Propofol

Relation between Brain Concentrations, Electroencephalogram, Middle Cerebral Artery Blood Flow Velocity, and Cerebral Oxygen Extraction during Induction of Anesthesia

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Background: The potential benefit of propofol dose regimens that use physiologic pharmacokinetic modeling to target the brain has been demonstrated in animals, but no data are available on the rate of propofol distribution to the brain in humans. This study measured the brain uptake of propofol in humans and the simultaneous effects on electroencephalography, cerebral blood flow velocity (V_{mca}), and cerebral oxygen extraction.

Methods: Seven subjects had arterial and jugular bulb catheters placed before induction. Electroencephalography and V_{mca} were recorded during induction with propofol while blood samples were taken from both catheters for later propofol analysis. Brain uptake of propofol was calculated using mass balance principles, with effect compartment modeling used to quantitate the rate of uptake.

Results: Bispectral index (electroencephalogram) values decreased to a minimum value of approximately 4 at around 7 min from the onset of propofol administration and then slowly recovered. This was accompanied by decreases in V_{mca}, reaching a minimum value of approximately 40% of baseline. Cerebral oxygen extraction did not change, suggesting parallel changes in cerebral metabolism. There was slow equilibrium of propofol between the blood and the brain ($t_{1/2keo}$ of 6.5 min), with a close relation between brain concentrations and bispectral index, although with considerable interpatient variability. The majority of the decreases in V_{mca}, and presumably cerebral metabolism, corresponded with bispectral index values reaching 40–50 and the onset of burst suppression.

Conclusion: Description of brain distribution of propofol will allow development of physiologic pharmacokinetic models for propofol and evaluation of dose regimens that target the brain.

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ALTHOUGH propofol is well established as a sedative–hypnotic agent in anesthetic practice, uncertainties still exist about its pharmacokinetics and pharmacodynamics. The pharmacokinetics in systemic blood are well described[1] and have been incorporated into devices, such as the Diprifusor® (AstraZeneca, London, United Kingdom), which deliver target controlled infusions, targeting concentrations in the blood.[2] A limitation of this approach, however, has been that blood concentrations are a poor predictor of anesthetic effect during intravenous loading doses. Attempts have been made to instead target an effect site.[3] Most commonly, this involves the linking of a theoretical effect compartment to a systemic compartment kinetic model with a fixed rate constant (k_{eo}), with estimations of the time course of concentrations in that compartment determined by measurement of some electroencephalographic effect of propofol. Published data using this technique usually provide $t_{1/2keo}$ values of around 2–3 min.[4–9]

Physiologic pharmacokinetic modeling instead utilizes a more anatomical approach to defining the time course of distribution and effect of drugs, accounting for physiologic changes that can alter drug distribution between organs. Development of these models requires actual data on drug distribution in specific organs, but in the case of propofol there are few data available about the true rate of equilibrium between the blood and the brain, the anatomic site of effect for anesthesia. Indirect examination using arteriojugular bulb gradients in humans,[10] and studies in a sheep preparation utilizing mass balance principles to determine brain concentrations of propofol,[11] both suggest that distribution to the brain is slow. Subsequent physiologic pharmacokinetic modeling using the sheep data[12,13] has provided insights into optimal dosing strategies, such as the relation between administration rates and dose. This type of modeling has potential applications to dosing strategies for propofol in humans, but data on propofol distribution to the brain are not available.

To examine this issue, it was decided to adapt the techniques used in sheep to a human model, with the addition of electroencephalographic measurements. This provided an opportunity to measure both the rate of cerebral uptake of propofol and the relation between brain concentrations and a range of cerebral parameters. The specific aims of this study were to measure the rate of propofol distribution into the brain, to quantitate this

using compartmental modeling, and to determine the relation between brain concentration and effects on middle cerebral artery flow velocity, cerebral oxygen extraction, and electroencephalographic parameters.

Methods and Materials

Institutional Ethics Committee approval was received prior to commencement of studies. Subjects approached for inclusion in the studies were those weighing between 55 and 80 kg, aged between 18 and 50 yr, and scheduled to undergo elective orthopedic surgery at Harborview Medical Center (Seattle, WA). Exclusion criteria included significant cardiorespiratory, renal, or hepatic disease, recreational drug use, regular use of sedative–hypnotics, symptomatic esophageal reflux disease, propofol allergy, and anticipated difficult intubation.

Patient Preparation

Seven patients fulfilling the selection criteria were studied (5 men and 2 women). After informed consent was obtained, patients had standard monitors connected (electrocardiogram, noninvasive blood pressure, oximetry) and breathed 50% oxygen *via* plastic mask. A cannula (Angiocath BD, Sandy, UT) was placed in a forearm vein, and patients received a dose of midazolam (Versed, Roche, Nutley, NJ) to induce sedation. For blood sampling, a 20-gauge arterial catheter (Angiocath) was placed in the distal radial artery in the opposite arm to the intravenous cannula, and a 16-gauge 5.25″ catheter (Angiocath) was placed in the right internal jugular vein and passed retrograde into the jugular bulb for sampling of cerebral venous blood. Lidocaine was used to provide local anesthesia for cannula insertion. Catheters were connected to a three-way tap and flushed with heparinized saline. The right middle cerebral artery was insonated using a transcranial Doppler (Multidop; DWL Neuroscan, Sterling, VA). The method has been previously described.[14] Briefly, the optimal signal was obtained transtemporally at a depth between 50 and 55 mm, and the position of the probe was fixed using the Lam Rack® (DWL Neuroscan),[15] thus ensuring a constant angle of insonation throughout the study period. Built-in computer software automatically computes the mean flow velocity expressed in centimeters per second based on the maximal spectral outline of the velocity profile. Blood flow velocity (V_{mca}) was continuously measured. Electroencephalographic parameters (Bispectral Index [BIS] and burst suppression) were measured using the Aspect 2000 monitor (Aspect Medical Systems, Natick, MA), incorporating software V2.21 and low impedance electrodes (Zip electrodes; Aspect Medical Systems) on a right fronto-temporal montage, and downloaded every 5 s onto a personal computer using the Hyperterminal program (Microsoft Corp., Redmond, WA).

Following a 5-min baseline period, 1% propofol (Diprivan; AstraZeneca, Wilmington, DE) was administered *via* continuous infusion through the intravenous catheter using a volumetric infusion pump (Flo-Gard; Baxter, Deerfield, IL) at 110 mg/min for 5 min and then 10 mg/min for 20 min, while electroencephalography, electrocardiography, and V_{mca} were continuously measured, and noninvasive blood pressure was measured at 3-min intervals. The electroencephalography signal was discarded from one patient because of persistent artifact. Blood samples (1.5 ml) for later measurement of propofol concentrations were taken from the arterial and jugular bulb catheters at the following intervals: arterial— 0, 0.5, 1, 2, 3, 4, 5, 5.5, 6, 7, 8, 10, 12, 15, 20, 25, 30, and 35 min; jugular bulb— 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 15, 20, 25, 30, and 35 min. An additional 0.5 ml was taken at 0, 3, 5, 10, 15, 20, 25, and 35 min and placed on ice for hematocrit and gas tension measurement immediately after the study was completed.

During induction, a laryngeal mask was inserted when an adequate plane of anesthesia was reached, and the patients artificially ventilated to normocarbia on approximately 50% oxygen in air. Mean arterial pressure was maintained at greater than 60 mmHg using phenylephrine, if needed. On completion of the study at 35 min, anesthesia was maintained with a propofol infusion, a nondepolarizing muscle relaxant was administered, an endotracheal tube was placed, the jugular bulb catheter was removed, and surgery was allowed to commence.

Propofol Assay

Blood samples were centrifuged at 10,000 rpm for 5 min, and plasma was extracted and stored at −20°C. Propofol was assayed using gas chromatography.[16] In all cases, linear regression of a standard curve covering the range of drug concentrations 0.2–50 mg/l produced an R^2 value of 0.97 or greater. The limit of sensitivity of the assay was 0.2 mg/l.

Data Analysis

Values of V_{mca} were averaged at 30-s intervals and expressed as percent of baseline values. Oxygen extraction across the brain, as reflected by the arteriovenous oxygen content difference, was calculated at each time point blood gas analysis was performed from the arteriojugular bulb content difference, using the following formula for oxygen content: $(1.34 \times Hb \times So_2) + 0.003 \times Po_2$.

Brain Concentrations

Brain concentrations were calculated using mass balance principles in a manner analogous to that used previously in sheep.[17] For each subject, the net flux of propofol into the brain was calculated from the arteriojugular bulb concentration difference and estimations of cerebral blood flow (CBF), using the relative changes in V_{mca}, and assum-

ing a baseline CBF of 55 ml · 100 g^{-1} · min^{-1}. The total amount of propofol in the brain was calculated from the integral of the net propofol flux over time, and the brain concentration was calculated assuming a brain mass of 1,400 ml. To simplify mass balance calculations, jugular bulb propofol values were calculated at the time points 0.5, 1.5, 5.5, and 6.5 min by linear interpolation.

Modeling

To quantify the rate of equilibrium between blood and the brain, we chose to apply effect compartmental modeling to the blood and brain concentration data. One-, two-, and three-compartment models were fitted to the concentration data. For effect compartment modeling, a single rate constant (k_{eo}) described the rate of distribution between the central compartment and the brain. A partition coefficient (R) accounted for the different solubility of propofol in blood and the brain. The models were implemented as sets of differential equations (Appendix 1) and were solved using the Scientist modeling package (Scientist for Windows, Version 2; Micromath, Salt Lake City, UT). Curve fitting using a least squares algorithm was performed with the Scientist modeling package and mean values of propofol concentrations. The best fit was judged by the maximization of the Model Selection Criteria (MSC) of this package, with higher values denoting improved fit.

To compare the findings in the current study with previously reported data, a simulation of the dose regimen used here was performed using a three-compartment model and the parameters of Marsh *et al.*,[18] which are used in the commercial target controlled infusion system Diprifusor®. To examine the relation between theoretical effect site concentrations and the brain concentrations from this study, two k_{eo} values (1.21 and 0.20) previously derived using the Marsh model and electroencephalography[5,7] were incorporated into the model. As we were interested in comparing the time course of concentrations in the theoretical effect site with those in the brain rather than absolute values, concentrations were normalized to peak concentrations to allow a visual comparison of relative changes over time. BIS values were graphed as a percent reduction from baseline, again to allow a visual comparison of changes over time.

Statistical Analysis

Data from all subjects were pooled and expressed as mean and SEM. Measured parameters were examined for changes over time using repeated-measures analysis of variance, with a value of $P < 0.05$ considered significant. Pharmacokinetic analysis was performed using the Scientist program, as outlined in the modeling section.
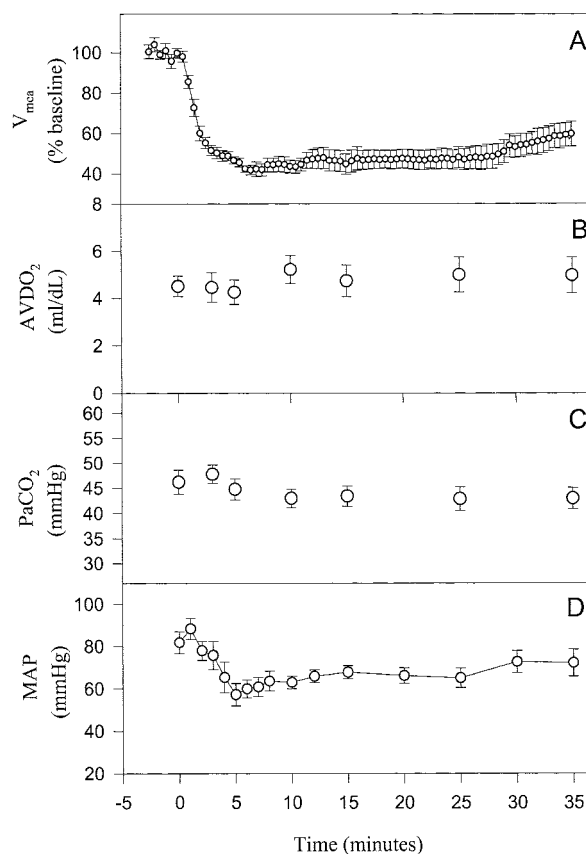

Fig. 1. The time-course of cerebral blood flow velocity (V$_{mca}$) (*A*), arteriovenous oxygen content difference, (*B*), arterial carbon dioxide partial pressure (*C*), and mean arterial pressure (*D*) after administration of propofol, commencing at time 0. Data are expressed as mean and SEM.

Results

Pharmacodynamics

During baseline measurements, the mean V$_{mca}$ values were 53, 42, 37, 55, 52, 57, and 82 cm/s in subjects 1–7, respectively, following sedation with midazolam in doses of 9, 2, 10, 5, 2, 8, and 15 mg, respectively. Administration of propofol produced a significant decrease in V$_{mca}$ ($P < 0.0001$), reaching a minimum of $41.8 \pm 2.3\%$ of baseline at 6 min from onset of propofol administration (fig. 1A). There were no significant changes in arteriovenous oxygen content difference over time ($P = 0.49$; fig. 1B), consistent with parallel changes in CBF and CMRO$_2$. After artificial ventilation was commenced, arterial carbon dioxide tension decreased by approximately 4 mmHg ($P = 0.003$) and then remained stable (fig. 1C). Mean arterial pressure decreased significantly ($P < 0.0001$) but never fell below 60 mmHg (fig. 1D). Phenylephrine support was only required briefly in two subjects. Arterial hemoglobin oxygen saturation was always in the range of 99–100%, and hemoglobin concentration remained constant ($P = 0.86$).

Bispectral Index values prior to the commencement of propofol administration were around 80, consistent with
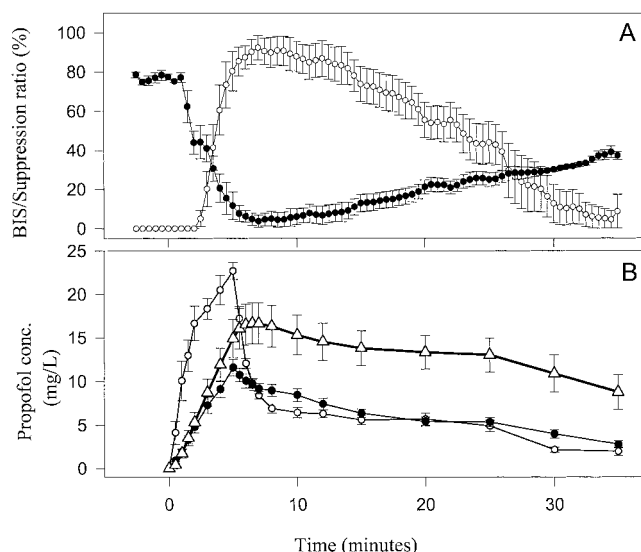
Fig. 2. (*A*) The time course of Bispectral Index (BIS; filled circles) and the suppression ratio (open circles) following propofol administration. (*B*) Arterial (open circles), jugular bulb (filled circles), and calculated brain concentrations (triangles) following administration of propofol. Data are expressed as mean and SEM.

moderate sedation from midazolam. There were rapid and significant decreases in BIS values ($P < 0.0001$) after propofol was commenced, reaching minimum mean values in the range of 3.8–4.9 between 6.5 and 7.5 min after commencement of propofol administration (fig. 2A). Burst suppression was induced, with the suppression ratio reaching maximum mean values in the range of 90.2–92% between 6.5 and 7.5 min. Burst suppression had almost completely recovered (with a suppression ratio of 4–5%) by 35 min, at which time BIS and V_{mca} levels were still markedly depressed at 60–65% of baseline.

Pharmacokinetics

The time course of propofol concentrations measured in arterial and jugular bulb blood, and calculated brain concentrations, are shown in figure 2B. There was a large and sustained arteriojugular bulb gradient throughout the initial 5-min loading dose of propofol, and this is reflected in the prolonged and delayed increase in brain concentrations.

A two-compartment model provided the best fit of arterial concentrations, with an MSC of 4.03 (fig. 3A). This provided parameter values as follows: $V_1 = 7.36$ (SD 0.450), $k_{12} = 0.397$ (SD 0.051), $k_{21} = 0.095$ (SD 0.031), $k_{10} = 0.356$ (SD 0.058). A three-compartment model also provided a good fit (MSC = 3.7), but the third compartment was poorly defined, perhaps because of the relatively short duration of sampling used. Addition of an effect compartment provided a reasonable fit of brain concentrations (MSC = 4.0; fig. 3B), and a k_{eo} of 0.108 (SD 0.005), a $t_{1/2keo}$ of 6.45 min, and a partition

coefficient of 2.11 (SD 0.059). Simulations using the Marsh model produced a similar time course of blood concentrations to that found in the current study (fig. 3A). The use of published values of k_{eo}, however, produced a different time course of effect compartment concentrations when compared with brain concentrations (fig. 3B). Comparison of the relative changes over time of BIS *versus* predicted effect site concentrations and brain concentrations revealed brain concentrations to most closely follow BIS (fig. 3C).

Concentration versus *Effect*

The relations between calculated brain concentrations and effect are shown in figure 4. There was a linear relation between the mean brain concentrations and mean BIS values throughout the study with minimal hysteresis (fig. 4A), although it was clear that there was considerable interindividual variation in this relation. Burst suppression was not evident until mean brain concentrations of greater than 5.5 mg/l were reached (fig. 4B), with concentrations of around 15 mg/l required to
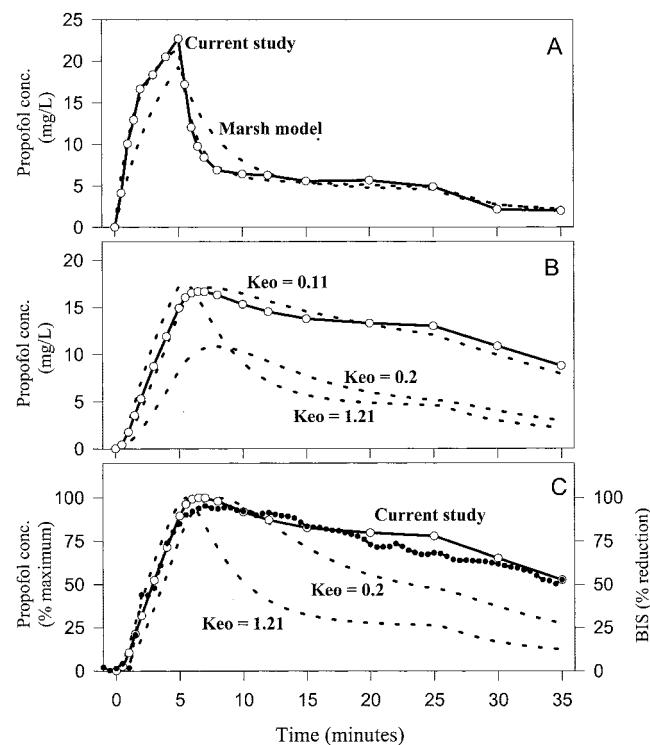
Fig. 3. (*A*) Mean arterial concentrations of propofol from the current study (circles and solid line), accompanied by the best fit of a two-compartment model (dotted line), and blood concentrations predicted by the Marsh model (dotted line). (*B*) Mean calculated brain concentrations of propofol from the current study (open symbols and solid line), accompanied by the best fit of the effect compartment model (dotted line), and effect site concentrations predicted by the Marsh model and two different k_{eo} values (dotted lines). (*C*) Calculated brain concentrations (solid line and circles) and predicted effect site concentrations (dotted lines) normalized to peak concentrations, and the mean percent reduction in Bispectral Index (solid circles).
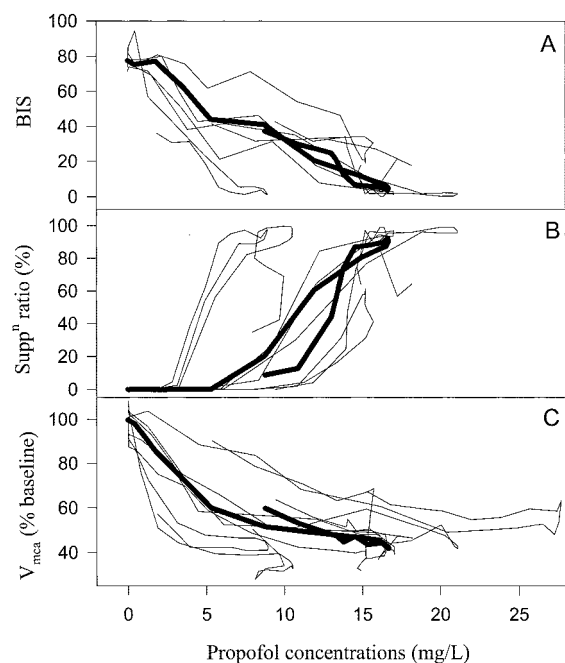
Fig. 4. The relation between calculated brain concentrations of propofol and Bispectral Index (BIS) (*A*), suppression ratio (*B*), and cerebral blood flow velocity (V_{mca}) (*C*). Thin lines represent individual subjects, and thick lines represent mean values.

produce near maximal suppression, although again considerable variation was evident. Near maximal depression of V_{mca} (and from the constant cerebral oxygen extraction, presumably $CMRO_2$), however, was achieved with concentrations of nearly half that value (fig. 4C).

Additional information regarding this is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

Discussion

Propofol and Cerebral Blood Flow–CMRO₂

Propofol produces dose-dependent decreases in both CBF and $CMRO_2$.[19-22] Although it is widely assumed that decreases in CBF are simply coupled to $CMRO_2$, there has been a trend in some studies for CBF decreases to exceed those of $CMRO_2$.[21,22] This, and evidence that propofol anesthesia in patients with brain tumors is associated with lower SjO_2 values than patients receiving inhaled anesthesia,[23] raises the question of a direct effect of propofol on cerebral vessels. The relation between CBF and $CMRO_2$ can be assessed from cerebral oxygen extraction, and the minimal changes in this parameter in the current study across a very broad range of brain concentrations and depths of anesthesia is consistent with the concept that coupling of flow and metabolism is preserved with propofol, even when near electrical silence is achieved. It should be noted that decreases in mean arterial pressure and slight hypocarbia accompanied the decrease in V_{mca} in the current study and could potentially have influenced the recorded results. In fact,

MAP remained above the usually accepted lower limit of autoregulation, and, if anything, the changes in both these parameters would have exaggerated any reduction in CBF. It therefore appears unlikely that propofol administration decreases CBF in excess of metabolism, at least in healthy individuals.

The data presented here also provide an opportunity to look at the relation between brain concentrations, electroencephalography, and V_{mca}, a relevant relation if electroencephalographic monitoring is to be used to estimate the degree of depression of CBF and $CMRO_2$ for neuroprotection. It has previously been reported that 50% burst suppression with propofol was associated with near maximal depression of CBF, but that further decreases could be achieved with electrical silence.[22] This is consistent with the findings in the current study but, as shown in figure 4, it is apparent that the majority of V_{mca} depression was achieved around the time of onset of burst suppression. While further decreases in V_{mca}, and presumably $CMRO_2$, were achieved, this required a near doubling of brain concentrations and is likely to be associated with increasing cardiovascular depression. It is interesting to relate these data to studies with barbiturates, where maximal cerebral protective effects with barbiturates do not require electrical silence to be achieved.[24] Although other protective mechanisms exist with these drugs, one can hypothesize that the majority of $CMRO_2$-related protective effects, at least with propofol, may be achieved without excessively deep anesthesia. The BIS would appear to be a valuable parameter to monitor in this setting, as the data presented here show the majority of depression of V_{mca} is reached at BIS values of 40–50 and maximal depression at a BIS of around 10–20.

Brain Uptake

The finding here of delayed cerebral uptake of propofol is consistent with previous data from sheep.[25] This similarity between species is not particularly surprising considering the dependence of propofol uptake on relative CBF values, CBF responses, and cardiac output, parameters with similar values and responses across both species. A previous study of propofol in humans estimated cerebral uptake by examining the time course of arterial and jugular bulb concentrations during the slow administration of propofol at induction of anesthesia.[10] The prolonged arteriojugular bulb gradients had suggested that equilibration was slow, but the absence of estimations of CBF changes, the dependence of propofol brain uptake on CBF, and the large decreases in CBF that accompany administration of propofol meant that calculations of the time course of brain concentrations were not possible. In the current study, V_{mca} was used as a surrogate for hemispheric blood flow for calculation of cerebral kinetics. Since normally the MCA carries between 75 and 80% of hemispheric blood flow,

it is reasonable to assume this relation during the study, provided that propofol does not greatly alter the intracerebral distribution of blood flow. In healthy individuals, this assumption is probably valid and supported by animal data showing a relatively homogeneous effect of propofol on cerebral metabolism.[26]

Concentrations versus *Electroencephalography*

It was clear that the time course of arterial concentrations was a poor predictor of cerebral effects during rapid intravenous loading of the brain but that mean brain concentrations were closely related to mean BIS values (fig. 3). The BIS, of course, is derived from a combination of electroencephalography parameters using an algorithm based on multiple observations of the relation between electroencephalography and signs of anesthesia,[27] and reasonable correlation with the few available specific clinical endpoints of anesthesia has been observed.[28,29] It is interesting to note the close relation between the time course of brain concentrations and BIS in the current study over a much wider range of depths of anesthesia than could be tested clinically, which does seem to support the effectiveness of the algorithm selected. An assumption that anesthetic effects are related to its global concentration in the brain would seem logical and is supported by data showing global brain concentrations to be closely related to antinociceptive effects in sheep.[11]

The variability between patients in brain concentrations *versus* BIS, highlighted in figure 4, is of some interest. Published data on dose–response relations with the BIS demonstrate considerable interpatient variation.[28-30] The current study has allowed determination of concentrations closer to the biophase, and the data shown here would suggest that a considerable proportion of that variation may lie within the brain. An alternate explanation is that the variability in the magnitude of brain concentrations is spurious. It could be a product of interpatient differences in baseline CBF, which we assumed to be equal, but the consistent baseline BIS values and carbon dioxide tensions between patients are against this being a large source of error. Equally, differences in brain volumes in adults were unlikely to account for the degree of variation. A contribution of an interaction between midazolam and propofol also cannot be excluded. Sedation for catheter insertion and TCD application was chosen for ethical reasons. Administration was restricted to initial intravenous titration to effect for simplicity, but it was notable that this provided very stable BIS values during the preinduction period (fig. 2A), suggesting it was unlikely to significantly distort the time course of the rapid changes in electroencephalographic effect in the period of acute brain uptake and elution.

Pharmacokinetic Modeling

Brain concentrations can be effectively used in physiologic pharmacokinetic modeling to devise optimal dose regimens,[13] and we plan to use the data obtained in the current study to examine this issue in humans. We chose to apply compartmental analysis to these concentrations only with the intention that this might allow some simple quantitation of the blood:brain disequilibrium. We also chose to visually examine the relation between brain concentrations and effect site concentrations predicted by compartmental models. The compartment model we used was selected because of its incorporation into the only commercial device currently on the market (the Diprifusor®) and in devices that display predicted brain concentrations. It is therefore the model to which clinicians have most exposure. It should be noted that, because of a blood:brain partition coefficient for propofol of greater than 1 (also reported in animals[31]), "real" rather than the "apparent" concentrations were modeled.

Values for $t_{1/2keo}$ for propofol obtained from blood concentration–electroencephalography analysis center around 2–3 min, and the figure derived in the current study is a great deal higher. It is apparent from figure 3C, however, that the value of k_{eo} is not particularly critical for predictions during the onset of anesthesia in dose regimens such as a loading dose over 5 min used in the current study. It was clear, however, that predicted effect compartment concentrations and brain concentrations diverged during the early "maintenance" phase of anesthesia. This suggests that effect site concentrations reported in the studies referred to previously may not closely reflect brain concentrations. It is interesting to consider the possible explanations for this discrepancy.

First, effect compartment modeling uses electroencephalography in its modeling process, while only brain concentrations were utilized in the current study. The close relation between brain concentrations and BIS throughout the study (fig. 3C), however, suggests that the use of electroencephalography would have little impact on k_{eo}.

Second, it is worth noting that propofol was administered relatively slowly in the current study, while rapid bolus administration was used in many of the studies from which k_{eo} values are derived. It is possible, in the case of propofol, that effect compartment models may lose accuracy when applied to administration rates different from those from which they were derived. This, in fact, is suggested by a study of repeat administration at different dose rates in humans[32] and from compartmental analysis in sheep[33] and may relate to physiologic factors, such as cardiac output and CBF, which can affect drug distribution. Indeed, it might be that the slow elution of propofol demonstrated in the current study, but a time to peak concentration which is hardly different to effect compartment models, relates to propofol induced decreases in CBF which have a more pro-

nounced effect on elution than uptake. This area warrants further examination.

Third, it is possible that global brain concentrations are not reflective of the anesthetic effects of propofol, as a result of the large central nervous system distribution volume and prolonged uptake into sites unrelated to sites of anesthetic action. Against this is the close brain concentration–BIS relation in figure 3. Lastly, the influence of midazolam may have been significant. It seems likely that decreases in CBF can reduce the rate and magnitude of drug uptake into the central nervous system,[34] and a midazolam-mediated decrease in CBF might have induced a slower rate of uptake and elution. Against this is the fact that a substantial decrease in CBF would be required, and evidence that CBF decreases following the doses of midazolam used in the current study should only be in the order of 10–15%.[35]

As BIS values provide a reasonable prediction of clinical anesthetic effect with propofol,[26,27] it would appear that pharmacokinetic models targeting brain concentrations have potential utility in devising dose regimens for propofol. Studies of the time course of brain concentrations in animals have been used to develop physiologic models that can account for variation in physiologic parameters such as cardiac output and CBF, as well as the impact of factors such as speed of administration on dose requirements.[12,13] The data presented here provide an opportunity to develop such models in humans. It remains to be seen whether the performance of these models provides an advantage over techniques such as effect compartment modeling, and such studies are currently underway.

In conclusion, the data presented here reveal a prolonged equilibrium between blood and the brain after intravenous injection of propofol, with a close relation between brain concentrations and BIS. Pharmacokinetic models incorporating this information therefore have potential utility when devising dose regimens to target the brain.

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Appendix 1

The differential equations for the effect compartment model used to fit arterial and brain concentrations. The symbol "'" in the Scientist program refers to differentiation over time.

IndVars: T

DepVars: C_1, C_{er}

Params: V_1, k_{21}, k_{12}, k_{el}, k_{eo}, R

$V_1 \cdot C_1' = doserate + (k_{21} \cdot A_2) - (k_{el} \cdot V_1 \cdot C_1) - (k_{12} \cdot V_1 \cdot C_1)$

$A_2' = (k_{12} \cdot V_1 \cdot C_1) - (k_{21} \cdot A_2)$

$Ce' = k_{eo} \cdot (C_1 - C_e)$

$C_{er} = R \cdot C_e$

//dose1

dose1 = 500

start1 = 0

tau1 = 5

doserate1 = pulse (dose1, start1, tau1)

//dose2

dose2 = 250

start2 = 0

tau2 = 25

doserate2 = pulse (dose2, start2, tau2)

doserate = doserate1 + doserate2

//initial conditions

$C_1 = 0$

$T = 0$

$A_2 = 0$

$C_e = 0$