 1189-1195, 1986

Dundee JW, McCollum JSC, Robinson FP. Propofol – an overview of over 1500 administrations. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986a

Dundee JW, Moore J. Alterations in response to somatic pain associated with anaesthesia I: the effect of thiopentone and pentobarbitone. British Journal of Anaesthesia 32: 407-414, 1960

Dundee JW, Robinson FP, McCollum JSC, Patterson CC. Sensitivity to propofol in the elderly. Anaesthesia 41: 482-485, 1986b

Dye D, Watkins J. Suspected anaphylactic reactions to Cremophor EL. British Medical Journal 280: 1353, 1980

Fahy LT, van Mourik GA, Utting JE. A comparison of the induction characteristics of thiopentone and propofol (2,6-di-isopropyl phenol). Anaesthesia 40: 939-944, 1985

Fragen RJ, Weiss HW, Molteni A. The effect of propofol on adrenocortical steroidogenesis: a comparative study with etomidate and thiopental. Anesthesiology 66: 839-842, 1987

Gauss A, Fösel T, Altemeyer K-H, Heinrich H. Hamodynamische veränderungen während der einleitung einer intubationsnarkose-ein vergleich. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986

George CF. Drug kinetics and hepatic blood flow. Clinical Pharmacokinetics 4: 433-448, 1979

Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as zero-order intravenous infusions in humans. Anesthesia and Analgesia 64: 1256-1263, 1987

Gepts E, Claeys AM, Camu F. Pharmacokinetics of propofol ('Diprivan') administered by continuous intravenous infusion in man: a preliminary report. Postgraduate Medical Journal 61: 51-52, 1985a

Gepts E, Claeys AM, Camu F, Smekens L. Infusion of propofol ('Diprivan') as a sedative technique for colonoscopies. Postgraduate Medical Journal 61: 120-126, 1985b

Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35868. British Journal of Anaesthesia 56: 617-626, 1984

Goodman NW, Black AMS, Carter JA. Some ventilatory effects of propofol as a sole anaesthetic agent. British Journal of Anaesthesia 59: 1497-1503, 1987

de Grood PMRM, Harbers JBM, van Egmond J, Crul JF. Anaesthesia for laparoscopy. Anaesthesia 42: 815-823, 1987a

de Grood PMRM, Mitsukuri S, van Egmond J, Rutten JMJ, Grul JF. Comparison of etomidate and propofol for anaesthesia in microlaryngeal surgery. Anaesthesia 42: 366-372, 1987b

de Grood PMRM, Ruys AHC, van Egmond J, Booij LHDJ, Crul JF. Propofol ('Diprivan') emulsion for total intravenous anaesthesia. Postgraduate Medical Journal 61: 65-69, 1985

Grounds RM, Lalor JM, Lumley J, Royston D, Morgan M. Propofol infusion for sedation in the intensive care unit: preliminary report. British Medical Journal 294: 397-400, 1987a

Grounds RM, Maxwell DL, Taylor MB, Aber V, Royston D. Acute ventilatory changes during i.v. induction of anaesthesia with thiopentone or propofol in man. British Journal of Anaesthesia 59: 1098-1102, 1987b

Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Anaesthesia 40: 735-740, 1985

Guedes Y, Rakotoseheno JC, Leveque M, Egreteau JP. Changes in intra-ocular pressure in the elderly during anaesthesia with propofol. Anaesthesia, in press, 1988

Gunawardene RD, White DC. Propofol and emesis. Anaesthesia, in press, 1988

Hartung H-J. Intrakranielles druckverhalten bei patienten mit schädel-hiru-trauma nach propofol-bzw. Thiopental-applikation. Anaesthetist 36: 285-287, 1987

Hartung E, Freye E. Comparison of propofol – N_2O/O_2 versus enflurane-N_2O/O_2 anaesthesia for long-lasting abdominal operations. Anaesthesia, in press, 1988

Hazeaux C, Tisserant D, Vespignani H, Hummer-Sigiel M, Kwau-Ning V, et al. Retentissement électroencéphalographique de l'anesthésic au propofol. Annales Français d'Anesthesie et Réanimation 6: 261-266, 1987

Henriksson B-Å, Carlsson P, Hallén B, Hägerdal M, Lundberg D, et al. Propofol vs thiopentone as anaesthetic agents for short operative procedures. Acta Anaesthesiologica Scandinavica 31: 63-66, 1987

Herregods L, Rolly G, Bogaert M. EEG and EMG monitoring during propofol induction and maintenance of anaesthesia. International Journal of Clinical Monitoring and Computing, in press, 1988

Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. Anaesthesia 42: 360-365, 1987

Homer TD, Stanski DR. The effects of increasing age on thiopental disposition and anaesthetic requirements. Anesthesiology 62: 714-724, 1985

Hunter SJ, Spencer I, McLaren CAB. Propofol ('Diprivan') induction and maintenance of anaesthesia. Postgraduate Medical Journal 61: 101, 1985

Jessop E, Grounds RM, Morgan M, Lumley J. Comparison of infusions of propofol and methohexitone to provide light general anaesthesia during surgery with regional blockade. British Journal of Anaesthesia 57: 1173-1177, 1985

Kay B. Propofol and alfentanil infusion: a comparison with methohexitone and alfentanil for major surgery. Anaesthesia 41: 589-595, 1986

Kay B, Healy TEJ. Propofol ('Diprivan') for outpatient cystoscopy: efficacy and recovery compared with althesin and methohexitone. Postgraduate Medical Journal 61: 108-114, 1985

Kay B, Stephenson DK. Dose-response relationship for disopropofol (ICI 35868; Diprivan). Anaesthesia 36: 863-867, 1981

Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. British Journal of Anaesthesia 58: 1075-1079, 1986

Kay NH, Uppington J, Sear JW, Allen MC. Use of an emulsion of ICI 35868 (propofol) for the induction and maintenance of anaesthesia. British Journal of Anaesthesia 57: 736-742, 1985

Kenyon CJ, McNeil LM, Fraser R. Comparison of the effects of etomidate, thiopentone and propofol on cortisol synthesis. British Journal of Anaesthesia 57: 509-511, 1985

Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol in elderly patients. British Journal of Anaesthesia, in press, 1988

Knell PJW, McKean JF. An investigation of the pharmacokinetic profile of propofol ('Diprivan') after administration for induction and maintenance of anaesthesia by repeat bolus doses in patients having spinal anaesthetic block. Postgraduate Medical Journal 61: 60-61, 1985

Lambert A, Mitchell R, Robertson WR. Effect of propofol, thiopentone and etomidate on adrenal steroidogenesis *in vitro*. British Journal of Anaesthesia 57: 505-508, 1985

Ledderose H, Rester P, Carlsson P, Peter K. Recovery time and side effects following propofol infusion versus isoflurane in ENT patients with regional block. Anaesthesia, in press, 1988

Ledingham IM, Finlay WEI, Watt I, McKee JI. Etomidate and adrenocortical function. Lancet 1: 1434, 1983
Ledingham IM, Watt I. Influence of sedation on mortality in critically ill multiple trauma patients. Lancet 1: 1270, 1983
Lippmann M, Paicius R, Gingerich S, Owens R, Mok MS, et al. A controlled study of the haemodynamic effects of propofol *vs* thiopentol during anaesthesia induction. Anesthesia and Analgesia 65: 589, 1986
Logan MR, Duggan JE, Levack ID, Spence AA. Single-shot i.v. anaesthesia for outpatient dental surgery. British Journal of Anaesthesia 59: 179-183, 1987
Mackenzie N, Grant IS. Comparison of propofol with methohexitone in the provision of anaesthesia for surgery under regional blockade. British Journal of Anaesthesia 57: 1167-1172, 1985a
Mackenzie N, Grant IS. Propofol ('Diprivan') for continuous intravenous anaesthesia: a comparison with methohexitone. Postgraduate Medical Journal 61: 70-75, 1985b
Mackenzie N, Grant IS. Propofol for intravenous sedation. Anaesthesia 42: 3-6, 1987
Major E, Verniquet AJW, Waddell TK, Savege TM, Hoffler DE, et al. A study of three doses of ICI 35868 for induction and maintenance of anaesthesia. British Journal of Anaesthesia 53: 267-272, 1981
Mangez JF, Menguy E, Rowe P. Sedation par propofol à debit constant cheze le traumatisé cranien. Annales Français de Anesthesie et Réanimation 6: 336-337, 1987
Martinelli G, diMarco MG, Begliomini B, Franceschelli N, Viganò E, et al. Preliminary results with propofol (Diprivan, ICI 35868) in boluses and continuous infusion. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986
McCollum JSC, Dundee JW. Comparison of induction characteristics of four intravenous anaesthetic agents. Anaesthesia 41: 995-1000, 1986
McCollum JSC, Dundee JW, Carlisle RJT. Premedication: effect on induction of anaesthesia with propofol. British Journal of Anaesthesia 58: 1330P, 1986
McCollum JSC, Dundee JW, Halliday NJ, Clarke RSJ. Dose response studies with propofol ('Diprivan') in unpremedicated patients. Postgraduate Medical Journal 61: 85-87, 1985
McCollum JSC, Milligan KR, Dundee JW. Has propofol an antiemetic action. British Journal of Anaesthesia 59: 654P, 1987
McLeod B, Boheimer N. Propofol ('Diprivan') infusion as main agent for day case surgery. Postgraduate Medical Journal 61: 105-107, 1985
Melloni C, Martinelli G. Diprivan in continuous infusion for body surface surgery. 7th European Congress on Anaesthesiology, Vienna, 7-13 September, 1986
Milligan KR, O'Toole DP, Howe JP, Cooper JC, Dundee JW. Recovery from outpatient anaesthesia: a comparison of incremental propofol and propofol-isoflurane. British Journal of Anaesthesia 59: 1111-1114, 1987
Mirakhur RK, Shepherd WFI, Darrah WC. Propofol or thiopentone: effects on intraocular pressure associated with induction of anaesthesia and tracheal intubation. British Journal of Anaesthesia 59: 431-436, 1987
Monk CR, Coates DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. British Journal of Anaesthesia 59: 954-960, 1987
Morcos WE, Payne JP. The induction of anaesthesia with propofol ('Diprivan') compared in normal and renal failure patients. Postgraduate Medical Journal 61: 62-63, 1985
Newman LH, McDonald JC, Wallace PGM, Ledingham IMcA. Propofol infusion for sedation in intensive care. Anaesthesia 42: 929-937, 1987
Nies AS, Shand DG, Wilkinson GR. Altered hepatic blood flow and drug disposition. Clinical Pharmacokinetics 1: 135-155, 1976
O'Toole DP, Milligan KR, Howe JP, McCollum JSC, Dundee JW. A comparison of propofol and methohexitone as induction agents for day case isoflurane anaesthesia. Anaesthesia 42: 373-376, 1987
Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. Postgraduate Medical Journal 61: 23-27, 1985
Product Monograph on Diprivan, ICI Pharmaceuticals, 1986
Profeta JP, Guffin A, Mikula S, Dolman J, Kaplan JA. The haemodynamic effects of propofol and thiamylal sodium for induction in coronary artery surgery. Anaesthesia and Analgesia 66: S142, 1987
Ravussin P, Guinard JP, Ralley F, Thorin D. Effect of propofol on cerebro-spinal fluid pressure and cerebral perfusion pressure in patients undergoing craniotomy. Anaesthesia, in press, 1988
Rhodes C, Longshaw S. Autoradiographic distribution study of a short-acting anaesthetic ICI 35868. Acta Pharmacologica et Toxicologica 41: 132-133, 1977
Robertson WR, Reader SCJ, Davison B, Frost J, Mitchell R. On the biopotency and site of action of drugs affecting endocrine tissues with special reference to the anti-steroid effect of anaesthetic agents. Postgraduate Medical Journal 61: 145-151, 1985
Robinson FP. Propofol ('Diprivan') by intermittent bolus with nitrous oxide in oxygen for body surface operations. Postgraduate Medical Journal 61: 116-119, 1985
Rolly G, Versichelen L, Huyghe L, Mungroop H. Effect of speed of injection on induction of anaesthesia using propofol. British Journal of Anaesthesia 57: 743-746, 1985
Sampson IH, Lefkowitz M, Cohen M, Mikula S, Kaplan JA. A comparison of propofol and methohexital for anesthesia by continuous infusion. Anesthesia and Analgesia 66: S150, 1987
Schaer H. Disoprivan zur Einleitung und Unterhaltung von Kurznarkosen. Anaesthetist 35: 531-534, 1986
Schüttler J, Schwilden H, Stoeckel H. Pharmacokinetic-dynamic modelling of diprivan. Anesthesiology 65: A549, 1986
Schüttler J, Stoeckel H, Schwilden H. Pharmacokinetic and pharmacodynamic modelling of propofol ('Diprivan') in volunteers and surgical patients. Postgraduate Medical Journal 61: 53-54, 1985
Sear JW, Shaw I, Wolf A, Kay NH. Infusions of propofol to supplement N_2O/O_2 for the maintenance of anaesthesia. Anaesthesia, in press, 1988
Servin F, Haberer JP, Cockshott ID, Farinotti R, Desmonts JM. Propofol pharmacokinetics in patients with cirrhosis. Anesthesiology 65: A554, 1986
Siani C, Zattoni J, Bozzo N, Tercero E, Altomonte M, et al. Intracranial pressor response and systemic haemodynamics during controlled infusion of 6 and 12 mg/kg/hour of Diprivan in neurosurgical patients. 3rd Italian/French Meeting on Neuroanaesthesia, Capri, 16-17 May, 1986a
Siani C, Zattoni J, Verado T, Dolcini G, Balestrero MA, et al. Response of intracranial pressure and systemic haemodynamics to 0.35, 0.80 and 2.5 mg/kg i.v. 'Diprivan' in conscious and normoventilated neurosurgical patients. 3rd Italian/French Meeting on Neuroanaesthesia, Capri, 16-17 May, 1986b
Simons PJ, Cockshott ID, Douglas EJ, Gordon EA. Disposition in male volunteers of a subanaesthetic intravenous dose of an oil in water emulsion of ^{14}C-propofol. Xenobiotica, in press, 1988
Simons PJ, Cockshott ID, Douglas EJ, Gordon EA, Hopkins K, et al. Blood concentrations, metabolism and elimination after a subanaesthetic intravenous dose of ^{14}C-propofol ('Diprivan') to male volunteers. Postgraduate Medical Journal 61: 64, 1985
Spelina KR, Coates DP, Monk CR, Prys-Roberts C, Norley I, et al. Dose requirements of propofol by infusion during nitrous

oxide anaesthesia in man. British Journal of Anaesthesia 58: 1080-1084, 1986

Stark RD, Binks SM, Dutka VN, O'Conner KM, Arustein MJA, et al. A review of the safety and tolerance of propofol ('Diprivan'). Postgraduate Medical Journal 61: 152-156, 1985

Stephan H, Sonntag H, Schenk HD, Kettler D, Khambatta HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. British Journal of Anaesthesia 58: 969-975, 1986

Stephan H, Sonntag H, Schenk HD, Kohlhausen S. Einfluß von Disoprivan (Propofol) auf die durchblutung und den sauerstaffverbrauch des gehirus und die CO_2 - reaktivität der hirngefäße beim menschen. Anaesthesist 36: 60-65, 1987

Streisand JB, Nelson P, Bubbers S, Stocking-Korzen R, Posthuma W, et al. The respiratory effects of propofol with and without fentanyl. Anesthesia and Analgesia 66: S171, 1987

Taylor MB, Grounds RM, Mulrooney PD, Morgan M. Ventilatory effects of propofol during induction of anaesthesia: comparison with thiopentone. Anaesthesia 41: 816-820, 1986

Thomson SJ, Yate PM. Bradycardia after propofol infusion. Anaesthesia 42: 430, 1987

Uppington J, Kay NH, Sear JW. Propofol ('Diprivan') as a supplement to nitrous oxide-oxygen for the maintenance of anaesthesia. Postgraduate Medical Journal 61: 80-83, 1985

Valanne J, Korttila K. Comparison of methohexitone and propofol ('Diprivan') for induction of enflurane anaesthesia in outpatients. Postgraduate Medical Journal 61: 138-143, 1985

Vanacker B, Dekegel D, Dionys J, Garcia R, Van Eeckhoutte L, et al. Intraocular pressure changes using propofol as an intravenous anaesthetic agent. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986

van Aken H, Meinshausen E, Prien T, Brüssel T, Heinecke A, et al. Haemodynamic effects of anaesthesia induction with propofol and N_2O in man. 7th European Congress of Anaesthesiology, Vienna, 7-13th September, 1986

Vermeyen KM, Erpels FA, Janssen LA, Beeckman CP, Hanegreefs GH. Propofol-fentanyl anaesthesia for coronary bypass surgery in patients with good left ventricular function. British Journal of Anaesthesia 59: 1115-1120, 1987

Versichelen L, Vermeulen H, deSomer A, Rolly G. 'Diprivan' as an induction and maintenance agent in ENT surgery. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986

Vinik HR, Shaw B, MacKrell T, Hughes G. A comparative evaluation of propofol for the induction and maintenance of general anaesthesia. Anesthesia and Analgesia 66: S184, 1987

Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anaesthetic etomidate. New England Journal of Medicine 310: 1415-1421, 1984

Walmsley AJ, McLeod B, Ponte J. The new formulation of ICI 35868 (propofol) as the main agent for minor surgical procedures. European Journal of Anaesthesiology 3: 19-26, 1986

Williams JP, McArthur JD, Walker WE, Tennissen E, Rietsema K, et al. The cardiovascular effects of propofol in patients with impaired cardiac function. Anesthesia and Analgesia 65: S166, 1986

Youngberg JA, Texidor MS, Smith D, Ramadhyani U. A comparison of induction and maintenance of anaesthesia with propofol to induction with thiopental and maintenance with isoflurane. 7th European Congress of Anaesthesiology, Vienna, 7-13 September, 1986

Zattoni J, Siani C, Balestrero MA, Davini D, Surace M, et al. Hypotensive effect of 0.35 and 0.80 mg/kg 'Diprivan' on intracranial and systemic arterial pressure during anaesthesia for neurosurgery under controlled ventilation. 3rd Italian/French Meeting on Neuroanaesthesia, Capri, 16-17 May, 1986

Zuurmond WWA, van Leeuwen L, Helmers JH. Recovery from propofol infusion as the main agent for outpatient arthroscopy. Anaesthesia 42: 356-359, 1987

Authors' address: *Mark S. Langley*, ADIS Drug Information Services, Suite 15c, Manchester International Office Centre, Styal Road, Manchester M22 5WL (England).