■ LABORATORY INVESTIGATIONS

The Cerebral Pharmacokinetics of Meperidine and Alfentanil in Conscious Sheep

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Background: Different opioids have different delays (hysteresis) between their concentrations in blood and their cerebral effects. Possible mechanisms include differences in their rate of penetration into the brain and differences in their distribution volume in the brain. There have been few *in vivo* studies of the cerebral kinetics of opioids to differentiate these mechanisms.

Methods: The cerebral kinetics of meperidine and alfentanil were examined using conscious sheep that were fitted with long-term monitoring equipment to measure relative changes in cerebral blood flow and opioid concentration gradients across the brain through frequent sampling of arterial and sagittal sinus blood. The data were compared using hybrid physiologic modeling with membrane-limited (consistent with mechanism 1) and flow-limited (consistent with mechanism 2) models of cerebral kinetics.

Results: Alfentanil had a variable effect on relative cerebral blood flow, whereas meperidine induced a transient increase. The arteriovenous concentration gradients were small after alfentanil but large after meperidine. The flow-limited model gave acceptable descriptions of observed sagittal sinus concentrations for alfentanil and meperidine, whereas the membrane-limited model collapsed to a flow-limited model. The half-lives of equilibrium between blood and brain were 6.3 and 0.8 min for meperidine and alfentanil, respectively.

Conclusions: The rate of penetration of both opioids into the brain was rapid and not rate-limiting. Large differences in the cerebral distribution volume of meperidine and alfentanil accounted for the respective delays in their peak brain concentration relative to blood. (Key words: Pharmacokinetics: alfentanil; modelling. Brain. Meperidine.)

THE pioneering work of Scott *et al.*[1] provided insight into the relation between the blood concentrations of two opioids and their effect on the electric activity of the brain, and also into reported delays (hysteresis) between blood opioid concentrations and pharmacologic effect (effect delay). The effect delay varies widely among opioids.[1-3] The article by Scott *et al.*[1] and an accompanying editorial by Hug[4] raised several issues regarding the mechanism of the hysteresis for opioids. Attention has focused on the relation between blood and brain (or central nervous system) concentrations of opioids as an explanation for these delays. Depending on the opioid, one of two possible mechanisms have been proposed:[5] 1) Differences in the delay may be due to differences in their rate of penetration into the brain, which is thought to relate to their lipophilicity, and 2) opioids penetrate the brain rapidly, but differences in the relative solubility (distribution volume) of the opioid in the brain result in differences in the time required for blood–brain equilibration. Large tissue distribution volumes fill more slowly and take longer to reach their peak concentration compared with small volumes.[6]

Distinguishing between these mechanisms requires knowledge of the cerebral kinetics of opioids. The most simple model compatible with the first mechanism would be a two-compartment, membrane-limited model of the brain. The second mechanism would be compatible with a single-compartment, flow-limited model. Currently, however, there is limited information on the cerebral kinetics of opioids in the literature. An exception is the work of Bjorkman *et al.*,[7,8] who reported differences between the apparent volume of a single-flow compartment fitted to the directly measured brain concentrations of fentanyl and alfentanil in the rat. These data and the theoretical analysis of meperidine by Davis and Mapleson[9] have suggested that a single flow-limited compartment is an adequate description of the brain for these opioids. However, there have also been reports of membrane-limited kinetics for drugs and organ combinations previously thought to be flow limited.[8,10]

UPTON *ET AL.*

We recently developed a model using conscious sheep fitted with monitoring instruments,[11,12] through which the cerebral pharmacokinetics and pharmacodynamics of drugs can be examined simultaneously with continuous measurement of an index of cerebral blood flow (CBF) using an ultrasonic Doppler technique.[13] We chose to study the cerebral kinetics of meperidine and alfentanil because of our previous experience with these agents in this preparation and because they differ in their lipophilicity (alfentanil > meperidine).[14] They also appear to differ in their effect delay. Changes in evoked potentials after meperidine is given to goats are delayed relative to its blood concentrations with a half-life of about 6 or 7 min.[2] In contrast, the half-life of effect delay for alfentanil is more rapid, with values of about 1 min reported for changes in the electric activity of the brain in human.[1] Thus we used our preparation to examine the hypothesis that differences in the magnitude of these delays would be reflected in differences in the cerebral kinetics of these two drugs, and we examined the suitability of single flow-limited compartment and membrane-limited two-compartment models to distinguish between the two proposed mechanisms of cerebral uptake. We also examined the effects of any opioid-induced changes in CBF on subsequent pharmacokinetic calculations of their cerebral kinetics.

Materials and Methods

Animal Preparation

Approval was obtained from our institutional Animal Ethics Committee, and animals were cared for in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes issued by the National Health and Medical Research Council of Australia.

Adult female Merino sheep with a nominal weight of 50 kg and that were aged between 1 and 2 yr were fitted with long-term monitoring instruments. Anesthesia was induced using intravenous thiopental (20 mg/kg), a cuffed endotracheal tube was inserted into the trachea, and the lungs were ventilated with a mixture of 1% or 2% halothane in oxygen. Each animal was placed in the "sphinx" position, and the head was shaved and soaked in a povidone-iodine antiseptic solution. All surgical procedures then were performed during full aseptic conditions.

An ultrasonic Doppler flow probe was placed on the dorsal sagittal sinus to measure an index of CBF using

the method described previously.[13] Briefly, a midline longitudinal incision was made in the scalp, and a 19-mm trephine hole was made at the caudal junction of the frontal and parietal bones to expose the dorsal sagittal sinus. The ultrasonic Doppler transducer (20 MHz; Tritonics Medical Instruments, Iowa City, IA) was secured on the sagittal sinus at the rostral edge of the trephine hole. In addition, a 3-French blood sampling catheter (Cook, Brisbane, Australia) was placed in the sagittal sinus, as described by Lindsay and Setchell[15] and Hales,[16] with its tip placed "downstream" of the probe. The bone plug from the trephine hole was replaced and secured using a titanium plate and 1-mm stainless steel screws. The fact that dorsal sagittal sinus blood is pure brain effluent in sheep has been discussed extensively in a previous report.[13]

After this procedure, the anesthetized sheep were placed on their backs for cannulation of the remaining blood vessels, as described by Runciman *et al.*[17] The right carotid artery and jugular vein were exposed through a neck incision. Using a modified Seldinger technique, two 7-French catheters (multipurpose A1 catheter; Cordis Corp., Miami, FL) were placed *via* the carotid artery into the ascending aorta, with their tips located approximately 2 cm above the aortic valves for arterial blood sampling. Through the jugular vein, a 7-French catheter (multipurpose A1 catheter, Cordis Corp.) was placed in the right atrium for drug injection. The positions of these catheters were confirmed under direct vision using a fluoroscope with the injection of intravascular contrast (Conray 420 [70% iothalamate]; May and Baker Ltd., Dagenham, UK) into the corresponding blood vessels. The sheep were allowed to recover from anesthesia and housed in metabolic crates with free access to food and water. The catheters were flushed continuously with 0.9% saline processed in heparin (5 IU/ml) at a rate of 3 ml/h using a gas-powered system.[17] The sheep were allowed to recover fully for 1 week; this period also allowed the Doppler flow probe to become firmly embedded in scar tissue, which ensured good acoustic coupling.

Study Design

On the day of the experiments, the sheep were given either meperidine (300 mg over 4 min; David Bull Laboratories, Mulgrave, Victoria, Australia) or alfentanil (1,000 mg over 4 min; lot no. 86L16/177, Janssen Pharmaceutica, Beerse, Belgium) as constant-rate infusions into the right atrium. It is not known if these doses are equipotent in sheep; they were chosen based on pilot

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studies that showed these were the highest possible without producing prolonged profound dysphoria noted elsewhere.[18] Five studies were performed for each drug in four and five sheep for meperidine and alfentanil, respectively. For each study, the following data were collected.

Cerebral Blood Flow Measurements. The CBF method was not calibrated to give units of flow in the animals studied but was used to provide an index of relative changes in CBF. The Doppler shift in the sagittal sinus was measured using the Doppler flow probe and a flow meter (Department of Bioengineering, University of Iowa[19]) and was recorded for 3 min before the start of the drug infusions and for 20 min (alfentanil) or 40 min (meperidine) after the infusions using an analog-to-digital card (Metrabyte DAS 16-G2) and a personal computer (486-based IBM compatible). For subsequent calculations, baseline CBF for the region drained by the sagittal sinus sampling catheter was assumed to be 40 ml/min based on previous calibrated measurements in our preparation (range, 31–53 ml/min[13]).

Blood Gas Analysis. When the results from initial studies suggested that meperidine altered CBF, additional arterial blood samples were taken in three of the meperidine studies for blood gas analysis (Ciba-Corning 278; Ciba Corning Diagnostics, Medfield, MA) to investigate the mechanism of this change.

Cerebral Pharmacokinetics. After the start of the administration of the dose, 0.5-ml arterial and sagittal sinus blood samples were taken at regular intervals of as little as 30 s to yield a total of 24 samples per blood sampling site. All animals were subjected to the same sampling regimen, which is shown in figure 3. The samples were assayed for meperidine or alfentanil.

Drug Analysis

Meperidine was assayed using a single-extraction technique and gas chromatography with nitrogen-phosphorous detection.[20] Alfentanil was assayed using a double-extraction technique and high-pressure liquid chromatography with ultraviolet detection.[21] All assays were calibrated using five-point standard curves prepared in blood taken from the same animal before drug administration. The R^2 value of these standard curves exceeded 0.995 for every assay. The limit of sensitivity of the assays was approximately 0.1 and 0.05 μg/ml for meperidine and alfentanil, respectively.

Data Analysis

Pharmacokinetic Analysis. The measured effluent drug concentrations from the brain were compared with those predicted by two structural models representing the two mechanisms of cerebral uptake discussed previously: mechanism 1, a two-compartment model with membrane limitation, and mechanism 2, a single flow-limited compartment.[8]

The models were constructed as differential equations using the Scientist for Windows software package (Version 2, Micromath Scientific Software, Salt Lake City, UT).

Membrane-limited Model. The membrane-limited model represented the brain as nominal capillary and parenchymal compartments separated by a membrane barrier. The volume of the capillary compartment was assumed conservatively to be 5% of the total volume of the brain,[22] and permeability (PS) was defined as a clearance using standard capillary permeability nomenclature.[23] The differential equations describing this system were as follows:

$$V_{cap}\frac{dC_{ss}}{dt} = Q_{cbf}(C_{art} - C_{ss}) + PS(C_p - C_{ss})$$

$$V_{brain,1}\frac{dC_p}{dt} = PS(C_{ss} - C_p) \tag{1}$$

where V_{cap} is the volume of the capillary compartment, Q_{cbf} is cerebral flow, $V_{brain,1}$ is the apparent volume of the parenchymal compartment, and C_p is the concentration in the parenchymal compartment. The parameters $V_{brain,1}$ and PS were determined from least-squares curve fitting of the observed sagittal sinus concentrations (C_{ss}). Empirical forcing functions were used to represent the other measured variables of the model. The observed arterial blood concentrations (C_{art}) were fitted to a triexponential equation, and the observed CBF (Q_{CBF}) values were fitted to a fifth-order polynomial, which accounted for any drug-induced changes in flow.

When the ratio of PS/Q_{cbf} is greater than 3, this model is essentially flow-limited; when the ratio of PS/Q_{cbf} is less than 1, this model is essentially membrane-limited; and intermediate values are flow- and membrane-limited.[24]

Flow-limited Model. The single flow-limited compartment model was based on the following equation, where $V_{brain,2}$ is the apparent volume of the compartment representing the entire brain:

$$V_{brain,2}\frac{dC_{ss}}{dt} = Q_{cbf}(C_{art} - C_{ss}) \tag{2}$$

$V_{brain,2}$ was determined from least-squares curve fitting

of the observed sagittal sinus concentrations (C_{ss}). Empirical forcing functions were used to represent the other measured variables (C_{art}, Q_{cbf}) of the model as for the previous model.

The modeling was also repeated for the individual meperidine data sets without accounting for any observed drug-induced changes in CBF (*i.e.*, assuming flow did not change from its baseline value [$Q_{cbf,base}$]). For comparison with other data, the following kinetic parameters were calculated from these data sets:

The first-order rate constant (k) of the compartment:

$$k = \frac{Q_{cbf,base}}{V_{brain,2}} \qquad (3)$$

The mean transit time (MTT) of the drugs in the brain:[25]

$$MTT = \frac{V_{brain,2}}{Q_{cbf,base}} \qquad (4)$$

The half-time of equilibration ($t_{1/2,equil}$) between blood and the brain[6]:

$$t_{1/2,equil} = \frac{0.693}{k} \qquad (5)$$

The brain–blood partition coefficient (R) was calculated by assuming that the real volume of the region of the brain drained by the sagittal sinus catheter (V_{real}) was 75 ml:[13]

$$R = \frac{V_{brain,2}}{V_{real}} \qquad (6)$$

Curve Fitting. The goodness of fit of both models was determined by a least-squares method based on maximization of the Model Selection Criteria (MSC), which is essentially the Akaike Information Criterion scaled to allow for the comparison of data sets of different magnitudes (manual; Scientist for Windows 2.0, Micromath Scientific Software). The MSC was calculated using the following equation:

$$MSC = lr \left(\frac{\sum_{i=1}^{n} w_i \left(Y_{obs_i} - \overline{Y_{obs}} \right)^2}{\sum_{i=1}^{n} w_i \left(Y_{obs_i} - Y_{cal_i} \right)^2} \right) - \frac{2p}{n} \qquad (7)$$

where w_i is a weighting term and p is the number of parameters. No weighting was considered necessary

because there was no evidence that the data were heteroscedastic.

Statistical Analysis

Data were analyzed using two-factor analysis of variance or paired *t* tests as indicated, and probability values less than 0.05 were considered significant.

Results

The CBF measurements for one meperidine study were atypical and inconsistent with the simultaneous blood concentrations. The method of measurement was presumed to be faulty, and these flow measurements were excluded from the analysis. For one alfentanil study, the sagittal sinus concentrations were atypical in that they were very low and never exceeded the arterial concentrations. This animal did not have an abnormal response to the alfentanil, even though these measured concentrations would suggest a continuously increasing concentration of alfentanil in the brain. The cause of this observation is uncertain but may have been a result of entry of the catheter into the transverse sinus, thus sampling systemic and brain effluent blood. The data set was excluded from the analysis. Thus the total number of studies analyzed was five and four for meperidine and alfentanil, respectively.

Cerebral Blood Flow

Figure 1 shows the effect of the drugs on CBF, expressed as a percentage of baseline. Meperidine had a relatively consistent effect on CBF; that is, it increased to 140% of baseline by the end of the infusion and returned to baseline by 40 min. This change was significant (by analysis of variance; $P < 0.05$; n = 4). Alfentanil had a more variable effect on CBF, and although the peak mean recorded values were similar to those after meperidine, because of the variability this was not significant (by analysis of variance; $P = 0.23$; n = 4).
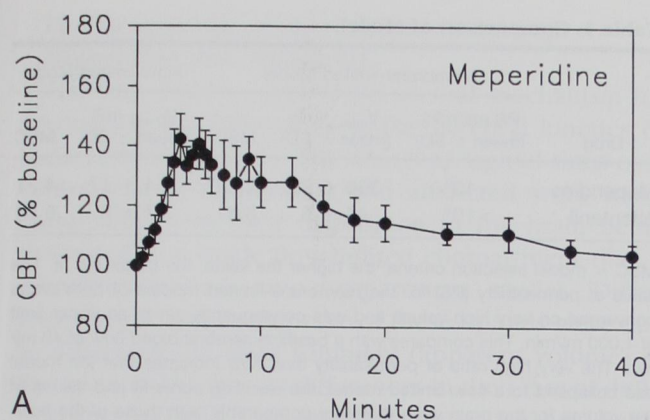
Blood Gas Analysis

Meperidine caused a significant (by analysis of variance; $P < 0.05$; n = 3) increase in arterial carbon dioxide tension to 111% of baseline, which was greatest at the end of the study (fig. 2).
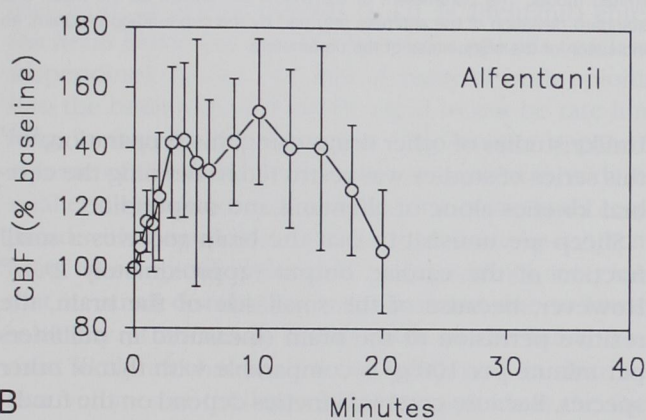
Cerebral Pharmacokinetics

The concentration data were highly reproducible among animals, as shown by the small standard errors

Fig. 1. (A) The effect of meperidine on cerebral blood flow expressed as a percentage of baseline. (B) The effect of alfentanil on cerebral blood flow expressed as a percentage of baseline. In both cases, the data are the mean and SEMs of four animals.
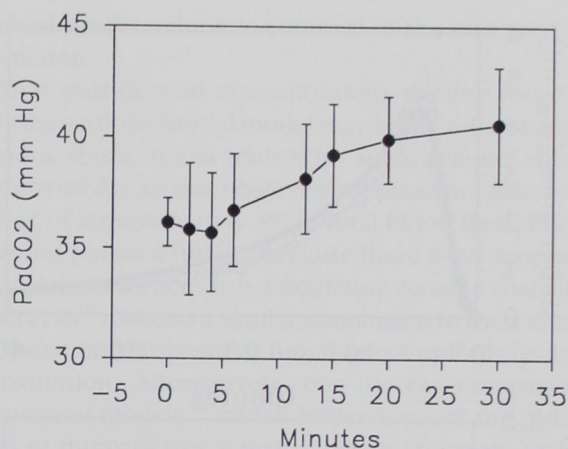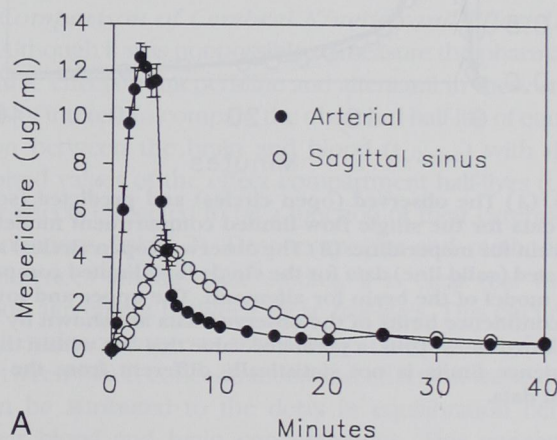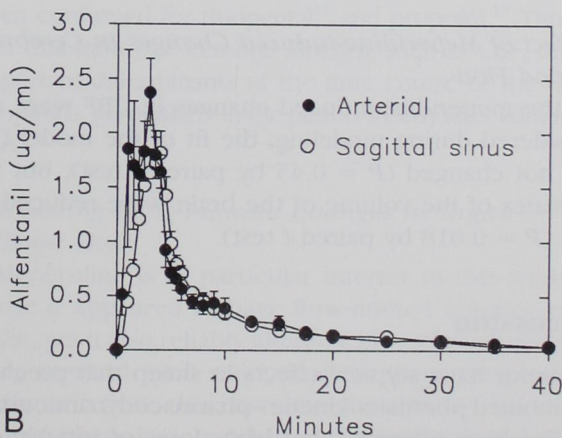

Fig. 2. The effect of meperidine on the carbon dioxide tension in arterial blood. The data are the mean and SEMs for three animals.

Fig. 3. (A) The observed arterial and sagittal sinus concentrations of meperidine. (B) The observed arterial and sagittal sinus concentrations of alfentanil. The data are the mean and SEMs of five and four animals, respectively.

in figure 3. For this reason, pharmacokinetic analysis was based on the mean data for all the animals after initial trials showed no advantages of an animal-by-animal analysis. Meperidine was characterized by a large arteriovenous difference during the infusion, which reversed in the postinfusion period. These differences were smaller for alfentanil. The single flow-limited compartment model gave acceptable descriptions of the observed sagittal sinus concentrations (fig. 4) for meperidine and alfentanil, respectively, and was preferred over the membrane-limited model, which gave high values of membrane permeability (table 1), thereby collapsing to a flow-limited model. However, even for the flow-limited model, there were systematic nonrandom trends in the residuals, suggesting that this model was not a complete description of the data. Table 2 shows the estimated and calculated cerebral pharmacokinetic parameters for each drug for the flow-limited model.
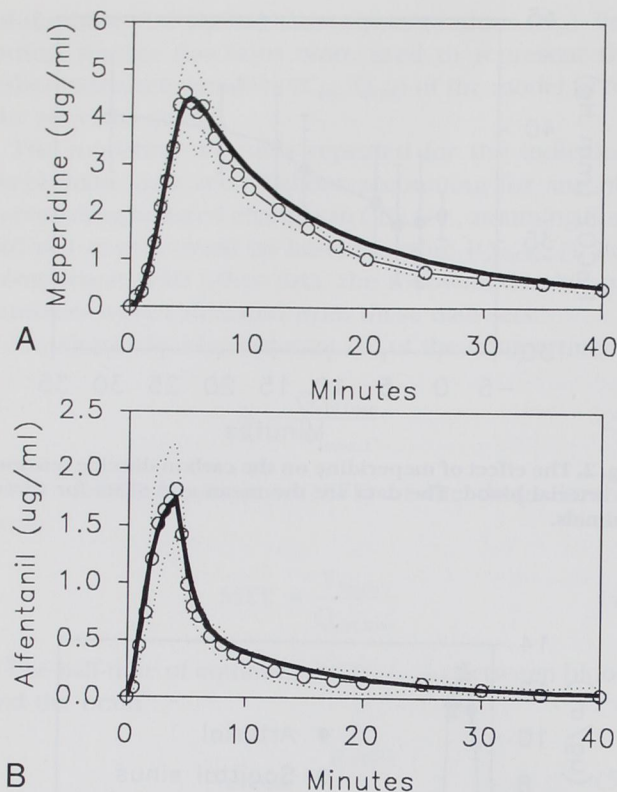
Fig. 4. (A) The observed (open circles) and predicted (solid line) data for the single flow-limited compartment model of the brain for meperidine. (B) The observed (open circles) and predicted (solid line) data for the single flow-limited compartment model of the brain for alfentanil. The upper and lower 95% confidence limits of the observed data are shown by the fine dotted lines. Thus, a predicted value that lies within these confidence limits is not statistically different from the observed data.

Table 1. Comparison of Models

Drug	Membrane-limited Model			Flow-limited Model	
	PS (ml/min) (mean ± SD)	$V_{brain,1}$ (ml) (mean ± SD)	MSC	$V_{brain,2}$ (ml) (mean ± SD)	MSC
Meperidine	$>10^3$	366 ± 20	4.22	364 ± 17	4.31
Alfentanil	$>10^3$	44 ± 5	3.41	47 ± 8	5.55

MSC = model selection criteria; the higher the value, the better the fit. The value of permeability (PS) for the membrane-limited models of both drugs converged on very high values and was consequently set to an upper limit of 1,000 ml/min. This compares with a baseline cerebral blood flow of 40 ml/min. The very high ratio of permeability over flow indicates that the model had collapsed to a flow-limited model; the resulting curve-fit and values of the volume for the brain were therefore comparable with those of the flow-limited model. The parameters of the model are shown as the mean and standard deviation of the estimate returned by the curve-fitting program, an indication of the uniqueness of the parameters.

Unlike studies of other drugs using this preparation,[11,12] this series of studies was restricted to defining the cerebral kinetics alone of alfentanil and meperidine.

Sheep are unusual in that the brain receives a small fraction of the cardiac output (approximately 2%).[26] However, because of the small size of the brain, the relative perfusion of the brain (measured in milliliters per minute per 100 g) is comparable with that of other species. Because cerebral kinetics depend on the fundamental physiologic properties of the brain and its relative (not total) blood flow, the cerebral kinetics of drugs in sheep are likely to be similar to that in other species. Previously, we studied the cerebral kinetics of propofol and thiopental in this preparation[11,12] and found them to be similar to those reported in other species.

Effect of Meperidine-induced Changes in Cerebral Blood Flow

If the meperidine-induced changes in CBF were not considered during modeling, the fit of the model (R^2) was not changed ($P = 0.45$ by paired t test), but the estimates of the volume of the brain were reduced by 15% ($P = 0.018$ by paired t test).

Discussion

Opioids have atypical effects in sheep that preclude a combined pharmacokinetic–pharmacodynamic analysis. We have observed that high doses of intravenous opioids in sheep have a stimulatory effect that induces dysphoria, and other investigators have noted these effects and shown that they are blocked by droperidol.[18]

Table 2. The Cerebral Pharmacokinetics of Meperidine and Alfentanil as Described by the Single Flow-limited Compartment Model

Calculated Pharmacokinetic Parameters	Meperidine	Alfentanil
Apparent volume (ml)	364 ± 17	47 ± 8
Rate constant (min^{-1})	0.11 ± 0.005	0.85 ± 0.14
Mean transit time (min)	9.1 ± 0.4	1.2 ± 0.2
Brain: blood partition coefficient	4.84 ± 0.22	0.62 ± 0.10
Equilibrium half-time (min)	6.3 ± 0.3	0.8 ± 0.1
Keo (published values) (min)	6–7*	1†

The fitted value of the apparent volume of the brain is shown with its standard deviation, which indicates the confidence of the least-squares estimate. The remaining parameters were calculated from the apparent volume as described in the text.

* Reported for cerebral evoked potentials in goats.[2]

† Reported for EEG changes in humans.[1]

The Mechanism of the Cerebral Uptake of Meperidine and Alfentanil

The data clearly support the second mechanism for accounting for differences in the cerebral kinetics of these opioids (table 1). The observed sagittal sinus concentrations of meperidine and alfentanil were more compatible with their disposition in the brain being described as a single flow-limited compartment than a membrane-limited, two-compartment model. Differences in the cerebral uptake of these opioids were due to differences in their solubility (apparent volume) in the brain rather than to differences in their rate of diffusion into the brain. This discounts the widely held belief that more lipophilic opioids (such as alfentanil) enter the brain faster than do less lipophilic opioids (such as meperidine). Rather, the rate of entry of both opioids into the brain was sufficiently rapid to not be rate limiting in their cerebral kinetics. The smaller apparent volume of alfentanil in the brain is consistent with its smaller distribution volume in the rest of the body compared with meperidine.[14] Given the relative lipophilicities of these opioids (alfentanil > meperidine), it is clear that its small distribution volume is not due to lower solubility of alfentanil in the lipids of the brain. The most likely mechanism for the differences in distribution volumes in the brain for these opioids is the fact that apparent tissue volumes are influenced by the ratio of binding of alfentanil in blood and brain.[27]

Morphine, with even lower lipophilicity than these two opioids, may be an exception to this rule. Some data suggest long effect delays (34 min),[3] which may imply a diffusion limitation in its cerebral uptake.

Models of Cerebral Kinetics for Opioids

There are some important issues with respect to the choice of an appropriate model to describe cerebral kinetics. Although the present data are sufficient to exclude the membrane-limited model in favor of the flow-limited model, it is clear that the flow-limited model has nonrandom deviations from the observed data (fig. 4), which suggests a small but systematic structural flaw in the model. However, these deviations were not compatible with membrane limitation because this model collapsed to a flow-limited model by producing estimates of membrane permeability much greater than blood flow (table 1). Simulations of the behavior of membrane-limited models will show that by nature they predict that postinfusion sagittal sinus concentrations will decline more slowly than those predicted by a flow-

limited model, which is contrary to the observed phenomenon.

That postinfusion concentrations decline more rapidly than a flow-limited model may imply a direct arteriovenous shunt. Initial trials with such a model showed improved fits to the observed meperidine data with a shunt of approximately 4% of total blood flow, but this was not pursued further because there is no supporting anatomic evidence. It is fascinating to note that Bjorkman et al.[8] reached a similar conclusion in their analysis of tissue unit disposition functions of opioids using deconvolution. Alternatively, one- or two-compartment dispersion models,[28] which better account the distribution of intravascular transit times in an organ, may improve the fit of the model, but unfortunately the application of these models to the current data is technically difficult because it requires curve fitting in the Laplace domain. Further analysis is in progress.

Comparison of Cerebral Kinetics and Effect Delay

Although it was not possible to measure the pharmacodynamic effects of meperidine and alfentanil in these studies, it is of interest to compare the observed half-life of equilibration between the brain and blood ($t_{1/2,equil}$) with the reported values of the effect compartment half-lives ($t_{1/2,keO}$) for effects expected to be a function of their cerebral concentrations (table 2). Despite species and methodologic differences among these studies, it is clear that there is good agreement between these half-lives. This circumstantial evidence suggests that a large component of the lag between blood concentrations and effects of these opioids can be attributed to the delay in equilibration between their blood and brain concentrations. This concept has been confirmed for thiopental[11] and propofol.[12] Thus factors that influence cerebral kinetics, such as CBF, may be important determinants of the time course of the effects of opioids, particularly in the period shortly after administration.

Modeling Drug-induced Changes in Organ Blood Flow

Meperidine is of particular interest in this study because it appeared to have flow-limited kinetics in the brain, yet it also reliably altered CBF. Although the modeling method used accounted for these drug-induced changes in flow, this raises the question to what extent should physiologic models of cerebral pharmacokinetics account for this phenomenon. Bjorkman et al.[29] showed that ketamine can reduce CBF and confirmed the need to account for organ blood flow changes in

direct mass balance calculations. In the present study, not accounting for drug-induced flow changes did not alter the fit of the flow-limited model to the data, but it did alter the estimate of the apparent volume of the brain by approximately 15%. This would suggest that the transient flow changes observed produced only insignificant changes in the shape of the predicted sagittal sinus concentrations and implies that these models are relatively insensitive to transient flow changes, at least when the apparent tissue volume is relatively large. However, the magnitude of estimated parameters can be erroneous, and ignoring drug-induced changes in organ blood flow cannot be recommended when examining organ drug kinetics.

Opioid Effects on Cerebral Blood Flow and Carbon Dioxide Tension

The possible causes of the CBF increases observed in this study include a direct cerebral vasodilatory effect, drug-induced stimulatory effect, and cerebral vasodilation resulting from increases in carbon dioxide tension. Carbon-dioxide–independent increases in CBF or intracranial pressure after administration of several opioids, including alfentanil, have been recorded previously, whereas a nearly equal number of studies have found no effect.[30-32] It is difficult to interpret the CBF findings in the current study because of drug-induced changes in ventilation and carbon dioxide tension, but the different time courses of CBF and carbon dioxide tension after meperidine administration suggest that mechanisms other than hypoventilation may be involved. It is likely that the stimulatory effect of opioids in sheep contributed significantly to CBF increases and to the time course of carbon dioxide tension changes. Significant opioid-induced dysphoria[18] was observed in all sheep in the current study during the first few minutes after administration of meperidine or alfentanil. Considerable variation in CBF associated with stimulation was previously recorded in awake sheep,[13] and the time course of the CBF increases displayed in figure 1 appeared to follow the time course of the drug's dysphoric effects. Further, simultaneous stimulation of ventilation may explain the minimal change in carbon dioxide tension for the first 10 min after meperidine administration. Probably this was replaced by ventilatory depression once dysphoria subsided.

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