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Brain and Blood Concentrations of Propofol After Rapid Intravenous Injection in Sheep, and Their Relationships to Cerebral Effects

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SUMMARY

The time-course of propofol concentrations in the blood and brain following rapid administration of three doses were examined using a sheep preparation and regional pharmacokinetic techniques. These were compared to the time-course of cerebral effects of propofol reported previously. There were marked differences between the time-course of propofol concentrations in arterial blood and the brain, with a close relationship between the time-course of brain concentrations and effects on depth of anaesthesia and CBF. There was evidence that the effect of propofol on cerebral blood flow altered its own rate of elution from the brain. Hysteresis between arterial propofol concentrations and cerebral effects following rapid IV administration therefore appears to have a pharmacokinetic basis, and conventional compartmental pharmacokinetic analysis using blood concentrations alone may fail to accurately predict the time-course of both brain propofol concentrations and depth of anaesthesia.

Key Words: ANAESTHESIA: cerebral blood flow; PHARMACOLOGY: propofol, pharmacokinetics

Propofol is a substituted phenol commonly used in anaesthetic practice, and is administered both via slow IV infusion for maintenance of anaesthesia and by rapid IV "bolus" to quickly increase the depth of anaesthesia. The systemic pharmacokinetics of this drug have been extensively investigated and these data used to develop dose regimens, in an attempt to provide optimal profiles of depth of anaesthesia while minimizing such side-effects as hypotension.

Dose regimens for maintenance of anaesthesia are most frequently derived from compartmental models fitted to the time-course of drug concentrations in blood, and these generally allow relatively accurate prediction of blood propofol concentrations and depth of anaesthesia[1].

Compartmental modelling may prove inaccurate, however, following rapid administration of drugs such as at induction of anaesthesia[2]. Regional pharmacokinetic studies of the time-course of the concentrations of drugs following bolus administration have demonstrated large and prolonged disequilibria between drug concentrations in blood and even highly perfused organs, and have confirmed that under these conditions organ drug effects may be accurately predicted by organ but not blood drug concentrations[3]. The time-course of changes in blood and organ concentrations following rapid administration are a product of complex interactions between such variables as injection profiles, cardiac output, blood flow to well perfused tissues and rates of diffusion; factors not addressed by conventional compartmental pharmacokinetic analysis[4].

While disequilibria between propofol concentrations in blood and anaesthetic effect at induction of anaesthesia is acknowledged in the literature, its causes remain partly speculative in the absence of data on the time-course and determinants of distribution of propofol to the brain[1,5,6]. We have previously examined the cerebral effects of propofol in a chronically instrumented sheep preparation[7]. This is a supplementary report to that study and examines the time-course of propofol concentrations in the brain and blood which were measured simultaneously in these sheep.

METHODS AND MATERIALS

Animal Preparation

All experimental protocols were approved by the Ethics Committee of the University of Adelaide and

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Institute of Medical and Veterinary Sciences (Adelaide). Female Merino sheep of similar ages and body mass were used, and animals were initially prepared with catheters and a flow probe under general anaesthesia[8]. For sampling of arterial blood and for measurement of arterial pressure, two 7F catheters (Multi-purpose A1 catheter, Cordis Corporation, Miami, FL, U.S.A.), were placed in the carotid artery and positioned under radiographic control with their tips at the origin of the brachiocephalic trunk. One 7F catheter, for drug administration, was placed in the jugular vein and positioned with its tip in the right atrium. Catheters were fastened to the strap muscles of the neck using a small plastic plate and exteriorized.

A 19 mm trephine hole was made in the skull and a 1 mm diameter 20 MHz piezoelectric Doppler transducer (Titronics Medical Instruments, Iowa City, Iowa, U.S.A.) placed over the sagittal sinus for cerebral blood flow (CBF) measurement. A 4F catheter (Cook Incorporated, Bloomington, U.S.A.), for sagittal sinus blood sampling, was inserted into the sagittal sinus approximately 1 cm rostral to the Doppler probe and positioned so the tip lay approximately 4 cm from the probe. The catheter and Doppler probe wire were exteriorized and the bone plug replaced. Sheep were then recovered from anaesthesia and housed in metabolic crates, with catheters continuously flushed with heparinized saline.

Experimental Design

Studies were commenced a week after surgery to allow wound healing. For each study, sheep breathing room air remained in their metabolic crates with their weight partially supported by a sling. Cerebral blood flow and an index of depth of anaesthesia were measured in each study as described below.

Cerebral blood flow was measured using a venous outflow method of Upton et al[9], with a directional pulsed Doppler flowmeter (Bioengineering, University of Iowa, U.S.A.) connected to the sagittal sinus transducer. It has been shown that this method measures the velocity of blood from approximately 70% of the brain, predominantly that from the cerebral cortices, and it has been shown that blood velocity correlated well with blood flow over a wide range of CBF values as a result of constant vessel cross-sectional area and the absence of turbulent flow[9]. Because the Doppler signal therefore remains proportional to actual flow at all times, it was considered unnecessary in this study to calibrate the Doppler signal against flow in each animal at the end of each series of experiments. The flowmeter output was recorded using an analog to digital card (Metrabyte DAS 16-G2) and a personal computer (Microbits 486-based IBM compatible) using a sampling rate of 1 Hz.

An index of the anaesthetic effect of propofol was measured at 30-second intervals using the threshold of response to a noxious stimulus. A ramped pulsed electrical DC current was applied to the lower hind limb of the sheep through two subcutaneous 26 gauge needles using a modified peripheral nerve stimulator (Digistim 3, Neuro Technology, Houston, Texas, U.S.A.), and the current threshold required to produce limb withdrawal observed and recorded[10].

In each study, after the baseline variables were recorded for three minutes and baseline arterial blood samples taken, either 50 mg, 100 mg or 200 mg of propofol was administered intravenously over two minutes using a syringe pump (Model 33, Harvard Apparatus Ltd, Kent, England). All variables were recorded for 40 minutes and 1 ml blood samples were taken from the catheters at the following times: arterial 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12.5, 15, 17.5, 20, 25, 30, 35, 40 minutes; sagittal sinus 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12.5, 15, 17.5, 20, 25, 30, 35, 40 minutes, and stored in glass tubes to which heparin (25 IU) had been added. Blood samples were then frozen and stored at –5°C. Each dose was administered to five different sheep, but because of probe or catheter failure, a total of eight sheep were studied. Two sheep received all doses in random order, three sheep received two doses and three sheep received only one dose. In sheep receiving more than one dose, at least 48 hours was allowed between studies.

Propofol Assay

Propofol concentrations in whole blood were assayed using a modification of the high-performance liquid chromatography (HPLC) and fluorescence detection technique of Mather and co-workers[11]. For solvent extraction, thymol (2.5 µg, internal standard), KH_2PO_4 (100 µl) and n-heptane (200 µl) were added to the sample which was then vortex-mixed and centrifuged. An aliquot of the supernatant heptane layer was transferred to glass vials and the heptane evaporated at 40°C in a partial vacuum. The residue containing the propofol and thymol was reconstituted in the acetonitrile-water-acetic acid (45-55-0.5) mobile phase (100 µl) and 10 µl samples injected into the chromatograph using an autoinjector (Perkin Elmer IS100). For chromatography, a liquid chromatography pump (Perkin-Elmer Series 410)

was connected in series with an HPLC column (Activon Goldpak ODS E18, Sydney, Australia) to a fluorescence detector (Perkin-Elmer LS40) using an excitation wave length of 210 nm and emission wavelength of 320 nm.

Standard curves were prepared by adding known amounts of propofol to sheep blood samples taken prior to drug administration. In all cases linear regression of a five-point standard curve covering the range of drug concentrations encountered in the studies produced an R^2 value of 0.995 or greater. The limit of sensitivity was approximately 0.02 μg ml^{-1}.

Mass Balance Calculations

The equations for calculation of organ concentrations have been described previously and have been extensively validated[12-14]. For each animal the net flux of propofol into the brain was calculated from the arterio-sagittal sinus concentration difference and the CBF. As the Doppler probe could not be calibrated in all animals and because sagittal sinus blood velocity is closely related to blood flow under a wide range of values of CBF, a baseline CBF of 40 ml/min was assumed in all animals. This figure was the mean CBF in a series of sheep of similar age and weight in which all Doppler probes were calibrated[9]. The total amount of propofol in the brain was calculated from the integral of the net propofol flux over time, and the brain concentration calculated assuming a brain mass in the area drained by the sagittal sinus of 75g. This figure is the brain mass from which sagittal sinus blood drains, estimated from sheep in the validation of methodology mentioned previously. To simplify mass balance calculations, sagittal sinus propofol values were calculated at the time points 0.25, 0.75, 1.25 and 1.75 minutes by linear interpolation.

Data Analysis

Although CBF was measured at 1 Hz, for practicality the Doppler output in individual animals was averaged at 30-second intervals. For measurement of depth of anaesthesia, current threshold values at each time point in individual animals were expressed as the per cent increase above the average baseline values. Data at each time point for all animals were then pooled and expressed as mean and standard error of the mean (SEM).

To examine for dose-dependent effects on arterial concentrations (drug input to the brain), the arterial concentrations were normalized for dose by scaling all values following the 50 mg and 200 mg doses by a factor of 2 and 0.5 respectively.

To examine for concentration-dependent kinetics in the brain, the effect of different arterial concentrations (input to the brain) after each dose was removed by normalization. The curves of sagittal sinus and brain concentrations were scaled by the ratio of actual peak arterial concentration and the peak mean arterial concentration after the 100 mg dose.

The relationship between propofol concentrations and cerebral effects was examined by plotting blood and brain concentrations against both current threshold increase and CBF following the 100 mg dose, the only dose which produced a significant change in depth of anaesthesia quantifiable for the entire duration of the study. The drug concentration-effect curves were examined for the presence of hysteresis using the following method. For individual animals each plot was divided into two sections at the point of peak propofol concentration so that one section represented concentration-effect relationships when concentrations were increasing, and the other when they were decreasing. The area under the curve (AUC) in each section was calculated using the trapezoidal method and the values for all animals were pooled. Hysteresis was considered present when the pooled areas for the sections representing ascending and descending concentrations were statistically different when compared using a paired t-test[3].

RESULTS

Propofol Concentrations

The time-course of the propofol concentrations for each dose were highly reproducible between animals and are shown in Figure 1. Peak arterial concentrations of 1.5, 9.3 and 17.1 μg.ml^{-1} for the 50, 100 and 200 mg doses respectively were reached at two minutes following all doses of propofol, and decreased very rapidly after drug administration was ceased, with no propofol detectable at the limit of detection in arterial blood two minutes after administration of any dose was ceased. After values were normalized for dose, peak arterial concentrations were similar after the 100 mg and 200 mg doses, but lower after the 50 mg dose, suggesting a dose-dependent effect on drug input to the brain (Figure 2). The time-course of arterial concentrations, however, was similar when values were normalized for peak concentration (Figure 3).

Sagittal sinus concentrations increased and decreased more slowly than arterial values, reaching maxima of 0.4, 2.3 and 4.5 μg.ml^{-1} after each dose respectively, all at 2.5 minutes (Figure 1). Scaling for peak arterial concentrations demonstrated that the

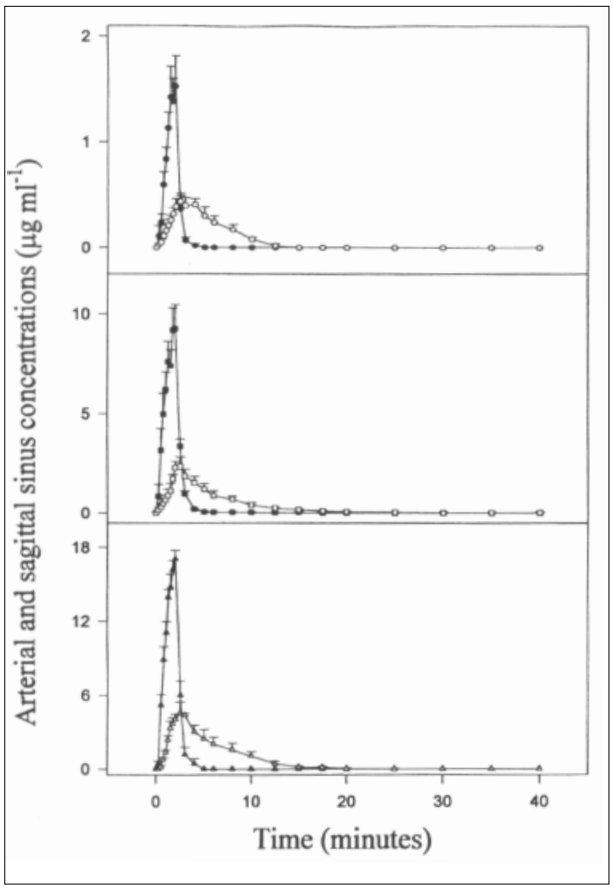

FIGURE 1: Arterial (filled symbols) and sagittal sinus (open symbols) propofol concentrations, mean (SEM) following IV administration of 50 mg (circles), 100 mg (squares) and 200 mg (triangles).

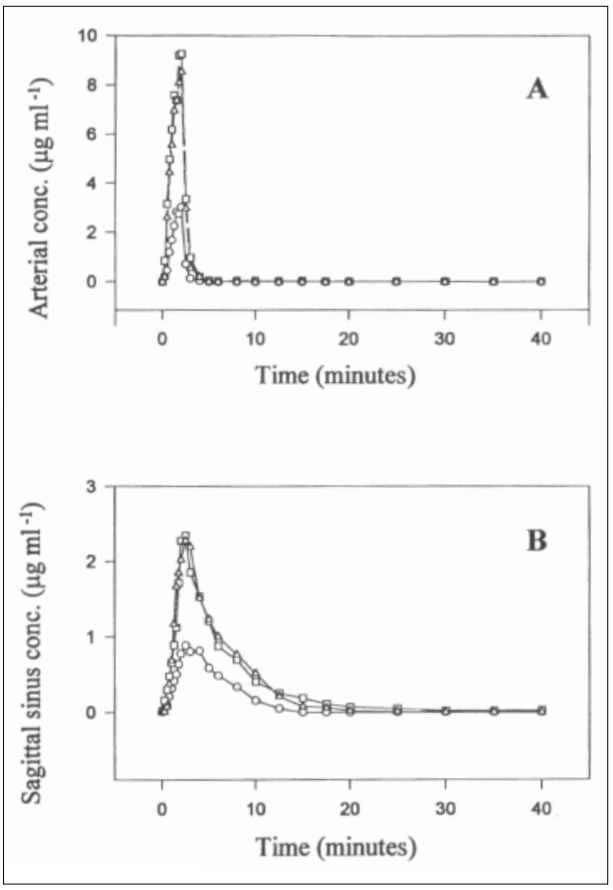

FIGURE 2: Arterial (A) and sagittal sinus (B) propofol concentrations normalized for dose following IV administration of 50 mg (circles), 100 mg (squares) and 200 mg (triangles).

relatively small peak sagittal sinus concentration after the 50 mg dose was secondary to relatively low arterial concentrations (Figure 3), and therefore that brain uptake of propofol was proportional to arterial concentrations.

The time-course of brain concentrations was similar to that in the sagittal sinus, with concentrations peaking at 0.97, 4.9 and 9.2 $\mu g.g^{-1}$ at 2.5 minutes, but with a slower decrease after administration was ceased (Figure 4). Scaling for peak arterial concentration (Figure 3) revealed similar peak brain concentrations for all doses but more rapid elution after the 50 mg dose.

Concentration-Effect Relationships

The effects of propofol on CBF and current threshold have previously been reported in detail[7]. In brief, it was shown that the propofol caused a transient dose-dependent decrease in CBF. Current threshold increased minimally after the 50 mg dose but transiently increased after the 100 mg dose to reach a maximum of 174% above baseline at five minutes. The 200 mg dose produced a greater and more prolonged increase, but the maximal effect could not be quantified because there was a period during which no withdrawal response was induced by the maximum current which could be safely delivered. Therefore, only data from the 100 mg doses was used for comparison with the simultaneously measured propofol concentrations.

Following the 100 mg dose there was significant anti-clockwise hysteresis in the relationship between both arterial and sagittal sinus concentrations and depth of anaesthesia ($P=0.033$ and $P=0.012$ respectively), but no significant hysteresis between brain concentrations and depth of anaesthesia ($P=0.37$; Figure 5). Depth of anaesthesia returned to baseline levels while there were still significant brain concentrations of propofol. Similarly, CBF changes were poorly related to arterial propofol concentrations with significant anti-clockwise hysteresis ($P=0.04$), but closely related to sagittal sinus and brain concentrations with no significant hysteresis ($P=0.94$, $P=0.66$ respectively; Figure 6).

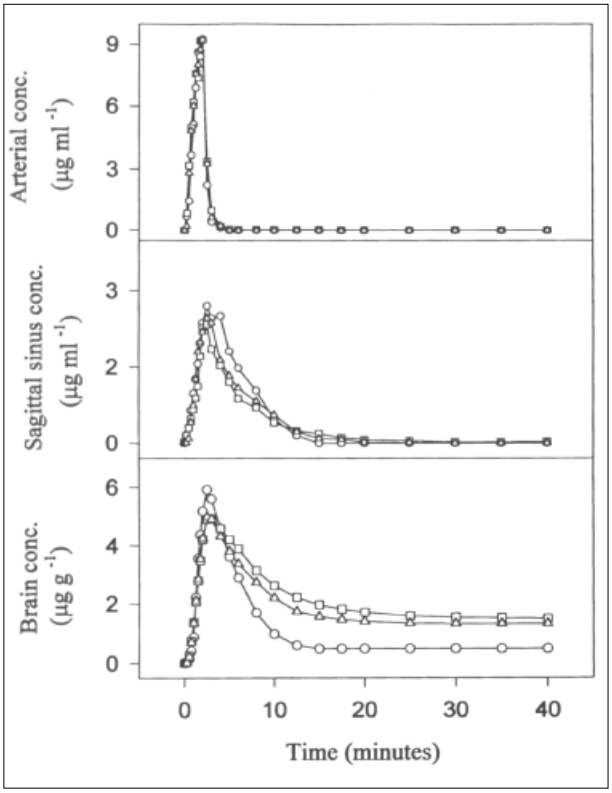

FIGURE 3: Arterial, sagittal sinus and brain propofol concentrations normalized for peak arterial concentrations following IV administration of 50 mg (circles), 100 mg (squares) and 200 mg (triangles).

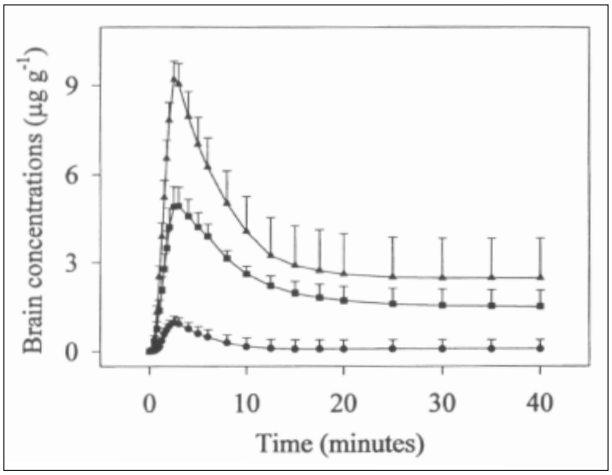

FIGURE 4: Brain drug concentrations, mean (SEM) following IV administration of 50 mg (circles), 100 mg (squares) and 200 mg (triangles).

DISCUSSION

Although examination of the systemic pharmacokinetics of propofol can readily be performed in man, the invasive techniques involved in measuring specific organ pharmacokinetics, particularly in the case of the brain, generally limit these studies to animal preparations. Chronic instrumentation of the sheep used in this study allows calculation of the time-course of drug concentrations in the brain with simultaneous measurement of drug effects following rapid administration, but without the influence of concomitant anaesthetic agents on both cerebral drug kinetics and dynamics. This has not previously been possible for anaesthetic drugs.

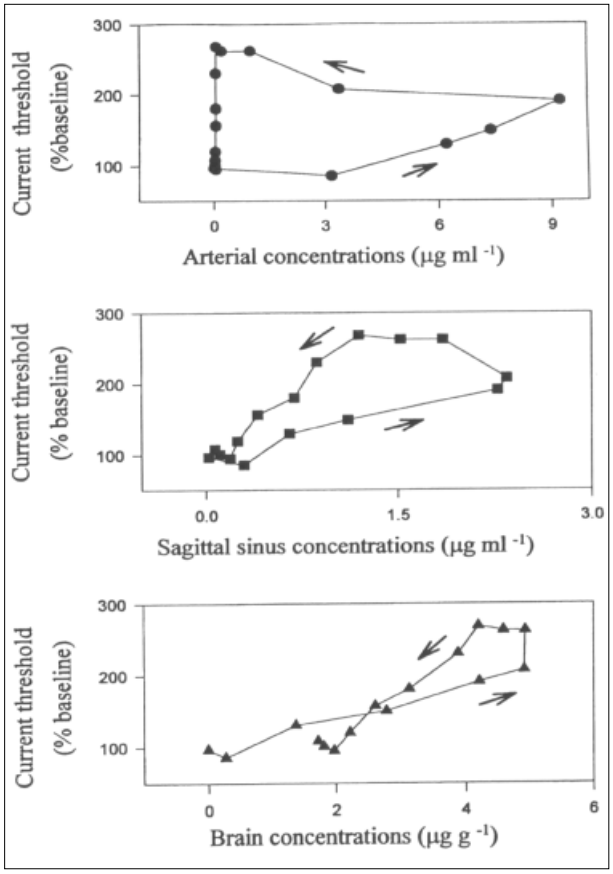

FIGURE 5: The relationship between mean arterial (circles), sagittal sinus (squares) and brain (triangles) propofol concentrations, and current threshold following IV administration of 100 mg over two minutes. There is no significant hysteresis between brain concentrations and current threshold.

Arterial Kinetics

If the propofol concentrations emerging from the lungs were linear with dose, the concentrations normalized for dose shown in Figure 2 should be superimposable, which is clearly not the case for the 50 mg dose. It is possible that lung extraction of propofol may account for the relatively small quantity of drug emerging from the lung after the 50 mg dose, If that were the case, the similar normalized arterial curves following the 100 mg and 200 mg doses would suggest that this process is non-linear and probably

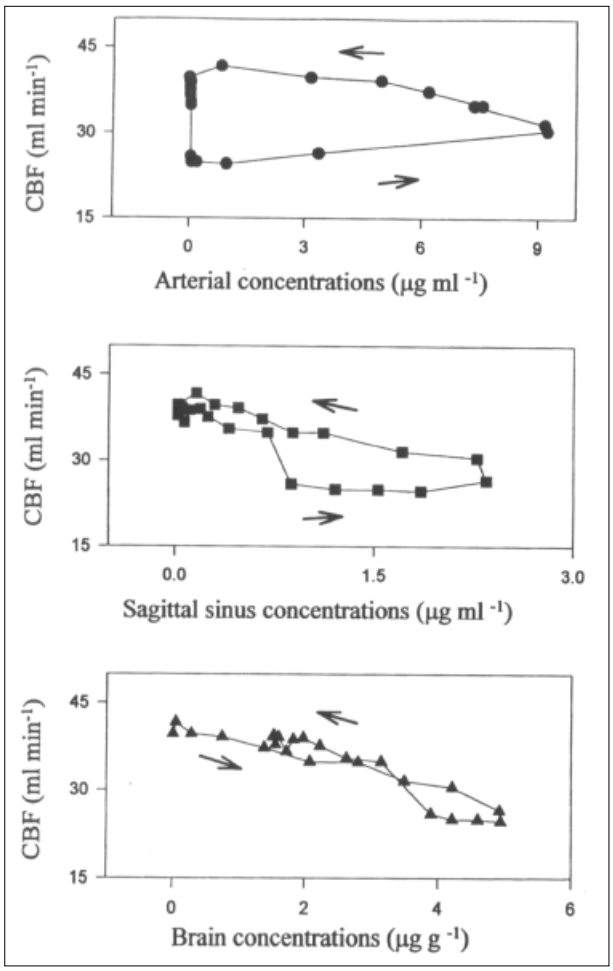

FIGURE 6: The relationship between mean arterial (circles), sagittal sinus (squares) and brain (triangles) propofol concentrations, and CBF following IV administration of 100 mg over two minutes. There is no significant hysteresis between brain or sagittal sinus concentrations and CBF.

saturable at clinically significant doses. Pulmonary extraction of propofol following rapid administration of subanaesthetic doses could therefore produce unexpectedly low brain concentrations, but is likely to be of little significance following doses used to induce anaesthesia. Large and saturable lung uptake of drugs is well described and thought to represent a process of simple diffusion of highly lipophilic drugs[15-17]. Substantial removal of propofol from the circulation by the lung has also been previously described[11,18], and because of the high lipid solubility of propofol, may represent a similar distribution process.

It is possible that propofol-induced changes in cardiac output could also influence the shape of the arterial concentration curve. The effect of changes in cardiac output on first-pass pulmonary arterial concentration curves entering the lung has previously been examined for tracers such as indocyanine green[19], with findings that pulmonary arterial peak heights were inversely related to cardiac output. Thus, it is possible that drug-induced cardiac depression might underlie the higher peak concentrations after the larger doses of propofol administered in this study. This is unlikely however, as the large increase in normalized peak concentrations after the 100 mg and 200 mg doses compared to the 50 mg dose (Figure 2), would require that increasing the dose of propofol from 50 mg to 100 mg induced approximately a threefold reduction in cardiac output, and that increasing the dose to 200 mg produced no further decrease in cardiac output. This does not fit the pattern of cardiovascular effects previously described for propofol or unpublished data from our laboratory, suggesting that cardiac output changes following all three doses are minimal when the drug is administered at these slow rates. Studies of the lung uptake and elution of this drug over a prolonged time period using pulmonary artery sampling and frequent measurement of cardiac output would be necessary to accurately examine the time-course of lung uptake and elution of propofol and also to determine whether lung metabolism of propofol contributes significantly to this process.

Cerebral Kinetics

The influence of variable brain input of propofol was removed by normalizing for the magnitude of the peak arterial concentrations. Fortunately this resulted in arterial curves which were essentially superimposable, so the concentration dependence of the cerebral kinetics could be examined and the similar-time courses of the normalized sagittal sinus and brain concentration curves revealed by this analysis confirms that brain uptake of propofol is fundamentally linear (Figure 3). There is, however, a relatively more rapid elution from the brain after the 50 mg doses and this may reflect propofol influencing its own distribution. Uptake and elution of highly lipid soluble drugs such as propofol into well perfused organs is frequently assumed to be predominantly flow-limited, and hence any changes in organ blood flow induced by a drug can potentially alter its own organ distribution. Such a phenomenon has been described in a regional pharmacokinetic study of the brain uptake of ketamine and midazolam[20]. The previously reported relatively small decrease in CBF induced by the 50 mg doses and the similar magnitude of CBF changes after the two higher doses[7] may thus explain the relatively rapid elution from the brain after drug administration was ceased following

the 50 mg doses and the similar but slower rate of elution after the 100 mg and 200 mg doses. This effect cannot readily be accounted for by conventional compartmental modelling techniques upon which propofol dose regimens have generally been based, but requires complex physiological modelling techniques. This type of analysis may also lead to better understanding of the influence of pathological changes in CBF on propofol dose requirements. There is an underlying assumption here that uptake and elution of lipid soluble drugs such as propofol is flow-limited and it is planned to test this in future studies using this sheep preparation.

Concentration-Effect Relationships

The hysteresis between arterial drug concentrations and cerebral effect is the classical picture associated with disequilibria due to organ drug uptake following rapid drug administration, and this is confirmed by the close relationship between the time-course of calculated brain propofol concentrations and effects on both CBF and depth of anaesthesia (Figures 5 and 6). This relationship suggests that propofol concentrations in the areas of brain from which effluent venous blood drains through the sagittal sinus are in pseudo-equilibrium with concentrations at the drug's sites of action, and that the rate of drug distribution into the brain rather than any drug receptor interaction explains the hysteresis between blood propofol concentrations and cerebral effects previously described[1].

From data previously published, baseline CBF was assumed to be 40 ml/min in all animals, but this would not alter the presence or absence of the observed hysteresis because errors in the magnitude of CBF would influence only the magnitude of calculated brain concentrations, but not the time-course[13]. As it is the time-course which is critical to the relationship between calculated concentrations and effects displayed in Figure 5, only changes in the slope, but not the shape, of the curve would be induced by variations in baseline CBF.

It is unlikely that changes in CBF distribution after propofol administration could influence the accuracy of brain concentration calculations by altering the area of brain from which blood drains to the sagittal sinus. It is clear that CBF changes follow cerebral metabolic rate, and regional measurement of cerebral metabolism has shown little regional variation[21].

Possible explanations for the return to baseline levels of current threshold while a significant quantity of propofol remained in the brain (Figure 5) include a lower limit of brain concentration before an effect is detectable or a change in drug-receptor interaction with time. The first phenomenon appears most likely, particularly as brain drug concentrations of approximately 1 $\mu g.g^{-1}$ following the 50 mg doses produced little change in current threshold from baseline. A change in drug-receptor interaction or "acute tolerance" is possible, but there was no evidence of development of tolerance in a recent study when propofol was repeatedly administered to rats[22]. Studies to examine this phenomenon by determining the relationship between current threshold and brain propofol concentrations during prolonged propofol administration are planned.

Although it is generally believed that the CBF changes seen following propofol and thiopentone administration are secondary to drug-induced decreases in cerebral metabolic rate, propofol-induced changes in cerebral perfusion pressure have complicated previous studies[23,24]. These decreases in CBF, however, have been shown to be independent of perfusion pressure when mean arterial pressure has been maintained with peripheral vasoconstricting agents[25]. In the current study, changes in mean arterial pressure were minimal after all doses of propofol, with a statistically insignificant decrease of 11 mmHg after the 100 mg dose being reported in the previous paper[7]. This small decrease, and the fact that cerebral autoregulation appears preserved after propofol administration[26,27], suggests that arterial pressure did not contribute to the observed CBF changes. The close relationship between the time-course of propofol concentrations in the brain and CBF changes demonstrated in the current study therefore supports the hypothesis that propofol-induced changes in CBF are a result of cerebral effects.

In summary, this study demonstrates that there are marked disequilibria between propofol concentrations in the blood and brain after rapid administration of this drug to sheep, and that the time-course of the effects of propofol on CBF and anaesthetic effect are closely related to the time-course of propofol concentrations in the brain but not the arterial blood. There is evidence that brain uptake and elution of propofol is a complex process and may be significantly affected by such factors as lung drug uptake and drug-induced CBF changes, confirming that dose regimens using conventional compartmental pharmacokinetic modelling based on the concentration of propofol in blood may fail to accurately predict propofol brain concentrations and anaesthetic effects following rapid administration. It may therefore be appropriate to consider the time-course and deter-

minants of brain concentrations of induction agents when devising dose regimens of short-acting intravenous induction agents.

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