Propofol in patients with cardiac disease

Norman R. Searle MSc MDCM FRCPC,
Philippe Sahab MD FRCPC

Propofol is an intravenous anaesthetic which is chemically unrelated to other iv anaesthetics. Most anaesthetists are now becoming familiar with propofol's pharmacokinetic and pharmacodynamic properties. It has proved to be a reliable drug that can be used safely for induction and maintenance of anaesthesia for most surgical procedures and unlike other anaesthetic agents, it can especially be extended into the postoperative setting or intensive care unit for sedation. Propofol's greatest attributes are its pharmacokinetic properties which result in a rapid, clear emergence and lack of cumulative effects even after prolonged administration. Compared with other iv anaesthetics, the induction dose of propofol has a relatively higher incidence of respiratory depression, short-lived apnoea and blood pressure reduction that may occasionally be marked. Possible mechanisms for the hypotension may relate to (1) its action on peripheral vasculature (vasodilatation), (2) decreased myocardial contractility, (3) resetting of the baroreflex activity and (4) inhibition of the sympathetic nervous system outflow. In vitro studies indicate that propofol depresses the immunological reaction to bacterial challenge as well as the chemotactic activity. Clinical studies, in cardiac surgery, have demonstrated that propofol, in association with an opioid, is a logical anaesthetic choice. Propofol is about to receive approval for continuous iv sedation. Comparative studies of propofol and midazolam have clearly demonstrated the superiority of propofol in terms of rapid recovery and precise control of the level of sedation.

Le propofol est un nouvel agent anesthésique iv qui se distingue des autres agents par sa structure chimique. Les anesthésistes sont maintenant familiers avec les propriétés pharmacocinétiques et pharmacodynamiques du propofol. Il s'est révélé efficace et sécuritaire comme agent d'induction et de maintien de l'anesthésie pour diverses procédures chirurgicales. Contrairement aux autres anesthésiques iv, le propofol peut être retenu comme agent de sédation en période postopératoire ou pour faciliter la ventilation mécanique aux soins intensifs. Ses atouts principaux relèvent de ses propriétés pharmacocinétiques qui expliquent sa rapidité d'émergence et l'absence d'accumulation même à la suite d'une administration prolongée. En contrepartie, le propofol occasionne une plus grande incidence de dépression respiratoire, d'apnée et une chute de la tension artérielle qui, occasionnellement, peut être sévère. Les mécanismes probables pour expliquer cette chute de tension sont: 1) la vasodilatation périphérique (diminution des résistances périphériques), 2) la diminution de la contractilité myocardique, 3) un réajustement de l'activité des barorécepteurs et 4) une inhibition du système nerveux sympathique. Une dépression du système immunitaire peut se manifester à la suite d'une infusion prolongée. Des études in vitro suggèrent une dépression de la réponse immunologique ainsi qu'une diminution de la réponse chémotactique des leucocytes. Des études cliniques chez des patients subissant une chirurgie cardiaque ont démontré que le propofol, en association avec un opiacé, est une alternative anesthésique acceptable. Le propofol va recevoir l'approbation pour l'administration intraveineuse continue à visée sédative. Des études comparatives entre le propofol et le midazolam ont démontré la supériorité du propofol en termes de rapidité de récupération de l'anesthésie et du contrôle précis du niveau de sédation.

Key words
ANAESTHESIA: cardiac;
ANAESTHETICS, INTRAVENOUS: propofol;
PHARMACOLOGY.

From the Department of Anaesthesia, Montreal Heart Institute, 5000 Belanger Street East, Montreal, Quebec, Canada H1T 1C8.

Address correspondence to: Dr. Norman Searle, Department of Anaesthesia, Montreal Heart Institute, 5000 Belanger Street East, Montreal, Quebec, Canada H1T 1C8.

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Contents

In 1990, a new intravenous anaesthetic unrelated to the barbiturates or other anaesthetic induction agents was approved for clinical use in Canada. Its chemical structure is 2,6-diisopropylphenol, propofol or Diprivan™ (Figure 1). The North American experience with propofol is relatively short, even though it was first used as an induction agent in 1977. Within a few years, propofol created enormous interest because of its pharmacokinetic characteristics and clinical effects.

The drug is virtually insoluble in aqueous solutions. It was initially formulated as a 1% solution in 15% Cremophor EL. Unfortunately, the solvent caused a high incidence of pain on injection and was implicated in several hypersensitivity reactions. Reintroduction of propofol awaited the development of a lecithin-containing formulation. Presently, it is formulated as a 1% weight/volume in an emulsion of 10% soya bean oil, 2.25% glycerol and 1.2% purified egg phosphatide.

Studies with the new emulsion have shown several advantages over existing induction agents. The most interesting property is the ease of titration by continuous infusion for the maintenance of general anaesthesia or sedation. While anaesthetists' interest grew, clinical trials using propofol infusions were extended to patients in the extremes of age as well as in various pathophysiological states (i.e, cardiac, hepatic and renal dysfunction). This review will summarize the current pharmacokinetic and pharmacodynamic behaviour of propofol and then will focus on specific areas of clinical use such as: (1) cardiac anaesthesia, (2) sedation in the intensive care unit (ICU) and postoperative care. The clinical use of propofol in general surgery and in other specific settings has been reviewed by others.[1,2]

GLOSSARY
Brain retraction pressure (BRP)
Cardiac index (CI)
Cardiopulmonary bypass (CPB)
Central volume (Vc)
Cerebral spinal fluid pressure (CSFP)
Cerebral perfusion pressure (CPP)
Cerebral blood flow (CBF)
Cerebrovascular resistance (CVR)
Coronary artery bypass surgery (CABG)
Intensive care unit (ICU)
Intracranial pressure (ICP)
Systemic vascular resistance (SVR)
Volume of distribution (Vd)

Pharmacokinetics of propofol

Single bolus administration

The mean standard induction dose in 95% of unpremedicated ASA I and II patients is 2.5 $mg \cdot kg^{-1}$. Induction time, measured by loss of the eyelash reflex, varied from 22 to 125 sec. Following a single bolus injection of propofol, blood concentrations of propofol decline rapidly due to extensive redistribution[3] (Figure 2). Kinetic data from several studies in volunteers, ASA I and II patients, elderly patients, hepatic and renal impaired patients are best described by an open three-compartment model: (1) rapid distribution of propofol from blood into highly perfused tissues such as brain, heart, lungs and liver ($t_{1/2\alpha}$ 1.8–4.1 min), (2) redistribution and metabolic clearance of propofol ($t_{1/2\beta}$ 21–69 min) and (3) slow return of the lipophilic drug from more poorly perfused tissue to blood ($t_{1/2\gamma}$ 184–834 min).[4–7]

Following the administration of a single bolus of 2.5 $mg \cdot kg^{-1}$ the mean central volume (Vc) ranges from 22 to 41 L, while the mean apparent volume of distribution (Vd) of 387 to 771 L is much larger. This high Vd reflects the high octanol/water partition coefficient while the high plasma protein binding (97–99%) may explain the large Vc. Large discrepancies in volumes are to be expected with a lipophilic drug. Campbell *et al.*[8] showed in three patients in whom the sampling period exceeded 42 hr apparent elimination half-life (55.6 hr) and apparent volume of distribution (1370 L) greatly exceeding previously published estimates. This suggests that previous estimates were biased by the relatively short duration of blood sampling (i.e, 8–12 hr). This prolonged terminal half-life probably represents the rate of drug efflux from the peripheral lipid stores. The clinical implications of these observations are not as important for bolus administration as for prolonged infusion (i.e., > 8 hr).

The total body clearance following a single bolus of propofol varies between 1.3 to 2.2 $L \cdot min^{-1}$. This high clearance rate far exceeds liver blood flow, suggesting that extrahepatic and/or extrarenal metabolism (possibly in the lung) may contribute to the elimination of propofol.[5,9]

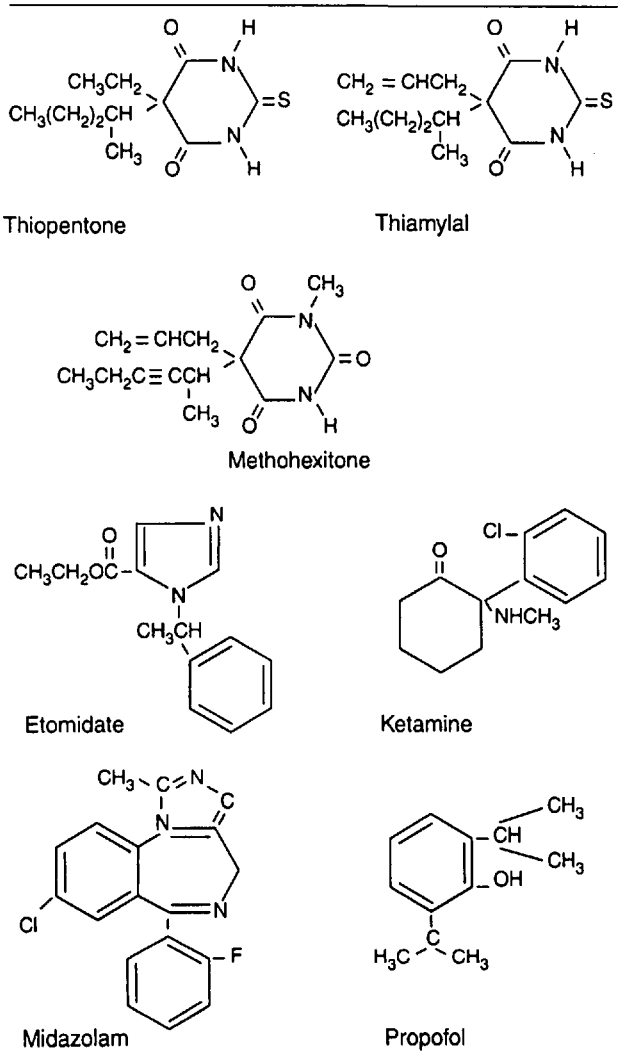

FIGURE 1 Structural formulae of different intravenous anaesthetic agents.

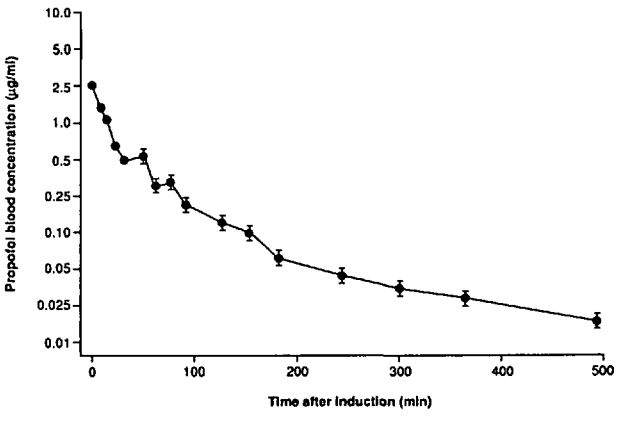

FIGURE 2 Mean blood propofol concentrations following induction doses of 2.5 mg · kg^{-1} in six normal female patients.[3]

Comparing male with female patients, Kay *et al.*[6] was unable to demonstrate any difference in Vd and clearance while White[9] found an increase in clearance counterbalanced by an increase in the Vd in women. In the former study, the ratio of the steady-state volume of distribution to Vd during the elimination phase was lower in women than in men. This difference was attributed to a possible retention of propofol in poorly perfused fat deposits.

The effect of liver cirrhosis on propofol pharmacokinetics indicates that even in patients with reduced hepatic metabolism, the clearance of propofol from blood is similar to that of normal patients.[10] As stated previously, extrahepatic mechanisms may be involved in propofol metabolism and these mechanisms may play an important role in the cirrhotic patient and during the anhepatic phase of orthotopic liver transplantation.[11]

Renal impairment does not appear to modify propofol pharmacokinetics. This issue has been addressed in uraemic patients undergoing either major abdominal surgery or renal transplantation. Indeed, after single bolus administration, no important pharmacokinetic differences were found between uraemic and normal subjects.[12,13]

Acute isovolumic haemodilution (average haematocrit 32.3%) did not affect propofol pharmacokinetic behaviour in eight men undergoing prostatectomy except for an increase of 27% in the Vc.[14] The authors concluded that the induction dose of propofol following isovolumic haemodilution does not require modification.

Aging is known to influence the pharmacokinetics of barbiturates (thiopentone and methohexitone) and etomidate. Also, in elderly patients there is a tendency for total body water, cardiac output and hepatic blood flow to be less than in young patients.[15] In 12 elderly patients (aged 65 to 80 yr), Kirkpatrick *et al.*[7] found a lower clearance rate and smaller Vc than in younger control patients (aged 18 to 35 yr), while the plasma protein binding of propofol and Vd were similar in both groups. This reduction in clearance suggests that metabolism of propofol is diminished in the elderly, possibly as a result of the reduction in the hepatic blood flow and/or cardiac output that occur with aging. Thus, a lower induction dose and a slower maintenance rate of administration are suggested in the elderly to avoid the haemodynamic and respiratory effects.

Concurrent drug administration such as fentanyl (100 µg) prior to induction of anaesthesia increased the blood concentration of propofol and reduced the Vd.[5] This higher plasma propofol concentration may be related to either competitive metabolism between propofol and fentanyl or a reduction in the total blood supply to the liver. More recent studies have shown no difference in the pharmacokinetic profile when fentanyl was administered five minutes before induction[16] and also with alfenta-

nil infusion.[17] The use of inhalational agents on the kinetics of a single bolus injection of propofol (2.5 $mg \cdot kg^{-1}$) reduced the elimination phase (36%), Vd (16%), $t_{1/2\beta}$ (24%) and $t_{1/2\gamma}$ (35%).[5]

When a subanaesthetic dose of ^{14}C-labelled propofol was given *iv* to male volunteers, 88% of the administered radioactivity was recovered in the urine, while less than 2% was excreted in the faeces.[18] Metabolites of propofol are the 1 and 4 glucuronide and/or 4 sulphate conjugates. Metabolism of propofol is rapid since 81% of the radioactivity is found in the metabolites of propofol after 30 min.

Emergence from anaesthesia after a single bolus injection (200 mg) in volunteers occurred in about ten minutes corresponding to a mean blood propofol concentration of 1.1 $\mu g \cdot ml^{-1}$.[19] Similarly emergence from anaesthesia from single bolus injection, repeated bolus administration or a continuous intravenous infusion of propofol occurred at the same average plasma concentration of 1.0 $\mu g \cdot ml^{-1}$ while complete orientation of patients was achieved at a plasma concentration of 0.5 $\mu g \cdot ml^{-1}$.[9,20,21] Plasma propofol concentrations for emergence and complete orientation were independent of age, sex, and type or length of the surgical procedure.

Repeated boluses or constant infusion

Given the pharmacokinetic profile of propofol, a rational approach to its administration for the maintenance of anaesthesia would be a continuous infusion to minimize the peaks and valleys in its blood concentrations without significant accumulation. Knell and McKean[20] showed that repeated propofol boluses of 1 $mg \cdot kg^{-1}$ every six minutes for 75 min following an induction dose of 2.5 $mg \cdot kg^{-1}$, in patients with spinal anaesthesia, showed little or no accumulation in propofol blood concentration.

Pharmacokinetic indices derived during three constant infusion rates (3, 6 and 9 $mg \cdot kg^{-1} \cdot hr^{-1}$) for patients undergoing surgery with regional anaesthesia agreed with those reported during single bolus dose administration and demonstrated that the pharmacokinetics of propofol were linear over the range of the infusion rates studied.[4]

The pharmacokinetics of propofol, administered by infusion at a constant rate of 6 $mg \cdot kg^{-1} \cdot hr^{-1}$, were not affected by an infusion of alfentanil to achieve a plasma concentration of 30 $ng \cdot ml^{-1}$.[17] However, in this study the plasma alfentanil concentration was higher than expected for the infusion rate which was derived from previous pharmacokinetic data. It appears that propofol may affect the disposition kinetics of alfentanil by either decreasing the Vd and/or decreasing elimination but more studies are needed to clarify this.

In ten patients undergoing hypothermic CPB, Massey *et al.*[22] found that clearance, Vd and terminal half-life were similar to those found in non-cardiac patients. A concentration of >1 $\mu g \cdot ml^{-1}$ was achieved within 15 min of starting the infusion (4 $mg \cdot kg^{-1} \cdot hr^{-1}$) and remained constant throughout surgery. Russell *et al.*[23] though reported a decreased plasma propofol concentration at the onset of CPB with a gradual rise in propofol level during the hypothermic period. Rewarming during CPB caused a gradual decline to prebypass plasma propofol concentration. These differences may have been caused by the different sampling sites (radial artery versus bypass oxygenator), acute haemodilution with a crystalloid pump prime, lack of redistribution of propofol from tissues into blood and the physiological changes that result from the onset of bypass.

As alluded to in the previous section, prolonged infusion of propofol may have clinical implications once terminated. Bailie *et al.*[24] recruited 12 patients requiring long-term sedation for mechanical ventilation. Propofol infusion lasted for a mean duration of 85.6 hr at a mean rate of 2.58 $mg \cdot kg^{-1} \cdot hr^{-1}$. After termination of the infusion, propofol blood concentrations declined rapidly with an overall mean decrease of 50% over the first ten minutes. Albanese *et al.*,[25] for a 72-hr propofol infusion at 3 $mg \cdot kg^{-1} \cdot min^{-1}$, showed that the plasma concentration decreased by 50% in six of the nine patients within the first ten minutes. According to the theoretical model proposed by Hughes *et al.*[26] of context-sensitive half-time, they predicted that propofol plasma concentration, at steady state, would decrease by 50% after approximately 50 min. Clearly, there is some discrepancy between this theoretical model predicting a 50% decrease in plasma concentration and the concrete findings by Bailie *et al.* and Albanese *et al.* One possible explanation may relate to the propofol pharmacokinetic values used to derive the context-sensitive half-time.

Pharmacodynamic behaviour

Haemodynamic effects

The cardiovascular depressant properties of propofol appear to be similar to or greater than those of barbiturates. Mackenzie and Grant[27] compared propofol (2.5 $mg \cdot kg^{-1}$), methohexitone (1.5 $mg \cdot kg^{-1}$) and thiopentone (5 $mg \cdot kg^{-1}$) in unpremedicated ASA I and II patients undergoing minor urological surgery. Compared with the methohexitone group, the propofol group had more patients who showed $>20\%$ decrease in systolic blood pressure although all agents increased heart rate (HR) by the same percentage. In another comparative study in 96 ASA I patients, methohexitone and propofol increased cardiac index (CI) measured by pulsed

Doppler ultrasound) while etomidate depressed CI by 16%.[28] Thiopentone had no effects on CI and systemic vascular resistance (SVR). Methohexitone and propofol decreased SVR by an average of 20% while etomidate caused a 12% increase in SVR. Claeys *et al.*[29] studied the haemodynamic effects of propofol, given as a single dose of 2 $mg \cdot kg^{-1}$ and followed immediately by a continuous infusion of 6 $mg \cdot kg^{-1} \cdot hr^{-1}$ in ten elderly ASA II or III patients breathing room air spontaneously. Decreases in systolic and diastolic arterial pressures were observed two minutes after induction (28% and 19% respectively) and during infusion (30% and 25%) and were related to a 21% decrease in SVR. Cardiac output (CO), HR and stroke volume (SV) remained unaffected throughout the study period. Carlier *et al.*[30] showed that, in the absence of N_2O, systemic blood pressures decreased by 20%, CO and SV by 22% while HR and SVR remained unchanged after 2.5 $mg \cdot kg^{-1}$ propofol. Addition of N_2O did not alter any haemodynamic variables. Similar haemodynamic findings to that of Carlier *et al.*[30] have been reported in ASA I–III patients.[14,31] The discrepancies between these latter studies and that by Claeys *et al.*[29] may well reside in their respective study protocols. As suggested by Carlier *et al.*,[30] patients in Claeys' study had a greater increase in $PaCO_2$ i.e., respiratory acidosis. This respiratory acidosis may have masked some cardiodepressive effects of propofol.

The haemodynamic response to 0.0, 0.25, 0.50, 0.75 and 1.0 MAC isoflurane administered in a random fashion concurrently with a constant propofol infusion in normocapnic ASA I and II patients, demonstrated a dose-dependent decrease in mean arterial pressure while CO, SV and HR were not affected.[32] Pulmonary capillary wedge pressure and central venous pressure were minimally altered, while intrapulmonary shunting and PaO_2 remained constant.

Peripheral vasodilatation

A reduction in blood pressure following induction of anaesthesia is observed with most induction agents, including propofol. The mechanisms implicated in the cardiovascular effects of a drug are the result of a complex interaction between: (1) baroreflex activity (heart rate), (2) direct peripheral vasodilatation, (3) central sympathetic nervous system outflow, (4) myocardial contractility, and (5) the underlying pathophysiological state of the myocardium.

In vitro hepatic portal vein and aorta taken from rats were used to investigate the direct action of propofol on the vascular smooth muscle.[33] Propofol caused a dose-related decrease of potassium-induced tone in both types of vessels. Portal veins required significantly lower propofol concentrations to produce similar changes than in the isolated aortic preparation. The possible interaction with endothelium-derived relaxing factor (EDRF) was also explored using endothelium-denuded rings from rat aorta and pulmonary artery rings in which EDRF/nitric oxide (NO) synthase was inhibited.[34] Propofol caused vasodilatation in aortic and pulmonary artery rings, whereas thiopentone had no effect. Propofol seemed to induce direct vasodilatation with a gradual attentuation probably due to a decreased basal release of EDRF. Furthermore, indomethacin-treated rings showed potentiation of an endothelium-dependent vasoconstriction with thiopentone and produced a decrease in propofol-induced dilatation. These results are consistent with the induction of some cyclooxygenase vasodilating metabolites by propofol and thiopentone. The latter findings are in contrast to those of Chang and Davis,[35] who found that vasodilatation produced by propofol is not endothelium-dependent but is likely to be due to blockade of voltage-gated influx of extracellular calcium.

Rouby *et al.*[36] and Boer *et al.*[37] demonstrated that propofol caused profound peripheral vascular dilatation that contributed to the decline in mean arterial blood pressure in patients whose CO was respectively controlled with artificial hearts or cardiopulmonary bypass. Muzi *et al.*[38] reported that propofol-induced hypotension also appeared to be mediated to a large extent by vasodilatation in human volunteers. Ebert *et al.*[39] also reported reduced forearm vascular resistance in association with a 76% decrease in efferent sympathetic nervous activity with propofol while etomidate showed no change. Propofol in contrast to halogenated agents does not inhibit hypoxic pulmonary vasoconstriction in patients undergoing left-sided thoracotomy.[40] These studies inferred that the haemodynamic depression observed with propofol could be attributed primarily to alterations in peripheral arterial and/or venous tone. Despite these well-designed studies, other investigators have found SVR to be unchanged,[14,30,31,41] while Naeije *et al.*[42] reported that vascular tone was related to the concentration of oxygen. During hyperoxia, SVR was increased while the opposite occurred during hypoxaemia. Thus, depending on the concentration of oxygen used in the various studies, the effect on SVR of propofol may have been masked.

Myocardial contractility

The direct effects of propofol on myocardial contractility remain controversial despite extensive study. Several of these studies are summarized in Table I. Mulier *et al.*[43] and Gauss *et al.*[44] used transoesophageal echocardiography to indirectly assess myocardial contractility. They reported that induction doses of propofol appeared to decrease inotropic state in ASA I and II patients. In halothane-anaesthetized swine, graded increase in plasma

TABLE I Effects of various intravenous anaesthetic agents with emphasis of propofol on myocardial contractility

References	*Species*	*iv Anaesth.*	*Bolus or plasma concentration*	*Infusion*	*LVdP/dt*	*SV*	*% SS*	*EF*	*Comments*
De Hert *et al.*[47]	Dog	T	20 mg · kg^{-1}	20–70 mg · kg^{-1} · hr^{-1}			−30% to 80%		Percent change from control. Propofol values did not worsen with critical stenosis applied
		E	1.5 mg · kg^{-1}	2.4–14.4 mg · kg^{-1} · hr^{-1}			−2.7% to −85%		
		P	15 mg · kg^{-1}	6–21 mg · kg^{-1} · hr^{-1}			−9% to −30%		
Diedericks *et al.*[48]	Dog	P	5 mg · kg^{-1}	200–500 μg · kg^{-1} · min^{-1}	−29%	−29%	−50%		Results compared with baseline values and after LAD critical stenosis
Diedericks *et al.*[49]	Dog	P	5 mg · kg^{-1}	300 μg · kg^{-1} · min^{-1} + N_2O	−13%		−6%		Also significant post-systolic shortening occurred with the addition of N_2O and LAD stenosis
			5 mg · kg^{-1}	300 μg · kg^{-1} · min^{-1} + N_2O + LAD stenosis	−20%		−30%		
Belo *et al.*[55]	Dog (*In situ*)	T	Intracoronary perfusion	20 μg · ml^{-1}			−11%		There was no difference in the propofol group but the high dose thiopentone was significant
				40 μg · ml^{-1}			−33%		
		P	Intracoronary perfusion	5 μg · ml^{-1}			0%		
				10 μg · ml^{-1}			−13%		
Ismail *et al.*[56]	Dog (*In situ*)	P	Intracoronary perfusion	150–1200 μg · min^{-1}			−3.8% to −25%		Percent systolic shortening significantly different for doses >300 μg · min^{-1} (these concentrations fall outisde the therapeutic range)
Lepage *et al.*[51]	Human	M	2 mg · kg^{-1}	100 μg · kg^{-1} · min^{-1}				−15%	
		P	2 mg · kg^{-1}	100 μg · kg^{-1} · min^{-1}				+3%	
Puttick *et al.*[50]	Dog	P	5 mg · kg^{-1}	200–500 μg · kg^{-1} · min^{-1}	−10% to −38%		−8% to −18%		Depression in myocardial contractility did not fully recover 60 min after cessation of propofol infusion
Pagel *et al.*[52]	Dog	P	5 mg · kg^{-1}	15–120 mg · kg^{-1} · hr^{-1}	−19% to −48%	−30% to −41%	−19% to −25%		Dose-dependent decrease in preload recruitable stroke work from −22% to −49% indicating negative inotropic effects of propofol
Brüssel *et al.*[46]	Dog	E	0.3 mg · kg^{-1}	Nil	dF/dt −1% to +5%				Effect of a single induction dose
		P	2.5 mg · kg^{-1}	Nil	dF/dt −18% to −24%				
Mayer *et al.*[53]	Dog	P	5 mg · kg^{-1}	Nil - Myocardial segments					Relative changes in different myocardial segments in relation to a single bolus administration of propofol
				(a) normal			−15%		
				(b) collateral dependent			−13%		
				(c) ischaemic			−27%		
Riou *et al.*[59]	Rat (*In vitro*)	P	Plasma concentration	1 μg · ml^{-1} + dF/dt	−6%				Authors found that propofol impaired isotonic relaxation
				− dF/dt	−3%				
				3 μg · ml^{-1} + dF/dt	0%				
				− dF/dt	+2%				
				10 μg · ml^{-1} + dF/dt	−1%				
				− dF/dt	−2%				
Goodchild *et al.*[58]	Dog	P	Plasma concentration	3.44 μg · ml^{-1}	0				Chloralose-anaesthetized dogs with bilateral vagotomy and bilateral common carotid ligation. All dogs received an *iv* infusion of butylium and propanolol. Difference only at 75.74 mg · ml^{-1}
				9.07 μg · ml^{-1}	0				
				21.78 μg · ml^{-1}	−17%				
				75.74 μg · ml^{-1}	−35%				
Pagel *et al.*[60]	Dog	K	10 mg · kg^{-1}	25 mg · kg^{-1} · hr^{-1}	−24%	−19%	−21%		Ketamine impaired left ventricular diastolic function while propofol did not
				50 mg · kg^{-1} · hr^{-1}	−34%	−20%	−36%		
				100 mg · kg^{-1} · hr^{-1}	−54%	−34%	−55%		
		P	10 mg · kg^{-1}	25 mg · kg^{-1} · hr^{-1}	−10%	−16%	−9%		
				50 mg · kg^{-1} · hr^{-1}	−15%	−16%	−12%		
				100 mg · kg^{-1} · hr^{-1}	−24%	−13%	−14%		

dF/dt = left ventricular early systolic rate of increase in force; E = etomidate; EF = ejection fraction; LAD = left anterior descending coronary artery; LVdP/dt = left ventricular rate of change of pressure with respect for time; M = methohexitone; P = propofol; T = thiopentone; % SS = percent systolic shortening.

concentrations of propofol resulted in progressive decline in myocardial contractility.[45] Similarly in ketamine-anaesthetized mongrel dogs, propofol demonstrated an average 16.3% and 23.5% decrease in left ventricular force and early systolic rates of increase force (dF/dt) respectively while etomidate showed no change.[46] As shown in Table I, several studies[47-54] have provided evidence to support the contention that propofol-induced hypotension is mediated principally by depression of myocardial contractility, others have shown little effect in ventricular performance.[55-59] There is one *in vitro* study that reported no alteration in left ventricular diastolic function with propofol, contrary to ketamine which caused, in a dose-dependent fashion, left ventricular diastolic dysfunction.[60]

Animal models of critical coronary artery constriction have shown that all intravenous anaesthetic agents were associated with a dose-dependent decrease in end-diastolic length indicating a decrease in left ventricular filling pressure.[47-50] Regional myocardial function in normal and ischaemic segments remained unaltered for etomidate, while thiopentone showed a dose-dependent decrease in systolic shortening in normal segment and worsening in ischaemic region.[47] Propofol showed similar decrease in systolic shortening in normal myocardium but did not worsen in the ischaemic region.[47] The latter report has not been substantiated; most report worsening of myocardial shortening with propofol.[50,53] The addition of nitrous oxide during a basal infusion of propofol caused mild global myocardial depression but in the presence of a critical coronary stenosis, myocardial contractility was severely perturbed.[49] Finally, the recovery of myocardial contractility in ischaemic segments did not parallel the decrease in plasma propofol concentration[45] and persisted even after 60 min of recovery.[50]

Baroreflex activity

Haemodynamic responses to anaesthesia are related, at least in part, to the action of anaesthetic agents on sympathetic nervous system activity and on the baroreflex response. Most of these agents have a disruptive effect on these systems and responses which may disturb the adaptive responses in certain stressful circumstances. Several clinical studies have shown that propofol used alone for induction and/or maintenance of anaesthesia does not change baroreflex sensitivity as assessed by the change in the slope of the pressor and depressor curve,[61-63] but a marked and sustained alteration of the baroreflex set-point was observed, in such a way as to allow unchanged heart rate at lower arterial pressure.

However, Ebert *et al.*[39] found that propofol depressed both pressor and depressor baroreflex responses, while etomidate did not. The heart rate following induction of anaesthesia was unchanged after etomidate, but after propofol, the heart rate increased in response to a decrease in blood pressure. In the same study, the sympathetic neural outflow after etomidate was unchanged whereas after propofol the sympathetic vasoconstrictor outflow decreased. This suggests that the sympathetic inhibition that occurs during propofol administration may contribute to the hypotension. Propofol-mediated decreases in sympathetic activity, i.e., increased venous compliance, decreased afterload and myocardial contractility, might be the unifying mechanism that explains these various observations. This has been substantiated in another study which showed that propofol infusion depressed the baroreflex activity in a dose-dependent fashion with a delayed recovery following termination of infusion.[64]

The use of a vagolytic drug before propofol to prevent or limit the decrease in blood pressure has also been investigated. In one study,[65] glycopyrolate produced no clinical benefit in preventing the decrease in blood pressure while Skues *et al.*[66] showed, for a comparable increase in heart rate, that glycopyrolate-treated patients had a higher arterial blood pressure than those treated with atropine. The reason for the difference between glycopyrolate and atropine is unknown. Selective muscarinic (M_1) agonist stimulation can increase sympathetic ganglionic activity and thus increase blood pressure and glycopyrolate exerts an anticholinergic action through selective antagonism of M_2 leaving the M_1 receptor unopposed while atropine antagonizes both M_1 and M_2 receptors.

Myocardial metabolism and blood flow

In patients with known coronary artery disease, imbalance between myocardial oxygen supply and demand may result in intraoperative myocardial ischaemia and subsequent postoperative myocardial infarction. During cardiac surgery, tracheal intubation, sternotomy and sternal spread are the major physical stresses that may result in a haemodynamically related ischaemic response.[67,68] Much controversy has surrounded the role of some anaesthetic agents in directly causing myocardial ischaemia.

The effect of propofol (200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) as the sole anaesthetic or in combination with fentanyl (10 $\mu g \cdot kg^{-1}$) on myocardial blood flow and metabolism was investigated in patients undergoing coronary artery bypass surgery (CABG).[69] Following induction of anaesthesia, mean arterial blood pressure was reduced by 15% along with a 19% and 25% decrease in cardiac index and stroke volume index respectively while heart rate increased by 18%. Myocardial blood flow decreased by 26% in association with a 31% reduction in myocardial oxygen consumption. Surgical stimulation led to the return of haemodynamic variables toward baseline except for

a further decrease in cardiac index. Myocardial lactate production was increased in only one patient. Combining a higher fentanyl dose (30 $\mu g \cdot kg^{-1}$) with a constant propofol infusion (mean dosage 4.45 $mg \cdot kg^{1} \cdot hr^{-1}$) did not alter baseline coronary sinus blood flow, myocardial oxygen consumption and myocardial lactate extraction.[70] In a comparative study between sufentanil-propofol and sufentanil-enflurane, the haemodynamic and myocardial metabolic profiles were similar apart from hypotension during induction of anaesthesia with the administration of the propofol bolus.[71]

Electrophysiological action

The sporadic reporting of severe bradycardia following the administration of propofol suggested that this anaesthetic may possess some activity on the cardiac conduction system.[72,73] The direct effects of propofol on the sinoatrial node and atrioventricular conduction have been assessed in animal studies.[74,75] The reduction of cytosolic calcium entry by propofol and the possible influence on the cytosolic calcium mobilization may contribute to the observed shortening of the duration of action potential and the negative inotropic effect of this anaesthetic.[75] The effects of propofol on calcium currents appear to be similar to those of halothane.

In vitro experiments on isolated rabbit sinoatrial node preparation have shown that propofol had only small effects on atrial conduction at 10 $\mu g \cdot ml^{-1}$, but that it reduced conduction drastically at 33 $\mu g \cdot ml^{-1}$ and caused complete block at 100 $\mu g \cdot ml^{-1}$.[74] The effects of propofol on sinoatrial nodes (rabbits and guinea pigs) were relatively slight at the concentrations likely to be seen in clinical practice.[74,75] In humans with rhythm or conduction disturbances (atrial fibrillation or supraventricular tachycardia), propofol modified sinus node automaticity via central parasympathetic process. These effects are more likely to occur during surgical procedures associated with vagal stimulation or when propofol is used with other drugs known to stimulate cholinergic activity. Since the bradycardia observed clinically is reversible by administration of atropine, it is probably due to a centrally mediated increase in vagal tone. Saarnivaara *et al.*[76] reported that methohexitone, propofol and midazolam all prolonged QTc in patients with a normal control QTc interval. Contrary to these results, the QTc interval in patients with a prolonged control QTc tended to be shortened only with midazolam, but was not worsened by propofol or methohexitone.

Cerebral physiology and metabolism

Measuring local cerebral glucose utilization in anatomically discrete regions of the rat brain in response to different doses of propofol showed a dose-dependent decrease in overall mean local cerebral glucose utilization.[77,78] Although all brain substructures were involved, forebrain structures showed greater sensitivity to the depressant action of propofol than did hindbrain regions. Furthermore, certain regions were assayed and demonstrated a 60 to 90% decrease in local cerebral glucose utilization.[78] Upon cessation of propofol infusion, the majority of brain areas rapidly returned to normal glucose uptake and no alteration in the energy state was seen for the different infusion rates of propofol studied.[77] Propofol anaesthesia reduced the glucose uptake in 35 regions of the rat brain and cervical spinal cord by approximately 40 to 70%.[79] Thus, propofol produces metabolic responses similar to those of the barbiturates.

The effect of propofol on cerebral blood flow (CBF), the uptake of oxygen by the brain ($CMRO_2$) and on the response of the cerebral vasculature to CO_2 in 11 patients prior to undergoing extracorporeal circulation has been evaluated.[80] Propofol caused a 24% and 17% decrease in mean arterial pressure and cardiac index respectively. Cerebral perfusion pressure (CPP) declined by 25% during normoventilation, increased by 8% with hyperventilation and decreased again by 12% after hypoventilation. During normocapnia, CBF decreased by 51% and was accompanied by a 55% increase in cerebrovascular resistance (CVR) and a 36% decrease in $CMRO_2$. Hyperventilation to a $PaCO_2$ of 30 mmHg caused a 43% increase in CVR and CBF decreased 25% further while $CMRO_2$ remained unchanged. Hypoventilation to a $PaCO_2$ of 50 mmHg was followed by a 67% increase in CBF, a 44% decrease in CVR and a 38% decrease in $CMRO_2$. It can be assumed from these findings that the reactivity of the cerebral vessels to changes in $PaCO_2$ is maintained during anaesthesia with propofol.

In a study of 23 patients without increased intracranial pressure (ICP), propofol, 1.5 $mg \cdot kg^{-1}$, followed by an infusion, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, decreased lumbar cerebral spinal fluid pressure (CSFP) by 37%.[81,82] The CPP remained above 70 mmHg despite a decrease in mean arterial pressure and CSFP. These values returned to baseline after tracheal intubation, application of pin holders and skin incision. As propofol increases CVR, the decrease in CSFP may be attributed to a decrease in cerebral blood volume. As with barbiturates, the response to propofol is transient, demonstrating its rapid redistribution and metabolism. When associated with a suitable opioid, propofol can obtund the CSFP and mean arterial pressure responses to intubation and noxious stimulation. Evaluation of propofol in patients with and without elevated CSFP has shown that the higher the CSFP, the greater the decrease in CSFP.[82] However, during induction and after tracheal intubation, CSFP remains higher in patients with intracranial hypertension. When propo-

fol, 2 mg · kg^{-1}, was administered over 90 sec to six comatose patients with elevated ICP (>25 mmHg) it caused a decrease in ICP but also lowered CPP below 50 mmHg in four patients. In another study on human brain retraction pressure (BRP), propofol reduced BRP by an average of 3.3 mmHg but also caused a 22.9 mmHg reduction in CPP.[83]

Kalkman *et al.*[84] showed that propofol preserved the early posterior tibial nerve somatosensory cortical evoked potential peaks more than did a combination alfentanil-nitrous-oxide. Propofol appears to have no effect on the time latencies of the brain stem auditory evoked potentials but showed attenuation in amplitude and increased latency of the cortical middle potential of the auditory response.[85]

Brain electrical activity, neurological outcome, and neuronal damage following incomplete ischaemia in rats showed that propofol improved neurological outcome and decreased neuronal damage compared with a group of rats receiving nitrous oxide and fentanyl. The cerebral protection of propofol was independent of plasma glucose concentration.[86] These findings are in contrast to those of Weir *et al.*[87] in cats, where propofol failed to improve the neuropathological outcome following incomplete ischaemia while improving post-ischaemic CBF, extracellular fluid acidosis, hyperkalaemia and a late improvement in calcium ion activity.

There are conflicting data with respect to the anticonvulsive properties of propofol. When propofol was titrated to achieve conscious sedation in 11 treated epileptic patients, six showed no change and five showed either a reduction in epileptic activities or complete suppression of the paroxystic discharges.[88] Hufnagel *et al.*[89] in 12 of 20 epileptic patients, observed maximal suppression of brain activity in the epileptogenic areas with ten patients showing suppression of spontaneous interictal activity, but in five patients induction of epileptiform activity was generated with only one patient convulsing. Several studies have shown that propofol shortens the duration of seizures in patients undergoing electroconvulsive therapy.[90,91] Experiments carried out in rodents to assess the protection afforded by propofol and thiopentone against induced epileptiform seizures showed that both anaesthetic drugs were effective at sedative doses.[92,93] In an animal model of induced status epilepticus, bolus administration of propofol followed by an infusion completely suppressed electrical and clinical seizures in rabbits. This suggests that propofol may be useful in patients with status epilepticus when other agents have failed.[94,95]

Respiration

Induction and maintenance of anaesthesia with propofol alters many respiratory variables. Several investigations have focused on the frequency and duration of apnoea following an induction dose of propofol. Apnoea for longer than 60 sec and a decrease in respiratory rate were observed more frequently after propofol than after thiopentone or methohexitone.[96] The incidence of apnoea seemed to be influenced by the state of hyperventilation or hyperoxia prior to induction since the incidence was 96% after breathing 100% oxygen and only 68% after breathing room air.[97] Furthermore, the duration of apnoea was twice as long in patients breathing 100% oxygen. During hypoxic and hypercapnic challenge, propofol had a greater depression of the afferent chemoreceptor acivity compared with thiopentone and etomidate.[98]

Minute ventilation, tidal volume, mean inspiratory flow rate and functional residual capacity are all decreased during propofol anaesthesia.[99,100] During maintenance of anaesthesia, propofol may also depress the hypercapnic or ventilatory drive. Allsop *et al.*[101] showed that in unpremedicated and papaveretum premedicated patients minute ventilation was depressed and a shift to the right of the carbon dioxide curve was present in both groups. Unpremedicated patients showed no change in the slope of their hypercarbic drive while the papaveretum group had a decrease in the carbon dioxide response to only 55% of the awake value. Recent results have shown that in mechanically ventilated COPD patients, propofol induces bronchodilatation.[102]

The effects of a sedative-hypnotic dose of propofol to maintain conscious sedation or light sleep have not been shown to cause respiratory depression.[103]

Premedication and dose of propofol

In most clinical situations, propofol is used in combination with premedication, opioid analgesics or inhalational anaesthetics, and consequently the possibility of additive or synergistic effects on haemodynamic variables is of interest.[104] In randomized non-blinded studies, the decrease of blood pressure by propofol was not modified by benzodiazepine and/or intramuscular opioids[105] while previous intravenous administration of an opioid analgesic potentiated the hypotensive response of an induction dose of propofol.[106]

Speed of injection

Varying the speed of injection or infusion rate only increased induction time, reduced the incidence of apnoea and total dose administered in the slower infusion groups, while the reductions in systolic and diastolic blood pressures were similar.[107-109] Satisfactory and reliable anaesthesia was obtained even if propofol was administered rapidly. In young and elderly patients, Peacock *et al.*[110] showed that the cardiorespiratory effects of propofol were related to the dose administered and not to the rate of

administration. Interestingly, in their study, induction of anaesthesia in both groups was achieved with smaller doses than had been recommended previously.

Oxygen-free radical scavenging

Oxygen-free radicals are highly reactive compounds causing peroxidation of lipids and proteins and are thought to play an important role in the pathogenesis of reperfusion abnormalities including myocardial stunning, irreversible injury, and reperfusion arrhythmias. Potential sources of free radicals during ischaemia and reperfusion have been identified in myocytes, vascular endothelium, and leukocytes. Free radicals cause injury to processes involved in regulation of the intracellular Ca^{++} concentration. Inhibiting free radical accumulation during myocardial ischaemia/reperfusion with free radical scavengers and inhibitors reduced the severity of myocardial stunning, irreversible injury, and reperfusion arrhythmias in many, but not all, studies.[111] Propofol has free radical scavenging properties resembling those of the endogenous antioxidant α-tocopherol (vitamin E).[112] Its antioxidant activity has been shown in rat liver microsomes and mitochondria at blood concentration seen during clinical anaesthesia or sedation.[113]

Propofol also inhibits the activity of glutamate in the synaptosomes of rat brain.[114] This causes inhibition of calcium influx in neurons which may offer effective protection against ischaemic or hypoxic injury that may occur during cardiopulmonary bypass.[115] These properties of propofol offer theoretical advantages to its use in neuro and cardiac anaesthesia, particularly since free radical mediated tissue injury may contribute to many disease processes.

The immune response

Some anaesthetic agents may inhibit various immune functions but because they are usually administered for a short time, their effects are generally short-lived and reversible. However, this may be relevant if the agent is administered continuously for several days as might be seen in the ICU.

At anaesthetic concentrations, propofol and thiopentone produced 50% inhibition in neutrophil polarization, which is a structural change of neutrophils induced after chemotactic challenge by bacteria.[116] Complete inhibition could be attained with higher concentrations. Midazolam produced no effect at clinically tested concentrations. The lipid carrier alone (10% Intralipid) increased neutrophil polarization. Human serum albumin confers some degree of protection at normal propofol concentrations but failed to do so at high concentrations. In another *in vitro* study, random and chemotactic stimulated locomotion of human neutrophils were adversely affected at clinical concentrations.[117] Although these experiments were carried out *in vitro*, they indicate that inhibition of the immune response may have serious repercussions if the agent is administered continuously to patients with known infection or to immunocompromised patients. Aseptic techniques must be applied to the handling of the drug. Propofol contains no antimicrobial preservatives and the vehicle supports the growth of micro-organisms. Asepsis must be maintained throughout the infusion period but no established guidelines for changing *iv* tubing and/or solution are available except those for administration of Intralipid.

Coagulation

Because fat emulsions may alter coagulation and fibrinolysis there is concern over the short- and long-term use of propofol.[118,119] At present, short-term use of the emulsion formulation has not shown any haematological changes even in the presence of nitrous oxide.[120] Very few studies have addressed this issue in the context of prolonged infusion. In one postoperative sedation study, an increase in prothrombin time (18 to 19.4 sec) was reported in ten critically ill patients eight hours after stopping the infusion[121] while no change in prothrombin time, platelet count or fibrinogen concentration was seen after four days of propofol infusion in 14 agitated patients requiring sedation for mechanical ventilation.[122] Patients in the former study had other underlying conditions that may have contributed to their already abnormal prothrombin time. More studies on prolonged infusion are needed especially in area where platelet dysfunction may occur, i.e., following cardiac surgery and in the ICU.

Allergic reactions

The previous formulation of propofol in Cremophor EL was associated with an unacceptable incidence of pain on injection and anaphylactoid reactions. The administration of the new emulsified preparation may produce skin flushing but is not associated with increases in plasma histamine, immunoglobulin or complement C_3 concentrations.[123] *In vitro* testing of ketamine, thiopentone and propofol failed to reduce, in human basophils, the release of histamine and *de novo* synthesis of leukotriene C_4 but propofol induced release of histamine from mast cells derived from skin and lung origin but not from heart.[124] In another *in vitro* study using basophils from normal and atopic patients, Laxenaire *et al.*[125] showed a slightly higher incidence of histamine release from atopic patients for propofol, thiopentone and chlormethiazole but at much higher than clinical concentrations. Inevitably, reports of allergic reactions occurred with increased use. Initial reporting came from Europe[126,127] and now from the American continent.[128]

Recently 14 patients who had a life-threatening reaction following propofol exposure (either alone or in combination with other drugs) were investigated within 4–6 wk of their incident.[129] Three different immunological tests were carried out: (1) skin testing to propofol and the solvent Intralipid, (2) leucocyte histamine release test and (3) radioimmunoassay of immunoglobulin E to propofol and to muscle relaxant. Results identified 13 of 14 patients who had at least one positive test supporting hypersensitivity to propofol. Nine of 14 patients reported previous allergic histories (atopy, allergic reaction to either antibiotics, lidocaine, muscle relaxants or colloid).

Patients with known allergic reaction to eggs are generally allergic to egg protein or albumin and not to lecithin (the egg phosphatides which are present in the emulsion propofol). Unfortunately, patients are generally unable to discern to which egg protein they are allergic. Until more information is available, it would be prudent to avoid using propofol in these patients.

Clinical Use

Cardiac anaesthesia

The combination of propofol with an appropriate opioid in patients undergoing CABG reduced cardiac work while coronary blood flow and myocardial lactate extraction remained unchanged.[70,71] However, even with smaller boluses of propofol (1 $mg \cdot kg^{-1}$) at induction during CABG, occasional severe reductions in arterial pressure were observed[130] and myocardial lactate extraction was decreased in one patient.[69] Using a similar propofol induction dose, preceded by 8 $\mu g \cdot kg^{-1}$ of fentanyl, Vermeyen *et al.*[131] noted a mean reduction in systolic blood pressure of 28% combined with a 25% reduction in SVR. Although no evidence of ischaemia was seen, a reduction of blood pressure of this magnitude may be hazardous. The authors speculated that the haemodynamic response may be related to the bolus administration overshooting target blood concentration. Utilizing a different administration protocol to achieve a plasma propofol concentration of 3 $\mu g \cdot ml^{-1}$ rapidly without overshooting blood concentration, Roberts *et al.*[132] did not observe any reduction in the haemodynamic variables. When the latter regimen was preceded by 3 $\mu g \cdot kg^{-1}$ of fentanyl, this prevented any haemodynamic response to tracheal intubation. Russell *et al.*[23] followed a standard cardiac induction technique (fentanyl 25 $\mu g \cdot kg^{-1}$ and diazepam 0.1 $mg \cdot kg^{-1}$) with a two-stage infusion of propofol to maintain anaesthesia. Ten minutes before skin incision propofol was started (10 $mg \cdot kg^{-1} \cdot hr^{-1}$) and continued for 15–20 min after sternal spread and then reduced to 3 $mg \cdot kg^{-1} \cdot hr^{-1}$ until the end of surgery. This regimen afforded excellent haemodynamic stability throughout surgery. Using a low-dose infusion of propofol to achieve a plasma concentration of 1 $\mu g \cdot ml^{-1}$, in association with alfentanil for induction and maintenance of anaesthesia, afforded comparable haemodynamic stability.[133] One must remember that this plasma concentration of propofol stands at the threshold value where patients are expected to emerge from anaesthesia.

The absence of explicit recall (the deliberate recollection of an experience) for intraoperative events does not preclude learning process during general anaesthesia.[134] Bethune *et al.*,[135] in CABG patients, tested for implicit recall (the influence of a response by recall of a previous experience without remembering being influenced) during infusion of propofol or methohexitone as an hypnotic supplement to opioid-based anaesthetic. Patients were exposed to an auditory tape throughout the surgery and immediate postoperative period. No patients had explicit recall of any events during the surgery. The propofol group who heard the tape during the surgery had significant implicit recall which was absent in the methohexitone group. This confirms that auditory perception can occur during clinical anaesthesia, and that suppression of auditory awareness or learning is a function of both the degree of sedation and of surgical stimulation. Unfortunately, blood plasma concentrations of propofol or methohexitone were not determined and the propofol infusion seemed to be low, i.e., 2 $mg \cdot kg^{-1} \cdot hr^{-1}$ (33 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Overall, the use of a propofol infusion, combined with a moderate dose of fentanyl, for the maintenance of anaesthesia during cardiac surgery provided good control of haemodynamic variable. To date, in patients with good left ventricular function, weaning from CPB with this technique does not appear to be a problem. Aside from reducing SVR during CPB,[37] there are no data linking CPB pressure and propofol plasma concentrations. Myocardial contractility has been addressed earlier (see Myocardial contractility).

Cardiac surgical patients traditionally occupy high-dependency beds in the ICU for up to 48 hr because of lingering effects of CPB, anaesthesia and intense postoperative sedation and this is expensive. When propofol anaesthesia was used during CPB and maintained until haemodynamic stability and bleeding stopped, only 7% of 245 cardiac patients required ICU admission.[136] All these patients were brought initially to the recovery room and the average time for tracheal extubation was two hours from the time of arrival. Only those with persistent bleeding and/or haemodynamic instability were admitted to ICU, the remaining 93% were discharged to the ward the day of the operation. Thus, propofol anaesthesia combined with an appropriate opioid may prove to be very cost-effective.

TABLE II Propofol for postoperative sedation

References	*n*	*Agent*	*Patients*	*Satisfactory level of sedation (%)*	*Spontaneous ventilation (min)*	*Tracheal extubation (min)*	*Amount of analgesic*	*Comments*
Grounds *et al.*[100]	30	M	Post-CABG	81	197 ± 22.5	226.1 ± 22.8	15.9 ± 2.1	Propofol was superior in all categories and less papaveretum was used
	30	P	Post-CABG	91	13.6 ± 2.7	24.9 ± 2.9	5.7 ± 1.36	
Snellen *et al.*[144]	20	M	Post-CABG	53	66 ± 16	243 ± 44		Patients receiving propofol needed more supplementary doses and increments of infusion rate
	20	P	Post-CABG	59.6	24 ± 7	154 ± 33		
McMurray *et al.*[145]	50	M	Post-CABG	56		127.9 ± 9.9	Morphine	Propofol group was superior to midazolam in all categories
	50	P	Post-CABG	86		11.9 ± 2.5	0.72 mg · kg^{-1} 0.57 mg · kg^{-1}	
Aitkenhead *et al.*[146]	47	M	Critically ill patients	93		148 (n = 18)		Results of tracheal extubation only available from 39 patients
	53	P	Critically ill patients	94		5 (n = 21)		

M = midazolam; P = propofol.

Sedation in intensive care

Most patients transferred from the operating room after CABG or major surgery are hypothermic and vasoconstricted. Those patients require ventilation and sedation for a limited time. The sedative technique must be reliable and allow a rapid and full recovery. The technique chosen should maintain a constant level of sedation, yet one which is readily adjustable without haemodynamic side effects.

In the ICU, satisfactory sedation can be achieved reliably and safely using either sedatives or hypnotics. The ideal sedative drug must provide a fast and smooth onset; an adjustable depth and predictable duration of sedation; be free of side effects; provide a pleasant recovery without rebound sedation. These pharmacodynamic requirements depend on such pharmacokinetic characteristics as: (1) a small initial volume of distribution, (2) a short context-sensitive half-time, (3) a high plasma clearance and (4) inactive metabolites.

The efficacy and dependability of propofol infusion for prolonged sedation has been reported (Table II).[100,121,122] The advantages of propofol are: (1) satisfactory level of sedation with minimal adjustment in the infusion rate, (2) adequate level of sedation reached rapidly, (3) cumulative effects, tachyphylaxis or other untoward effects are not observed, (4) recovery time and rate of decrease in blood propofol concentration after 24–96 hr of infusion are unchanged, (5) less analgesic was consumed, and (6) quicker return of spontaneous ventilation and more rapid tracheal extubation than after midazolam.

The mood-altering and psychomotor effects of propofol have been investigated in ten volunteers.[137] Propofol produced mood alteration in a dose-dependent fashion that persisted for 30 min after termination of the infusion. Only with the high-dose propofol infusion were the psychomotor functions and anterograde amnesia impaired.

Most studies, using a prolonged infusion of propofol, did not show inhibition of adrenal steroidogenesis or cause any clinically important changes in the plasma lipid profile. There has been one report following four days of propofol administration where the urine turned green.[138] Green urine is a well-known effect of phenols but the discoloration does not affect renal function.

Presently, the possibility of withdrawal phenomenon following the prolonged use of propofol has been raised in several case reports and in patients with a history of substance abuse.[139] This phenomenon will have to be investigated by more detailed studies.

Cardioversion

Cardioversion under propofol causes more hypotension and apnoea but with a faster recovery and quicker orientation with a greater acceptance by the patient (more pleasant feeling)[140] than after etomidate. The latter provided more haemodynamic stability but had serious drawbacks such as myoclonus, which interfered with the ECG interpretation, and the possibility of recall.[141] Midazolam showed a longer induction time and delayed recovery with considerable inter-individual variability.[142] Thiopentone was satisfactory although recovery was somewhat delayed

compared with propofol in most studies,[140,141] but it was faster in one study.[143]

Summary

Propofol has proved to be a reliable anaesthetic agent that can be used safely for induction and maintenance of anaesthesia for most surgical procedures and, unlike other agents, it can also be used for an adjustable sedation in the postoperative and/or intensive care settings. Clinical trials of propofol infusion with an appropriate opioid have been evaluated in special groups such as cardiac patients and produces similar haemodynamic results as high-dose opioid anaesthesia. Furthermore, propofol's evanescent action may enable the degree of sedation to be controlled more accurately and recovery of full consciousness to be achieved more quickly than with other intravenous anaesthetic agents. This has particular relevance in the management of patients after cardiac or neurological surgery, burned patients and for restless patients requiring mechanical ventilation. Overall, comparative studies have demonstrated that propofol is at least as effective as other intravenous anaesthetics with potential advantages and disadvantages in individual situations.

The rapid, clear emergence and the lack of cumulative effects even after prolonged anaesthesia are its greatest features. The disadvantages include a relatively high incidence of short-lived apnoea, respiratory depression and blood pressure reduction that may occasionally be marked. However, the magnitude of these effects was such that their management was relatively straightforward in most cases. Other possible interactions with the immune, coagulation systems as well as allergic potential are summarized. Clinical data on its possible role in cerebral protection during CPB is not yet available other than its potential scavenging effect on the free radicals.

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