PHARMACOKINETICS OF PROPOFOL ADMINISTERED BY INFUSION IN DOGS UNDERGOING SURGERY

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SUMMARY

We have investigated the pharmacokinetics of propofol in seven beagle dogs undergoing surgery for implantation of s.c. tissue pouches. Blood concentrations of propofol were measured using high pressure liquid chromatography with fluorescence detection. After premedication with acepromazine and papaveretum and induction of anaesthesia with propofol 4 mg kg\(^{-1}\) i.v., anaesthesia was maintained with propofol 0.4 mg kg\(^{-1}\) min\(^{-1}\) and 67% nitrous oxide in six dogs. In the seventh dog, the infusion rate was increased to 0.6 mg kg\(^{-1}\) min\(^{-1}\) in order to achieve surgical anaesthesia. The mean elimination half-life was 322.3 (sem 27.0) min, mean volume of distribution at steady state 6.510 (0.524) litre kg\(^{-1}\), mean body clearance 50.1 (3.9) ml kg\(^{-1}\) min\(^{-1}\) and mean residence time 131.6 (8.9) min. The blood propofol concentrations achieved using this standard dosing regimen showed wide variation among individuals. All dogs recovered rapidly from anaesthesia. The mean time to extubation was 7.6 min and to standing unaided was 30.7 min from the end of the infusion. (Br. J. Anaesth. 1993; 70: 546–551)

KEY WORDS

Anaesthetics, intravenous: propofol.

We have previously reported the pharmacokinetics of propofol in the dog, which remains a popular model in medical research, despite a tendency to favour small laboratory animals for experimental purposes. When propofol is administered as either a single bolus or as a bolus before maintenance of anaesthesia with halothane, body clearance was greater in dogs than in man, elimination half-life was shorter and recovery from anaesthesia equally rapid [1]. However, the sampling period in that study was relatively short (6 h). Campbell and colleagues [2] have suggested that, when blood samples are collected over a relatively short period of time, this apparently rapid elimination may be misleading. These and other workers have reported longer elimination half-lives and lower clearance values which suggested that elimination of propofol from the body was relatively slower than reported previously [2–5]. This could be significant when propofol is used by infusion for the maintenance of anaesthesia in long surgical procedures. Albanese and colleagues [6] reported a mean elimination half-life of 1878 min and an increased clearance value in patients undergoing long-term infusions, but in this study there was considerable interpatient variation.

Consequently, we decided to investigate the pharmacokinetics of propofol infusion in dogs undergoing identical body surface surgery, in order to identify the blood concentrations required to maintain surgical anaesthesia and to define pharmacokinetic parameters using a longer sampling regimen. The work was carried out under Home Office Licence PPL 60/01048.

METHODS

Pharmacokinetic studies in dogs given a single bolus dose of propofol have been carried out [1] and the mean results for volume of the central compartment (Vc) and body clearance (Cl) were used to estimate a loading dose (Xd) and infusion rate for this study as follows:

\[
Xd = C_{ss} Vc, \quad \text{Infusion rate} = Cl C_{ss}
\]

where \(C_{ss}\) is the target concentration at steady state and infusion rate = Cl \(C_{ss}\). On the basis of a pilot infusion study carried out in bitches undergoing ovarohysterectomy, the target range for \(C_{ss}\) was set at 5–7 \(\mu g\) ml\(^{-1}\).

We studied seven beagle dogs (three male) aged 8–9 months, weights 16–26.5 kg and free from clinical signs of disease. They were to be anaesthetized for implantation of four s.c. tissue cages in the flank region. Before anaesthesia, routine biochemical and haematological screening was carried out on each dog.

Food was withheld for all animals for 12–16 h, but water was freely available until 3 h before induction of anaesthesia. All dogs were premedicated with acepromazine maleate (ACP; CVet) 0.05 mg kg\(^{-1}\) and papaveretum (Omnopon; Roche) 0.4 mg kg\(^{-1}\), given together i.m. 30 min before induction of anaesthesia. Propofol (Rapinovet; Pitman Moore) 4 mg kg\(^{-1}\) was injected as a bolus via a preplaced cannula located in the right cephalic vein. After tracheal intubation, the dogs were allowed to breathe spontaneously a mixture of 67% nitrous oxide in

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oxygen via a Magill non-rebreathing system with a fresh gas flow rate of 200 ml kg\(^{-1}\) min\(^{-1}\).

One minute after induction, a zero order i.v. infusion of propofol 0.4 mg kg\(^{-1}\) min\(^{-1}\) was begun using a volumetric infusion pump (Flo-Gard 6200; Baxter) and continued for 60 min. If anaesthesia was inadequate, the infusion rate was increased until the desired plane of anaesthesia was achieved. In all animals, the non-steroidal antiinflammatory drug flunixin meglumine (Finadyne; Schering Plough Animal Health) 1 mg kg\(^{-1}\) was injected s.c. 2 h after the infusion was terminated.

Venous blood samples (1.5 ml) were collected from a cannula located in the left cephalic vein, immediately before and during the infusion, and after it was terminated. Times of collection during the infusion were 2, 5, 10, 15, 20, 40 and 60 min. After the infusion was stopped, samples were taken at 2, 5, 10, 20, 30, 45, 60 min and then at 2, 3, 4, 6, 9, 20 and 24 h. Samples, collected in tubes containing potassium oxalate, were cooled immediately and stored at 4°C until analysis. All samples were assayed within 2 weeks of collection and previous investigations have shown that blood stored in this way retains in excess of 98% of its original propofol concentration. Whole blood concentrations of propofol were measured by high pressure liquid chromatography with fluorescence detection [7]. The limit of detection was approximately 5 ng ml\(^{-1}\) and the intra-assay coefficient of variation was 2.9%.

Routine monitoring was carried out during anaesthesia. Heart rate and ventilatory frequency, systemic arterial pressure, end-tidal partial pressure of carbon dioxide (\(P\text{CO}_2\)) and oxygen saturation were measured at 5-min intervals. Arterial pressure was monitored using a Dinamap pressure monitor (Critikon Canada Inc.) with an appropriately sized cuff placed over the middle coccygeal artery. \(P\text{CO}_2\) was monitored on a breath-by-breath basis using a carbon dioxide analyser (Normocap; Datex). Oxygen saturation was measured using a pulse oximeter (Ohmeda) located on the tongue.

Recovery times (tracheal extubation, head lift, sternal recumbency and standing unaided) were measured from the time the infusion was switched off. The blood concentration of propofol at the time of tracheal extubation and head-lift was calculated retrospectively by extrapolation from each individual propofol concentration–time curve.

The apparent elimination half-life, \(T^\beta\) was calculated from the terminal log-linear portion of the post-infusion decay curve of blood concentration of propofol vs time, using the curve stripping programme CSTRIP [8]. The non-compartmental pharmacokinetic parameters, volume of distribution at steady state (\(V^\infty\)), clearance (\(CL\)) and mean residence time (MRT) were calculated according to standard methods using the statistical moment theory [9]. Area under the blood concentration (\(t^C_0\))-time (\(t\)) plots to infinity (AUC), and the area under the first moment curve (\(AUMC = t^C_0\times t\)) were calculated from the first to the last blood propofol sample using the trapezoidal rule. An estimate of the infinite part of the curve was obtained from \(t^C_0/\beta\), where \(t^*\) = last measured blood concentration of propofol and \(\beta\) = overall elimination rate constant. An estimate of the infinite part of the AUMC plot was obtained from \(t^C_0\times t/\beta\). MRT corrected for infusion duration, was calculated from AUC and AUMC (\(MRT = AUMC/AUC - T/2\)) where \(T\) is the infusion time. \(V^\infty\) was calculated from \(CL\times MRT\) [10].

RESULTS

Six of the seven dogs had a constant rate infusion, while the seventh required two increases in infusion rate. Consequently, results for blood propofol concentrations are expressed as a mean for six animals (dogs Nos 1–6). Blood concentrations of propofol varied between 3.77 and 5.52 µg ml\(^{-1}\) as the infusion was started. A mean concentration of 5 µg ml\(^{-1}\) (range 3.34–6.60 µg ml\(^{-1}\)) was achieved within 10 min, indicating a rapid approach towards the target concentration range, although the between-animal variation was large. The propofol concentration increased gradually over the next 50 min until the infusion was switched off, at which point the mean concentration was 5.84 (SEM 0.54) µg ml\(^{-1}\) (range 4.0–7.1 µg ml\(^{-1}\)) (fig. 1A). In dogs Nos 1–6, surgery began within 15 min of the start of the infusion, at which time the blood concentrations of propofol were in the range 3.5–5.8 µg ml\(^{-1}\). After cessation of the infusion, the blood concentration of propofol declined in a polyexponential manner (fig. 1B). Measurable blood concentrations of propofol were present in all dogs for 25 h.

Tracheal intubation was not possible immediately after induction in dog No. 7, and after 10 min the infusion rate was increased to 0.5 mg kg\(^{-1}\) min\(^{-1}\). Four minutes later, the infusion rate was increased again to 0.6 mg kg\(^{-1}\) min\(^{-1}\) in order to achieve surgical anaesthesia. At 15 min, this animal had a blood concentration of propofol 5.4 µg ml\(^{-1}\) and intubation was successful. When surgery began 20 min after the start of the infusion, the blood concentration of propofol was 5.82 µg ml\(^{-1}\). The rate of infusion was reduced to 0.5 mg kg\(^{-1}\) min\(^{-1}\) after 40 min and again 6 min later to 0.4 mg kg\(^{-1}\) min\(^{-1}\). At the end of the infusion period the blood concentration of propofol was 7.9 µg ml\(^{-1}\). During surgery, although no movement was recorded and cardiovascular variables remained stable, an increase in ventilatory frequency was evident as s.c. tunnelling was performed.

Clinically, all animals were in a light plane of anaesthesia. A brisk palpebral reflex was present for the first 30–40 min of the infusion in five dogs and on occasions spontaneous blinking was noted.

The mean elimination half-life for all seven dogs was 322.3 (27.0) min, mean clearance 50.1 (3.9) ml kg\(^{-1}\) min\(^{-1}\), \(V^\infty\) 6.510 (0.524) litre kg\(^{-1}\) and MRT 131.6 (8.9) min. The pharmacokinetic variables for each dog are shown in table I.

Mean values for physiological parameters are shown for six dogs, omitting dog No. 7 which received a greater total dose of propofol than the other six animals. Systolic arterial pressure decreased from 130 (5) mm Hg 5 min before induction to a smallest value of 111 (3) mm Hg 5 min after
induction (fig. 2). Thereafter, it remained relatively stable, varying between 112 and 121 mm Hg. The diastolic pressure followed a similar pattern (fig. 2) with a maximum decrease of 20% recorded 5 min after induction. During anaesthesia, the heart rate varied minimally from a preinduction value of 85 beat min⁻¹ (fig. 2). Post-induction apnoea was recorded in one dog, spontaneous ventilation returning after 3 min. *P*CO₂ values increased from a mean value of 5.9 (0.4) kPa 5 min after induction to 6.7 (0.3) kPa, while ventilatory frequency remained largely unchanged from preinduction values (fig. 3).
out anaesthesia, but was considered acceptable in induction of anaesthesia with a bolus injection of respiratory depression persisting into the recovery end of the infusion, indicating that there was little COI this group of spontaneously breathing dogs. 

Achieve surgical anaesthesia within 20 min in all (range 2.1-2.9 µg ml\(^{-1}\)) and at head lift (min)

Recovery from anaesthesia was rapid in all dogs (Table II). One dog remained in lateral recumbency for 55 min, but appeared fully conscious. The mean blood concentration of propofol at extubation was 2.3 µg ml\(^{-1}\) (range 2.1-2.9 µg ml\(^{-1}\)) and at head lift 2.1 µg ml\(^{-1}\) (range 1.7-2.7 µg ml\(^{-1}\)).

**DISCUSSION**

The combination of a bolus dose followed by a relatively rapid infusion of propofol allowed us to achieve surgical anaesthesia within 20 min in all dogs. Respiratory depression was evident throughout anaesthesia, but was considered acceptable in this group of spontaneously breathing dogs. P\(\text{E}_\text{CO}_2\) had returned to a mean of 5.3 kPa within 5 min of the end of the infusion, indicating that there was little respiratory depression persisting into the recovery period.

Arterial hypotension occurs commonly during induction of anaesthesia with a bolus injection of propofol, and this has been attributed to a decrease in systemic vascular resistance [11-13]. However, more recently Puttick and colleagues [14] have demonstrated that reduction in preload and myocardial contractility contributed to propofol-induced hypotension in a group of open chested dogs. In the present study, the greatest changes in systolic and diastolic arterial pressures were recorded 5 min after induction of anaesthesia. However, these dogs had received acepromazine, a phenothiazine tranquilizer, as part of the premedicant 30 min before the induction of anaesthesia. In addition to its tranquilizing properties, this drug causes moderate hypotension in the dog as a result of peripheral vasodilatation [15], which would contribute to the hypotension recorded during induction and maintenance of anaesthesia.

Previous studies of propofol in humans and experimental animals have shown that individual variations in blood concentrations of propofol may occur [14, 16]. Similarly, in the present study, marked variation in blood concentrations of propofol occurred, despite the identical infusion rate. Such variation was not reflected clinically, however, as six dogs appeared to be in a similar anaesthetic plane. The exception was dog No. 7: the trachea could not be intubated until the blood concentration of propofol reached 5.4 µg ml\(^{-1}\).

In man, there seems to be wide variation in blood concentrations of propofol associated with the abolition of response to surgical stimulus, with the concurrent use of other drugs making comparisons difficult [17-19]. Turtle and others reported that a propofol concentration of 5.9 µg ml\(^{-1}\) abolished movement to skin incision in 95% of patients who had received lorazepam as a premedicant [20]. This value is similar to that found in our dogs, which had been sedated with a neuroleptanalgesic mixture. However, the additional analgesic activity of this mixture must be set against the substantially lower efficacy of nitrous oxide in dogs [21] compared with man.

Gepts and co-workers [22] administered propofol to patients by continuous infusion at a maximum rate of 0.15 mg kg\(^{-1}\) min\(^{-1}\) and found that there was an initial increase in blood concentration over 10 min, followed by a slower rate of increase over the infusion period. After the infusion they measured a long third phase (355 min), which they suggested was unlikely to play a significant role in the rate of recovery of consciousness because blood concentrations were so small. In our canine study, blood concentrations of propofol followed a similar pattern, but we consider that a zero order infusion of this magnitude (0.4 mg kg\(^{-1}\) min\(^{-1}\)), if maintained for long periods, could result in delayed recovery from anaesthesia because of cumulation of propofol in tissue stores. Limited clinical experience of prolonged infusion of propofol to dogs supports this view [23].

During the post-infusion decay of propofol from blood, three of seven animals showed small secondary peaks, dogs Nos 1 and 2 at 240 min and dog No. 4 at 45 min, all of which were less than 20% of the previous sample value. This is in contrast with...
infusion studies in man which have demonstrated occasional profound increases in blood concentration of propofol during the recovery period [5, 6, 18].

Previous studies in the dog have reported a $T_{1/2}$ of 90.9 min with a high clearance value of 58.6 ml kg$^{-1}$ min$^{-1}$ [1]. This clearance is in excess of liver blood flow [24] and lends weight to the argument for an extrahepatic site of metabolism. Morgan, Campbell and Crankshaw [3] suggested that, in humans, clearance values from single bolus studies were an overestimate of the true body clearance when applied to infusion studies, but we have shown that in the dog the mean clearance for propofol by infusion, 50.1 ml kg$^{-1}$ min$^{-1}$, is similar to that found in single bolus studies. However, the elimination half-life was considerably greater than that calculated from single dose studies. This is probably a reflection of the fact that samples were collected over a much longer period of time. Similar findings have been demonstrated in patients undergoing long-term mechanical ventilation who received propofol by infusion [6] and other workers investigating the pharmacokinetics of propofol from infusion studies have reported a variety of prolonged half-lives of 13.1–44.7 h [3].

The volume of distribution was large, 6.5 litre kg$^{-1}$, confirming the extensive distribution of propofol from blood into tissues, and is not unexpected for such a highly lipophilic drug. These values are greater than those recorded in humans by some groups [18, 22, 25], but less than that reported by Albanese and coworkers [6].

Blood concentration of propofol at awakening has been measured in man and the evidence suggests that, when propofol is given by infusion, the range is 0.74–1.66 µg ml$^{-1}$ [22]. In a study carried out in pregnant women, it was reported that patients who received a greater infusion rate during surgery opened their eyes at the same time (mean 6 min) as those that received a lesser infusion rate, although the blood concentrations of propofol were significantly greater (1.74 µg ml$^{-1}$ vs 1.24 µg ml$^{-1}$) [26]. It is difficult to assess time of awakening in dogs. We regard the ability to maintain head-lift as the criterion for awakening in animals, although it may not be totally comparable to eye opening in man. The blood concentrations of propofol at awakening obtained in these dogs, greater than recorded in humans and from dogs given a single bolus dose of propofol [1], probably reflect the greater infusion rate used in this study, but the recovery times compare favourably.

In conclusion, we have shown that although the elimination half-life of propofol in dogs was considerably longer than that recorded from single bolus dose studies, body clearance was high. In addition, there was considerable between-animal variation in blood concentrations of propofol measured during a zero order infusion and in blood concentrations required to maintain anaesthesia for body surface surgery.

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