Recirculatory model of fentanyl disposition with the brain as the target organ

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Background. The factors affecting the concentrations of fentanyl in the brain after intravenous administration have not been completely quantified.

Methods. A model integrating the role of brain, lung and systemic kinetics was developed based on data from conscious instrumented sheep. Brain kinetics were inferred from arterio-sagittal sinus concentration gradients and cerebral blood flow, and lung kinetics from the pulmonary artery-aortic gradient and cardiac output. The best models of the lung and brain were incorporated into a recirculatory model of the whole-body disposition of fentanyl. The validity of the model structure was tested by its ability to describe published data on the effect of hypo-, normo- and hypercarbia on the blood and brain concentrations of fentanyl in anaesthetized dogs.

Results. The cerebral kinetics of fentanyl were consistent with partial membrane limitation: the time to 50% equilibration with arterial blood was 10.0 min. Lung kinetics had two distinct components: a shallow compartment that was 50% equilibrated with blood in 0.72 min, and a loss term probably representing sequestration. Despite its simplicity, the recirculatory model was an adequate description of the sheep data. The dog data could be described if cerebral blood flow and cardiac output in the model were allowed to differ between hypo-, normo- and hypercarbic states. The required flow changes were in good agreement with the known effect of these states in the dog.

Conclusions. A recirculatory model with the brain as a target organ defined the quantitative relationship between the brain concentrations of fentanyl and the circulatory state.

Keywords: brain, cerebral blood flow; heart, cardiac output; pharmacokinetics, brain; pharmacokinetics, fentanyl; pharmacokinetics, lung; pharmacokinetics, models

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The therapeutic effects of commonly used opioids are known to be mediated largely via mu opioid receptors that are expressed predominantly in the central nervous system (CNS). While pharmacokinetic analysis of fentanyl disposition has often focused on the blood concentrations of fentanyl, it is known that the time course of some opioid effects (e.g. analgesia and changes in the electroencephalogram [EEG]) are delayed relative to the time course of the arterial blood concentrations, and the size of this delay is an important determinant of some clinical properties of opioids.1–3 The half-life of this delay has been reported to be 4.7–6.6 min for fentanyl in humans.4–6

The mechanism of the delay is unclear, but on theoretical grounds it may have a contribution from the equilibrium delay between the arterial and CNS concentrations of fentanyl, or a delay between CNS opioid concentration (the biophase) and the occupancy of opioid receptors due to slow dissociation from receptors, or a delay between receptor occupancy and the initiation of subsequent opioid effects.

The first process could be investigated by defining the cerebral kinetics of fentanyl (assuming that the brain is representative of the CNS). We have previously determined the cerebral kinetics of alfentanil, pethidine7 and morphine8 using a chronically instrumented sheep preparation. Cerebral kinetics were inferred by hybrid modelling of the concentrations of these opioids in sagittal sinus blood leaving the brain. In this paper, we report the analogous data for fentanyl.

There is also increasing interest in defining the role of recirculatory models in pharmacokinetic analyses, particularly for drugs that are administered via intravenous bolus or...
short infusion and whose disposition is affected by the state of the circulation. When kinetics are viewed from a recirculatory viewpoint, it is the kinetics of a drug in the lungs and the cardiac output that determine the initial drug concentrations in arterial blood (and elsewhere). We have previously developed recirculatory models of the disposition of thiopentone, propofol, lidocaine and verapamil in sheep. Lung kinetics in each case were determined from simultaneous pulmonary artery and arterial blood sampling and concurrent measures of cardiac output.

Therefore we proposed the development of a similar recirculatory model for fentanyl. Fentanyl is of interest in this context as it is often given via intravenous bolus or short infusion in the peri- and postoperative periods, as well as in the setting of patient-controlled analgesia. The circulatory states of many patients receiving fentanyl are affected by disease or concurrent anaesthesia. These models offer the potential both to describe and to predict the effect of changes in cardiac output and cerebral blood flow, such as those that occur in hypo- and hypercarbia.

The specific aims of the study were to determine the lung and cerebral kinetics of fentanyl during and after its i.v. administration (600 μg over 4 min) to chronically instrumented sheep, to determine the systemic kinetics of fentanyl during and after a 120 min i.v. infusion in sheep, to use the above data to develop a recirculatory model of the kinetics of fentanyl in sheep, with particular emphasis on predicting the time course of fentanyl concentrations in the brain, and to test the ability of the basic structure of the model to describe previously published data on the effect of hypo- and hypercarbia on the blood and brain concentrations of fentanyl in dogs.

This may provide greater understanding of the processes governing the concentrations of fentanyl in its most important target tissue.

Methods

Experimental methods

Animal preparation

In brief, female Merino sheep of similar age and body mass (~50 kg) were instrumented under general anaesthesia as described previously. Catheters were chronically implanted via the femoral vessels in the abdominal aorta (for sampling of arterial blood), the right atrium (for drug administration), the pulmonary artery (for blood sampling and thermodilution measurement of cardiac output) and the dorsal sagittal sinus (the appropriate site for sampling cerebral venous blood in sheep). A Doppler transducer was placed over the sagittal sinus using a previously validated method to provide an index of cerebral blood flow. The sheep were recovered from anaesthesia and housed in metabolic crates, with their catheters maintained with a saline–heparin lock (0.9%–50 iu ml−1). All experimental protocols were approved by the Animal Ethics Committee of the University of Adelaide.

Study design

Seven short-infusion studies (fentanyl 150 μg min−1 for 4 min) and five long-infusion studies (fentanyl 50 μg min−1 for 120 min) were conducted in separate sheep. Fentanyl was purchased from Astra Pharmaceuticals, North Ryde, NSW, Australia, and was infused intravenously via a right atrial catheter.

For each study, instrumented sheep were placed in slings inside their metabolic crates and were prepared for physiological measurements and blood sampling as described below. After a period of baseline measurements, the fentanyl infusion was begun at time zero. The sheep were extubated and spontaneously breathed room air throughout. For each study, the following pharmacodynamic and pharmacokinetic data were collected.

Pharmacokinetic measurements

The cerebral pharmacokinetics was determined from simultaneous measurements of arterial and sagittal sinus drug concentrations and an index of cerebral blood flow, as used previously in this preparation. For the short-infusion studies, arterial and sagittal sinus blood samples (0.5 ml) were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 15, 20, 30, 45, 60 and 75 min. All times are referenced to the start of the infusions. The lung pharmacokinetics was determined in an analogous manner from pulmonary arterial samples taken at the same times as the arterial samples, as used previously in this preparation.

The methods were the same for the long-infusion studies, but the arterial, sagittal sinus and pulmonary artery blood samples were taken at 0, 1, 3, 6, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 121, 123, 126, 130, 135, 140, 145, 150, 160, 170, 180, 195, 210, 225 and 240 min.

Cardiovascular measurements

Immediately prior to fentanyl infusions, cardiac output was measured three times using a thermodilution method. The values were averaged to give baseline cardiac output. For the long infusions, cardiac output was also measured at 20, 60, 120, 140, 180 and 240 min.

Arterial blood pressure was recorded continuously via a pressure transducer on one of the arterial catheters. Changes in cerebral blood flow were measured using the Doppler flow probe and a flowmeter (Bioengineering, University of Iowa, IA, USA). Both were recorded for 5 min prior to the start of drug infusion (baseline) and throughout the infusion using an analogue–digital card (Metrabyte DAS 16-G2) and a personal computer (486-based IBM compatible).

Additional arterial blood samples were taken immediately prior to the infusions and at regular intervals after the start of the infusion for blood gas analysis (ABL System 625, Radiometer, Sweden). Arterial oxygen tension, arterial carbon dioxide tension and arterial oxygen saturation were recorded.

Drug analysis

Fentanyl was assayed using a double extraction technique and high-performance liquid chromatography with UV
detection. All assays were calibrated using standard curves prepared in blood taken from the same animal prior to drug administration. The $R^2$ value of these standard curves exceeded 0.992 for every assay, and the average value was 0.998. The average limit of detection of the assays was 2.94 ng ml$^{-1}$. The coefficients of variation of the assay ($n = 3$) at 5, 10 and 25 ng ml$^{-1}$ were 19.6%, 10.4% and 8.3%, respectively.

Modelling methods: model structure and estimating parameter values

General

Modelling was performed using ‘Scientist’ software (Version 2.01, Micromath, Utah, USA). Models were written as differential equations, and were integrated using the Episode (Stiff) algorithm. Curve-fitting used a least-squares algorithm and model comparisons were made using the Model Selection Criteria (MSC) of this software. This is essentially the Akaike Information Criterion scaled for the size of the dataset and has been described in detail previously. In brief, MSC$<1$ is a poor fit, and MSC$>5$ is an excellent fit. An MSC of 2–3 would be considered good for most biological systems. No data weighting was used for the sheep data. Data weighting was chosen by considering the contribution of any heterogeneity to the variance of the data and the range of concentrations to be fitted.

The data used for modelling were the average concentration at each time point for all sheep of either the short- or long-infusion groups, as indicated. This minimized the contribution of intra-individual variability and helped model discrimination.

Hybrid modelling to determine a submodel of fentanyl kinetics in the brain

The arterial and sagittal sinus concentrations from the short-infusion studies were used to determine an appropriate model of the cerebral kinetics of fentanyl. The sagittal sinus concentrations in blood leaving the brain are a function of the rate that fentanyl is entering the brain (the product of the arterial fentanyl concentrations and cerebral blood flow) plus the influence of any kinetic processes within the brain. In hybrid modelling, the kinetic processes within the brain are represented by a model, and the rate of entry of fentanyl into the model is made to match that observed in vivo by fitting empirical continuous functions to the observed arterial concentrations and cerebral blood flow. The form (e.g. exponential or polynomial) of these ‘forcing’ functions is unimportant, provided that they interpolate the observed data accurately. They are necessary because the numerical integration used to solve the model requires continuous functions rather than discrete data points. With appropriate forcing functions in place, the sagittal sinus concentrations can be curve-fitted to estimate the parameter(s) of the model, and the relative values of the MSC can be used to decide which model is the most appropriate description of cerebral kinetics.

Five different models of brain kinetics were examined: a null model, where the sagittal sinus concentration equalled the arterial concentration, which tested the hypothesis that the concentration difference across the organ was due to random fluctuations; a single flow-limited compartment defined by a single distribution volume and organ blood flow; a two-compartment ‘tank in series’ model; a single flow-limited compartment with an apparent first-order loss representing either deep distribution or metabolism; a two-compartment membrane-limited model with a permeability term describing distribution into a deep compartment.

These models are shown in pictorial form in Figure 1 and the detailed equations are given in the Appendix. The measured arterial concentrations were fitted to multi-exponential forcing functions, and the measured changes in cerebral blood flow were fitted to a polynomial forcing function, but with the baseline value based on previous measurements. This latter assumption was made to produce sensible units for parameter values.

Hybrid modelling to determine a submodel of fentanyl kinetics in the lungs

A modelling process analogous to that used for the brain, the pulmonary artery and arterial concentrations from the short-infusion study was used to determine an appropriate model of the lung kinetics of fentanyl from those shown in Figure 1. The detailed equations are given in the Appendix. The arterial fentanyl concentrations leaving the lungs were curve-fitted to determine model parameters.

Recirculatory modelling of systemic kinetics

The cerebral and lung kinetic submodels providing the best fit of the data were incorporated into a recirculatory model to...
describe the time course of the systemic arterial concentrations (Fig. 2). The basic form of this model was adapted from recirculatory models of other drugs developed using this experimental preparation.\textsuperscript{15,17} Recirculation was incorporated by adding a tissue pool with a total body clearance term, with recirculated drug returned to the venous mixing compartment of the model. This venous compartment nominally accounts for the dispersion (broadening) of the concentration peak of an intravenously injected drug between the injection site and the pulmonary artery, and was fixed at a value of 0.255 litres.\textsuperscript{22}

The unknown parameters of the recirculatory model were the volume of the tissue pool ($V_{\text{pool}}$), the total body clearance ($Cl_{\text{tot}}$) and the cardiac output ($Q_{\text{CO}}$ estimated from the data for comparison with the measured value). The best estimates of these parameters were determined by fitting the arterial concentrations for the long-infusion studies. The remaining lung and brain parameters of the recirculatory model were fixed at the values determined by the hybrid modelling described above.

Model analysis via validation and simulation

Validation of the cerebral kinetic model

The best cerebral kinetic model derived from the short-infusion data was used to predict the time course of the sagittal sinus concentrations for the long-infusion studies. This was compared with the observed concentrations, and the mean prediction error was calculated.

Equilibration times

Simulations using the best submodels of the brain and lungs were used to calculate the time required for the brain and lung concentrations to reach 50% and 95% equilibration with afferent blood (arterial and pulmonary artery, respectively). The input into each organ was a step change of afferent concentration (e.g. 0 to 1) with no recirculation.

Simulations of the effect of cardiac output and cerebral blood flow

The final recirculatory model was also used to examine the effect of altered cardiac output and cerebral blood flow on the peak concentrations of fentanyl in the brain after a 4 min intravenous infusion of the same dose. Changes in flow were as documented in Table 5.

Altered cardiac output and cerebral blood flow: modelling published data in the dog

Previously published literature has reported the effect of hypo-, normo- and hypercarbia on the blood and brain concentrations of fentanyl in anaesthetized dogs after intravenous administration of fentanyl 250 \(\mu\)g over 1 min.\textsuperscript{23} The ability of the basic structure of the recirculatory model (Fig. 2) to account for the effect of these three circulatory states on fentanyl disposition was tested.

The process used essentially repeated that described above for sheep. The data of Ainslie and colleagues\textsuperscript{23} were interpolated from Figures 1 and 2 of their paper. First, hybrid modelling was used to fit the various models of cerebral kinetics discussed previously (Fig. 1) to the brain concentration data for all three circulatory states with cerebral blood flow as an unknown. The fitted cerebral blood flows for each state were compared with the results of McPherson and colleagues\textsuperscript{24} who reported the effect of hypo-, normo- and hypercarbia on cerebral blood flow in the anaesthetized dog. If the model is a good description of the data, there should be good agreement between the fitted and measured cerebral blood flow in this preparation.

Secondly, a recirculatory model (Fig. 2) was fitted simultaneously to the arterial fentanyl data (with 1/y weighting to account for the relatively wide concentration range) for all three circulatory states. The brain submodel was fixed as the best model determined as described in the previous paragraph. Cardiac output, volume of the lung ($V_{\text{lung}}$), volume of the tissue pool ($V_{\text{pool}}$) and total body clearance ($Cl_{\text{tot}}$) were estimated from the data. Cardiac output and clearance were assigned separate parameters for each circulatory state, and therefore were estimated for each state. The fitted cardiac outputs were compared with the data of Carson and colleagues\textsuperscript{25} and Kontos and colleagues\textsuperscript{26} who reported the effects of hypo-, normo- and hypercarbia on cardiac output in the anaesthetized dog. If the model is a good description of the data, there should be good agreement between the fitted and measured cerebral output in this preparation.

Statistical analysis

The object of the data analysis was to define the response of the average animal. Therefore data were reported as either mean (SEM) or 95% confidence intervals (95% CI) as needed for clarity. Measurements at a given time point were recorded as significantly different from baseline if the mean baseline value lay outside the 95% confidence intervals of the measurement at that time.

Estimates of model parameters are reported with their standard deviation as returned by the curve-fitting program.
Recirculatory pharmacokinetics of fentanyl

This is calculated from the Hessian matrix of the fit and indicates the precision of the estimate.

Results

Deviations from the protocol were as follows. In one short-infusion study, sagittal sinus samples could not be collected because of catheter failure, and in another short-infusion study mean arterial blood pressure could not be collected for the same reason. Occasionally, a sample could not be collected from catheters at any of the sites. These data were treated as missing values. In one experiment cardiac output could not be measured for either the short- or long-infusion studies because of technical problems.

Haemodynamic and other measurements

All sheep became mildly agitated and dysphoric with the administration of fentanyl. The general pattern of the haemodynamic measurements was consistent with this agitation, but agitation was more apparent for the short infusions. Cerebral blood flow was significantly elevated to a maximum of 144% of baseline (95% CI, 100–187) 10 min after the start of the short-infusion studies, and to 116% of baseline (95% CI, 108–124) for the long infusions. For both infusions, it had returned to baseline by the end of the studies. Mean arterial pressure was significantly elevated to a maximum of 120% of baseline (95% CI, 106–134) at 5 min for the short-infusion studies, and was unchanged from baseline for the long-infusion studies. The average baseline cardiac output for the short-infusion studies was 6.7 l min\(^{-1}\) (95% CI, 5.7–7.8). For the long-infusion studies it was 6.8 l min\(^{-1}\) (95% CI, 5.0–8.6), but was increased during the early part of the infusion with a maximum value of 8.0 l min\(^{-1}\) (95% CI, 5.3–10.8), although this was not statistically different from baseline.

Confidence interval analysis showed that arterial oxygen tension, arterial carbon dioxide tension and arterial oxygen saturation were unchanged from baseline following the administration of fentanyl for the short infusions. There were minor reductions in arterial oxygen tension and saturation at some time points during the long infusions (Table 1).

The time courses of the observed fentanyl concentrations for the short-infusion studies are shown in Figure 3. The data for 45, 60 and 75 min were generally below the limit of detection and were not included in subsequent analysis. Concentration differences across the lung (pulmonary artery–arterial) were evident during the infusion, but were minimal at other times. Concentration differences across the brain (arterial – sagittal sinus) were evident during the infusion, and the difference was reversed in the post-infusion period.

Modelling methods: model structure and estimating parameter values

Submodel of fentanyl kinetics in sheep brain

The parameters of the cerebral submodels are shown in Table 2. The membrane-limited model was clearly the best fit of the data; the line of best fit is shown in Figure 3B. The value of PS\(_{\text{brn}}\) (0.240 l min\(^{-1}\)) was greater than the cerebral blood flow (0.04 l min\(^{-1}\)), indicating that membrane limitation was partial. Thus the fentanyl concentrations in the deep compartment of the model (V\(_{2,\text{brn}}\)) were delayed only slightly relative to those of the compartment including sagittal sinus blood (V\(_{1,\text{brn}}\)), but the total time course of uptake was bi-exponential (since the model has two compartments).

Submodel of fentanyl kinetics in sheep lung

The parameters of the submodels of the lungs are shown in Table 3. The optimal model of these data was less clear, as the MSC values of some models were similar, with a general consensus that the lung included a single distribution volume of \(~6\) litres. The best model added a small unidirectional loss (equivalent to an extraction ratio of \(~10\%) to this volume which may represent a deep distribution that was essentially irreversible on the timescale of the study. The line of best fit for this model is shown in Figure 3C.

Recirculatory modelling of systemic kinetics in sheep

The recirculatory model was an adequate fit of the data (Fig. 4A). The final parameter values of the recirculatory model are shown in Table 4. The cardiac output estimated from the fentanyl concentration data (9.4 l min\(^{-1}\)) was within the 95% confidence interval of the measured peak cardiac output for the same dataset (5.3–10.8 l min\(^{-1}\)). This indicates that pharmacokinetic data can be used to estimate cardiac output in some circumstances.

Model analysis via validation and simulation

Validation of the cerebral kinetic model

The observed sagittal sinus concentrations for the long-infusion studies are shown in Figure 4B. The predicted sagittal sinus concentrations for this study based on the best (membrane-limited) cerebral submodel were in good agreement with the observed concentrations, and were within the 95% confidence intervals of the data. The mean prediction error was \(-0.48\). Thus the model was able to account for an independent dataset not used for its development.

Equilibration times

Simulations using the best (membrane-limited) cerebral submodel showed that the times to 50% equilibration were 8.0 min and 10.0 min for the first (V\(_{1,\text{brn}}\)) and second (V\(_{2,\text{brn}}\)) compartments, respectively, and the times to 95% equilibration were 41 min and 43 min, respectively. Simulations using the best (flow with loss) lung model showed that the equilibration times of the first lung compartment (V\(_{1,\text{lng}}\)) with pulmonary artery blood were rapid: 50% equilibration in 0.72 min, and 95% equilibration in 3.1 min.

Simulations of the effect of cardiac output and cerebral blood flow

The simulations using the final recirculatory model based on sheep data showed that altered cardiac output and cerebral blood flow had a major effect on the peak fentanyl concentrations achieved in the brain (Table 5). Low cardiac outputs and high cerebral blood flows were associated with
High peak brain concentrations for the non-steady-state conditions of the simulation.

Altered cardiac output and cerebral blood flow: modelling published data in the dog

A ‘two tank in series’ model was the best description of the cerebral kinetics for the data of Ainslie and colleagues in Table 1.

Table 1 Blood gas measurements. Arterial oxygen tension ($P_{aO2}$), arterial oxygen saturation ($SO_2$) and arterial carbon dioxide tension ($P_{aCO2}$) are shown as mean and 95% confidence limits for the short and long fentanyl infusion studies in sheep. *Mean baseline value lies outside the confidence interval of the measurement at a later time.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>$P_{aO2}$ (kPa)</th>
<th>$SO_2$ (%)</th>
<th>$P_{aCO2}$ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short (4 min) infusion studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14.7</td>
<td>10.5</td>
<td>18.8</td>
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<tr>
<td>4</td>
<td>14.1</td>
<td>12.3</td>
<td>15.9</td>
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<tr>
<td>10</td>
<td>13.8</td>
<td>11.2</td>
<td>16.3</td>
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<tr>
<td>30</td>
<td>13.8</td>
<td>11.2</td>
<td>16.4</td>
</tr>
<tr>
<td>Long (120 min) infusion studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14.1</td>
<td>13.3</td>
<td>14.9</td>
</tr>
<tr>
<td>20</td>
<td>12.6</td>
<td>9.8</td>
<td>15.4</td>
</tr>
<tr>
<td>60</td>
<td>11.8*</td>
<td>10.6</td>
<td>13.0</td>
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<tr>
<td>120</td>
<td>12.4</td>
<td>10.1</td>
<td>14.7</td>
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<tr>
<td>160</td>
<td>12.2</td>
<td>10.2</td>
<td>14.1</td>
</tr>
<tr>
<td>180</td>
<td>12.9*</td>
<td>12.0</td>
<td>13.8</td>
</tr>
<tr>
<td>240</td>
<td>12.4</td>
<td>11.0</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Table 2 Models of the cerebral kinetics of fentanyl in sheep. The goodness of fit of the models of fentanyl kinetics in the brain when fitted to the short-infusion data. MSC, model selection criteria (the higher the number, the better the fit). Parameters are apparent distribution volume ($V_{1,brn}$), first-order loss ($PS_{loss,brn}$), membrane permeability ($PS_{brn}$) and deep-compartment volume ($V_{2,brn}$) in the brain as described in Figure 1 and the Appendix. The data are shown as the mean (SD) returned by the curve-fitting program.

<table>
<thead>
<tr>
<th>Model</th>
<th>MSC</th>
<th>$V_{1,brn}$ (litres)</th>
<th>$PS_{loss,brn}$ (l min$^{-1}$/C$0_1$)</th>
<th>$PS_{brn}$ (l min$^{-1}$/C$0_1$)</th>
<th>$V_{2,brn}$ (litres)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>-0.60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow</td>
<td>2.07</td>
<td>0.415 (0.039)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tank in series</td>
<td>2.03</td>
<td>0.415 (0.040)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow + loss</td>
<td>2.03</td>
<td>0.414 (0.039)</td>
<td>&lt;10$^{-5}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membrane (fixed $V_{1,brn}$)</td>
<td>2.30</td>
<td>0.0045</td>
<td>0.240 (0.072)</td>
<td>0.490 (0.057)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Models of the lung kinetics of fentanyl in sheep. The goodness of fit of the models of fentanyl kinetics in the lungs when fitted to the short-infusion data. MSC, model selection criteria (the higher the number, the better the fit). Parameters are apparent distribution volume ($V_{1,lng}$), first-order loss ($PS_{loss,lng}$), membrane permeability ($PS_{lng}$) and deep-compartment volume ($V_{2,lng}$) in the lungs as described in Figure 1 and the Appendix. The data are shown as the mean (SD) returned by the curve-fitting program.

<table>
<thead>
<tr>
<th>Model</th>
<th>MSC</th>
<th>$V_{1,lng}$ (litres)</th>
<th>$PS_{loss,lng}$ (l min$^{-1}$/C$0_1$)</th>
<th>$PS_{lng}$ (l min$^{-1}$/C$0_1$)</th>
<th>$V_{2,lng}$ (litres)</th>
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<tbody>
<tr>
<td>Null</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Flow</td>
<td>2.01</td>
<td>7.64 (0.90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tank in series</td>
<td>1.79</td>
<td>2.32 (3.58)</td>
<td>4.26 (4.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow + loss</td>
<td>2.32</td>
<td>6.25 (0.77)</td>
<td>0.67 (0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Membrane</td>
<td>2.29</td>
<td>6.37 (0.99)</td>
<td>1.32 (0.54)</td>
<td>14.6 (11.2)</td>
<td></td>
</tr>
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</table>

Fig 3 (A) Measured pulmonary artery, aortic and sagittal sinus concentrations of fentanyl for short-infusion studies in sheep. Data are mean (SE); no error bar is shown if it is smaller than the symbol. (b) The time course of the arterio-sagittal sinus concentration difference (across the brain) for these studies and its 95% confidence interval. The solid line is the line of best fit for the membrane-limited model of Table 2. (c) Time course of the pulmonary artery–arterial concentration difference (across the lungs) for these studies and its 95% confidence interval. The solid line is the line of best fit for the ‘flow with loss’ model of Table 3. If the 95% confidence interval of the difference at a given time point does not include zero, then the concentration difference is statistically significant at that time.
Recirculatory pharmacokinetics of fentanyl

Fig 4 (A) Measured arterial concentrations of fentanyl for the long-infusion studies in sheep with 95% confidence intervals. The solid line is the best-fit concentration for the recirculatory model for the parameter values shown in Table 4. (B) Measured sagittal sinus concentrations of fentanyl for the long-infusion studies with 95% confidence intervals. The solid line is the predicted concentration for the membrane-limited model of Table 2. The good agreement between the observed and predicted measurements validates the cerebral model for a different dataset (long infusion) than that from which model parameters were estimated (short infusion).

<table>
<thead>
<tr>
<th>Model</th>
<th>MSC</th>
<th>$Q_{CO}$ (l min$^{-1}$)</th>
<th>$V_{pool}$ (litres)</th>
<th>$C_l_{tot}$ (l min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recirculatory</td>
<td>2.41</td>
<td>9.4 (1.0)</td>
<td>211 (25)</td>
<td>2.62 (0.17)</td>
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</tbody>
</table>

Table 4 Parameter values for the final recirculatory model for sheep. The final recirculatory model was fitted to the arterial concentrations for the long-infusion dataset. Values for cerebral and lung kinetics were fixed at values determined separately by hybrid modelling of individual datasets as shown in Tables 2 and 3. MSC, model selection criteria (the higher the number, the better the fit). The parameters are cardiac output ($Q_{CO}$), tissue pool volume ($V_{pool}$) and total body clearance ($C_l_{tot}$). Parameters are shown with the standard deviation (sd) returned by the curve-fitting program.

Table 5 Predicted effect of cardiac output and cerebral blood flow on peak concentrations of fentanyl after short infusions were affected by cardiac output and cerebral blood flow. This was confirmed by fitting the model to published data on the effect of hypo- and hypercarbia on serum and brain fentanyl concentrations in the dog. To fit these data, the model estimated values of cardiac output and cerebral blood flow that were in good agreement with the known effects of hypo- and hypercarbia on these flows.

<table>
<thead>
<tr>
<th>Cerebral blood flow (ml min$^{-1}$ [100 g]$^{-1}$)</th>
<th>Concentration (%)</th>
<th>CO=3 l min$^{-1}$</th>
<th>CO=6 l min$^{-1}$</th>
<th>CO=9 l min$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>71</td>
<td>64</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>118</td>
<td>100</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>151</td>
<td>125</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

that it was able to describe the brain concentration data for all three circulatory states. The MSC was 4.90, 4.27 and 5.04 for the hypo-, normo- and hypercarbic data, respectively. The corresponding half-lives of cerebral equilibration were 5.54 min, 3.85 min and 1.12 min, respectively. These half-lives are compared with previously published data on the effect of hypo-, normo- and hypercarbia on cerebral blood flow in Figure 5. There is good agreement between the two, suggesting that the observed effect of hypo-, normo- and hypercarbia on the cerebral kinetics of fentanyl can largely be explained by the known changes in cerebral blood flow.

The dog recirculatory model was able to describe the serum and brain concentration data in hypo-, normo- and hypercarbic states in the dog (Fig. 6). The cardiac outputs estimated from the concentration data were 1406 (sd 106) ml min$^{-1}$, 2136 (232) ml min$^{-1}$ and 5988 (993) ml min$^{-1}$ for the hypo-, normo- and hypercarbic data, respectively (Table 6). This is in agreement with the known effects of these states on cardiac output in the dog (Fig. 5).

**Discussion**

In summary, the CNS concentrations of fentanyl in sheep were found to be delayed relative to those in arterial blood, with the magnitude of the delay being similar to that reported between arterial blood concentrations and EEG effects for fentanyl. The initial CNS concentrations of fentanyl in sheep could be described by a recirculatory model that incorporated lung kinetics and the influence of cerebral blood flow and cardiac output. This model predicted that the peak brain concentrations of fentanyl after short infusions were affected by cardiac output and cerebral blood flow. This was confirmed by fitting the model to published data on the effect of hypo- and hypercarbia on serum and brain fentanyl concentrations in the dog. To fit these data, the model estimated values of cardiac output and cerebral blood flow that were in good agreement with the known effects of hypo- and hypercarbia on these flows.

**Opioid effects in sheep**

The dysphoric effect of opioids, and fentanyl in particular, in sheep has been reported previously. The dysphoria appeared to be accompanied by sympathetic stimulation, evident by the rise in blood pressure, but there was accommodation to the dysphoric effect with time. The dysphoria compromises the measurement of analgesia in sheep, particularly for methods with a behavioural component. However, the dysphoria would be expected to have only a minor effect on the temporal relationship between the blood and brain concentrations of fentanyl.

**Cerebral kinetics of fentanyl**

The global brain concentrations of a drug can be a significant determinant of its CNS effects if it dissociates rapidly from its CNS receptors and if it has no active metabolites. This is the case for fentanyl: the half-life of receptor dissociation of fentanyl is of the order of seconds, and the metabolites of fentanyl have limited analgesic activity in vivo. This is consistent with an early study that showed a close temporal relationship between brain concentrations of fentanyl and...
analgesic effects, although in this study the relationship was not quantified.

There are two important aspects of cerebral kinetics that dictate the time course of brain concentrations of a drug: the cerebral distribution volume(s), which can also be expressed as a brain–blood partition coefficient in the steady state, and the time required to fill these volumes. In the present study, the cerebral distribution volume was 0.490 litres. With a nominal real volume of 0.065 litres, this equates to a partition coefficient of 7.5 (i.e. 0.49/0.065). This is higher than the value of 4 (0.66) measured directly at steady state in rats, and 4.9 under non-steady-state conditions, which may reflect species differences.

The second aspect (the time required to fill the volume) has a theoretical maximum value governed by cerebral blood flow for the case where fentanyl diffusion across the blood–brain barrier is extremely rapid. Neither the present study (Table 2) nor earlier modelling in rats supports this completely flow-limited model of cerebral kinetics for fentanyl. This slight diffusion limitation on cerebral uptake has been observed in our preparation for drugs as diffusible as nitrous oxide, but the physical location of the diffusion barrier is not yet known.

Table 6 Parameter values for final recirculatory model fitted to the dog data of Ainslie and colleagues. A recirculatory model was fitted concurrently to all three (hypo-, normo- and hypercarbia) datasets. Parameter values for cerebral kinetics (not shown) were those determined separately by hybrid modelling of individual datasets. Separate values of cardiac output (CO) and total clearance (ClTot) were allowed for each of the three datasets, while the apparent volumes of the lung (Vlung) and tissue pool (Vpool) were common to all datasets. Data are shown as the parameter value (SD) as returned by the curve-fitting program. A weighting of 1/y was used, although the choice of weighting schemes influenced parameter estimates by less than 0.5%.

<table>
<thead>
<tr>
<th>Dataset</th>
<th>CO</th>
<th>Vlung</th>
<th>Vpool</th>
<th>ClTot</th>
</tr>
</thead>
<tbody>
<tr>
<td>All three</td>
<td>2.96 (106)</td>
<td>3048 (297)</td>
<td>21432 (2018)</td>
<td>391 (24)</td>
</tr>
<tr>
<td>Hypocarbia</td>
<td>1406 (106)</td>
<td>391 (24)</td>
<td>21432 (2018)</td>
<td>391 (24)</td>
</tr>
<tr>
<td>Normocarbia</td>
<td>2136 (232)</td>
<td>1210 (339)</td>
<td>21432 (2018)</td>
<td>1210 (339)</td>
</tr>
<tr>
<td>Hypercarbica</td>
<td>5988 (993)</td>
<td>955 (106)</td>
<td>21432 (2018)</td>
<td>955 (106)</td>
</tr>
</tbody>
</table>
However, the deviation from flow-limited behaviour was minor. In our study, 50% equilibration of the blood compartment was observed in 8.0 min, and of the deep compartment in 10.0 min. Again, these values are slower than the equilibrium half-lives of 5.5 min estimated from the steady-state data in rats, but are closer to the value (7 min) calculated from non-steady-state rat data extrapolated to humans. 

There have been few studies in the literature that have quantified the relationship between the brain concentrations of fentanyl and analgesic effects. However, the effect delay half-life of fentanyl between blood concentration and changes in the EEG have been reported as 6.4 (1.3) min, 4.71 (1.5) min and 6.6 (1.3) min. The broad similarity between the cerebral equilibration half-lives and these half-lives of effect delay suggest that a large component of the effect delay is due to the time required for cerebral equilibration. Therefore one would expect it to be influenced by factors affecting cerebral kinetics, such as cerebral blood flow.

On comparison with other opioids, the delay between arterial blood concentrations and brain concentrations/CNS effects of fentanyl is relatively long, being slower than alfentanil (~1 min) and pethidine (~6 min) and similar to that of morphine (~10 min) in the same preparation. The disequilibrium caused by this delay for fentanyl would be most evident in the first 30 min after rapid bolus administration (e.g. bolus loading doses in the perioperative and recovery period, or when used for patient-controlled analgesia) but not on longer timescales (e.g. when used via infusion as the main anaesthetic). The contribution of this disequilibrium should be accounted for when interpreting the blood concentrations of fentanyl in studies of shorter timescales.

There is indirect evidence of active transport of fentanyl out of the brain by p-glycoprotein. In contrast, it has been proposed that there is net active transport of fentanyl into the brain. Unfortunately, the present study does not provide any information about whether there were active or passive components of the cerebral uptake measured in sheep.

**Lung kinetics of fentanyl**

The interpretation of studies of lung kinetics is complicated by a number of methodological issues; however, the present data and that in the literature are reconcilable if fentanyl kinetics in the lungs is considered to have two distinct components: a rapidly equilibrating flow-limited volume (~6 litres in sheep, equivalent to a partition coefficient of ~4) and a slower deep distribution component (evident as the loss term PSoss,lng in Table 3). This is in general agreement with studies of the lung kinetics of fentanyl in humans. The first-pass extraction of fentanyl in the lungs measured using double-indicator techniques has been reported to be 83% and 71%, but this method is only an indirect measure of pulmonary distribution volume and is consistent with the first component of uptake. However, during a long infusion of fentanyl, a deeper distribution volume in the lungs appears to fill with fentanyl, producing large lung–blood partition coefficients at near steady state (e.g. a coefficient of ~15 after 6 h of infusion).

**Recirculatory model of fentanyl**

The recirculatory model is a parsimonious description of the kinetics of fentanyl and is suitable for predicting the peak blood and brain concentrations of fentanyl after short intravenous administration. It is these peak concentrations that are likely to dictate the maximum therapeutic and adverse effects of fentanyl. The basic form of the model dictates that both cardiac output and cerebral blood flow are significant determinants of peak brain concentrations of fentanyl after administration of short infusions (Table 5), with relatively large changes in peak concentration possible over a plausible physiological range for these flows.

The data of Ainslie and colleagues from studies in dogs provided an opportunity to test this prediction. The dog model could only be developed because the sheep data limited the assumptions that needed to be made, particularly by supporting the use of single compartments for the lung and tissue pools. It is a feature of recirculatory models that lung kinetics must be understood and represented correctly if the representation of the effect of cardiac output in the model is to be accurate. The preferred model for the brain for these dog data differed from that found for the sheep data. It is likely that the optimal type of model is also a function of whether cerebral kinetics is inferred from brain concentrations (Ainslie data) or from cerebral venous concentrations (sheep data). However, it is clear (Fig. 5) that the differences in cerebral blood flow required by the model to fit the data are in good agreement with the known changes in cerebral blood flow with hypo-, normo- and hypercarbia in the dog. Furthermore, when this model of cerebral kinetics is incorporated into a recirculatory model, the differences in cardiac output required by the model to fit the data are in good agreement with the known changes in cardiac output in the same species. This supports the concept that recirculatory models of this level of complexity are able to describe the major processes involved in the interactions between fentanyl concentrations in its target tissue and in the circulatory state. It is the difference in cerebral blood flow and cardiac output that largely account for the effect of hypo-, normo- and hypercarbia on the concentrations of fentanyl in the brain after acute intravenous administration. This may have implications with respect to how the fentanyl dose should be modified for different patient groups.

**Appendix. Detailed equations for models**

**Submodels of brain and lungs**

The basic form of the equations describing these models has been published previously, but are reproduced in...
Table A1 Equations describing submodels of brain and lungs

<table>
<thead>
<tr>
<th>Model</th>
<th>Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null model</td>
<td>$C_{out} = C_{in}$</td>
</tr>
<tr>
<td>Flow-limited model</td>
<td>$V_1 \frac{dC_{in}}{dt} = Q \left( C_{out} - C_{in} \right)$</td>
</tr>
<tr>
<td>Tank in series model</td>
<td>$V_2 \frac{dC_1}{dt} = Q \left( C_2 - C_1 \right)$</td>
</tr>
<tr>
<td>Flow with loss model</td>
<td>$V_2 \frac{dC_1}{dt} = Q \left( C_{out} - C_1 \right)$</td>
</tr>
<tr>
<td>Membrane-limited model</td>
<td>$V_2 \frac{dC_{pool}}{dt} = Q \left( C_{in} - C_{pool} \right) + PS_{inj} \cdot C_{out}$</td>
</tr>
</tbody>
</table>

Table A1 in a general form. $C_{in}$ and $C_{out}$ are the afferent and efferent drug concentrations of an organ and $Q$ is organ blood flow (Table A1). $V_1$ is the volume of the first compartment of the models, and $V_2$ and $C_2$ are the volume of and concentration in the second compartment (if appropriate). PS is the permeability term for loss or exchange from the first compartment. For the brain kinetic models, the parameters of the above models are labelled by the subscript brn, $C_{in}$ is the arterial concentrations, $C_{out}$ is the sagittal sinus concentration and $Q$ is cerebral blood flow. For the lung models, the subscript is lng, $C_{in}$ is the pulmonary arterial concentrations, $C_{out}$ is the arterial concentration and $Q$ is the cardiac output.

Recirculatory model

The series of differential equations for the recirculatory model in sheep are given below. They are written in a format common to many differential-equation-solving programs, where $C'$ indicates a derivative with respect to time (dC/dt). In general, $C$ denotes concentration, $V$ denotes volume and $Q$ denotes blood flow.

$C_{inj} = \text{dose rate}/QCO$

$V_{mix} \cdot C_{pa}' = \left( QCO \cdot C_{inj} - C_{pa} \right) + Q_{pool} \cdot C_{pool} + Q_{brn} \cdot C_{SS}$

$V_{1\text{lung}} \cdot C_{art}' = \left( QCO \cdot C_{pa} - C_{art} \right) - PS_{lng} \cdot C_{art}$

$V_{1\text{brn}} \cdot C_{SS}' = Q_{brn} \cdot C_{SS} + PS_{brn} \cdot C_{2\text{brn}}$  

$V_{2\text{brn}} \cdot C_{2\text{brn}}' = PS_{brn} \cdot C_{SS} - C_{2\text{brn}}$

$Q_{pool} = \left( QCO - Q_{brn} \right)$

$V_{pool} \cdot C_{pool}' = Q_{pool} \cdot C_{art} - Q_{pool} \cdot C_{pool} - C_{\text{art}}$

Acknowledgement

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Recirculatory pharmacokinetics of fentanyl

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