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The Cerebral and Systemic Kinetics of Thiopentone and Propofol in Halothane Anaesthetized Sheep

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SUMMARY

The cerebral and systemic kinetics of intravenous thiopentone (250 mg over 2 minutes, n=5) and propofol (100 mg over 2 minutes, n=6) were determined in sheep anaesthetized with halothane (2.0%) and mechanically ventilated to an end-expired carbon dioxide tension of 40 mmHg. The sheep were previously instrumented with arterial and sagittal sinus (effluent from the brain) blood sampling catheters. Systemic kinetics were inferred from the time-course of the arterial blood concentrations, and cerebral kinetics from the time-course of the arterio-sagittal sinus concentration difference across the brain. Under halothane anaesthesia, the peak arterial concentrations of each drug occurred at the end of the two-minute infusion, and was 42.3 mg/l and 12.3 mg/l for thiopentone and propofol, respectively. Propofol had a significantly larger systemic clearance (3.19 l/min) than thiopentone (0.99 l/min). The brain concentrations of propofol equilibrated more slowly with the arterial concentrations than those of thiopentone. The extraction ratio across the brain near the end of the infusions (1.5 min) were 0.85 and 0.46 respectively. These data were also compared to analogous previously published data for initially conscious sheep. The systemic kinetics of thiopentone were little affected by halothane anaesthesia. For propofol, halothane anaesthesia was associated with a statistically significant reduction in clearance (50% of awake), a slower initial half-life (247% of awake), and the emergence of a second slower half-life in some sheep. The cerebral kinetics of both drugs were subtly altered by halothane anaesthesia.

Key Words: ANAESTHETICS INTRAVENOUS: thiopentone, propofol, pharmacokinetics, halothane; ANAESTHETIC GASES: halothane

There is a large body of evidence documenting the effect of general anaesthesia on drug disposition[1]. Major perturbations can include altered cardiac output and regional blood flows, and depression of the activity of drug-metabolizing enzymes. While pharmacokinetic studies of drugs ideally should be conducted in conscious individuals, more complex, invasive studies must be conducted in anaesthetized animal preparations. Furthermore, for those drugs commonly administered in the peri-operative period, it is desirable to have some understanding of their kinetics in both conscious and anaesthetized individuals.

We have previously reported a series of studies of the cerebral kinetics of thiopentone and propofol in halothane-anaesthetized sheep in which cerebral blood flow was altered by changing arterial carbon dioxide tension[2]. Cerebral kinetics were measured at low, normal and high states of cerebral blood flow, but only data for the low and high flow states were analysed. These were the most suitable data sets with which to discriminate between various models of the cerebral kinetics of these drugs. However, the previously unpublished measurements for the normal cerebral blood state in these studies are of interest for another reason, as the arterial carbon dioxide tension (40 mmHg) is directly comparable to that of conscious animals. With the exception of the presence of halothane anaesthesia, these were studies identical with respect to dose, duration of injection and blood sampling regimen to previously published studies of the cerebral kinetics of thiopentone[3] and propofol[4] in initially conscious sheep. In this paper we therefore report these new data measured under halothane anaesthesia, and compare them to previously published data for initially conscious sheep. The systemic kinetics of thiopentone and propofol in sheep will

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also be examined in more detail. These new data will contribute to an understanding of the mechanisms governing the systemic and cerebral kinetics of these agents, and their perturbation by halothane, and will also provide insight into whether halothane-anaesthetized experimental preparations can be used to study the cerebral kinetics of thiopentone and propofol.

MATERIALS AND METHODS

Animal preparation

The experimental conditions have been reported previously[2]. In summary, female Merino sheep of similar ages and body mass (approximately 50 kg) were used, and were instrumented under general anaesthesia. Catheters were chronically implanted in the carotid artery (for sampling of arterial blood), in the right atrium (for drug administration), and in the dorsal sagittal sinus (the appropriate site for sampling cerebral venous blood in sheep[5]). A Doppler transducer was placed over the sagittal sinus using a previously validated method to provide an index of cerebral blood flow[5]. The sheep were recovered from anaesthesia and housed in metabolic crates, with their catheters continuously flushed with heparinized saline. All experimental protocols were approved by the Animal Ethics Committee of the University of Adelaide.

Study Design

At a later date, the sheep were again anaesthetized (halothane, 2.0% inspired), intubated and mechanically ventilated. For the thiopentone studies, anaesthesia was induced with intravenous propofol (200 mg): for the propofol studies they were induced with intravenous thiopentone (1000 mg). Blood pressure was monitored throughout the anaesthetic and maintained near the baseline value with infusions of normal saline as necessary. After waiting at least 1.5 hours, which previous work has shown was sufficient for the induction agent to reach insignificant concentrations in blood[3,4], ventilation rate was adjusted to give an end expired carbon dioxide tension ($P_{ET}CO_2$ of 40 mmHg Model OIR 7101, Nihon Kohden Corporation, Tokyo, Japan). Once $P_{ET}CO_2$ had stabilized, either thiopentone (250 mg over 2 min) or propofol (100 mg over 2 min) were infused intravenously. Arterial blood (0.5 ml) was sampled at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12.5, 15, 17.5 and 20 minutes after the start of the infusion, Sagittal sinus samples (0.5 ml) were taken at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12.5, 15, 17.5 and 20 minutes. All times are hereafter referenced to the start of the two-minute infusions.

At the end of the study, the sheep were recovered from anaesthesia and returned to their metabolic crate. The study design was a "cohort" study, with thiopentone studied in five different sheep and propofol in six different sheep. One sheep was common to both the thiopentone and propofol studies.

Drug Analysis

All drug concentrations were determined as whole blood concentrations. Thiopentone samples were assayed using a method based on protein precipitation and separation using a high pressure liquid chromatograph with UV detection as previously described[3]. The limit of quantification was approximately 0.1 mg/l. Propofol samples were assayed using a previously described method[4] based on basic extraction and separation using a high pressure liquid chromatograph with fluorescence detection. The limit of quantification was approximately 0.02 mg/l. For each drug, standard curves were prepared with concentrations that spanned the expected concentration range in drug-free blood taken prior to drug administration. The level of precision of both assays was such that the r^2 value for linear regression of the standard curve was more than 0.995 in all cases.

Data Analysis

Systemic kinetics

Systemic kinetics were inferred from the time-course of the arterial drug concentrations. These were described in terms of

1. the peak concentration achieved,
2. the area under the concentration time curve (AUC) determined by trapezoidal integration with extrapolation to infinity of the terminal exponential phase,
3. systemic clearance as given by AUC over total dose.

The post infusion decline in concentrations were also fitted to single exponential or bi-exponential equations using the "Scientist for Windows" modelling program (Micromath Scientific Software, Utah, U.S.A.). The rate constants of these exponentials were expressed as half-lives. Fitting a single exponential equation to the data produced one half-life term, while a bi-exponential produced two (fast and slow) half-life terms.

The equivalent analysis was also performed on previously published arterial concentration data for the same dose of thiopentone[3] and propofol[4] in initially conscious sheep.

Cerebral kinetics

The uptake and elution of the drugs in the brain were described in a model independent manner by calculating the extraction ratio (E) of each drug across the brain at times representative of the intra-infusion period (1.5 min) and the immediate post-infusion period (3 min). The following formula was used, where C_{art} and C_{sag} were the arterial and sagittal sinus drug concentrations, respectively, at the desired time point.

$$E = 1 - \frac{C_{sag}}{C_{art}} \quad \ldots (1)$$

Cerebral kinetics were also examined using hybrid modelling, which describes cerebral kinetics independently of any influence of the time-course of the arterial concentrations entering the brain. The details of this method have been described previously[2]. The arterial concentrations entering the organ were fitted to empirical forcing functions that closely matched the observed data. These were used as input functions for the model of cerebral kinetics—the parameter values for the model were then estimated by curve-fitting the sagittal sinus concentrations in blood emerging from the brain. Two models of cerebral kinetics were examined—a membrane limited model, and a single flow-limited compartment model (Figure 1). As the true value of cerebral blood flow was not known (the method used only measures relative changes in flow within an animal), cerebral blood flow was incorporated as an unknown term into the parameters of the models (Figure 1).

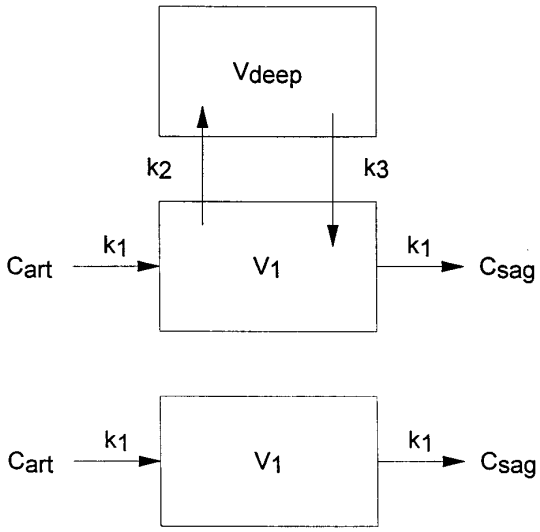

FIGURE 1: Schematic representations of the models of cerebral kinetics fitted to the data. Upper: Membrane limited model. The model has 2 compartments—a "vascular compartment" into which drug is delivered via arterial blood (C_{art}) and leaves via sagittal sinus blood (C_{sag}), as governed by the rate constant k_1 (min^{-1}). Drug can also enter and leave a deeper compartment via rate constants k_2 and k_3, respectively (also min^{-1}). These three rate constants were the fitted parameters. They can also be defined in terms of cerebral blood flow (Q), and volumes of the two compartment (V_c and V_{deep}, respectively): $k_1=Q/V_c$; $k_2=PS/V_c$; $k_3=PS/V_{deep}$, where PS is the permeability term (l/min) for the membrane barrier. Lower: Single-flow limited compartment model. This is analogous to the above model without the deep compartment.

Statistical Analysis

The general method used for statistical analysis was based on the calculation of the appropriate mean value and its upper and lower 95% confidence intervals assuming a t-distribution[6]. T-tests were also used to compare kinetic parameters between the awake and halothane anaesthetized states.

RESULTS

The mean $P_{ET}CO_2$ at the start of the propofol infusions in halothane anaesthetized sheep was 41.5 (SD 10.6) mmHg, which was comparable to the measured peak arterial partial pressure in the initially conscious sheep of 41 mmHg[7].

The arterial and sagittal sinus (effluent from the brain) blood concentrations measured under halothane anaesthesia are shown in Figure 2—both drugs reached their peak arterial concentration at the end of the two minutes infusion.

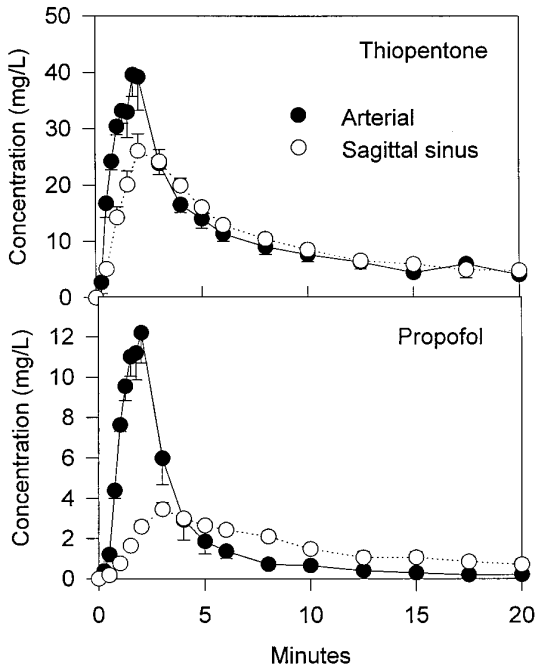

FIGURE 2: The mean arterial and sagittal sinus concentrations of thiopentone (upper panel) and propofol (lower panel) observed when doses of 250 or 100 mg, respectively, were infused intravenously over 2 min to halothane anaesthetized sheep. Data are shown as mean and standard error.

Systemic kinetics

The parameters describing the arterial concentrations under halothane anaesthesia are summarized in Table 1. Thiopentone showed a bi-exponential decline in concentration after the infusion. While three of six propofol studies showed a bi-exponential decline, the remainder showed a rapid mono-exponential decline. Propofol had a significantly larger systemic clearance than thiopentone.

TABLE 1

Summary of systemic kinetic parameters

Thiopentone	Halothane (n=5)	Awake (n=6)
Peak Conc (mg/l)	42.3 (30.1-54.5)	40.8 (29.4-52.2)
AUC (mg/l/min)	278 (142-412)	317 (205-428)
CI (l/min)	0.99 (0.62-1.37)	0.87 (0.56-1.18)
Fast $t_{1/2}$ (min)	0.97 (0.14-1.80)	0.43 (0.33-0.53)
Slow $t_{1/2}$ (min)	9.3 (5.9-12.8)	8.8 (6.6-11.1)
Propofol	**Halothane (n=6)**	**Awake (n=5)**
Peak Conc (mg/l)	12.3 (8.5-16.1)	9.5 (6.4-12.6)
AUC (mg/l/min)	35.0* (21.2-48.7)	16.6 (11.3-21.8)
CI (l/min)	3.19* (1.99-4.39)	6.36 (4.38-8.33)
Fast $t_{1/2}$ (min)	0.84* (0.49-1.19)	0.34 (0.26-0.42)
Slow $t_{1/2}$ (min)	3.6, 7.0, 5.8	na

Data are given as mean and 95% confidence intervals.
*Significantly different from awake, by t-test.

For comparison, the analogous data for the previously published conscious studies are also shown in Table 1. There were no statistically significant differences in the systemic kinetics of thiopentone between halothane anaesthetized and initially conscious sheep. For propofol, halothane anaesthesia was associated with a statistically significant reduction in clearance (50% of awake), a slower initial half-life (247% of awake), and the emergence of a second half-life in some sheep that was not present in the initially conscious group.

Cerebral kinetics

The intra-infusion and post-infusion extraction ratios of thiopentone and propofol across the brain under halothane anaesthesia are shown in Table 2. Both drugs were characterised by uptake into the brain during the infusion (positive extraction ratio). In keeping with previous observations, the brain concentrations of propofol equilibrated more slowly with the arterial concentrations than those of thiopentone, with the extraction ratio for propofol being almost twice that of thiopentone. For both drugs, uptake turned to elution within 1 to 2 minutes after the end of the infusion period (negative extraction ratio).

TABLE 2

Intra-infusion (1.5 min) and post-infusion (3 min) extraction ratios of thiopentone and propofol across the brain

Thiopentone	Halothane (n=5)	Awake (n=6)
1.5 min	0.46 (0.08)	0.45 (0.07)
3 min	–0.01* (0.06)	–0.20 (0.13)
Propofol	**Halothane (n=6)**	**Awake (n=5)**
1.5 min	0.85 (0.05)	0.84 (0.12)
3 min	0.42* (0.15)	–0.83 (0.38)

Data are given as mean and standard deviation.
*Significantly different from awake, by t-test.

The analogous extraction ratio data for the previously published studies in initially conscious sheep are also shown in Table 2. There were no differences in extraction between the two groups during the infusion, but halothane anaesthesia was associated with a significantly less elution (i.e., more positive extraction ratio) in the immediate post-infusion period.

Such differences in the model independent analysis of cerebral uptake, while relatively subtle, were reflected in the hybrid modelling of cerebral kinetics (Table 3). Under halothane anaesthesia, both the thiopentone and propofol data were fitted better by the membrane-limited model. The awake thiopentone data was better described by the single flow-limited compartment model. Therefore, for thiopentone, halothane anaesthesia was associated with an increase in turnover in the deep compartment, such that it collapsed to single compartment. In contrast, while the awake propofol data was better described by a membrane-limited model, the confidence intervals of the parameters of the membrane-limited models were significantly different between the awake and halothane anaesthetized groups. Halothane anaesthesia was associated with a smaller deep distribution volume (k_3/k_2=1.1 vs 1.35) and more rapid turnover in the deep compartment ($1/k_3$ =1.51 vs 8.2 min).

TABLE 3
Parameter values for cerebral kinetic models

Parameter and model	Thiopentone Halothane	Thiopentone Awake	Propofol Halothane	Propofol Awake
Membrane-limited				
MSC	**4.50**	2.97	**4.24**	**3.22**
k_1	2.01 (1.20-2.82)	1.12 (0.925-1.31)	0.334 (0.251-0.418)	0.24 (0.212-0.269)
k_2	1.31 (–0.010-2.64)	na	0.731 (0.115-1.35)	0.165 (0.063-0.267)
k_3	0.804 (0.338-1.76)	na	0.66 (0.31-1.01)	0.122 (–0.016-0.260)
Flow-limited				
MSC	2.83	**3.24**	2.24	2.23
k_1	1.07 (0.81-1.27)	1.11 (0.937-1.29)	0.181 (0.154-0.208)	0.197 (0.172-0.222)

The MSC is the Model Selection Criterion of the modelling package used (Scientist for Windows). It is an adaption of the Akaike Information Criterion, but in this case the higher value indicates a better fit. The MSC of the best model of the two examined is shown in bold. The parameters of the models (k_1, k_2 and k_3) are as defined in Figure 1. Data are given as best fit estimate of the parameter with its 95% confidence intervals returned by the curve-fitting program.

DISCUSSION

This study reports the systemic and cerebral kinetics of thiopentone and propofol under halothane anaesthesia, and an opportunistic comparison with conscious data. Limitations of the experimental design therefore include the fact that it was not a random cross-over study. However, previous experience has shown that the kinetics of drugs in sheep are relatively reproducible[3,4]. Furthermore they represent a relatively homogeneous study population as they were from the same flock and were of similar age and weight. In addition, the experimental design was not ideal for elucidating the mechanisms of the interaction of halothane with thiopentone or propofol, as the relative changes in key determinants of kinetics such as cardiac output and cerebral blood flow were not measured. Nevertheless, these data are valuable in that they document the magnitude of the interaction, and together with published literature, can be used to make some inferences about the mechanisms governing the effect of halothane on the kinetics of intravenous anaesthetics.

The systemic kinetics of thiopentone were little affected by halothane, while those of propofol were characterized by higher peak concentrations, a larger AUC and lower total clearance. Recent work has provided some insight into the determinants of the peak arterial concentrations achieved after an intravenous bolus or short infusion administration of a drug[9]. For drugs with a relatively high clearance, the first pass concentrations contribute significantly to the observed arterial concentrations—these in turn are a function of first-pass dilution with cardiac output and the kinetics of the drug in the lungs. A low cardiac output will produce higher peak concentrations—this has been shown experimentally for propofol[9], and via modelling analysis for thiopentone[10,11] and propofol[12]. Although cardiac output was not measured in the present study, the effect of halothane anaesthesia on cardiac output is well defined. In sheep, 1.5% halothane (albeit in the presence of other drugs) lowered cardiac output to 71% of control at 30 min after induction[13]. Higher concentrations of halothane markedly reduced cardiac output[14]. However, as the duration of anaesthesia increases there is a tendency for cardiac output to return to control values[13]. In the present study, measurements were made at least 1.5 h after the start of halothane anaesthesia. This, and the fact that the systemic kinetics of thiopentone were unchanged compared to awake, suggest that cardiac output was unaltered between the awake and halothane anaesthetized group at the time of the drug infusion. This being the case, a mechanism other than lowered cardiac output would need to be invoked to explain the higher peak propofol concentrations observed under halothane anaesthesia. It has previously been reported that propofol was extracted across the lungs of initially conscious sheep in a non-linear manner (i.e., the extraction was reduced or abolished at higher propofol concentrations[15]), and that propofol has a high first pass lung clearance in sheep[16]. The observed changes in systemic kinetics of propofol under halothane anaesthesia (higher peak concentrations, higher AUC and lower clearance) are consistent with this lung extraction being reduced or abolished. Reductions in hepatic clearance, although often associated with halothane anaesthesia, are known to have only a minor impact on the initial concentrations of these drugs after short infusion administration[12].

The cerebral kinetics of both drugs under halothane anaesthesia differed subtly from those measured in initially conscious sheep. This was apparent for the model-independent analysis, which showed that halothane affects the elution of thiopentone and propofol in the brain more than their uptake. However, extraction ratio is a relatively crude measure of organ kinetics, as its magnitude depends on the time-course of the arterial drug concentrations entering the organ. Thus, it is possible to have

changes in extraction even when organ kinetics have not changed, if there are differences in the systemic kinetics of the drug. This was overcome by hybrid modelling of the cerebral kinetics, which describes cerebral kinetics independently of any influence of the time-course of the arterial concentrations entering the brain. This confirmed that there were direct changes in the cerebral kinetics of thiopentone and propofol under halothane anaesthesia.

On first principles, these changes could be due to either altered cerebral blood flow or altered cerebral distribution volumes under anaesthesia. The influence of cerebral blood flow changes on the cerebral kinetics of thiopentone and propofol have been examined previously[2]. Although their rate of uptake into the brain was consistent with slight membrane limitation, the rate of equilibration of cerebral drug concentrations with those in arterial blood was found to increase with increased blood flow. Unfortunately, comparative data on absolute cerebral blood flow in conscious and halothane-anaesthetized sheep are not available—the flow method used in the present study measures relative blood flow within an animal. However, when carbon dioxide tension is controlled for (as in the present study) it has been found that halothane anaesthesia increases cerebral blood flow to approximately 150% of control values[17,18]. It is also known that in contrast to isoflurane, halothane produces relatively homogeneous changes in cerebral blood flow throughout regions of the brain[19].

If cerebral blood flow was increased under halothane anaesthesia to 150% of baseline in the present study, this should be reflected in the k_1 rate constant of the membrane-limited model. This was in fact the case—k_1 increased under halothane anaesthesia to 179% and 139% of awake values (Table 1) for thiopentone and propofol, respectively. Thus, it seems plausible that some of the changes in cerebral kinetics can be explained by the altered cerebral blood flow under halothane anaesthesia. However, it is evident from the inconsistent changes in the other parameters (k_2, k_3) that the effect of halothane anaesthesia is complex. These changes in cerebral kinetics will not be fully understood until the physical nature or mechanism of the apparent membrane limitation in the cerebral kinetics of thiopentone and propofol is better understood. In the interim, it should be concluded that the differences in the cerebral kinetics of thiopentone and propofol between the initially conscious and halothane-anaesthetized states are sufficiently large that one cannot be inferred from the other. The possible interaction between the lung kinetics of propofol and halothane also requires further investigation as a mechanism for why the systemic kinetics of propofol but not thiopentone were affected by halothane anaesthesia.

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