A model of the kinetics and dynamics of induction of anaesthesia in sheep: variable estimation for thiopental and comparison with propofol

R. N. Upton and G. L. Ludbrook

Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, University of Adelaide, North Terrace, Adelaide, SA 5005, Australia

We describe a six-compartment kinetic and dynamic physiological model of induction of anaesthesia with thiopental. The model included an accurate account of initial drug distribution by representing the inter-relationships between initial vascular mixing, lung kinetics and cardiac output, and the use of the brain as the target organ for anaesthesia (two-compartment sub-model with slight membrane limitation). It also accounted for thiopental-induced reductions in cerebral blood flow and cardiac output. Parameters for the model were estimated using hybrid modelling from an extensive in vivo data set collected in sheep. Simulations were used to compare the properties of the thiopental model with an analogous previously published model of propofol. Differences in the blood:brain equilibrium half-lives of thiopental (1.22 min) and propofol (4.32 min) contributed to significant differences in the predicted optimal rate of bolus injection of each agent for inducing anaesthesia in sheep.

Keywords: anaesthetic techniques, induction; model, pharmacokinetic; anaesthetics i.v., thiopental; anaesthetics i.v., propofol; thiopental, pharmacokinetics; pharmacodynamics; sheep

Accepted for publication: December 23, 1998

Onset and offset of anaesthesia after bolus injection of an i.v. anaesthetic occur rapidly (within minutes) and are thought to be related to uptake of the agent into, and its redistribution from, the central nervous system. It is clear that physiological–pharmacokinetic models can account for this redistribution process better than traditional compartment models, and can provide good descriptions of the time course of the concentrations of an anaesthetic in various tissues in the hours after a bolus injection. However, none of these previous physiological models was intended to be a detailed description of the rapid uptake and elution of anaesthetic in the brain after i.v. bolus injection that underlies induction of anaesthesia, the principal clinical use of this class of drug. Consequently, several limitations are apparent when these types of physiological models are extended into this initial distribution period. In general terms, these limitations appear to be: (1) obtaining blood and/or tissue samples too late (e.g. 1–2 min after bolus injection) to characterize uptake of anaesthetic into well perfused tissues, including the brain; (2) using venous blood compartment volumes that are significantly greater than the true blood volume between, for example, a central venous injection site and the lungs. This underestimates peak concentrations after a bolus injection; (3) not measuring organ blood flow in the same animals in which drug concentrations were measured, which introduces errors and provides no insight into drug-induced changes in organ blood flow; (4) not having a dynamic component (e.g. a measure of depth of anaesthesia) or a target organ for these drugs effects (e.g. the brain).

We have recently developed a physiologically based kinetic–dynamic model of induction of anaesthesia with propofol. The model incorporated accurate descriptions of initial distribution by recognizing that it is comprised of the initial mixing of the anaesthetic with venous blood and cardiac output, and first-pass passage of the resultant concentration peak through the lungs and brain. Recirculation through the remainder of the body was represented as lumped compartments which greatly simplified the description of kinetic processes not fundamental to the induction process. The model was validated for propofol with regional kinetic data sets collected using a chronically instrumented sheep preparation. We believe this model addressed many of the previously identified limitations and captured the
A model of induction with thiopental

Fig 1 An overview of the structure of the model. The parameter values for thiopental are summarized in Table 1. The variables of the model are as follows: \( C_{pa} \) = pulmonary artery concentration, \( C_{art} \) = arterial concentration, \( C_{ss} \) = sagittal sinus concentration, \( C_{bp} \) = concentration in second compartment of brain, \( Q_{red} \) = percentage reduction in cerebral blood flow, \( A_{inc} \) = percentage increase in ‘anaesthesia’, as given by the algesimetry method. \( Q_{co} \) and \( Q_{b} \) are cardiac output and cerebral blood flow, respectively.

clinically relevant features of the induction process with propofol, while being of sufficient simplicity that it could be validated with relatively simple in vivo experiments.

The aims of this study were as follows: first, to estimate the parameters of the model for the barbiturate thiopental from previously published data collected using a chronically instrumented sheep preparation; second, to compare the variables of this thiopental model with our previous model of propofol; and third, to analyse the predictions of the models regarding any differences in the optimal method for induction of anaesthesia with each agent.

**Methods**

**Structure of the model**

The overall structure of the model is shown in Figure 1 and has been discussed in detail for propofol. It is a six-compartment recirculatory physiological model, with compartments for venous mixing and lung kinetics (through which cardiac output flows), the brain (a two-compartment model) and two-lumped tissue pools. To validate the model, the important sites for measurement of anaesthetic concentrations are the pulmonary artery (entering the lungs), aorta (leaving the lungs and entering the remaining organs) and the sagittal sinus (effluent from the brain in sheep). Blood flows of relevance are cardiac output and cerebral blood flow, which can be measured in sheep using thermodilution and ultrasonic Doppler methods, respectively.

**Parameter estimation—thiopental**

**General methods**

The final model was implemented as a set of differential equations, as described previously for propofol, using the Scientist software package (Scientist for Windows, Version 2, Micromath, Salt Lake City, USA). Parameters for each region of the model (e.g. lung or brain) were estimated by hybrid modelling of previously published data sets pertaining to the corresponding region of the body, as described previously. The input into each region (e.g. blood flow and afferent concentrations) was described by a series of empirical forcing functions, while the variables of the sub-model of the region were determined by least squares fitting of the measured output data (e.g. efferent concentrations). Curve-fitting was performed using a least squares algorithm with the Scientist modelling package; the best fit was judged by maximization of the ‘model selection criteria’ (MSC) of this package, which is the Akaike information criterion scaled to normalize for data sets of different magnitudes. The higher the value of MSC, the better the fit. The goodness of fit of individual data sets was also reported as an \( r^2 \) value. The hybrid modelling process for each of the regions of the model shown in Figure 1 are discussed in detail below.

**Venous mixing and baseline cardiac output**

Injection of drug into the cardiac output after i.v. injection was assumed to initially produce a square wave concentration peak in the pulmonary artery based on indicator dilution principles. This peak was then dispersed by passage through a hypothetical venous mixing compartment, the volume of which was set so that the degree of dispersion empirically matched experimental studies of the dispersion of intravascular indicators in the pulmonary artery when injected in the same manner in sheep. Based on these data, venous mixing volume was set at 0.255 litre, and baseline cardiac output was set at 5.6 litre min\(^{-1}\). The net effect is to produce an initial pulmonary artery concentration peak with the characteristics of a classical ‘dye dilution’ curve.

**Thiopental effect on cerebral blood flow**

We have previous data on the effect of thiopental 250, 500 and 750 mg (2-min infusion) on cerebral blood flow
in non-ventilated sheep. Increasing doses of thiopental increased the duration of depression of cerebral blood flow rather than the magnitude of depression. To account for these drug-induced changes in blood flow, the ability of linear, Emax and sigmoid Emax dynamic models to describe the relationship between cerebral blood flow and the observed sagittal sinus concentrations for this study were examined.

**Cerebral kinetics and depth of anaesthesia**

We have shown previously that after a dose of thiopental 250 mg over 2 min to sheep, an index of depth of anaesthesia produced by thiopental based on an algesimetry method was found to be related to sagittal sinus concentrations emerging from the brain with an effect delay half-life of 0.41 min (1.33 min for arterial blood). Hybrid modelling of sagittal sinus concentration and the index of depth of anaesthesia data from this previous study were used to investigate two options for accounting for this observation. First, cerebral kinetics and dynamics were represented by a single flow-limited compartment with depth of anaesthesia further delayed relative to the concentration in this compartment, with a half-life of 0.41 min. Second, cerebral kinetics and dynamics were represented by a two-compartment model, the first of which was in equilibrium with sagittal sinus blood, and with depth of anaesthesia related to the concentrations in the second compartment. The equilibrium delay of the second compartment would therefore account for the delay observed for depth of anaesthesia.

**Thiopental effects on cardiac output**

While propofol in standard anaesthetic doses had a minimal effect on cardiac output in sheep, this was not the case for thiopental. Previous work has shown that thiopental 750 mg over 2 min transiently reduced cardiac output for approximately 6 min to a minimum of 75% of baseline. Given the fundamental role of cardiac output in this type of model, it was felt the model should account for this observation. Hybrid effect compartment analysis with linear, Emax and sigmoid Emax dynamic models were used to compare the time course of changes in cardiac output with the observed sagittal sinus concentrations for this study were examined.

**Lung kinetics**

Three models of lung kinetics were tested for thiopental: a flow-limited model; a flow-limited model with first-order extraction; and a membrane-limited model, the equations of which have been reported previously. In this study, we used lung extraction in the traditional sense to indicate loss as a result of metabolism or essentially irreversible distribution rather than its use to describe first-pass distribution in dual indicator studies. These lung models were tested against data regarding the rate of rise of arterial concentrations of thiopental during 2-min infusions of 250, 500 or 750 mg in sheep, a method we used previously for estimating the distribution volume of propofol in the lungs. The lung models were also tested against data regarding the time course of thiopental concentrations in pulmonary arterial and arterial blood, and cardiac output, during and after a 2-min infusion of thiopental 750 mg in five chronically instrumented sheep. All but pulmonary artery concentrations of this data set have been published previously.

**Systemic kinetics**

The predictions of the model in the induction period have a large first-pass component and are not particularly sensitive to the details of systemic kinetics. Consequently, only two tissue pools were used to account for systemic kinetics, which received fixed fractions of 75% and 25%, respectively, of cardiac output (less cerebral blood flow), as reported previously for propofol. Kinetic variables were determined from a previously published data set of arterial concentrations of thiopental during, and for 300 min after, an infusion of 500 mg over 2 min in sheep. Clearance from the first tissue pool was set at a value of 0.5 litre min⁻¹ as determined in these studies, and values for volume of distribution of the lungs, and tissue pools 1 and 2 of the complete model were determined by curve-fitting of this data set.

**Parameter estimation—propofol**

In this study, the opportunity was taken to revise the previously published propofol model in two ways. First, the relationship between reduction in cerebral blood flow produced by propofol and concentrations in the brain was modelled previously as linear with a cut-off at 50% decrease from baseline. This was changed to a sigmoid Emax relationship using the method described above for thiopental, based on curve-fitting of a multiple dose rather than a single dose data set so that direct comparisons could be made with the thiopental model.

Second, the systemic kinetics of propofol, determined previously from a 45-min infusion data set, were re-examined by fitting both bolus (100 and 200 mg) and infusion (450 mg over 45 min) data concurrently. To better account for these data, the distribution of propofol into the second tissue pool was replaced with a clearance term (these can be indistinguishable in systemic kinetic analysis). This improved the ability of the model to describe the rate of decline of arterial concentrations after bolus doses, but did not greatly alter the predictions of the model with respect to the time course of anaesthesia.

**Simulations**

Various simulations, based on the final versions of the kinetic–dynamic models for thiopental and propofol and described below, were used to compare aspects of the kinetics and dynamics of induction of anaesthesia with each agent. We have shown previously that the anaesthetic effects of thiopental and propofol, as given by an algesimetry method, were related linearly to concentrations in the brain. Based on observations made in these previous studies, loss of consciousness in the simulations was
assumed to occur at apparent brain concentrations of 2 mg litre$^{-1}$ for propofol and 15 mg litre$^{-1}$ for thiopental.

**Brain equilibration times**

The final cerebral kinetic models for thiopental and propofol were used to simulate the rate of rise of cerebral concentrations after a step increase in arterial concentrations. The results were plotted and the time to 95% equilibration with arterial concentrations determined. The curves were also fitted to a single rising exponential function to determine to what extent they could be described by terms based on a single half-life, such as used in effect compartment modelling.

**Time course of brain concentrations at induction**

The general predictions of the models were demonstrated by simulating the time courses of brain concentrations of thiopental and propofol expected after injection of doses of each over 10 s (i.e. rapid induction) or 2 min (slow induction). The dose in each case was adjusted to produce a peak brain concentration of 15 mg litre$^{-1}$ for thiopental and 2 mg litre$^{-1}$ for propofol.

**Effect of duration of injection**

While duration of bolus injection of an induction agent is recognized as important clinically, and has been optimized empirically in this context, there has been very little kinetic information that can be used to provide a rational basis for the choice of duration of bolus injection. To examine this, the influence of duration of injection of thiopental was determined by simulations for a range of durations (from 10 s to 8 min) while varying the dose until a peak brain concentration of 15 mg litre$^{-1}$ was achieved in each case. The required dose, time to reach peak arterial and brain thiopental concentrations and the magnitude of peak arterial thiopental concentrations were then related to duration of injection. The data were plotted with analogous results for propofol using the revised model and based on a peak brain concentration of 2 mg litre$^{-1}$.12

**Effect of baseline cardiac output and cerebral blood flow**

We have predicted previously a marked dependence of duration of anaesthesia produced by a bolus dose of propofol on baseline values of cardiac output and cerebral blood flow. To compare this with thiopental, the models were used to analyse the dose requirements for each agent in order to achieve approximately the same time course of anaesthesia under conditions of altered baseline cardiac output and cerebral blood flow. First, the models were used to predict the time course of anaesthesia for each agent under normal conditions of cardiac output (CO) and cerebral blood flow (CBF) for equi-anesthetic doses of thiopental and propofol injected over 1 min. A curve-fitting routine was then used to determine the dose and duration of injection of each agent best able to duplicate the same time course of anaesthesia over a range of values of CO and CBF.

**Results**

**Parameter values**

Final parameter values of the models for thiopental and propofol are shown in Table 1. There were clear differences in the variables between drugs. Propofol had a relatively larger distribution volume in the lung, with mean transit times through the lungs of 0.76 and 0.44 min for propofol and thiopental, respectively. Propofol was extracted in a non-linear manner by the lungs, while thiopental was not. Tissue distribution volumes of thiopental were smaller than those of propofol, but were accompanied by a considerably lower total body clearance (clearance 0.5 litre min$^{-1}$ for thiopental compared with systemic clearance 4.94 litre min$^{-1}$ for propofol). Both drugs affected the circulatory system in the doses used—thiopental produced moderate reductions in cerebral blood flow, but significantly reduced cardiac output. Propofol did not alter cardiac output, but produced relatively greater reductions in cerebral blood flow.

**Thiopental effect on cerebral blood flow**

Figure 2 shows observed sagittal sinus (effluent from the brain) concentrations after thiopental 250, 500 and 750 mg plotted against observed percentage reduction in cerebral blood flow. Consistent with our previous observations, this plot showed minimal hysteresis and indicated that the maximum observed reduction in cerebral blood flow was approximately 20–25%. These data were best described by a sigmoid Emax dynamic model, the variables of which are shown in Table 1, and the fit of the data in Figure 2. The relatively small depression in cerebral blood flow is consistent with the fact that these sheep were not ventilated and therefore slightly hypercapnic.

**Cerebral kinetics and depth of anaesthesia**

We found that the two-compartment model produced a good fit to the data (Fig. 3) yielding precise parameter estimates (Table 1). As it was directly comparable with the model used for propofol, it was used in subsequent work. In common with propofol, the resultant value of membrane permeability of 0.063 litre min$^{-1}$ relative to a baseline cerebral blood flow of 0.04 litre min$^{-1}$ indicates that the model can be categorized as both membrane- and flow-limited. The equations of the final two-compartment cerebral kinetic–dynamic model incorporating cerebral blood flow and depth of anaesthesia effects are shown in the appendix.

**Thiopental effects on cardiac output**

Effect compartment analysis showed that changes in cardiac output lagged behind arterial concentrations of thiopental with an effect delay half-life of 0.58 min. The resultant collapsed hysteresis loop is shown in Figure 4. A sigmoid
Table 1 Parameters (and their standard deviations where appropriate) of the model for thiopental and previously reported parameters for propofol in sheep. The variables for the effect of propofol on cerebral blood flow and its systemic kinetics have been revised as indicated in the text. na indicates a parameter is not applicable to that model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Thiopental</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q )</td>
<td>Baseline cardiac output</td>
<td>5.6 litre min(^{-1})</td>
<td>5.6 litre min(^{-1})</td>
</tr>
<tr>
<td>( V_{\text{mix}} )</td>
<td>Volume of venous mixing compartment</td>
<td>0.255 litre</td>
<td>0.255 litre</td>
</tr>
<tr>
<td>( V_{\text{lag}} )</td>
<td>Apparent volume of the lung</td>
<td>2.49 (0.16) litre</td>
<td>4.23 (0.26) litre</td>
</tr>
<tr>
<td>( E_{\text{lag}} )</td>
<td>Extraction by the lung</td>
<td>0</td>
<td>Non-linear (10–60%)</td>
</tr>
<tr>
<td>( V_{\text{bc}} )</td>
<td>Apparent volume of first compartment of brain</td>
<td>0.039 litre</td>
<td>0.143 (0.011) litre</td>
</tr>
<tr>
<td>( V_{\text{bp}} )</td>
<td>Apparent volume of second compartment of brain</td>
<td>0.018 (0.007) litre</td>
<td>0.035 (0.009) litre</td>
</tr>
<tr>
<td>( PS )</td>
<td>Membrane permeability of the brain</td>
<td>0.063 (0.06) litre min(^{-1})</td>
<td>0.032 (0.009) litre min(^{-1})</td>
</tr>
<tr>
<td>( \dot{Q}_{\text{bb}} )</td>
<td>Baseline cerebral blood flow</td>
<td>0.04 litre min(^{-1})</td>
<td>0.04 litre min(^{-1})</td>
</tr>
<tr>
<td>( E_{\text{max}} \dot{Q} )</td>
<td>Emax of pharmacodynamic model for cerebral blood flow</td>
<td>21.62 (1.95)</td>
<td>40</td>
</tr>
<tr>
<td>( EC_{50,Q} )</td>
<td>EC(_{50}) of pharmacodynamic model for cerebral blood flow</td>
<td>19.5 (2.49)</td>
<td>1.15 (0.08)</td>
</tr>
<tr>
<td>( n_{Q} )</td>
<td>Hill coefficient of pharmacodynamic model for cerebral blood flow</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>( S_{A} )</td>
<td>Slope of linear pharmacodynamic model for anaesthesia</td>
<td>8.51 (0.27)</td>
<td>85 (3)</td>
</tr>
<tr>
<td>( k_{\text{eo}} )</td>
<td>Effect delay rate constant for cardiac output changes</td>
<td>1.19 (0.16)</td>
<td>na</td>
</tr>
<tr>
<td>( E_{\text{max}} k_{\text{eo}} )</td>
<td>Emax of pharmacodynamic model for cardiac output</td>
<td>60</td>
<td>na</td>
</tr>
<tr>
<td>( EC_{50,k_{\text{eo}}} )</td>
<td>EC(_{50}) of pharmacodynamic model for cardiac output changes</td>
<td>53.54 (3.04)</td>
<td>na</td>
</tr>
<tr>
<td>( n_{k_{\text{eo}}} )</td>
<td>Hill coefficient of pharmacodynamic model for cardiac output changes</td>
<td>2.44 (0.31)</td>
<td>na</td>
</tr>
<tr>
<td>( V_{1} )</td>
<td>Volume of tissue pool 1</td>
<td>0.63 (1.04) litre</td>
<td>87.5 (29.9) litre</td>
</tr>
<tr>
<td>( V_{2} )</td>
<td>Volume of tissue pool 2</td>
<td>33.67 (9.14) litre</td>
<td>na</td>
</tr>
<tr>
<td>( F )</td>
<td>Fraction of cardiac output going to ( V_{1} )</td>
<td>0.75</td>
<td>na</td>
</tr>
<tr>
<td>( Cl_{\text{tot}} )</td>
<td>Total systemic clearance</td>
<td>0.5 litre min(^{-1})</td>
<td>4.94 (1.98) litre min(^{-1})</td>
</tr>
</tbody>
</table>

Emax dynamic model was the best fit of these data, but was underdetermined for the value of Emax, the maximum drug effect. A value of 60% reduction in cardiac output was arbitrarily chosen as the maximum possible without gross cardiovascular disturbance (this would have little influence on the predictions of the model for normal doses). The magnitude of changes in cardiac output predicted by this model was compatible with the steady state observations of Runciman, Mather and Selby, in sheep (Fig. 4), showing that the model is accurate for dynamic and steady state changes in cardiac output.

Lung kinetics

In our previous work, we showed that propofol had non-linear extraction across the lung that was attributed to metabolism and moderate lung distribution volume. Unlike propofol, we found that the distribution volume of the lung could not be estimated from the rate of rise of these thiopental concentrations during a 2-min infusion, which we attributed to contamination of these ‘first-pass’ concentrations with recirculated thiopental from organs such as the heart and brain, in which thiopental has an extremely short mean transit time.

There were no differences in the time courses of the pulmonary artery and arterial concentrations during the

Fig 2 Concentration of thiopental in sagittal sinus blood (\( C_{ ss } \), effluent from the brain) plotted against its effects on cerebral blood flow, expressed as percentage reduction from baseline (\( \dot{Q}_{\text{red}} \)) for doses of 250, 500 and 750 mg in non-ventilated sheep. The fit of a sigmoid Emax model to the data is also shown by the solid line (MSC\(_{5}\) = 1.26, \( r^{2} = 0.864 \)). The fit of a linear model is shown by the broken line.

Fig 3 The fit of the combined cerebral kinetic–dynamic model to the observed mean data (MSC\(_{3}\) = 1.36, \( r^{2} = 0.973 \)). The main panel shows the predicted (lines) and observed (symbols) time courses of arterial (filled symbols) and sagittal sinus (open symbols) thiopental concentrations. The insert shows the simultaneous predicted (lines) and observed (symbols) changes in the current required for leg withdrawal (\( A_{\text{inc}} \), % increase from baseline) used as an index of depth of anaesthesia.

750 mg were superimposable when normalized for dose. Therefore, the lung kinetics of thiopental were linear over this dose range. Unlike propofol, we found that the distribution volume of the lung could not be estimated from the rate of rise of these thiopental concentrations during a 2-min infusion, which we attributed to contamination of these ‘first-pass’ concentrations with recirculated thiopental from organs such as the heart and brain, in which thiopental has an extremely short mean transit time.
A model of induction with thiopental

Fig 4 The dynamic model of thiopental effects on cardiac output. The predicted effect compartment concentration ($C_{\text{eff}}$) is shown with the change in cardiac output, expressed as percent reduction from baseline (COred). Open symbols show observed data and the line is the best fit of the model (MSC=3.47, $r^2=0.988$). The reduction in cardiac output measured by Runciman, Mather and Selby\(^\text{18}\) at a steady state arterial thiopental concentration in sheep (filled symbols) is shown for comparison with the dynamic data used for estimating variables. There is good agreement between the dynamic and steady-state data, suggesting the dynamic model is stationary.

750-mg infusion, as determined by analysis of 95% confidence limits of the concentration difference between these sites. This conservation of mass suggests that thiopental was not subject to metabolism or deep distribution in the lungs of sheep. Lung extraction could therefore be set at zero, and this excluded the ‘flow-limited with extraction’ and ‘membrane-limited’ models of the lungs for thiopental.

This left the ‘flow-limited’ model, but also suggested its distribution volume was too small to estimate from hybrid modelling of the pulmonary artery and arterial concentration data. The distribution volume of the lung was therefore estimated from arterial concentrations concurrently with volumes of the tissue pools as part of the systemic kinetic analysis, in a manner analogous to that used by others.\(^\text{27,28}\)

Systemic kinetics
Systemic kinetic variables were estimated with an adequate degree of confidence from the data (see Table 1), and were a good fit of the measured data (Fig. 5).

Simulations

Brain equilibration times
The larger distribution volumes of propofol in the brain suggest slower equilibration with arterial blood than thiopental, and this was confirmed in Figure 6. The times required for 95% equilibration of brain concentrations to step changes in arterial concentrations were 5.0 and 18.6 min for thiopental and propofol, respectively.

Time course of brain concentrations at induction.
As expected on the basis of its more rapid blood:brain equilibration, the brain concentration curve for thiopental for both rapid and slow induction increased more rapidly and peaked earlier than those of propofol (Fig. 7). Peak brain concentrations were achieved earlier (1.5 min) with rapid injection of thiopental, and this was delayed to 2.75 min when thiopental was injected slowly. However, rapid injection of propofol was unable to produce peak anaesthesia occurring any earlier than 2.75 min, which was only a marginal improvement compared with when it was injected slowly (4.0 min). In contrast with thiopental, the slower injection of propofol was associated with a significant dose reduction to achieve the same peak brain concentration. This phenomenon will be discussed in more detail below.

Effect of duration of bolus injection
Duration of injection had a profound effect on the concurrent times of peak brain and arterial concentrations, and the magnitude of peak arterial concentrations (Fig. 8A, B, C). Slower injection produced a dose-sparing effect for propofol but not for thiopental (Fig. 8D).

Effect of baseline cardiac output and cerebral blood flow
Both drugs required similar modifications of dose (2–3-fold) and duration of injection to achieve a similar time course of...
anaesthesia for different baseline values of cardiac output and cerebral blood flow (Table 2).

**Discussion**

This physiologically based analysis showed significant differences in the kinetics of induction of anaesthesia with thiopental and propofol. These differences could be attributed largely to differences in rate of blood:brain equilibration. Blood:brain equilibration for both anaesthetics was found to be a complex process with slight membrane limitation that was influenced by drug-induced changes in cerebral blood flow that, in theory, precluded description as a single rate constant inherent in effect compartment analysis, for example. In reality, fitting these curves to single exponential functions gave a reasonable approximation of the kinetics of blood:brain equilibration, with the exception of the early stages of the equilibration process for propofol. The approximate blood:brain equilibrium half-life for thiopental was 1.22 min, and for propofol 4.32 min, for a baseline value of cerebral blood flow. Clearly, long equilibration delays between the brain and arterial concentrations of an i.v. anaesthetic reduce the usefulness of a pharmacokinetic analysis based only on arterial blood concentrations in describing the induction process.

The value for the blood:brain equilibrium half-life of thiopental observed in sheep agreed well with values used previously, and with the half-life of blood:cerebral effect equilibration. The value for blood:brain equilibration for propofol has been less well characterized previously, although the jugular bulb data of Peacock and colleagues in humans is consistent with a relatively long equilibration time. Blood:effect equilibration half-lives \( T_{1/2, e_{oo}} \) of 2.57, 3.30 and 3.47 min have been reported for various effects based on changes in the EEG, although these values were relatively noisy. A value of 2.9 min was reported by Schuttler, Schwilden and Stoeckel, but it is not clear if arterial or venous blood concentrations were used. The use of venous concentrations would underestimate the value of \( T_{1/2, e_{oo}} \) compared with arterial samples.

The present model of thiopental kinetics has been optimized and validated for the initial period after i.v. injection of relevance to induction of anaesthesia. This allowed a novel mechanistic analysis of the effect of duration of bolus injection on the induction process, which is summarized in Figure 8. After bolus injection, both drugs were characterized by a transient high peak in arterial concentrations. This corresponds to mixing of injected drug with venous blood and cardiac output followed by first-pass passage of the drug through the lungs. The height of this peak was significantly affected by duration of bolus injection in a manner consistent with a direct indicator dilution effect. Increasingly rapid injection of the same doses of both drugs produced increasingly large transient peaks in arterial concentrations, and the relative increase in peak concentration was comparable between drugs (Fig. 8A).

For the full range of durations of injection, the time of peak arterial concentration occurred almost immediately after the end of injection for both thiopental (Fig. 8B) and propofol (Fig. 8C). However, the two drugs differed significantly in the time of peak brain concentrations over this range (Fig. 8B, C). The delay between the end of
A model of induction with thiopental

Fig 8 Effect of duration of injection of thiopental and propofol when titrating to a peak brain concentration of 15 mg litre\(^{-1}\) for thiopental and 2 mg litre\(^{-1}\) for propofol. The effects of duration of injection on peak arterial concentrations achieved for each drug (A); concurrent times to reach peak concentrations in arterial blood and brain for thiopental (B); concurrent times to reach peak concentrations in arterial blood and brain for propofol (C); and dose required (D).

Table 2 Effect of cardiac output (\(Q_{\text{co}}\)) and cerebral blood flow (\(Q_{\text{b}}\)) on the dose and duration of injection of thiopental required to achieve approximately the same time course of anaesthesia. Values are expressed as a percentage of the value for a cardiac output of 6 litre min\(^{-1}\) and a cerebral blood flow of 0.04 litre min\(^{-1}\). Values in parentheses are the equivalent values for propofol.

<table>
<thead>
<tr>
<th>(Q_{\text{b}})</th>
<th>(Q_{\text{b}} = 0.02) litre min(^{-1})</th>
<th>(Q_{\text{b}} = 0.04) litre min(^{-1})</th>
<th>(Q_{\text{b}} = 0.08) litre min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Q_{\text{co}} = 3) litre min(^{-1})</td>
<td>78 (92)</td>
<td>69 (74)</td>
<td>65 (55)</td>
</tr>
<tr>
<td>(Q_{\text{co}} = 6) litre min(^{-1})</td>
<td>105 (132)</td>
<td>100 (100)</td>
<td>96 (87)</td>
</tr>
<tr>
<td>(Q_{\text{co}} = 9) litre min(^{-1})</td>
<td>124 (173)</td>
<td>119 (129)</td>
<td>115 (116)</td>
</tr>
</tbody>
</table>

Duration of injection

<table>
<thead>
<tr>
<th>(Q_{\text{b}})</th>
<th>(Q_{\text{b}} = 0.02) litre min(^{-1})</th>
<th>(Q_{\text{b}} = 0.04) litre min(^{-1})</th>
<th>(Q_{\text{b}} = 0.08) litre min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Q_{\text{co}} = 3) litre min(^{-1})</td>
<td>46 (9)</td>
<td>80 (66)</td>
<td>153 (209)</td>
</tr>
<tr>
<td>(Q_{\text{co}} = 6) litre min(^{-1})</td>
<td>14 (28)</td>
<td>100 (100)</td>
<td>179 (269)</td>
</tr>
<tr>
<td>(Q_{\text{co}} = 9) litre min(^{-1})</td>
<td>22 (4)</td>
<td>98 (106)</td>
<td>168 (272)</td>
</tr>
</tbody>
</table>

Achieving rapid loss of consciousness with propofol comparable with that for thiopental implies a higher dose than necessary has been used, and there may be subsequent excessive anaesthesia and adverse haemodynamic effects. It is now clear that the concentration of propofol required to produce loss of consciousness is considerably less than that required to prevent response to the stress of surgical stimuli, and presumably intubation. If loss of con-
consciousness is used as the sole end-point when titrating i.v. anaesthetics, significant differences in the time course of depth of anaesthesia after loss of consciousness, as predicted by these models, are masked from the anaesthetist. Infusion of propofol to an anaesthetic end-point (over approximately 4–6 min) may be more appropriate for induction of anaesthesia, particularly as light anaesthesia with propofol is much better tolerated than that with thiopental, and again the maximum anaesthetic effect would occur shortly after the end of infusion.

A significant feature of the present model was incorporation of cardiac output and cerebral blood flow as determinants of the induction process. For both drugs, it was predicted that increased baseline cardiac output would require higher doses and vice versa, which has also been concluded by analysis of another physiological model of thiopental. This raises the hypothesis that many of the factors known to affect the dose of an induction agent, such as body weight, age and the pathophysiological state of the circulation, may act largely as indirect determinants of cardiac output (and cerebral blood flow). For example, it is known that cardiac output decreases with age. A relationship between induction dose and cardiac output was shown by Christensen, Andresen and Jansen, and their data showed lower cardiac outputs for older patients. A common misconception with respect to cerebral blood flow is that the well documented autoregulation of cerebral blood flow with respect to arterial pressure means that cerebral blood flow is constant. In fact, there is evidence that cerebral blood flow is relatively labile in conscious subjects and may therefore be influenced by several factors in the anaesthetic environment, including other drugs, carbon dioxide tension secondary to assisted and unassisted ventilation rates, and neurogenic factors. These may influence the optimal dose of an induction agent.

Given the extensive validation of these models against data collected in sheep, the predictions of these models are likely to be accurate for this species. Although the data from sheep show many quantitative and qualitative similarities with data collected in humans, the predictions of these models should be regarded as important hypotheses requiring testing in humans. Effect compartment modelling of EEG changes in humans may provide a method of doing so, but at present this approach lacks the physiological interpretation of the present model. Limitations include poor description of the role of blood:brain equilibration, of initial mixing and lung kinetics, and of the role of cerebral blood flow and cardiac output that we believe are crucial for a clinically relevant interpretation of the kinetics of the induction process. To address these limitations, we are currently examining if relatively simple recirculatory models of the type presented here can be validated using data collected in humans.

Appendix

Equations of the combined cerebral kinetic–dynamic model incorporated into the final recirculatory model, as shown in Figure 1. Cerebral blood flow \( Q_{cb} \) is expressed as percentage reduction \( Q_{cb} = Q_{cb}(1 - \frac{C_{ss} - C_{bp}}{C_{ss} - C_{bp}}) \) from baseline \( Q_{cb} \) and is related to thiopental concentrations in the first compartment \( C_{ss} \) of the brain. Depth of anaesthesia is expressed as percentage increase from baseline \( A_{inc} \) and is related to the concentrations in the second (parenchymal) compartment \( C_{bp} \) of the brain. The descriptions of the other parameters of the model are given in Table 1. Note that \( C_{ss} \) is an abbreviation of \( dC_{ss}/dt \), as implemented in many differential equation solving programs.

\[
\begin{align*}
Q_{cb} &= \max Q \times (C_{ss} - nQ_0)/(EC_50 - nQ_0) + (C_{ss} - nQ_0) \\
Q_{cb} &= \max Q \times ((100 - Q_{cb}/100) \\
A_{inc} &= S \times C_{bp} \\
V_{bb} \times C_{ss} &= Q_{bb} \times (C_{ss} - C_{bp}) + PS \times (C_{bb} - C_{bp}) \\
V_{bp} \times C_{bp} &= PS \times (C_{ss} - C_{bp})
\end{align*}
\]

Acknowledgements

Supported by the National Health and Medical Research Council of Australia, the Royal Adelaide Hospital–Research Review Committee and Special Purposes Fund and the Ramaciotti Foundation. We thank Mr Cliff Grant, Ms Elke Gray and Ms Allison Martinez.

References

13. Upton RN, Grant C, Ludbrook GL. An ultrasonic Doppler venous outflow method for the continuous measurement of cerebral