A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables

R. N. UPTON AND G. L. LUDBROOK

Summary
We describe a six-compartment physiological model of the kinetics and dynamics of induction of anaesthesia with propofol in sheep. It includes a faithful description of initial bolus kinetics caused by accurate representations of the inter-relationships between initial vascular mixing, lung kinetics and cardiac output, the use of the brain as the target organ for propofol anaesthesia (two-compartment sub-model with slight membrane limitation), a description of the effects of propofol-induced changes in cerebral blood flow and a combined description of systemic kinetics as two tissue pools. Variables for the model were estimated from an extensive in vivo data set using hybrid modelling. Propofol was characterized by rapid transit through the lungs, but a slower transit time though the brain, leading to significant delay between arterial blood concentrations and cerebral effects. (Br. J. Anaesth. 1997; 79: 497–504).

Key words

The pharmacokinetics and pharmacodynamics of propofol have been studied widely as a tool for increasing insight into its clinical use. The majority of studies have focused on measurements of the time course of the concentration of propofol in blood, and various measures of cerebral pharmacodynamic effects, including changes in the EEG and clinical indicators of depth of anaesthesia.1–4 The resulting models of this process have been based typically on a two-, or more commonly, three-compartment systemic model with or without an effect compartment.5 6

While this approach can provide useful information, particularly with respect to targeting blood concentrations6 7 for longer term administration by infusion, the limitations of this compartmental approach for bolus kinetics (or for rapid changes in infusion rate) have been well documented in the pharmacokinetic literature.8–12 With respect to induction agents, these models fail to describe vascular mixing,13 14 lung kinetics8 15 and cerebral drug kinetics16 in the vital period immediately after bolus injection.17 Furthermore, these models are not suitable for describing the influence of the common physiological and pathophysiological conditions encountered in surgical patients.

These problems can be attributed to the lack of a physiological basis for these conventional compartmental models. Indeed, it has been shown that adding physiological descriptions of vascular mixing and lung kinetics improves their ability to describe initial bolus kinetics.18 19 In our laboratory we have recently proposed a model of the first-pass passage of lignocaine from its venous injection site to one of its target organs for toxic effects—the heart.20 This model embraced the importance of vascular mixing and lung kinetics, but also proposed a physiological site for drug action. Importantly, every aspect of this model was validated extensively using hybrid modelling techniques against an in vivo data set rather than arterial blood concentrations alone.

In this article, we extend this model to produce a physiologically realistic model of the kinetics and dynamics of induction of anaesthesia with propofol. The model is validated by comparison with recent experimental work from our laboratory using a chronically instrumented sheep preparation with which we have measured arterial and sagittal sinus (effluent blood from the brain) drug concentrations21 simultaneously with measurements of cerebral blood flow22 and an index of anaesthetic effects.23 24 The essential structure of the model is sufficiently general in its form that it can be used to provide qualitative insights into induction of anaesthesia with propofol. Consequently, in this article the model is described and validated. In an accompanying article, the properties of the model and determinants of the induction process are examined in detail.

Methods and results

STRUCTURE OF THE MODEL

An overview of the structure of the model is presented first. It is similar to that proposed...
previously,\textsuperscript{20} with the addition of recirculation. The justification of this structure will be apparent when the variables of the model are validated subsequently against the \textit{in vivo} experimental data.

The model is composed of six compartments in series and parallel (fig. 1). Consider the case where propofol is injected at a constant rate over a period $T$ (e.g. 20 s) into the peripheral venous circulation to produce a square wave concentration peak of duration $T$. This “slug” of propofol (after Crawford\textsuperscript{25}) travels in venous blood towards the lungs. The shape of this slug in the pulmonary artery is independent of the location of the injection site, and is determined in two steps in the model. First, the height of the square wave is adjusted for dilution with the remainder of cardiac output, with the new height given by the dose rate over cardiac output.\textsuperscript{14} 26 Second, dispersion of the peak because of intravascular mixing in transit from the injection site to the pulmonary artery is accounted for empirically by the passage of this peak through a small hypothetical well-stirred venous mixing compartment.

The peak then passes through the lungs where it is subject to distribution (described by a well-stirred compartment through which cardiac output flows) and a non-linear extraction term caused by metabolism. Emerging from the lungs in arterial blood, the peak is distributed to the remaining organs of the body. The brain was of special interest as the target organ for anaesthesia with propofol\textsuperscript{21}—the kinetics were represented by a two-compartment model. The first compartment (nominally including capillary blood) was flow-limited, with slight membrane limitation in transfer to the second compartment (nominally including the parenchyma). The resultant sub-model of the brain has characteristics of both flow and membrane limitation,\textsuperscript{27} and was modified further by a feedback loop accounting for propofol-induced reductions in cerebral blood flow. The maximum reduction in cerebral blood flow was set at 50\% of baseline. The cerebral dynamic effects of propofol—its anaesthetic effects and ability to reduce cerebral metabolic rate and therefore cerebral blood flow—were related linearly to the concentration of propofol in the second compartment of the brain.

The kinetics of propofol in the remainder of the body were of interest to account for the effects of recirculation only, and the remainder of the body was therefore grouped together as compartments representing two tissue pools. The first was nominally the well-perfused organs, such as the liver and kidneys, received 75\% of cardiac output (less cerebral blood flow) and included a first-order elimination process that represented hepatic clearance. The second received the remainder of the cardiac output and was nominally the poorly perfused tissues, such as muscle and fat. To complete the model, recirculated drug emerging from the brain and the tissue pools was returned to the venous circulation.

EQUATION SOLVING

The model was implemented as a set of differential equations (appendix 1) and was solved using the “Scientist” modelling package (Scientist for Windows, Version 2, Micromath, Salt Lake City, UT, USA), although any differential equation solver would be suitable. In general terms, the model could be used to predict the effect of propofol with respect to depth of anaesthesia and reductions in cerebral blood flow, and its concentrations in the brain parenchyma, pulmonary artery, aorta and sagittal sinus (venous effluent from the brain).

VARIABLE ESTIMATION

A shortcoming of many physiological models in the past has been the lack of a detailed \textit{in vivo} experimental data set of simultaneously measured regional drug concentrations \textit{and} blood flows with which to estimate the variables of the model. Our \textit{in vivo} data...
set\textsuperscript{21,24} allowed the use of hybrid physiological modelling\textsuperscript{28,29} to estimate the variables of the model. The process used has been reported in detail previously,\textsuperscript{20} but in general terms each component of the model (e.g. each compartment in fig. 1) is compared independently with the appropriate component of the data set. Input into each component is described by a series of empirical forcing functions that closely match the measured data, while the variables of the sub-model representing that component are determined by least squares fitting of the measured output data. For example, to model cerebral kinetics, arterial blood concentrations and cerebral blood flow (input to the brain) are fitted to empirical forcing functions. The variables of the chosen model of the brain (such as apparent volume of the brain) are then estimated by least squares curve-fitting by comparing the predicted and measured sagittal sinus concentrations (output of the brain). In this manner, the variables of large models can be estimated with a high degree of confidence independently of other aspects of the model. Detailed estimation of the variables is described below. The symbols and equations used are summarized in tables 1 and 2, and appendix 1.

Curve-fitting using a least squares algorithm was performed using 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.\textsuperscript{30} The higher the value of the MSC, the better the fit. The goodness of fit of individual data sets was also reported as an $r^2$ value.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$</td>
<td>Time</td>
</tr>
<tr>
<td>$C_{pa}$</td>
<td>Pulmonary artery concentration</td>
</tr>
<tr>
<td>$C_{art}$</td>
<td>Arterial concentration</td>
</tr>
<tr>
<td>$C_{ss}$</td>
<td>Sagittal sinus concentration</td>
</tr>
<tr>
<td>$C_{bp}$</td>
<td>Brain parenchyma concentration</td>
</tr>
<tr>
<td>$Q_{red}$</td>
<td>Percentage reduction in cerebral blood flow</td>
</tr>
<tr>
<td>$A_{inc}$</td>
<td>Percentage increase in “anaesthesia”</td>
</tr>
</tbody>
</table>

The fundamental indicator dilution basis of venous mixing is central to indicator methods for measuring cardiac output\textsuperscript{20} and has been confirmed experimentally in the context of bolus injection.\textsuperscript{14} However, dispersion of the peak in transit from the venous injection site to the pulmonary artery is a complex process.\textsuperscript{31} An empirical but accurate method of accounting for dispersion with a small venous mixing compartment has been validated previously in our preparation.\textsuperscript{20} The volume of the mixing compartment was shown to be 0.255 litre, and cardiac output itself has been measured repeatedly in our preparation—the baseline value was set at 5.6 litre min\textsuperscript{-1}.\textsuperscript{32} This baseline value was used for simulation of “normal” data sets; in reality it should be acknowledged that there is sheep-to-sheep and day-to-day variation in cardiac output.\textsuperscript{33}

**Venous mixing (lines 22–23 of appendix 1)**

The process used has been reported in detail previously that the initial arterial concentrations of propofol after bolus injection were non-linear at low doses\textsuperscript{21} and attributed this to non-linear extraction across the lung. The work of Mather and colleagues,\textsuperscript{34} also using sheep, provided more information on this process. They showed that extraction occurred after prolonged infusions, and was therefore likely to be a result of metabolism (or essentially irreversible distribution). Re-analysis of their data showed that this metabolism was greatest at low concentrations and appeared to become saturated at higher concentrations (extraction of 68\% at a steady state pulmonary artery concentration of 0.65 mg litre\textsuperscript{-1}, 26\% at 3.4 mg litre\textsuperscript{-1} and 15\% at 8.35 mg litre\textsuperscript{-1}, respectively). It was found that the relationship between the inverse of extraction (1/Extr) and the afferent pulmonary artery concentration ($C_{pa}$) could be described by the following equation ($r^2=0.987$; fig. 2):

$$\frac{1}{E_{lung}} = 0.007C_{pa} + 0.013 \quad (1)$$

The remaining task was to estimate the

**Lung kinetics (lines 26–28 of appendix 1)**

We have reported previously that the initial arterial concentrations of propofol after bolus injection were non-linear at low doses\textsuperscript{21} and attributed this to non-linear extraction across the lung. The work of Mather and colleagues,\textsuperscript{34} also using sheep, provided more information on this process. They showed that extraction occurred after prolonged infusions, and was therefore likely to be a result of metabolism (or essentially irreversible distribution). Re-analysis of their data showed that this metabolism was greatest at low concentrations and appeared to become saturated at higher concentrations (extraction of 68\% at a steady state pulmonary artery concentration of 0.65 mg litre\textsuperscript{-1}, 26\% at 3.4 mg litre\textsuperscript{-1} and 15\% at 8.35 mg litre\textsuperscript{-1}, respectively). It was found that the relationship between the inverse of extraction (1/Extr) and the afferent pulmonary artery concentration ($C_{pa}$) could be described by the following equation ($r^2=0.987$; fig. 2):

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value used</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{ose}$</td>
<td>Total dose</td>
<td>200 mg</td>
<td>Default only</td>
</tr>
<tr>
<td>$T$</td>
<td>Duration of injection</td>
<td>20 s</td>
<td>Default only</td>
</tr>
<tr>
<td>$Q_{t}$</td>
<td>Cardiac output</td>
<td>5.6 litre min\textsuperscript{-1}</td>
<td>Measured/hybrid modelling</td>
</tr>
<tr>
<td>$V_{max}$</td>
<td>Volume of the hypotetical venous mixing compartment</td>
<td>0.255 litre</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$V_{lung}$</td>
<td>Apparent volume of the lung</td>
<td>3.607 litre</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$E_{lung}$</td>
<td>Extraction by the lung</td>
<td>see equation (1)</td>
<td>Measured by Mather and colleagues\textsuperscript{14}</td>
</tr>
<tr>
<td>$V_{bc}$</td>
<td>Apparent volume of the brain capillary space</td>
<td>0.143±0.011 litre</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$V_{bp}$</td>
<td>Apparent volume of the brain parenchyma</td>
<td>0.035±0.009 litre</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$P_{S}$</td>
<td>Membrane permeability of the brain</td>
<td>0.032±0.009 litre min\textsuperscript{-1}</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$Q_{bb}$</td>
<td>Baseline cerebral blood flow</td>
<td>0.04 litre min\textsuperscript{-1}</td>
<td>Measured</td>
</tr>
<tr>
<td>$Q_{max}$</td>
<td>Maximum reduction in cerebral blood flow</td>
<td>50%</td>
<td>Assumed</td>
</tr>
<tr>
<td>$S_{o}$</td>
<td>Slope of linear pharmacodynamic model for cerebral blood flow</td>
<td>19.82±1.34</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$S_{a}$</td>
<td>Slope of linear pharmacodynamic model for anaesthesia</td>
<td>85±3</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$V_{1}$</td>
<td>Volume of tissue pool 1</td>
<td>15.67±2.95 litre</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$V_{2}$</td>
<td>Volume of tissue pool 2</td>
<td>570±131 litre</td>
<td>Hybrid modelling</td>
</tr>
<tr>
<td>$F$</td>
<td>Fraction of cardiac output going to V1</td>
<td>0.75</td>
<td>Assumed</td>
</tr>
<tr>
<td>$Cl_{lun}$</td>
<td>Hepatic clearance</td>
<td>1.12±0.25 litre min\textsuperscript{-1}</td>
<td>Measured by Mather and colleagues\textsuperscript{34}</td>
</tr>
</tbody>
</table>
distribution volume of the lung while taking into account this extraction (although it is relatively low at anaesthetic concentrations of propofol). Data for this purpose were the previously published initial increase in arterial concentrations of propofol measured during a 2-min infusion of propofol at a rate of 50 mg min\(^{-1}\). The time course of these arterial concentrations depends on two factors. First, in the absence of recirculation, concentrations increase to a steady-state value that depends only on the dose rate, cardiac output\(^1\) and magnitude of the extraction process described by equation (1). The rate that they reach this value depends only on the magnitude of vascular mixing and the distribution of propofol in the lungs.

Hybrid modelling of the vascular mixing and lung kinetics subsystems, with dose as the input and arterial concentration as the output, was used to estimate the unknown variables of this sub-model—cardiac output (as it was not measured in this series of studies) and distribution kinetics in the lung. Measurement of cardiac output in this way is analogous to its measurement using indicator dilution principles.\(^2\) Only data for the first 2 min of the infusion were used to ensure the measured concentrations were not distorted by recirculation, which is insignificant in this period.\(^3\) In accord with our previous model, the lung distribution kinetics were represented initially as a single compartment through which cardiac output flowed.\(^4\)

It was found that this simple model allowed unique estimates of both cardiac output (mean 4.26 (SD 0.25) litre min\(^{-1}\) for these studies) and the apparent volume of the lung (mean 3.61 (SD 0.30) litre), and accurately described the measured data \((r^2 = 0.997; \text{MSC} = 3.62)\) (fig. 3). This equates to relatively rapid transit of propofol through the lung, with a mean transit time of 0.85 min. For comparison, the mean transit time of the vascular mixing process was 0.06 min.

**Cerebral kinetics and dynamics (lines 31–38 of appendix 1)**

The models of cerebral kinetics and dynamics were developed concurrently in order to account for the following observations, and were compared with the previously published studies of the cerebral kinetic and dynamics of propofol after a dose of 100 mg infused over 2 min.\(^5\)\(^6\)

**Relationships between propofol concentrations and cerebral blood flow.** The pharmacokinetic modelling of anaesthetic agents is complicated as the majority of agents affect cerebral blood flow.\(^7\)\(^8\) It was felt that the model should account for our previous observation that propofol reduced cerebral blood flow commensurate with reductions in cerebral metabolism.\(^9\)\(^10\) The time course of these reductions was found to correlate linearly with the time course of mean brain concentrations of propofol (calculated using mass balance principles) but were delayed relative to the time course of arterial or effluent brain concentrations.\(^11\) Baseline cerebral blood flow in the model was also set at 40 ml min\(^{-1}\) in accord with our previous observations.\(^12\) The model should also be compatible with the observation that most anaesthetics can reduce cerebral blood flow only to a minimum of approximately 50% of baseline, consistent with abolishing synaptic function but not cellular respiration.\(^13\)

Unpublished data from our laboratory have shown that propofol has minimal effect on cardiac output in sheep for bolus doses of up to 200 mg, in agreement with a report of a minor effect of propofol on cardiac output at “normal” blood concentrations in open chested pigs.\(^14\) Therefore, the effects of propofol on cardiac output were not incorporated into the model.

**Relationships between propofol concentrations and the depth of anaesthesia.** To quantitate the time course of depth of anaesthesia after propofol administration in our preparation, we developed previously an algesimetry method based on the subcutaneous electrical current required to make a sheep withdraw its leg,\(^15\) a concept similar to that used in the determination of minimum alveolar concentration (MAC) for volatile anaesthetic agents. While this method is restricted to measuring light planes of anaesthesia, it was found that this index correlated linearly with the time course of mean brain concentrations of propofol calculated using mass balance principles,\(^16\) but again was delayed relative to arterial...
or sagittal sinus concentrations. The implication of these observations is that both this measure and other more traditional indicators of depth of anaesthesia, such as loss of consciousness and eyelash reflex, can be placed on the line of increasing brain concentrations thereby negating the temporal aspects of drug delivery to the brain.

The cerebral pharmacokinetic–pharmacodynamic model. Initial studies compared cerebral kinetics (as given by sagittal sinus concentrations and cerebral blood flow) with a single flow-limited compartment, and a membrane-limited two-compartment model, as used previously for thiopentone in this preparation. Both were good descriptions of the data, with a slight statistical preference for the membrane-limited ($r^2 = 0.995; \text{MSC} = 4.91$) over the flow-limited ($r^2 = 0.992; \text{MSC} = 4.55$) model. However, the flow-limited compartment model was excluded further as this requires that mean brain concentrations and effluent sagittal sinus concentrations are proportional, and are delayed to equal extents relative to the cerebral effects. This is at odds with the two observations discussed in the previous section.

A property of the membrane-limited model is that sagittal sinus concentrations cannot be used to provide precise information on concentrations in the second compartment of the brain. This information was provided by allowing these concentrations to be related to the dynamic effects of propofol (both cerebral blood flow and depth of anaesthesia). Initially, more complex $E_{\text{max}}$ and sigmoid $E_{\text{max}}$ dynamic models were examined, but it was found that the most appropriate model (i.e. highest value of $r^2$ and MSC together with precise estimates of variables) was one in which the concentration–effect relationships were linear with intercepts of zero, and the volume of the first compartment was set at the value determined for the kinetic data alone. An upper limit of 50% for reduction in cerebral blood flow was used, as discussed previously, on theoretical grounds only.

The resultant cerebral kinetic–dynamic model was a simple, yet elegant, description of the measured data, requiring estimation of only four variables ($V_b$, PS, $S_Q$, $S_A$) from three concurrent data sets (sagittal sinus concentrations, cerebral blood flow, depth of anaesthesia). Estimates of the variable values were precise (table 2). The kinetic component of the model was a good description of sagittal sinus concentrations ($r^2 = 0.948; \text{fig. 4}$), and the ratio of membrane permeability (PS) over flow of 0.8, places the model in the category of those that are both flow and membrane limited. The dynamic components of the model were also good descriptions of the data (fig. 4) with $r^2$ values of 0.964 and 0.983 for blood flow and depth of anaesthesia, respectively. The overall MSC value for the combined kinetic–dynamic model was 3.77, and the respective $r^2$ values listed above show that approximately 95% of the variability in all three data sets could be accounted for by the model.

Systemic kinetics (lines 45–46 of appendix 1)

The systemic kinetic variables of the model were estimated from pilot data from our sheep preparation describing arterial concentrations of propofol during and after a 45-min infusion of propofol at a rate of 10 mg min$^{-1}$ ($n = 3$ sheep). It was felt that two tissue pools were appropriate for systemic kinetics, the second pool accounting for the widely acknowledged “deep” distribution of propofol. These pools received fixed fractions of 75% and 25%, respectively, of cardiac output (less cerebral blood flow). Initial studies showed that the model was under-determined if clearance, as a result of elimination and deep distribution kinetics, was estimated simultaneously, which is consistent with our previous work showing that these processes are indistinguishable, even at steady state, in some circumstances. Fortunately, Mather and colleagues made direct measurements of propofol...
organ clearance in sheep, and found that with the exception of pulmonary extraction accounted for above, clearance was predominantly hepatic and was relatively constant (1.13 \( \pm \) 0.25 litre min\(^{-1}\)) with almost complete extraction of propofol by the liver. Consequently, clearance from tissue pool 1 was set at this value. The unknowns to be determined from the 45-min infusion data were therefore cardiac output and the volume of tissue pools 1 and 2. These were estimated with an adequate degree of confidence from the data (6.41 \( \pm \) 0.1 litre min\(^{-1}\), 15.7 (2.9) litre, 570 (131) litre, respectively), and were a good fit of the model (solid line). 

**COMPARISON WITH INDEPENDENT DATA SET**

The good fits of the data shown in figures 2–5 illustrate that the structure of the sub-models used were appropriate descriptions of the relevant data sets. To examine the overall integrity of the completed model, it was used de novo to predict a set of data that could be compared with an independent data set not used in the validation steps of the model. The data set chosen was pilot data \( (n = 3) \) of sagittal sinus concentrations of propofol after a 45-min infusion at a rate of 10 mg min\(^{-1}\). There was good agreement between simulated and measured concentrations (fig. 6), thereby showing that the model is capable of accurate de novo predictions.

**Discussion**

For describing bolus kinetics, traditional compartmental pharmacokinetic models invariably feature a central compartment to which drug is added instantaneously or as a very short infusion. A common problem has been highly variable estimates of this central volume, which appears to relate to the time\(^9\) and site\(^2\) of the first blood sample, and the physiological state of the patient. Two important points arise from this article. First, together with the work of others,\(^{18,19}\) it has shown that in physiological terms the central compartment is in fact a poor representation of the interactions between vascular mixing, lung kinetics and cardiac output, and that taking these factors into account can greatly improve the description of bolus kinetics. Second, the initial concentrations in the central compartment are poorly related to the important cerebral effects of propofol, and these are described better by using the brain as the target organ for these effects.

A drawback of the increased complexity of our model is the non-intuitive nature of the interactions between the various components, but this can be addressed by using a working version of the model to simulate various data sets.\(^{41}\) Importantly, this increased complexity allows determinants of the onset of anaesthesia to be described by variables directly relevant to the practice of anaesthesia (e.g. cardiac output and cerebral blood flow), which are examined in more detail in an accompanying article.\(^{41}\) A traditional problem of physiological models, that of estimating large numbers of variables from an under determined data set,\(^{29}\) has been circumvented by hybrid modelling of in vitro data such that all variables were estimated confidently and essentially independently of each other.

The limitations of the present model are in addition to those discussed for the previous model of first-pass concentrations,\(^{20}\) but in general amount to “fine tuning” of the model rather than structural flaws. These include the fact that it is based on animal data (discussed in more detail in our accompanying article\(^{41}\)), does not account for lag during passage through blood vessels (insignificant when drug transit times through organs are high relative to vascular transit times), has a poor description of injection site concentrations (not of direct clinical relevance) and does not account for protein binding (can be ignored in individuals if binding is linear and protein concentrations are constant after injection) or tachyphylaxis (overall role uncertain). It should also be remembered that the model does not account for the haemodynamic effects of propofol, which
may significantly influence its use, nor does it account for blood flow changes secondary to respiratory depression in unventilated animals.

The present model (and data upon which it is based) has several implications for other models of propofol kinetics. First, the model incorporates two sources of non-linearity: drug-induced cerebral blood flow changes and concentration-dependent lung extraction. Therefore, models that are entirely linear in their structure are likely to be in error when predicting the outcome of large changes in dose. Second, the model provides some insight into the nature of the commonly used effect compartment rate constant k_{eff} relating blood concentration (usually arterial) to a measured effect.\(^3\) In the case of propofol, our study revealed k_{eff} to be a composite of flow and permeability terms describing entry of propofol into brain tissue and, for the reasons described above, would not have the properties of linearity and first-order kinetics usually ascribed to k_{eff}. However, rough calculations show that the effect delay predicted by this model could be approximated by an effect half-life relative to arterial blood that ranged from 3.5 to 7 min. The slight membrane limitation in the model of the cerebral kinetics of propofol is supported by recent data in human.\(^4\)

In summary, we propose that the model provides useful insight into which kinetic and dynamic processes contribute to the onset and offset of anaesthesia with propofol.

**Appendix 1**

**EQUATIONS DESCRIBING THE MODEL**

The equations of the model, written in a form suitable for the differential equation solver and modelling environment "Scientist" (Scientist for Windows, Version 2, Micromath, Salt Lake City, UT, USA). The conventions used are common to many programming languages, but note that an apostrophe after a variable indicates a differential with respect to time (thus C' is dC/dt) and that the "pulse" function is used to generate a square wave input. Annotations are preceded by "//", and symbols are explained in detail in tables 1 and 2. The line numbers on the right are for reference purposes only. In this example, 200 mg is administered over 30 s.

```
// A physiological model of the kinetics and dynamics of induction of anaesthesia with propofol in sheep

IndVars: t
DepVars: Cpa, Cart,Css,Cbp,Qred,Ainc

Params: Qt,Vmix,Vlung,Vbc,Vbp,PS, SA, SQ,V1,V2,F,CLhep

//Dose— provision for 2 square wave injections

dose=200
start=0
bigT1=0.5
doaserate1=pulse(dose, start1, bigT1)

doaserate2=pulse(dose2, start2, bigT2)

//Venous mixing compartment, including addition of recirculation

Cinj=doaserate1+doaserate2

//Lung kinetics
```

**Acknowledgements**

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