PHARMACOKINETICS OF AN INFUSION OF PROPOFOL DURING CARDIAC SURGERY

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SUMMARY
We have measured whole blood concentrations and pharmacokinetics of propofol administered as a constant rate infusion during cardiac surgery. Ten patients undergoing elective cardiac surgery involving cardiopulmonary bypass (seven myocardial revascularization and three aortic valve surgery) received a continuous infusion of propofol 4 mg kg\(^{-1}\) h\(^{-1}\) to supplement alfentanil analgesia. Whole blood propofol concentrations were measured by high pressure liquid chromatography. A concentration greater than 1 \(\mu g\) ml\(^{-1}\) was achieved within 15 min of starting the infusion and remained constant throughout surgery. Volume of distribution, clearance and terminal half-life were similar to those found in non-cardiac patients.

KEY WORDS

High doses of opioid drugs have been advocated as the sole anaesthetic agent for cardiac surgery [1, 2]. However, they may cause prolonged postoperative respiratory depression and, when used alone, there is a possibility of intraoperative awareness [3]. The use of a moderate dose of opioid supplemented by a hypnotic agent is a recognized solution to these problems [4]. Propofol has a pharmacokinetic profile which makes it suitable for both induction of anaesthesia and administration by continuous infusion. When used for induction of anaesthesia, propofol 2.5 mg kg\(^{-1}\) produces hypotension secondary to vasodilatation [5, 6]—a property undesirable in cardiac patients. However, an infusion of propofol is associated with less haemodynamic instability [7].

The aims of this study were: to establish that the dose of propofol infused routinely for cardiac surgery in our centre was sufficient to produce blood concentrations greater than the 1 \(\mu g\) ml\(^{-1}\) at which patients wake up after non-cardiac surgery [8, 9]; to determine if concentrations changed during cardiopulmonary bypass (CPB); and if the acute changes during and after CPB altered the pharmacokinetic values for propofol from those in non-cardiac patients.

PATIENTS AND METHODS
After local Ethics Committee approval was granted, written consent was obtained from 10 patients (mean age 46 yr (range 17–62 yr); mean weight 84 kg (range 60–127 kg)) undergoing elective cardiac surgery involving CPB (seven myocardial revascularization, three aortic valve surgery). None had biochemical evidence of hepatic or renal impairment and all had angiographic evidence of good left ventricular function with an estimated ejection fraction greater than 0.5. Established cardiac drug therapy was continued until surgery and premedication of papaveretum 15–20 mg and hyoscine 0.3–0.4 mg was given i.m. 1 h before anaesthesia.

Peripheral venous, radial arterial and internal jugular venous cannulation were performed under local anaesthesia before induction of general anaesthesia. After 3 min of preoxygenation, anaesthesia was induced over 2 min with i.v. midazolam 2–3 mg and alfentanil 50 \(\mu g\) kg\(^{-1}\). Muscle relaxation was produced and maintained with pancuronium 0.15 mg kg\(^{-1}\), the trachea intubated.
and the lungs ventilated to normocapnia with oxygen. Following induction, a zero-order i.v. infusion of propofol 4 mg kg\(^{-1}\) h\(^{-1}\) was started via a dedicated peripheral i.v. cannula using a syringe pump (MS 2000, Graseby Medical, Watford) and continued until the patient arrived in the intensive care unit. Analgesia was maintained by an i.v. infusion of alfentanil 60 \(\mu\)g kg\(^{-1}\) h\(^{-1}\) continued until the start of CPB and a supplement of alfentanil 50 \(\mu\)g kg\(^{-1}\) was given over 2 min at skin incision. A membrane oxygenator (M2000, Shiley) primed with Plasmalyte solution 2000 ml, 8.4% sodium bicarbonate 100 ml and 20% mannitol 100 ml was used for the CPB, during which patients were cooled to a nasopharyngeal temperature of 28 °C. An infusion of glyceryl trinitrate 1–5 mg h\(^{-1}\) was started on rewarming and continued until the end of surgery. No patient required inotropic support following surgery. The duration of propofol infusion from induction to CPB, during CPB and from the end of CPB to the end of infusion were recorded.

Blood samples of 5 ml were obtained from the radial artery cannula at 15, 20 and 30 min and subsequently at 15-min intervals after the start of infusion until CPB; at 5, 10 and 15 min and subsequently at 15-min intervals during CPB; and at 5, 10, 15, 20 and 30 min and subsequently at 15-min intervals after CPB until the end of the infusion. Additional samples were taken immediately before the start and the end of CPB to provide a baseline for the samples taken after these events. When the patient arrived in the intensive care unit a blood sample was taken, propofol was discontinued and further samples were taken at 5, 10, 15, 30, 45, 60, 75, 90 and 120 min and at 4-h intervals until 24 h after the end of the infusion.

Samples were collected in tubes containing potassium oxalate and stored at 4 °C until assay of total whole blood concentration of propofol by high pressure liquid chromatography. The method conforms largely to that described previously [10], with the modifications that the samples were extracted into a 75:25 cyclohexane:hexane solution and dried at 40 °C under oxygen-free nitrogen. The lower limit of detection was 0.02 \(\mu\)g ml\(^{-1}\). The inter-study coefficient of variation of the assay was 4% and intra-study coefficient of variation was 1.97%. These were not affected by the drug concentration within the range measured. The extraction recovery was greater than 95%.

Analysis of data
The total dose of propofol administered (DOSE) was calculated from the infusion rate and duration of infusion and a curve of whole blood concentration of propofol against time was drawn for each patient, thus allowing individual pharmacokinetic values to be derived. The mean concentration for the whole group at each of the sampling times was determined and curves of mean whole blood concentration against time were constructed for the intraoperative and early postoperative periods. Changes in concentrations during and after bypass with time were tested by analysis of variance and a \(P\) value of less than 0.05 was accepted as significant.

Non-compartmental analysis of the data for each patient was made by the statistical moments theory using the trapezoidal rule [11] and from this the area under the whole blood concentration (\(C(t)\)) against time curve to infinity (AUC) and the \(C(t) \times \text{time (t)}\) against time curve to infinity (AUMC) were measured. The mean residence time (MRT) corrected for the duration of infusion (\(T\)) was calculated using the formula:

\[
\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} - \frac{1}{2T}
\]

The characteristics of the terminal part of the decay curve were used to derive the elimination half-life (\(T_{1/2}\)) and constant (\(K_{el}\)). Clearance (\(Cl\)) and volume of distribution (\(V\)) of propofol for each patient were calculated using the formulae:

\[
\text{Cl} = \frac{\text{DOSE}}{\text{AUC}} \text{ and } V = \text{Cl} \times \text{MRT}
\]

RESULTS
The mean time from induction to CPB was 61.3 min (range 36–102 min). The target propofol concentration of greater than 1 \(\mu\)g ml\(^{-1}\) was achieved within the first sampling time at 15 min (fig. 1). The concentration remained greater than this with only a small increase throughout the period before CPB. The mean time of CPB was 87.7 min (range 39–126 min), during which patients were cooled to 28 °C and rewarmed subsequently to 37 °C. At the onset of CPB, no reduction in concentration of propofol was detected and values remained steady during CPB.

The mean time of infusion following CPB was 62.6 min (range 30–104 min) and nasopharyngeal temperature was maintained at 36–37 °C. Fol-
Fig. 1. Total whole blood concentrations of propofol during an infusion of 4 mg kg$^{-1}$ h$^{-1}$ in the times before, during and after cardiopulmonary bypass (mean, SD). * Mean of additional samples taken immediately before CPB, before stopping CPB and before stopping the infusion.

Fig. 2. Log total whole blood concentrations of propofol vs time after infusion (mean (+ range after 90 min)). Number of samples below the lower limit of detection is indicated in parentheses.

following CPB there was, again, no significant change in concentration of propofol (fig. 1).

Mean total infusion time was 211.5 min (range 137–281 min). After stopping the infusion there was a rapid decline in whole blood concentration of propofol, and by 30 min it was less than 1 μg ml$^{-1}$ (fig. 2).

The mean (SD) derived pharmacokinetic data of the 10 patients were: $V$ 626 (313) litre; $Cl$ 2.23 (0.55) litre min$^{-1}$; $T_{1/2}$ 356 (67) min; $K_{el}$ 0.00201 (0.00037) min$^{-1}$.

**DISCUSSION**

Propofol and alfentanil were delivered through a dedicated peripheral line to allow good mixing in venous blood before return to the right heart. It was accepted that delivery might be affected by poor peripheral perfusion during hypothermic CPB. However, when propofol is delivered centrally during open heart surgery it may be seen sometimes escaping into the pericardium in “milky” streams from leaks around the right atrial cannula.

In this laboratory, several different extraction solvents were investigated for more accurate results with lower coefficients of variation than the described methods. Of those tested, 75:25 cyclohexane:hexane gave the most accurate, cleanest peaks with the standard solutions. From investigations at different temperatures it was found that drying the solution at 40 ºC under oxygen-free nitrogen gave no denaturing of the drug and the drying time was reduced considerably compared with that at ambient temperature.

Following the start of the zero order infusion of
propofol, there was an initial fast increase in concentration, so that a whole blood concentration greater than 1 mg ml\(^{-1}\) was attained at 15 min, followed by a slower increase. However, in the limited time to CPB a steady concentration would not be achieved. The initial rate of increase in whole blood concentrations of propofol and the concentrations attained within the time period before CPB were faster than expected on the basis of pharmacokinetic principles, but were in agreement with a study of zero order infusions of propofol by Gepts and co-workers [10]. This may represent changes in \(V\) or \(T_{1/2}\) in these patients during induction and early anaesthesia.

Propofol concentration was not altered by the onset of CPB. This was to be expected because the extra 2.2 litre of crystalloid added to the circulation was small compared with the volume of distribution into which propofol is rapidly distributed [8–10]. This finding is in contrast with those of Russell and co-workers [12] who detected a reduction in concentration at 2–10 min. These differences may arise because they sampled from the pump oxygenator during bypass, not from the radial artery, and because changes in the concentration of propofol in the bypass system and the patient may not be comparable at times of rapid volume change. Also, although the sampling times were not specified by Russell’s group, they may have sampled sooner and more frequently than us. The whole blood concentration of propofol did not alter significantly during CPB, despite the presence of several factors which may alter drug disposition, including: altered regional blood flow secondary to hypothermia, vasoactive drugs and cessation of pulmonary blood flow causing a decrease in hepatic clearance, renal clearance and distribution volume; and haemodilution during CPB causing a decrease in protein binding and an increase in the distribution volume.

After CPB there was a non-significant increase in the concentration of propofol within the first 30 min, similar to that noted by Russell and co-workers [12]. This was probably because the concentration was increasing towards equilibrium before CPB and, despite the interruption, the increase was resumed after it. In addition, during CPB, propofol may have been sequestered in areas which were poorly perfused, such as the peripheries, lung and liver, and subsequently returned to the circulation to contribute to the increased concentrations.

Propofol was used as a hypnotic agent to supplement the analgesia provided by alfentanil. Previous studies in non-cardiac patients have shown that maintenance infusion rates of between 3.73 and 4.29 mg kg\(^{-1}\) h\(^{-1}\) [13–15], when combined with full regional analgesia, are associated with lack of awareness, and that patients wake up at whole blood concentrations of propofol about 1 mg ml\(^{-1}\) [7–9, 16]. In this study, after the first 15 min, the mean blood concentration of propofol throughout surgery exceeded 1 mg ml\(^{-1}\) and, when combined with the hypnosis of a papaveretum premedication and midazolam at induction, should have been adequate to provide hypnosis. Although on direct questioning, and in our clinical use of propofol infusions, no patient complained of awareness, more detailed evaluation is required.

The use of non-compartmental analysis of pharmacokinetic parameters for infusions of propofol has been validated in non-cardiac patients [10]. During cardiac surgery pharmacokinetic variables may change in the periods before, during and after CPB. However, the use of non-compartmental analysis was judged appropriate because all patients are subjected to each phase and it is the net effect that is important clinically. The \(V\) quoted is an overall volume of distribution, rather than that of equilibrium at steady state. It is clear that steady state was never achieved, as the duration of infusion was too short and the volume of distribution may have differed during the different phases. During CPB the addition and removal of crystalloid and blood, affecting plasma proteins and hence binding capacity, might be expected to affect the \(V\) of drugs. However, the mean \(V\) (626 litre) in this study was within the range reported in patients undergoing non-cardiac surgery (298–1008 litre) [8–10, 17] and presumably this is because the volumes of the fluid fluxes were small compared with the overall \(V\). Propofol is known to be 88% metabolized by conjugation [18], mainly in the liver, and drugs with a high hepatic extraction ratio given i.v. are usually sensitive to factors that affect hepatic blood flow (e.g. CPB) and to a lesser extent hepatic enzyme activity (e.g. hypothermia); however, in this study the clearance (2.23 litre min\(^{-1}\)) remained within quoted limits (1.3–2.3 litre min\(^{-1}\)). With the high clearance, whole blood concentrations of propofol decreased rapidly after the infusion was stopped and by 30 min were less than 1 mg ml\(^{-1}\). \(T_{1/2}\) (356 min) was longer than that measured after bolus injections of propofol in surgical patients.
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(184–309 min) [8, 9], but was in agreement with that measured after infusions (227–403 min) [10].

REFERENCES