

The Effect of Altered Cerebral Blood Flow on the Cerebral Kinetics of Thiopental and Propofol in Sheep

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Background: **Thiopental and propofol are highly lipid-soluble, and their entry into the brain often is assumed to be limited by cerebral blood flow rather than by a diffusion barrier. However, there is little direct experimental evidence for this assumption.**

Methods: **The cerebral kinetics of thiopental and propofol were examined over a range of cerebral blood flows using five and six chronically instrumented sheep, respectively. Using anesthesia (2.0% halothane), three steady state levels of cerebral blood flow (low, medium, and high) were achieved in random order by altering arterial carbon dioxide tension. For each flow state, 250 mg thiopental or 100 mg propofol was infused intravenously over 2 min. To quantify cerebral kinetics, arterial and sagittal sinus blood was sampled rapidly for 20 min from the start of the infusion, and 1.5 h was allowed between consecutive infusions. Various models of cerebral kinetics were examined for their ability to account for the data.**

Results: **The mean baseline cerebral blood flows for the "high" flow state were over threefold greater than those for the low. For the high-flow state the normalized arteriovenous concentration difference across the brain was smaller than for the low-flow state, for both drugs. The data were better described by a model with partial membrane limitation than those with only flow limitation or dispersion.**

Conclusions: **The cerebral kinetics of thiopental and propofol after bolus injection were dependent on cerebral blood flow, despite partial diffusion limitation. Higher flows produce higher peak cerebral concentrations. (Key words: flow-limited; membrane-limited; pharmacokinetics; intravenous anesthetic.)**

INTRAVENOUS anesthetics such as thiopental or propofol are characterized by a rapid rate of onset of central nervous system effects after intravenous bolus administration; this is consistent with the widely held notion that they are sufficiently lipophilic to diffuse rapidly into the brain. If the diffusion rate of an intravenous anesthetic in the brain greatly exceeds its rate of delivery to the brain by cerebral blood flow, the cerebral uptake of the anesthetic can be limited by cerebral blood flow. The brain can be thought of as a single distribution volume for the anesthetic, and higher cerebral blood flows are associated with more rapid uptake into the brain. This manifests as higher peak brain concentrations after bolus administration.

The extent to which the kinetics of intravenous anesthetics in the brain are limited by cerebral blood flow is important in physiologic pharmacokinetic models (which have been developed for thiopental (propofol has not been studied as extensively in this manner). Although a number of investigators have assumed flow-limited kinetics and represented the brain as a single flow-limited compartment,[1–3] others have found that the cerebral kinetics of thiopental are characterized by a diffusion barrier[4,5] and have invoked more complicated "membrane-limited" models of cerebral kinetics. For a series of barbiturates including thiopental, the permeability of the diffusion barrier decreases as their lipophilicity decreased.[6] If the permeability across the diffusion barrier is low, then higher cerebral blood flows are not associated with more rapid uptake into the brain. Peak brain concentrations after bolus administration are independent of cerebral blood flow. However, intermediate values for the permeability of the diffusion barrier can produce cerebral kinetics with elements of both flow- and membrane limitation.

An understanding of how cerebral blood flow influences the cerebral kinetics of these intravenous anesthetics may have clinical implications. Variations in cerebral blood flow caused by hyper- or hypoventilation, disease states, the coadministration of other drugs, blood pressures outside the autoregulated range, or neurogenic influences may account for some of the variability in the induction doses of intravenous anesthetics observed in patients. Furthermore, both thiopental and propofol reduce cerebral blood flow and may influence their own cerebral kinetics in a manner that could prolong washout from the brain after high doses. Finally, selective targeting of intravenous anesthetics into the brain by raising cerebral blood flow before induction (for example by coadministration of another drug) must be considered a theoretic possibility.

A criticism of earlier studies of the cerebral kinetics of thiopental[1–4] and propofol[7] is that kinetics were determined at only one value of cerebral blood flow. The most convincing evidence of flow-limited kinetics is from experiments in which cerebral kinetics are studied over a

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range of cerebral blood flows. We examined the cerebral kinetics of thiopental and propofol at both low and high states of cerebral blood flow achieved by altering ventilation rate in anesthetized, instrumented sheep. The study had two aims: first, to examine the extent to which the cerebral kinetics of thiopental and propofol are influenced by changes in cerebral blood flow; and second, to use the data to determine the optimal model of the cerebral kinetics of these agents—this would allow further refinement of, and increased confidence in, kinetic–dynamic models of the induction process.[8,9] The hypothesis to be examined is that these lipophilic agents rapidly diffuse into the brain, and their cerebral kinetics are therefore predominantly flow-limited and can be modeled as a single flow-limited compartment.

Methods

Animal Preparation

All experimental protocols were approved by the Animal Ethics Committee of the University of Adelaide. Female Merino sheep of similar ages and body masses (approximately 50 kg) were instrumented during general anesthesia as described previously.[7] In summary, catheters were implanted chronically 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.[10]). A Doppler transducer was placed over the sagittal sinus using a previously validated method to provide an index of cerebral blood flow.[10,11] The sheep were recovered from anesthesia and housed in metabolic crates, with their catheters continuously flushed with heparinized saline.

Study Design

At a later date, the sheep again were anesthetized (2.0% inspired halothane), intubated, and mechanically ventilated. Anesthesia was induced for the thiopental studies with 200 mg intravenous propofol, and for the propofol studies with 1,000 mg intravenous thiopental. Blood pressure was monitored throughout the duration of the anesthetic and maintained near the baseline value with infusions of normal saline as necessary. The index of cerebral blood flow was monitored continuously using the Doppler transducer and displayed in real time on the screen of a data-acquisition system. After 1.5 h for the induction agent to reach undetectable levels, three steady-state levels of cerebral blood flow (nominally low, medium, and high) were achieved consecutively and in random order by altering arterial carbon dioxide tension. The low state was achieved by hyperventilating the animal to an end-expiratory partial pressure of carbon dioxide (P_{CO_2}) of approximately 25 mmHg (capnograph model OIR 7101, Nihon Kohden, Tokyo, Japan). The high state was achieved by hypoventilating the animal until P_{CO_2} was greater than 70 mmHg. The medium state was achieved by selecting a ventilation rate that gave a P_{CO_2} of approximately 40 mmHg.

Once the end expired P_{CO_2} and new cerebral blood flow for each flow state had stabilized (approximately 5–10 min), either thiopental (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 min 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 min. Sufficient time (1.5 h) was allowed between the drug infusions at each cerebral blood flow state for the previous dose to reach undetectable levels in blood entering and leaving the brain.

At the end of the study, the sheep were recovered from anesthesia and returned to their metabolic crates. Thiopental was studied in five different sheep, propofol in six. One sheep was common to both the thiopental and propofol studies.

Drug Analysis

All drug concentrations were determined as whole blood concentrations. Thiopental samples were assayed using a method based on protein precipitation and separation using high-pressure liquid chromatography with ultraviolet detection as previously described.[3] The limit of quantification was approximately 0.1 mg/l. Propofol samples were assayed using a previously described method[7] based on basic extraction and separation using high-pressure liquid chromatography 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 before drug administration. An assay was rejected if the R^2 value for linear regression of the standard curve was less than 0.995.

Data Analysis

Cerebral Blood Flow Changes. The method used to measure cerebral blood flow gives an accurate account of relative changes in cerebral blood flow.[10] For each sheep, the Doppler output for each flow state was expressed as a percentage of the reading obtained in the baseline period of the "medium" flow state. To simplify the units of the parameters of the models, and to facilitate comparison of parameter values with previously published models, the baseline flow for this medium-flow state was normalized to 40 ml/min. However, discrimination between models necessitated only relative flow changes. This absolute flow agrees with measure-

ments made using the Kety-Schmidt nitrous oxide method in sheep.[11]

Model-independent Analysis. The differences in the uptake and washout of the drugs in the brain were examined in a model-independent manner by plotting the time courses of the mean arterial–sagittal sinus concentration difference for each flow state. The arteriovenous difference across an organ is the flux of drug into (or out of) the organ per unit blood flow.[12] However, the magnitude of this flux depends on the magnitude of the concentrations; the flux therefore was divided by the weighted mean arterial concentration for each study. This was calculated from the arterial area under the curve determined using the trapezoidal rule divided by the total duration of the study. This analysis allowed a comparison of the relative arteriovenous difference between the high- and low-flow states, and between the intra- and postinfusion periods. Although plotting the time course of extraction ratio across the brain would provide similar information, such plots are distorted by the large differences in the maximum possible extraction ratio in the intra- and postinfusion periods, which tend to $+1$ and $-\infty$, respectively.

General Modeling Methods. The ability of a range of cerebral kinetic models to account for the observed changes in kinetics if cerebral flow is altered was examined both for thiopental and propofol. The models were constructed using the Scientist for Windows software package (Micromath Scientific Software, Salt Lake City, UT) on a personal computer, and analysis was performed on the pooled data after initial inspection showed narrow 95% confidence intervals for the raw data (*i.e.*, the time courses of the mean concentrations were estimated with good precision).

A hybrid modeling method was used, which is discussed in more detail in previous work[8,13] and in the appendix, which can be found on the Web Enhancement. In brief, the cerebral kinetics were examined separately from kinetics in the remainder of the body by considering only the input to the brain (arterial drug concentration [C_{art}] and cerebral blood flow [Q_b]) and the output from the brain (sagittal sinus drug concentrations [C_{sag}]). The inputs to the models (C_{art}, Q_b) were fitted to empiric forcing functions (based on sums of exponentials or polynomials), and the parameters of the cerebral kinetic model (e.g., apparent volume of distribution in the brain) were estimated by curve-fitting the output (C_{sag}).

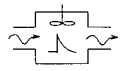
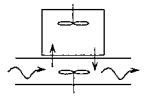
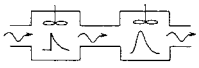
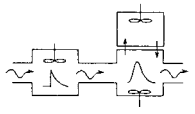
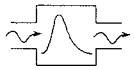
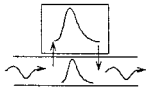
For the least-squares curve-fitting, the best model was defined as that with the highest model selection criterion (MSC) and with identifiable parameters. The MSC is essentially an inverse Akaike information criterion scaled to compensate for data sets of different magnitudes (according to the Scientist for Windows manual, Micromath Scientific Software, Salt Lake City, UT) and is calculated as follows if p is the number of parameters and n is the number of data points:

$$MSC = \ln\left(\frac{\sum_{i=1}^{n}(Y_{obs_i} - \overline{Y}_{obs})^2}{\sum_{i=1}^{n}(Y_{obs_i} - Y_{cal_i})^2}\right) - \frac{2p}{n} \quad \ldots \quad (1)$$

No weighting was used. A parameter was defined arbitrarily as nonidentifiable if the SD of the parameter returned by the fitting program was greater than the parameter estimate (*i.e.*, the coefficient of variation was greater than 100%). A model with nonidentifiable parameters is "underdetermined" for a given data set—that is, the data do not contain sufficient information to estimate the parameter with precision.

Several types of models were examined (table 1). A single-compartment flow-limited model[2,3] and a two-compartment membrane-limited model[4,6] were tested because these have been used previously in physiologic models of thiopental kinetics. A two-compartment "tanks in series" model[14,15] was tested because this type of

Table 1. Schematic summary of models

Single flow-limited compartment model. Defined only by cerebral blood flow (Q_b) and a single distribution volume (V_b)	
Traditional membrane-limited model. Adds a deeper distribution volume (V_{deep}) to the above model. Drug entry into this volume is defined by the permeability term (PS_{deep}).	
2 tanks in series model. Two flow-limited compartment models in series to add an element of dispersion.	
Compilation model. Adds a deeper distribution volume to the second compartment of a 2 tanks in series model.	
Single compartment dispersion model. Drug transit times through the compartment are represented as a Gaussian distribution.	
Two compartment dispersion model. As above but also incorporates statistical terms for drug transport into a deep tissue pool.	

model provides a simple method for accounting for dispersion of drug in transit through the brain.[16] A recently developed "compilation" model having elements of both dispersion and membrane limitation[16] also was tested. These models were solved in the time domain. Finally, more complex one- and two-compartment dispersion models[15,17–19] were tested. These models can account for dispersion arising from factors such as the spread of intravascular transit times through an organ. The dispersion models were written and solved in the Laplace domain, which greatly simplifies the solution of the fundamental equations underlying these types of models.[20] To reduce computational time, time-dependent changes in cerebral blood flow from baseline values were not accounted for when using models in the Laplace domain—the mean value for the flow state was used. We previously examined the implications of making this assumption for alfentanil and meperidine in the brain.[21] The goodness of the fit of cerebral kinetic models was unchanged, but parameters values were altered by approximately 15%. To account for this error, the membrane-limited model was solved in both the Laplace and time domains. This provided a common reference model between the two domains and the two methods of accounting for cerebral blood flow changes. The equations of the models are summarized in the appendix, which can be found on the Web Enhancement.

Simultaneous Modeling of High- and Low-flow States. To test each type of model for its overall ability to account for the data given the changes in cerebral blood flow, the model was fitted simultaneously to the data for the high- and low-flow states. Two cerebral kinetic models of the each type were coded in the modeling environment with the appropriate forcing functions describing the arterial and cerebral blood flow data for both the high- and low-flow states. However, the two models were coded with common parameters, and these then were estimated by simultaneous fitting of the respective sagittal sinus data for the high- and low-flow states (Web Enhancement appendix).

Separate Modeling of High and Low Flow States. The sagittal sinus data for the high- and low-flow states also were fitted separately to the flow-limited and membrane-limited models to test their ability to describe the data measured only at each cerebral blood flow state.

Simulations. To provide insight into the clinical implications of altered cerebral blood flow on the induction of anesthesia, the most appropriate models of cerebral kinetics for thiopental and propofol were incorporated into previously published models of the induction of anesthesia in sheep.[8,9] These models then were used to simulate the time course of the cerebral concentrations of thiopental and propofol (bolus dose over 10 s) for a range of cerebral blood flows from 10 to 80 ml/min (normal value 40 ml/min in sheep). All other parameters of the models were kept constant. The peak cerebral concentration and the time in which it was achieved were recorded.

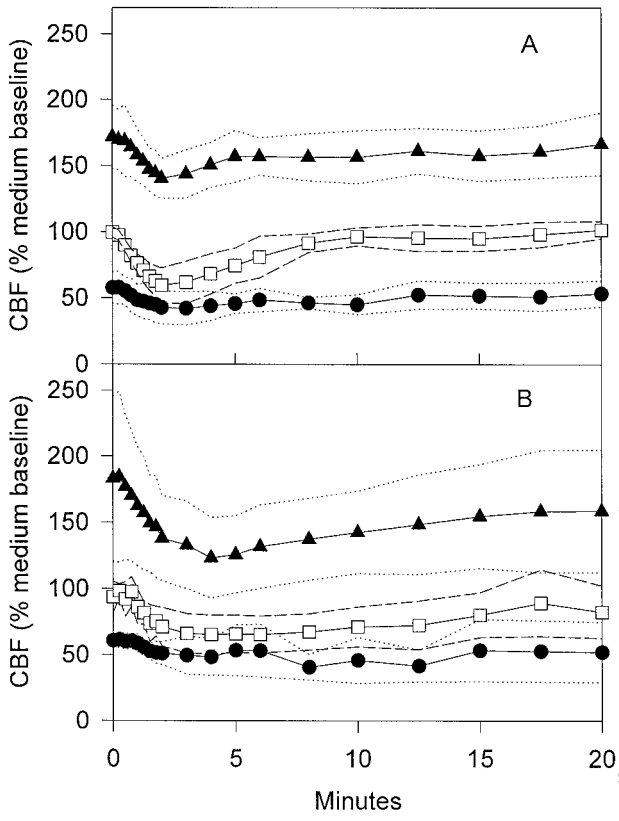


Fig. 1. The cerebral blood flow readings (mean and 95% confidence limits) expressed as percentages of the baseline readings for the medium flow state for thiopental (*A*) and propofol (*B*). In each case, the high-flow state is indicated by the filled triangles, the medium by the open squares, and the low by the filled circles.

Statistical Analysis

Statistical analysis was performed using a spreadsheet program (Excel 4.0, Microsoft Corporation, Redmond, WA). The general method used was based on the calculation the appropriate mean value and its upper and lower 95% confidence intervals, assuming a t distribution.[22,23] Comparing the data sets, values that lay outside the 95% confidence intervals of the mean were considered significantly different from the mean.

Results

Cerebral Blood Flow Changes

Altering the ventilation rate produced three statistically different levels of baseline cerebral blood flow without overlapping confidence intervals (fig. 1). Because of the additional effects of thiopental or propofol on cerebral blood flow there were transient reductions in flow from each baseline level. For both drugs, the values for the medium-flow state were felt to be too similar to those of the low-flow state to warrant analysis

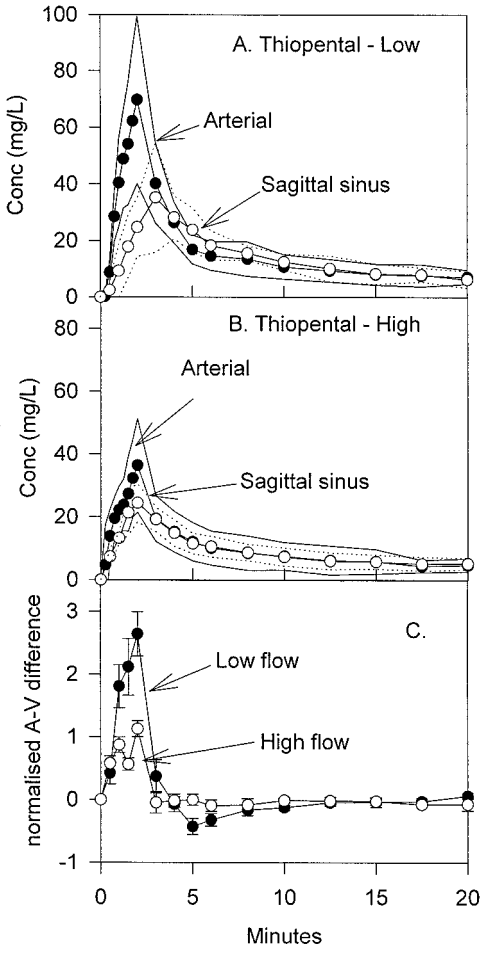


Fig. 2. The arterial and sagittal sinus concentrations (mean and 95% confidence limits) observed for the low-flow (*A*) and high-flow (*B*) states for thiopental. The time course of the normalized arteriovenous difference for each states is shown for comparison on the same graph (*C*); data are shown as the mean and SEM for clarity.

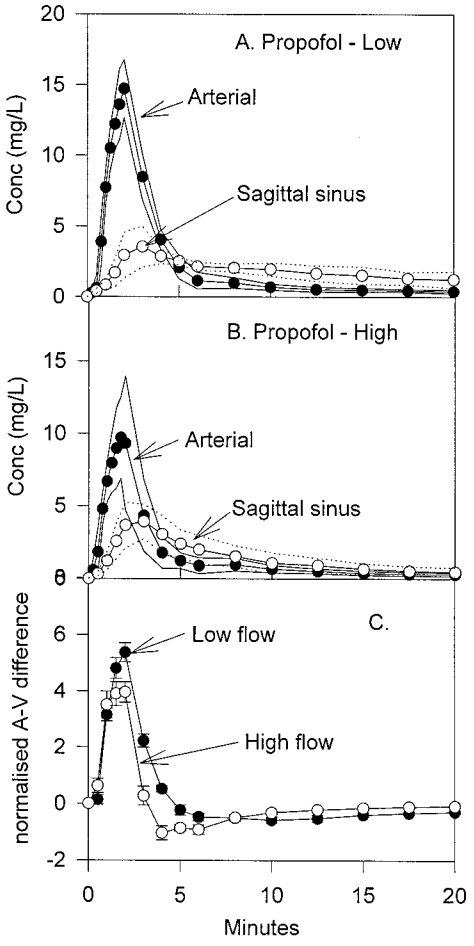


Fig. 3. The arterial and sagittal sinus concentrations (mean and 95% confidence limits) observed for the low-flow (*A*) and high-flow (*B*) states for propofol. The time course of the normalized arteriovenous difference for both states is shown for comparison on the same graph (*C*); data are shown as the mean and SEM for clarity.

of concurrent kinetics. Therefore, subsequent comparisons were made only between the kinetics measured during the high- and low-flow states—this provided the greatest ability to resolve the effect on cerebral blood flow changes on cerebral drug kinetics.

Model-independent Analysis

The mean arterial and sagittal sinus concentrations observed for the high- and low-flow states, and the time courses of the arteriovenous difference, for thiopental are shown in figure 2. The equivalent data for propofol are shown in figure 3. There were differences in the magnitude of the arterial concentrations between the low- and high-flow states for both drugs that can be attributed to differences in cardiac output between these states.

Characteristic differences were observed in the magnitude of the normalized arteriovenous difference between these two states, and these were consistent between the two drugs (figs. 2C and 3C). Most obviously, for both drugs the magnitude of the arteriovenous difference was greater for the low- than for the high-flow state. For thiopental, the normalized arteriovenous difference for the low-flow state lay outside the 95% confidence intervals of the high-flow state for the times 1, 1.5, 2, and 5 min. For propofol, these times were 2, 3, 4, 10, 12.5, 15, 17.5, and 20 min. For both drugs there were periods in which statistically significant differences in the arteriovenous difference could be attributed to the change in blood flow state.

Modeling

Simultaneous Modeling of High- and Low-flow States. The best fits of the simultaneous models are shown in table 2 for thiopental and table 3 for propofol. The membrane-limited model was the best fit of the cerebral kinetics for both drugs and was clearly superior to the flow-limited model. The observed data and best fits of the flow-limited and membrane-limited models are shown in figures 4 and 5 for thiopental and propofol,

Table 2. Thiopental Best-fit Models of Each Class

Model	MSC	Parameter	Parameter Description	Parameter Value
Time domain				
Traditional single flow-limited compartment	2.12	V_b	Volume of venous compartment	0.039 ± 0.003 L
Traditional membrane-limited	3.14	V_b	Volume of venous compartment	0.030 ± 0.002 L
		PS_{deep}	Permeability constant	0.007 ± 0.001 L/min
		V_{deep}	Volume of deep compartment	0.060 ± 0.022 L
Two tanks in series	2.05	V_1	Volume of first compartment	0.0001 L (fixed)
		V_b	Volume of venous compartment	0.39 ± 0.003 L
Complilation model	3.08	V_1	Volume of first compartment	0.0008 ± 0.002 L (nonidentifiable)
		V_b	Volume of venous compartment	0.028 ± 0.006 L
		PS_{deep}	Permeability constant	0.007 ± 0.002 L/min
		V_{deep}	Volume of deep compartment	0.060 ± 0.021 L
Laplace domain				
Membrane-limited	3.07	V_b	Volume of venous compartment	0.031 ± 0.003 L
		PS_{deep}/V_{deep}	Deep compartment rate constant	0.314 ± 0.139 min^{-1}
One compartment dispersion	2.19	V_b	Volume of venous compartment	0.072 ± 0.015 L
		τD_{ax}	Time constant for axial diffusion	1.39 ± 0.22 min
Two compartment dispersion	2.22	V_{deep}	Volume of deep compartment	0.107 ± 0.009 L
		τD_{ax}	Time constant for axial diffusion	1.43×10^{14} $\pm$ 7.81×10^{22} min
		PS_{deep}	Permeability constant	7.17×10^{8} $\pm$ 1.82×10^{10} L/min

A higher model selection criteria (MSC) indicates a better fit. Parameter values are given as mean±SD returned by the curve-fitting program. Baseline cerebral blood flow in the normal flow state was assumed to be 40 ml/min based on previous measurements.[10,11]

respectively. The models incorporating elements of dispersion (all but the first two models in table 1) did not provide a better fit of the data, suggesting that factors contributing to dispersion were not significant for these data.

Separate Modeling of High- and Low-flow States. The membrane-limited model was preferred over the flow-limited model for the separate fits of both the high- and low-states for both drugs, in agreement with the simultaneous fits (table 4). The MSC values were comparable to those of the simultaneous fits. This suggests that fitting data collected at only one flow state identified the most appropriate type of cerebral kinetic model.

However, for the membrane-limited model there were statistically significant differences in the values of some parameters between the high- and low-flow states and the simultaneous fits (table 5). This suggests that fitting data collected at only one flow may not produce a model that is consistent with cerebral kinetics over a range of

Table 3. Propofol Best-fit Models of Each Class

Model	MSC	Parameter	Parameter Description	Parameter Value
Time domain				
Traditional single flow-limited compartment	1.73	V_b	Volume of venous compartment	0.16 ± 0.01 L
Traditional membrane-limited	3.03	V_b	Volume of venous compartment	0.086 ± 0.010 L
		PS_{deep}	Permeability constant	0.058 ± 0.016 L/min
		V_{deep}	Volume of deep compartment	0.113 ± 0.010 L
Two tanks in series	1.65	V_1	Volume of first compartment	0.0001 L (fixed)
		V_b	Volume of venous compartment	0.163 ± 0.011 L
Compilation model	2.91	V_1	Volume of first compartment	0.0001 L (fixed)
		V_b	Volume of venous compartment	0.085 ± 0.011 L
		PS_{deep}	Permeability constant	0.058 ± 0.016 L/min
		V_{deep}	Volume of deep compartment	0.114 ± 0.022 L
Laplace domain				
Membrane-limited	2.59	V_b	Volume of venous compartment	0.093 ± 0.007 L
		PS_{deep}/V_{deep}	Deep compartment rate constant	0.573 ± 0.207 min^{-1}
One compartment dispersion	0.910	V_b	Volume of venous compartment	0.656 ± 0.574 L
		τD_{ax}	Time constant for axial diffusion	3.07 ± nc min
Two compartment dispersion	0.275	V_{deep}	Volume of deep compartment	2.70 ± 0.92 L
		τD_{ax}	Time constant for axial diffusion	9.05×10^{13} $\pm$ 6.12×10^{16} min
		PS_{deep}	Permeability constant	3.86 ± 213 L/min (nonidentifiable)

A higher model selection criteria (MSC) indicates a better fit. Parameter values are given as mean ± SD returned by the curve-fitting program. Baseline cerebral blood flow in the normal flow state was assumed to be 40 ml/min based on previous measurements.[10,11]

nc = number not able to be calculated during curve-fitting.

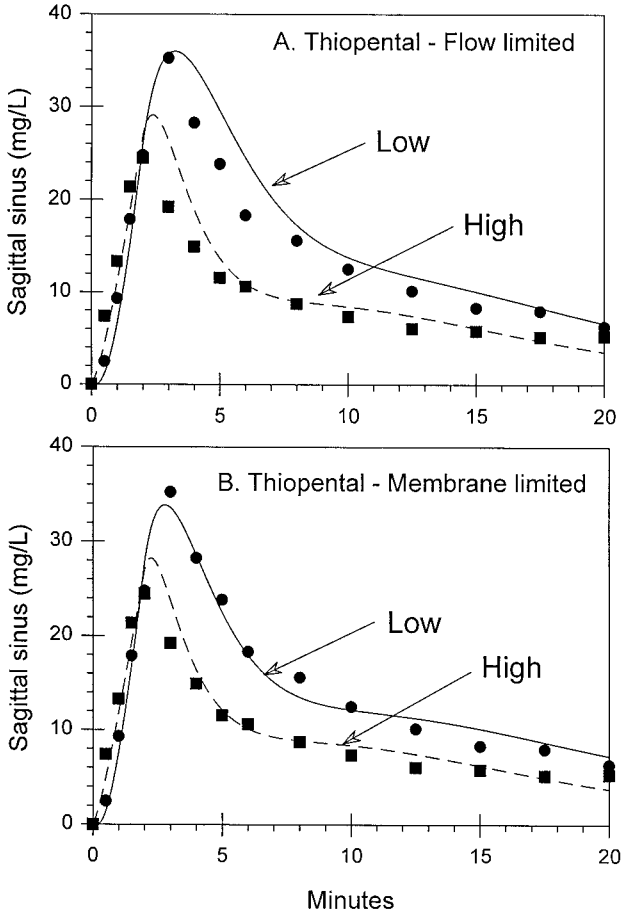


Fig. 4. The observed data (symbols) and best fits (lines) of the flow-limited (*A*) and membrane-limited (*B*) models for thiopental. Both high- and low-flow data are shown and were fitted simultaneously.

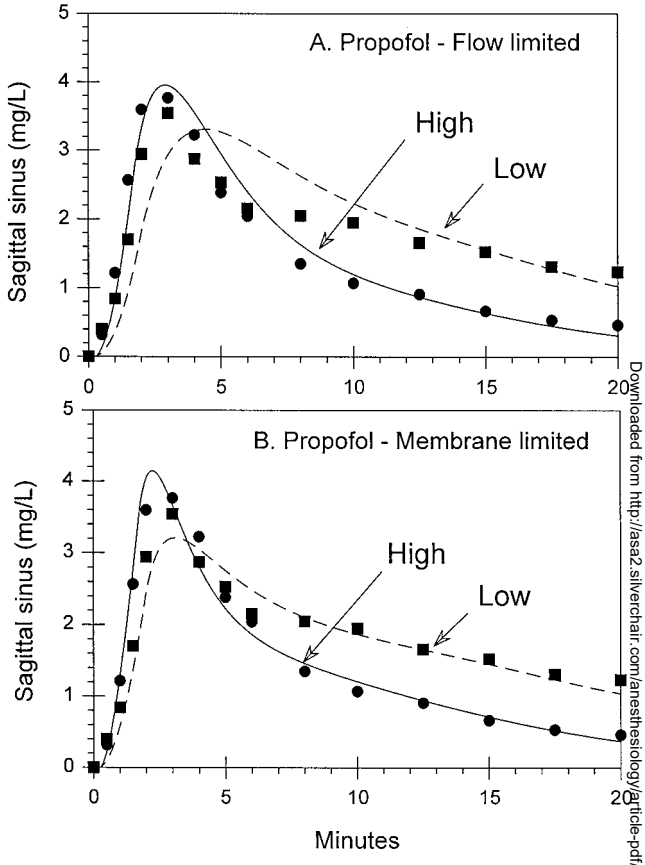


Fig. 5. The observed data (symbols) and best fits (lines) of the flow-limited (*A*) and membrane-limited (*B*) models for propofol. Both high- and low-flow data are shown and were fitted simultaneously.

cerebral blood flows. Note that the volume of the deep compartment of the brain for both drugs was relatively unaffected by changes in blood flow.

Simulations

The implications of altered cerebral blood flow for intravenous bolus administration of thiopental or propofol are summarized in figure 6. The data were qualitatively similar between drugs, showing relatively large changes in the magnitude of their peak cerebral concentrations and in the time to peak concentration if cerebral blood flow ranged between 25 and 200% of normal. The concentrations in both the venous and deep compartments were altered to a similar extent, illustrating the partial nature of the membrane limitation. Higher cerebral blood flows were associated with higher peak concentrations and shorter times to reach this concentration.

Discussion

The observed differences in the magnitude of the arterial concentrations between the low- and high-flow states for both drugs were consistent with differences in cardiac output between these states. This aspect of the arterial concentrations for propofol previously has been published and considered in detail.[24] In summary, higher cardiac outputs were observed in the high-flow state, which resulted in lower arterial concentrations because of greater first-pass dilution between the injection site and the aorta, and greater systemic clearance and distribution. These differences in concentration entering the brain are accounted for in both the model-independent and model-dependent analyses, provided cerebral up

Table 4. Model Selection Criteria (MSC) Values for the Flow-limited and Membrane-limited Models for Separate Fits of the High and Low Flow States, and for the Simultaneous Fit of Both Flow States

	Thiopental		Propofol	
	Flow-limited	Membrane-limited	Flow-limited	Membrane-limited
Separate low flow	2.21	3.59	0.85	2.92
Separate high flow	1.79	3.41	1.86	3.97
Simultaneous low and high flow	2.12	3.14	1.73	3.03

The higher the MSC, the better the fit.

Table 5. Parameter Values for the Membrane-limited Models for Separate Fits of the High and Low Flow States, and for the Simultaneous Fit of Both Flow States

	Flow-limited		Membrane-limited					
	V_b (L)		V_b (L)		PS_{deep} (L/min)		V_{deep} (L)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Thiopental	0.0406	0.0326	0.0331	0.0285	0.0051	0.0028	0.0761	−0.0059
low flow		0.0486		0.0377		0.0070		0.1581
Thiopental	0.0291*	0.0170	0.0104*	−0.0032	0.0259*	0.0099	0.0935	0.0452
high flow		0.0413		0.0241		0.0418		0.1412
Thiopental	0.0388	0.0326	0.0303	0.0257	0.0070	0.0040	0.0604	0.0152
simultaneous		0.0450		0.0345		0.0110		0.1057
Propofol low	0.1704	0.1278	0.0563	0.0351	0.0658	0.0365	0.1470*	0.1197
flow		0.2129		0.0777		0.0950		0.1758
Propofol	0.1758	0.1389	0.1144*	0.0961	0.0445	0.0255	0.1459*	0.1028
high flow		0.2127		0.1329		0.0635		0.1890
Propofol	0.1630	0.1411	0.0857	0.0642	0.0580	0.0259	0.1130	0.0890
simultaneous		0.1848		0.1073		0.0902		0.1370

Data are shown as mean and 95% confidence intervals (CI) returned by the curve-fitting program. See the 'Parameter Description' column of table 2 or 3 for definitions of abbreviations.

* Outside confidence interval of value for simultaneous fit of same drug.

take is linear. This assumption is crucial for the analysis of these data and has been verified previously for these drugs in sheep.[3,7]

A limitation of the study design is that altering flow by altering carbon dioxide tension also alters *p*H in both the blood and brain. For propofol, which essentially is unionized at physiologic *p*H, the effect of *p*H changes should be negligible. For thiopental with a pKa (the negative logarithm of the acidic dissociation constant) of 7.6, changes in the degree of ionization may be an issue, with systemic acidosis favoring cerebral uptake. A model incorporating ionization effects is under development in our laboratory.

It was shown in the current study that the cerebral kinetics of both thiopental and propofol were altered by changes in cerebral blood flow. After short-infusion administration, the model-independent analysis showed that higher cerebral blood flows were associated with smaller arteriovenous differences across the brain that are consistent with more rapid uptake in this flow state. This shows an effect of flow on kinetics but in itself does not differentiate between flow- and membrane-limited uptake. Introducing a second compartment with a membrane limitation to a model of cerebral kinetics can have either a small or large effect depending on the relative values of the permeability constant, the blood flow, and the volumes of the two compartments. For this reason, the ability of these models and others to account for cerebral kinetics were examined in detail.

Although the prevailing hypothesis is that these two anesthetics are sufficiently lipophilic that their entry into the brain is limited only by cerebral blood flow, this was not supported by the current study. The flow-limited model was not the best description of the data for either drug. The fit was improved by accounting for a second compartment with membrane limitation. Although it is

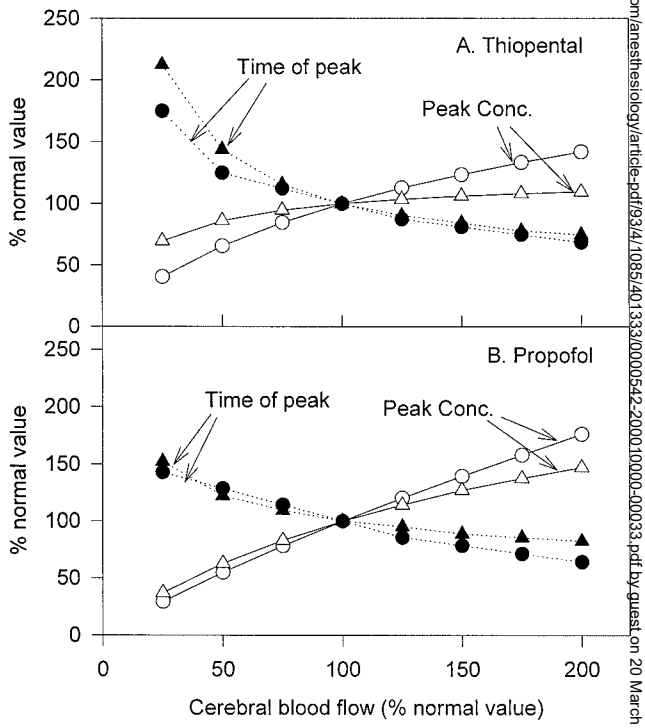


Fig. 6. (*A*) A simulation of the effect of altered cerebral blood flow in sheep (over the range between 25 and 200% of a baseline of 0.04 l/min) on the cerebral concentrations of thiopental after an intravenous bolus dose (201 mg over 10 s). All other parameters of the models were unchanged. The magnitude of the peak concentration is shown expressed as a percentage of the value for the baseline flow (open symbols, solid lines); the concurrent time to reach this concentration (also as a percentage of baseline) also is shown (filled symbols, dashed line). Circles and triangles indicate data for the venous and deep compartments of the brain, respectively. The times of the peak concentrations for venous and deep compartment at the normal flow were 0.8 and 3.20 min, respectively. (*B*) The equivalent data for propofol for a dose of (150 mg over 10 s). The times of the peak concentrations for venous and deep compartments at the normal flow were 0.7 and 3.15 min, respectively.

not possible to speculate on the physical location of the apparent diffusion barrier based on the current data, the same phenomenon has been observed in sheep with nitrous oxide,[25] which is more diffusible than either thiopental or propofol. Various models based on shunts or heterogenous perfusion were not able to account for the effect for nitrous oxide[25] and were not tried in the current study for this reason. It is known that there is little capillary recruitment in the brain (*i.e.*, most capillaries are always open)[26] and that the effect of hypercarbia is to increase the overall blood velocity in capillaries.[27] Other investigators also have reported better fits of tissue concentration data at a single flow level with membrane-limited models for relatively lipophilic drugs,[4,6,28] suggesting that the phenomenon is not unique to the current experimental preparation. For example, studies in rats have shown that thiopental appears to have a membrane barrier in the brain under normal flow conditions,[4,5] and the membrane limitation becomes more significant for barbiturates of decreasing lipophilicity.[6]

Although there was a statistical preference for the membrane-limited model, the parameters of the model were such that the final model still featured cerebral blood flow as a significant determinant of the cerebral kinetics of thiopental and propofol. This occurs if the membrane permeability term of the model (*PS*) is similar in magnitude to the blood flow term (*Q*). At low flows ($Q < PS$), such models appear flow-limited; at higher flows ($Q > PS$) the models appear membrane-limited.[29]

Models incorporating elements of drug dispersion (*e.g.*, resulting from the spread of intravascular transit times) within the brain did not account for the data better than the membrane-limited model. These dispersion models have proven useful for describing the kinetics of drugs in isolated perfused organ systems (Web enhancement appendix). However, the current data suggest that sources of dispersion do not contribute greatly to the observed arteriovenous concentration differences of thiopental or propofol across the brain in this experimental setting, in which the drugs are administered relatively slowly.

This study shows that cerebral kinetic data determined at only one cerebral blood flow are suitable to define the most appropriate form of a cerebral kinetic model: A membrane-limited model was preferred for both the high- and low-flow data sets if fitted separately. However, differences in the parameter values for these models suggest that this process cannot define a general model able to describe cerebral kinetics over a range of cerebral blood flows. Although the differences are not large in most cases, the general conclusion is that if a model is to be used to predict the outcome of blood flow changes, it should be validated over a range of blood flows.

Although it is difficult to confirm the current results in humans, the underlying physiology is similar between sheep and man and we previously showed agreement between predictions based on a sheep model and data collected in humans with respect to injection rate and onset of anesthesia.[30] In clinical practice, the effect of higher cerebral blood flows is predicted to manifest as higher peak brain concentrations after bolus administration, with decreases in the time needed to reach the peak concentration (fig. 6).

A useful contribution of the current animal studies of cerebral kinetics may be in providing a mechanistic basis for the effect compartment rate constant (k_{eo}) determined in humans from studies of the arterial concentrations of anesthetics and changes in the electroencephalogram. Animal studies have shown that anesthetic effects of thiopental and propofol are related to their cerebral concentrations, and that the delay between cerebral effects and arterial blood concentrations largely results from the time needed for cerebral equilibration.[3,7] The effect compartment concentration can be thought of as a surrogate for the average brain concentration for these drugs. Although the brain can be approximated as a single distribution volume and k_{eo} can be attributed to cerebral blood flow over cerebral distribution volume,[9] if the model is needed to account for the effects of cerebral blood flow changes, a more complicated effect compartment model with membrane limitation may be needed.

There is a perception that because cerebral blood flow is autoregulated with respect to blood pressure it can be considered a constant value. However, the available evidence suggests that cerebral blood flow can be influenced by a number of factors that are expected to vary in patients presenting for anesthesia, including hyper- or hypoventilation,[10] disease states, the coadministration of other drugs,[10] and blood pressures outside the autoregulated range or neurogenic influences. The current data provide a mechanistic basis on which the effect of these factors on the induction of anesthesia with thiopental or propofol can be interpreted and indicates that the magnitude of the effect would be clinically significant.

References

1. Saidman LJ, Eger EI: The effect of thiopentone metabolism on duration of anaesthesia. ANESTHESIOLOGY 1966; 27:118–26

2. Bischoff KB, Dedrick RL: Thiopental pharmacokinetics. J Pharm Sci 1968; 57:1346–51

3. Upton RN, Ludbrook GL, Grant C, Gray EC: In vivo relationships between the cerebral pharmacokinetics and pharmacodynamics of thiopentone in sheep after short-term administration. J Pharmacokinet Biopharm 1996; 24:1–18

4. Ebling WF, Wada DR, Stanski DR: From piecewise to full physiologic modelling: Applied to thiopentone disposition in the rat. J Pharmacokinet Biopharm 1994; 22:259–92

5. Wada DR, Bjorkman S, Ebling WF, Harashima H, Harapat SR, Stanski DR: Computer simulation of the effects of alterations in blood flows and body composition on thiopental pharmacokinetics in humans. ANESTHESIOLOGY 1997; 87:884–99

6. Igari Y, Sugiyama Y, Awazu S, Hanano M: Comparative physiologically based pharmacokinetics of hexobarbital, phenobarbital, and thiopental in the rat. J Pharmacokin Biopharm 1982; 10:53–75

7. Ludbrook GL, Upton RN, Grant C, Gray EC: Relationships between blood and brain concentrations of propofol and cerebral effects after rapid intravenous injection in sheep. Anaesth Intens Care 1996; 24:445–52

8. Upton RN, Ludbrook GL: A physiological model of the induction of anaesthesia with propofol in sheep. 1. Structure and estimation of parameters. Br J Anaesth 1997; 79:497–504

9. Upton RN, Ludbrook GL: A model of the kinetics and dynamics of the induction of anesthesia in sheep. Parameter estimation for thiopentone and comparison with propofol. Br J Anaesth 1999; 82:890–9

10. Upton RN, Grant C, Ludbrook GL: An ultrasonic doppler venous outflow method for the continuous measurement of cerebral blood flow in conscious sheep. J Cereb Blood Flow Metab 1994; 14:680–88

11. Doolette DJ, Upton RN, Grant C: Agreement between estimates of cerebral blood flow changes in the sheep by a real-time ultrasonic Doppler venous outflow method and Kety Schmidt calculations based on 15 minutes nitrous oxide wash-in. Clin Exp Pharmacol Physiol 1999; 26:736–40

12. Upton RN, Mather LE, Runciman WB, Nancarrow C and Carapetis RJ: The use of mass balance principles to describe regional drug distribution and elimination. J Pharmacokin Biopharm 1988; 16:13–29

13. Upton RN: A model of the first pass passage of drugs from their intravenous injection site to the heart: Parameter estimates for lignocaine in the sheep. Br J Anaesth 1996; 77:764–72

14. Beek WJ, Muttzall KMK: Transport Phenomena. London, Wiley, 1975

15. Roberts MS, Donaldson JD, Rowland M: Models of hepatic elimination: Comparison of stochastic models to describe residence time distributions and to predict the influence of drug distribution, enzyme heterogeneity, and systemic recycling on hepatic elimination. J Pharmacokinet Biopharm 1988; 16:41–83

16. Upton RN, Huang YF, Mather LE, Doolette DJ: The relationship between the myocardial kinetics of meperidine and its effect on myocardial contractility: Model independent analysis and optimal regional model. J Pharmacol Exp Ther 1999; 290:694–701

17. Weiss M: Moments of physiological transit time distribution and the time-course of drug distribution in the body. J Math Biol 1982; 15:305–18

18. Roberts MS, Rowland M: A dispersion model of hepatic elimination: 1. Formulation of the model and bolus considerations. J Pharmacokinet Biopharm 1986; 14:227–60

19. Weiss M, Roberts MS: Tissue distribution kinetics as determinant of transit time dispersion of drugs in organs: Application of a stochastic model to the rat hindlimb. J Pharmacokinet Biopharm 1996; 24:173–96

20. Wagner JG: Fundamentals of Clinical Pharmacokinetics, 1st Edition. Hamilton, IL, Drug Intelligence Publications, 1975, pp 231–46.

21. Upton RN, Ludbrook GL, Gray EC, Grant C: The cerebral pharmacokinetics of meperidine and alfentanil in conscious sheep. ANESTHESIOLOGY 1997; 86: 1317–25.

22. Gardner MJ, Altman DG: Statistics with Confidence, Confidence Intervals and Statistical Guidelines. London, British Medical Journal, 1989

23. Motulsky H: Intuitive Biostatistics. New York, Oxford University Press, 1995, pp 63–9

24. Upton RN, Ludbrook GL, Grant C, Martinez A: Cardiac output is a determinant of the initial concentrations of propofol after short-infusion administration. Anesth Analg 1999; 89:545–52

25. Doolette DJ, Upton RN, Grant C: Diffusion limited, but not perfusion limited, compartmental models describe cerebral nitrous oxide kinetics at both high and low flows. J Pharmacokinet Biopharm 1999; 26:649–72

26. Villringer A, Them A, Lindauer U, Einhaupl K, Dirnagl U: Capillary perfusion of the rat brain cortex: An in vivo confocal microscopy study. Circ Res 1994; 75:55–62

27. Abounader R, Vogel J, Kuschinsky W: Patterns of capillary plasma perfusion in brains of conscious rats during normocapnia and hypercapnia. Circ Res 1995; 76:120–6

28. Bjorkman S, Stanski DR, Harashima H, Dowrie R, Harapat SR, Wada DR, Ebling WF: Tissue distribution of fentanyl and alfentanil in the rat cannot be described by a blood flow limited model. J Pharmacokinet Biopharm 1993; 21:255–79

29. Piiper J, Scheid P: Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. Respir Physiol 1981; 46:193–208

30. Ludbrook GL, Upton RN: A physiological model of the induction of anaesthesia with propofol in sheep: 2. Model analysis. Br J Anaesth 1997; 79:505–13