Pharmacokinetics of propofol when given by intravenous infusion

DENIS J. MORGAN¹, GWEN A. CAMPBELL^{2,*} & DAVID P. CRANKSHAW²

¹Victorian College of Pharmacy, 381 Royal Parade, Parkville, Melbourne, Victoria, Australia, 3052 and

²Department of Surgery, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia, 3052

We have previously shown with i.v. bolus studies that the elimination of propofol is much slower than previously reported. Now we have studied the implications of this for prolonged i.v. infusion of propofol in seven patients who received continuous infusions of propofol for up to 9 h. Values of elimination half-life ranged from 13.1 to 44.7 h, systemic clearance from 1.02 to 1.63 l h⁻¹ and volume of distribution from 1390 to 3940 l and these were similar to those obtained with bolus administration. The large volume of distribution is consistent with the high octanol/blood partition coefficient, which was found to be 72.0. Despite the very long elimination half-life, blood propofol concentrations appeared to approach steady state within 20 min rather than the 4–5 half-lives normally expected. This is because for this drug, which displays multicompartment pharmacokinetics, the rate of initial rise of blood concentrations is governed primarily by the very short distribution half-life of the drug. Therefore, the long elimination half-life of propofol is probably of little significance in designing infusions regimens, but the lower systemic clearance should be taken into account to avoid unwanted accumulation.

Keywords propofol infusion pharmacokinetics

Introduction

Early pharmacokinetic studies of the intravenous anaesthetic agent propofol, administered as a single i.v. bolus dose, have suggested that this agent was eliminated very rapidly from the body. This was indicated by estimates of elimination half-life of 1.5–5 h and of systemic clearance which exceeded the commonly accepted value for human hepatic blood flow (1.5 l min⁻¹) by up to 50% (Cockshott *et al.*, 1987; Kay *et al.*, 1986; Servin *et al.*, 1988; Simons *et al.*, 1988). This apparent rapid elimination rate was probably a function of the relatively short duration of blood collection (8–12 h). A longer duration of blood collection (greater than 42 h) yielded much higher estimates of elimination half-life

(55 h) and much lower estimates of systemic clearance (1 l min⁻¹), indicating that the elimination of this drug from the body is slower than first thought (Campbell *et al.*, 1988).

This slow elimination of propofol is of little clinical significance for single bolus dose administration, because during the extended elimination phase blood propofol concentrations are very low. However, for continuous i.v. infusion of propofol, the low systemic clearance and long half-life would be expected to result in higher steady-state blood propofol concentrations and a longer time to achieve steady state. Several studies have examined the pharmacokinetics of propofol during continuous i.v. infusion for up

*Present address: Department of Anaesthetics, Dunedin Hospital, Dunedin, New Zealand

Correspondence: Dr D. J. Morgan, Victorian College of Pharmacy Ltd, 381 Royal Parade, Parkville, Melbourne, Victoria 3052 Australia

to 4 h, but all of them used a duration of post-infusion blood collection that was insufficient to define the pharmacokinetics of the drug adequately (Gepts *et al.*, 1987; Schafer *et al.*, 1988; Schuttler *et al.*, 1985).

In this study we have determined the pharmacokinetics of infused propofol using an appropriately long duration of post-infusion blood collection. It was our intention to compare these results with our data from i.v. bolus administration (Campbell *et al.*, 1988).

Methods

Seven male patients, aged 38–67 years (mean 55 years), weighing 49–81 kg (mean 67 kg) were studied (Table 1). The patients were undergoing major oral or neck surgery and were all classified as American Society of Anesthesiologists physical status category I or II, and none showed any clinical or biochemical evidence of hepatic, renal or cardiac dysfunction. The protocol was approved by the institutional research and ethics committee and all patients gave informed consent.

Premedication was with temazepam and pethidine or morphine. Anaesthesia was induced with thiopentone in patients 1–4 and with propofol (see below) in patients 5–7. Intubation was facilitated with suxamethonium (100 mg) followed by infusion of alcuronium or atracurium. All patients received N_2O/O_2 (67/33) during the procedure, and patients 1 and 3 also received a low concentration of enflurane.

Propofol was administered by i.v. infusion via an indwelling catheter in a peripheral vein in an aqueous emulsion formulation (10 mg ml⁻¹, Diprivan). The aim was to produce a stable arterial propofol concentration for the duration of the infusion. Patient 1 received a fixed rate infusion of 3.5 mg kg⁻¹ LBM h⁻¹ (LBM =

calculated lean body mass) for the duration of the infusion while the remaining patients received an initial loading infusion of decreasing rate over the first 15 min followed by a constant rate maintenance infusion. The maintenance rate ranged from 3.5–6.2 mg⁻¹ kg⁻¹ LBM h⁻¹, the duration of infusion ranged from 2.5–9.1 h and the total dose from 403–1800 mg (Table 1). Due to an inadvertent brief disconnection of the infusion line it was not possible to ascertain the total dose received by patient 7.

Blood (3 ml) was taken from an indwelling radial arterial cannula prior to the infusion and then at 15–30 min intervals until the end of the infusion. Venous blood was also collected post infusion at 5, 15, 30, 60 min and approximately 6, 12, 24 h and thereafter once daily for the subsequent 5 days. The total volume of blood removed was not greater than 1 ml kg⁻¹. Blood was collected, sealed in heparinized glass tubes and stored at 4° C until assayed. Propofol concentration in whole blood was assayed by high performance liquid chromatography as described previously (Campbell *et al.*, 1988; Plummer, 1987). The assay limit was 8 µg l⁻¹.

The octanol/blood partition coefficient of propofol was measured by adding 2 ml of freshly drawn drug-free blood (pH 7.4) to 2 ml of octanol containing 200 µg propofol. The mixture was gently shaken for 5 min, then centrifuged to separate the phases. The concentration of propofol in the blood was then measured as described above. The partition coefficient was taken as the ratio of calculated concentration of propofol in the octanol after shaking/measured blood propofol concentration.

The apparent elimination half-life ($t_{1/2}$) was estimated from the terminal log-linear portion of the post infusion profile of blood propofol concentration vs time. Systemic clearance (CL) was calculated from total dose/AUC, where AUC is the area under the time-blood concentration

Table 1 Patient details and pharmacokinetic parameters

Patient	Age (years)	Weight (kg)	Maintenance infusion rate (mg kg ⁻¹ LBM h ⁻¹)	Total dose (mg)	Infusion duration (h)	Sampling duration (h)	$t_{1/2}$ (h)	CL (l min ⁻¹)	V (l)
1	38	61	3.5	403	2.5	82	41.0	^a	^a
2	59	49	4.7	999	4.3	26	13.1	1.22	1390
3	53	81	4.7	1437	4.3	49	19.8	1.44	2460
4	63	68	5.2	1184	4.0	99	25.7	1.02	2270
5	67	75	6.1	1800	4.5	83.5	37.6	1.21	3940
6	41	73	6.1	1225	3.3	74.5	27.5	1.63	3870
7	65	64	4.1	NA	9.1	54	44.7	—	—

^a 6 and 12 h post-infusion plasma samples not available; CL and V calculated as approximately 1.01 l min⁻¹ and 3590 l, respectively, by taking 6 and 12 h plasma concentrations as equal to the 24 h plasma concentration.

curve from the start of the infusion, extrapolated to infinity in the usual manner (Gibaldi & Perrier, 1982). Volume of distribution (V) was calculated as $(CL \times t_{1/2})/0.693$ (Gibaldi & Perrier, 1982).

Results

After the initial 15 min loading period, blood drug concentrations were relatively stable, and generally ranged between 1.5–2.5 mg l⁻¹ (Figure 1a). Following cessation of infusion (Figure 1b), the blood drug concentration fell rapidly at first, but then more slowly so that measurable concentrations (8 µg l⁻¹) were still apparent up to 95 h later. Patient physical characteristics, maintenance infusion rate, dosage, duration of infusion, sampling duration and derived values are shown in Table 1. Values of systemic clearance ranged from 1.02 to 1.63 l h⁻¹, volume of distribution from 1390 to 3940 l and elimination half-life from 13.1 to 44.7 h.

The octanol/blood partition coefficient of propofol was found to be 72.0.

Discussion

Several pharmacokinetic studies have suggested that propofol is eliminated very rapidly from the body because of an extremely high systemic clearance (Cockshott *et al.*, 1987; Kay *et al.*, 1986; Servin *et al.*, 1988; Simons *et al.*, 1988). Use of a much longer duration of blood collection following i.v. bolus administration allowed us to make a more accurate estimate of the pharmacokinetic profile of propofol. In particular, more accurate definition of the area under the curve for propofol showed that propofol is eliminated much more slowly than previously thought (half-life 56 h, systemic clearance 1 l min⁻¹) (Campbell *et al.*, 1988). In some patients, however, it was not possible to define the area under the curve for propofol adequately because use of the bolus dose resulted in blood propofol concentrations that fell quickly below the limit of sensitivity of the blood propofol assay (8 µg l⁻¹). It was considered important to confirm these results for propofol when administered by continuous infusion where the higher doses used compared with

Figure 1 Blood propofol concentrations a) during a fixed rate infusion of 3.5 mg kg⁻¹ LBM for 2.5 h in patient 1 and b) following discontinuation of the infusion in patient 4.

bolus administration would facilitate detection of propofol in blood for a longer period, thus increasing the accuracy of the derived pharmacokinetic parameters.

The present study with infused propofol did confirm the finding of our previous study with bolus doses of propofol (Campbell *et al.*, 1988), in spite of the variability in anaesthetic technique and dose and duration of propofol. Systemic clearance, though relatively high ($1.02\text{--}1.63\text{ l min}^{-1}$), was of the same order as the commonly accepted adult value for hepatic blood flow (1.5 l min^{-1}) even allowing for some reduction during anaesthesia and surgery (Gelman, 1976). Therefore, as concluded with bolus dosing (Campbell *et al.*, 1988), there is no need to invoke the possibility of extrahepatic metabolism.

In spite of the relatively high systemic clearance, mean elimination half-life of propofol was relatively long (13.1–44.7 h). This was because of the extremely large volume of distribution (1390–3940). Such a large volume of distribution is consistent with the very large octanol/blood partition coefficient of propofol of 72.0. This value is similar to those of very highly lipid soluble anaesthetic gases, such as halothane (60), enflurane (36) and isoflurane (45), which are sequestered in adipose tissue and released very slowly thereafter (Eger, 1974). Propofol therefore contrasts with other intravenous anaesthetic agents, such as thiopentone and methohexitone, with octanol/blood partition coefficients of 13 and 10, respectively (calculated as the product of unbound fraction in blood and octanol/water partition coefficient (Dundee & Wyant, 1974)) and exhibits properties much more analogous to the volatile anaesthetic agents.

Calculation of the appropriate infusion rate of propofol to achieve a constant blood concentration using a previously overestimated systemic clearance of 1.81 l min^{-1} (Kay *et al.*, 1986) would result in a steady state blood concentration about 50% higher than that achieved using the clearance mean of 1.30 l min^{-1} observed in this study. Further, from the present study it would be expected to take in excess of 100 h (3–4 times the elimination half-life) for steady state to be reached, in contrast to some 5–15 h predicted by earlier studies.

In fact, the constant rate infusion (patient 1) resulted in an apparently constant concentration in less than thirty minutes. Similar observations have been reported previously in 13 patients (Gepts *et al.*, 1987). In an attempt to explain this apparent rapid approach to steady state despite the extremely long elimination half-life, we have

Figure 2 Computer simulation of blood propofol concentrations during a fixed rate infusion of 3.62 mg min^{-1} for 10 h, using long elimination half-life, low clearance pharmacokinetic parameters of Campbell *et al.* (1988) (—) and short elimination half-life, high clearance pharmacokinetic parameters of Kay *et al.* (1986) (-----).

compared simulated time-blood propofol concentration profiles based on the short elimination half-life (4.4 h), high systemic clearance (1.81 l min^{-1}) data of Kay *et al.* (1986), with our long elimination half-life, low clearance data (Campbell *et al.*, 1988) in Figure 2. The simulations were produced by using the equation for i.v. infusion into the central compartment of a three compartment pharmacokinetic model (Gibaldi & Perrier, 1982). Using a fixed rate infusion of 3.62 mg min^{-1} with high systemic clearance of 1.81 l min^{-1} , aimed at producing a steady-state blood concentration of 2 mg l^{-1} resulted in the curve shown by the broken line. In contrast, using the same infusion rate with a three compartment model, but with lower clearance and longer elimination half-life data (Campbell *et al.*, 1988) resulted in the curve shown by the solid line. Paradoxically, the initial rise for the long elimination half-life data (solid line) is much more rapid than that for the short elimination half-life data (broken line). The targetted concentration of 2 mg l^{-1} is also reached more rapidly, which corresponds to the clinical infusion data. The ultimate steady-state concentration for the long elimination half life data will be 3.4 mg l^{-1} in the simulation because of the lower systemic clearance, and this will not be completely reached for very many hours because of the very long elimination half-life. According to theory, the more rapid initial rise in plasma drug concentrations than predicted on the basis of the elimination half-life is due to the fact that, for this drug which displays multi-compartment pharmacokinetics, significant

elimination occurs before distribution equilibrium is achieved. For such drugs it is the half-life of the distribution phase and not that of the elimination phase that primarily determines the rate of rise of plasma concentrations (Rowland & Tozer, 1989).

This study confirms that, whether administered by i.v. bolus or by continuous infusion, the systemic clearance of propofol is lower and the elimination half-life is longer than previously

thought. For the calculation of regimens for intravenous infusion of propofol the prolonged elimination half-life is of little significance. The lower systemic clearance estimate should be taken into account, however, to avoid unwanted accumulation.

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