J. Pharm. Pharmacol. 2000, 52: 181–189
Received June 30, 1999
Accepted September 28, 1999

Development and Validation of a Recirculatory Physiological Model of the Myocardial Concentrations of Lignocaine after Intravenous Administration in Sheep

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Abstract

A recirculatory physiological model of the determinants of the myocardial concentrations of lignocaine after intravenous administration was developed in sheep and validated with the intention of analysing and predicting the outcome of altered dose regimens and various pathophysiological states on the initial myocardial concentrations of lignocaine.

The structure and parameters of the model were determined by hybrid modelling of the time-courses of the pulmonary artery, arterial and coronary sinus concentrations of lignocaine after the intravenous administration of 100 mg of lignocaine over 5 min to 5 chronically instrumented sheep. The model accounted for the determinants of the myocardial concentrations via compartments for venous mixing, the lung (a single-compartment model with a first-order loss) and the heart (a single flow-limited compartment). Recirculation and the remainder of the body were represented as a single tissue pool with a clearance term. The distribution volume of the heart was $0{\cdot}42 \pm 0{\cdot}009$ L, which gave a half-time of myocardium : blood equilibration of 2·37 min. The distribution volume of the lungs was $5{\cdot}40 \pm 0{\cdot}23$ L, with an apparent first-order loss of $1{\cdot}02\ \mathrm{L\ min^{-1}}$ representing deep distribution or metabolism. The validity of the model was tested by comparing the predictions of the model with the equivalent data collected in 6 sheep when lignocaine (89 mg) was administered via a complex dose regimen with a faster initial rate of infusion ($39{\cdot}1\ \mathrm{mg\ min^{-1}}$), declining exponentially to basal infusion rate ($7{\cdot}02\ \mathrm{mg\ min^{-1}}$) over 8 min. The predictions of the model were in general agreement with these data.

It is concluded that the model was sufficient to account for the effect of altered dose regimens of lignocaine on the time-course of its myocardial concentrations.

Lignocaine blocks sodium channels in nerve cells and the myocardium, the latter accounting for its clinical use by intravenous injection as an antiarrhythmic. It has been shown that rapid intravenous bolus injection of lignocaine was associated with transient depression of myocardial contractility in a conscious sheep preparation (Huang et al 1992). The reductions in contractility were temporally related to the time-course of the calculated concentrations of lignocaine in the myocardium, which also showed a transient peak after intravenous bolus administration (Huang et al 1993a). Other workers have shown that the prolongation of the QRS interval of the electrocardiogram by lignocaine is also temporally related to its concentration in the isolated rabbit heart (Mazoit et al 1993). Consequently, the myocardial concentrations of lignocaine appear to play an important role in determining the time-course of some of its clinically important myocardial effects.

The development of a model of the determinants of the myocardial concentrations of lignocaine would offer several potential advantages. Firstly, it could be used to facilitate the development of a dose regimen of lignocaine that minimises the transient peak in its myocardial concentration after intravenous bolus injection but that rapidly attains therapeutic concentrations in the myocardium. Secondly, it would provide insight into how disease states that alter the cardiovascular system (such as hypoxia or shock) affect lignocaine dose requirements.

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The most appropriate form of such a model is worthy of some comment. Traditional compartmental models have a number of limitations in describing drug concentrations after bolus administration, even when an effect compartment is used as a surrogate for a target organ. Principally, the initial distribution volume of these models has no physiological identity, and its size is highly dependent on the dose regimen and initial blood sampling schedule used in a particular experimental study (Chiou 1980). Consequently, models fitted to bolus or infusion data may not be directly comparable, as has been demonstrated for the intravenous anaesthetic, propofol (Vuyk et al 1995). Multi-organ physiological models (Benowitz et al 1974) can be used to overcome this lack of physiological reality, but are labour intensive and require determination of drug kinetics in a number of organs that do not directly influence the time-course of drug concentrations in the target organs responsible for drug effects. Furthermore, organ blood flow is often estimated rather than measured directly.

Hybrid recirculatory models (Krejcie et al 1994, 1997; Upton & Ludbrook 1997; Huang et al 1998) appear to offer some middle ground as they can accurately describe bolus kinetics while greatly reducing the number of organs in which drug kinetics and blood flow need to be determined. Of principal importance is the need to accurately represent the relationships between vascular mixing, cardiac output and lung kinetics (Krejcie et al 1994; Wada & Ward 1994), and the kinetics of the drug in the target organ of interest (e.g. the heart for lignocaine (Upton 1996)). The remainder of the body is lumped as one or two compartments, as for a traditional compartmental model.

The aim of this project was to develop a hybrid recirculatory physiological model of the determinants of the myocardial concentrations of lignocaine in an instrumented sheep preparation. To develop the model, its parameters were estimated from data collected when lignocaine was infused over five minutes to sheep. It was felt that the model would be useful for devising intravenous dose regimens that optimise the delivery of lignocaine to the heart if it was able to predict the consequences of rapidly changing dose regimens of lignocaine on the time-course of its myocardial concentrations. To validate the model, it was used to predict the outcome of a complex three-part short-infusion regimen of lignocaine. These predictions were compared with data collected when the complex regimen was administered to sheep. The model extends, and validates in-vivo, a previously published model of the first-pass kinetics of lignocaine (Upton 1996).

Methods

Experimental procedure

Six chronically instrumented sheep were prepared using a method described in detail elsewhere (Huang et al 1992). In summary, under anaesthesia and sterile surgical conditions, an ultrasonic Doppler flow probe was placed on the left main-stem coronary artery for measurement of an index of myocardial blood flow. Intravascular catheters were placed via the right carotid artery or jugular vein in the ascending aorta (for arterial blood sampling, arterial blood pressure and placement of left ventricle Miller manometer catheter), inferior vena cava (for drug administration), the coronary sinus (for sampling myocardial effluent blood after ligation of the hemiazygous vein) and in the pulmonary artery (Model TD1755H, Biosensors International, Singapore, for blood sampling and thermodilution cardiac output measurement). Following recovery from anaesthesia, the sheep were placed in mobile metabolic crates and their catheters were continuously flushed with heparinized (5 int. units mL^{-1}) 0·9% saline at a rate of 3 $mL\,h^{-1}$, using a gas-powered system. Post-operative analgesia was provided using intramuscular xylazine (0·05 $mg\,kg^{-1}$) as required (Grant et al 1996). All animals had free access to food and water.

At a later date, the sheep were administered 100 mg of lignocaine as an intravenous infusion over five minutes. Immediately before the infusions, cardiac output was measured three times using a thermodilution method. Their values were averaged to give the baseline cardiac output. Following the start of the infusions, 0·5-mL pulmonary artery, arterial and coronary sinus blood samples were taken until 20 min after drug administration, using an intermittent withdrawal method that ensured no contamination of blood samples with catheter deadspace (Huang et al 1991). The times of the pulmonary artery blood samples were 0·5, 1·5, 2·5, 4, 5, 6, 7, 10, 12·5, 15, 17·5 and 20 min after the start of the infusion. More rapid sampling was possible from the larger-bore coronary sinus catheter, with additional samples taken at 3, 5·5, 6·5 and 8 min. Even more rapid sampling was possible for the arterial catheter, with additional samples taken at 0·25, 1, 2, 3, 5·5, 6·5 and 8 min.

All blood samples were stored at −20°C and the whole-blood concentrations of lignocaine were later assayed using an internal standard gas chromatographic method (Nancarrow et al 1987). Samples were extracted into toluene under basic conditions, and the toluene injected into a gas chromatograph with a packed OV-17 column and a

nitrogen–phosphorous detector. The limit of sensitivity of the assay was approximately 0·1 mg L^{-1}.

Model development

The structure of the hybrid recirculatory model is shown in Figure 1 and is modified from a previously published first-pass model of lignocaine (Upton 1996). Similar models have been used previously to model data arising from this experimental preparation (Upton & Ludbrook 1997; Huang et al 1998; Upton & Ludbrook 1999).

In the previous first-pass model, the lung was represented as a single compartment with a fixed first-order extraction ratio of 32% (Upton 1996). In the present model, hybrid modelling was used to refine the submodel of the lung. The input to the lungs was taken to be the pulmonary artery concentrations (fitted to an empirical forcing function) and cardiac output (set at the measured baseline value); the output from the lungs (the arterial concentrations) was curve-fitted to determine model parameters.

Three different kinetic models of the lungs were fitted to the data: a single flow-limited compartment through which cardiac output flowed; a single flow-limited compartment with an apparent first-order loss representing either deep distribution or metabolism; and a two-compartment membrane-limited model with a permeability term describing distribution into a deep compartment.

The basic form of the equations describing these three models has been published previously (Huang et al 1998), but are reproduced below in a general form where C_{in} and C_{out} are the afferent and efferent drug concentrations of an organ, respectively, and Q is organ blood flow.

$$V_1 \cdot dC_{out}/dt = Q \cdot (C_{in} - C_{out}) \quad (1)$$

$$V_1 \cdot dC_{out}/dt = Q \cdot (C_{in} - C_{out}) - PS \cdot C_{out} \quad (2)$$

$$V_1 \cdot dC_{out}/dt = Q \cdot (C_{in} - C_{out}) + PS \cdot (C_2 - C_{out})$$
$$V_2 \cdot dC_2/dt = Q \cdot (C_{out} - C_2) \quad (3)$$

Where equations 1, 2 and 3 pertain to the three kinetic models described above, respectively; 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 from the first compartment.

Hybrid modelling was also used to examine the ability of these three models to describe the heart kinetics of lignocaine. In this case, the input to the heart was taken to be the arterial concentrations (fitted to an empirical forcing function) and myocardial blood flow (set at a previously measured baseline value), while the output from the heart (the coronary sinus concentrations) was curve-fitted to determine model parameters.

Recirculation was incorporated by adding a tissue pool with a total body clearance term as shown in Figure 1. The values of these additional parameters were determined by fitting the pulmonary arterial and arterial concentrations with the lung and heart kinetic parameters fixed at the values determined by the hybrid modelling described above. The recirculated drug was returned to the venous mixing compartment of the model, which accounts for

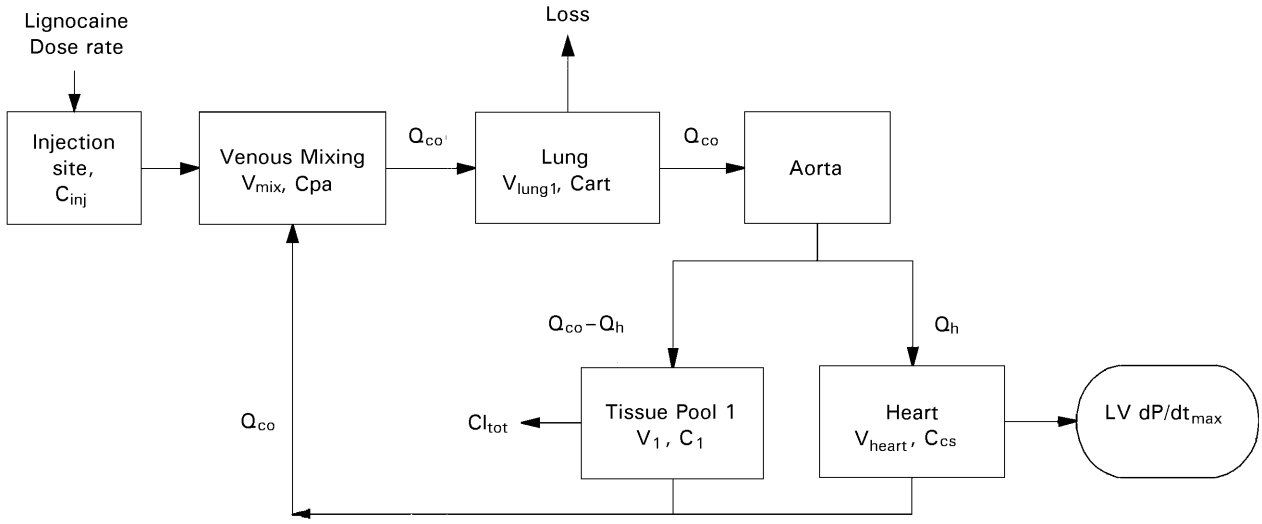

Figure 1. An overview of the recirculatory model of intravenous lignocaine administration to sheep. Q_{co} is cardiac output, Q_h is myocardial blood flow and LV dP/dt_{max} is the maximum rate of rise of left ventricular pressure, an index of myocardial contractility.

the dispersion (broadening) of the concentration peak of an intravenously injected drug between the injection site and the pulmonary artery (Upton & Huang 1993; Upton 1996). The volume of this compartment was initially set at 0·255 L based on the previous first pass model (Upton 1996), but was later changed to a fitted parameter.

A systemic model with a second tissue pool to account for any deep systemic distribution was also examined, as used previously for other drugs (Upton & Ludbrook 1999). In this model, the fraction of the cardiac output (less heart blood flow) going to the first and second pool was arbitrarily set at 70 and 30%, respectively (see below) and total clearance was set at $1{\cdot}26\,\mathrm{L\,min^{-1}}$ as previously determined by Mather et al (1986) in sheep.

Parameter estimation

The unknown parameters of the models were estimated from the appropriate concentrations using modelling software (Scientist for Windows, Version 2, Micromath, UT). The best fit was determined by maximising the model selection criteria (MSC). The MSC is essentially the Akaike information criterion scaled to compensate for data sets of different magnitudes (Scientist for Windows manual), and is calculated from the following formula:

$$\mathrm{MSC} = \ln\left(\frac{\sum_{i=1}^{n} w_i(y_{obs,i} - \overline{y_{obs}})^2}{\sum_{i=1}^{n} w_i(y_{obs,i} - y_{cal,i})^2}\right) - \frac{2p}{n} \qquad (4)$$

where w_i is a weighting term and p is the number of parameters. No weighting was considered necessary as there was no evidence that the data were heteroscedastic.

Model validation

It was felt that the model would be useful for devising dose regimens of lignocaine that target the heart if it was able to predict the consequences of rapidly changing dose regimens. To test this, a complex dose regimen was devised consisting of a three-stage infusion, with a faster initial infusion (Rate1) declining exponentially (Rate2) to a slower infusion (Rate3). The overall infusion rate was the sum of three separate components:

$$\mathrm{Rate1},\ \text{for } 0 < t < \tau 1 \qquad (5)$$

$$\mathrm{Rate2} = \mathrm{Rate1} \cdot e^{(-k(t-\tau 1))},\ \text{for } \tau 1 < t < \tau 2 \qquad (6)$$

$$\mathrm{Rate3},\ \text{for } 0 < t < \tau 2 \qquad (7)$$

Where $\tau 1$ is the stop time of the initial faster infusion, $\tau 2$ is the stop time of the slower infusion and k is the rate constant of the declining exponential infusion. The total dose given by such a system is given by the following formula:

$$\mathrm{Dose} = \mathrm{Rate1} \cdot \tau 1 + (\mathrm{Rate1}/k) + \mathrm{Rate3} \cdot \tau 2 \qquad (8)$$

The values used for the regimen were: Rate1 $= 39{\cdot}1\,\mathrm{mg\,min^{-1}}$; $\tau 1 = 0{\cdot}5$ min; $k = 2{\cdot}8\,\mathrm{min^{-1}}$; Rate3 $= 7{\cdot}02\,\mathrm{mg\,min^{-1}}$; and $\tau 2 = 8$ min, which gave a dose of 89 mg. These values were chosen empirically to produce a time-course of myocardial concentrations that avoided a high peak concentration by letting the concentrations rise slowly over three minutes to a constant target value, which was maintained for the following five minutes.

The parameters and the equations describing the complex dose regimen (equations 5–7) were programmed as a macro in a spreadsheet program (Excel 4.0, Microsoft Corporation), which was used to reset the infusion rate of a syringe pump (Model 33, Harvard Instruments, UK) via a serial interface at 1-s intervals so that pump rate matched the desired complex infusion rate. The complex infusion was then administered to 6 sheep prepared as described above. In an analogous manner to the 5-min infusion studies, pulmonary artery, arterial and coronary sinus blood samples were taken during and after the infusion and assayed for lignocaine as described above. The times of the pulmonary artery and coronary sinus samplings were 0·5, 1·5, 3, 4, 5, 6, 8, 8·5, 9, 9·5, 10, 12·5, 15, 17·5 and 20 min. Additional arterial samples were taken at 0·25, 1 and 2 min.

Pharmacodynamic measurements

In both the 5-min and complex infusion studies, the maximum rate of rise of left ventricular pressure (LV dP/dt_{max}), was measured using an acutely placed left ventricular catheter as previously described (Huang et al 1992) to quantitate a pharmacodynamic effect of lignocaine. The index of myocardial blood flow and mean arterial pressure were recorded continuously throughout the experiments.

Statistical analysis

To compare the observed and predicted data for the complex infusion, the predicted data was plotted with the mean and 95% confidence intervals of the observed data (calculated assuming a t-distribution; Gardner & Altman 1989). The predicted concentration at a given time-point was recorded as not statistically different to the observed concentrations

if it lay within the confidence intervals of the observed concentrations.

Results

In one sheep it was not possible to collect arterial blood samples for the 5-min infusion study due to a catheter failure. This sheep was not included in the pooled analysis so that the total number of animals studied was 5 and 6 for the 5-min and complex infusion regimens, respectively. In the first sheep studied, baseline cardiac output was not measured due to technical difficulties. For the other sheep, the mean baseline cardiac outputs and their 95% confidence intervals for the 5-min and complex infusion regimens were 6·36 (5·90–6·82) and 6·14 (5·59–6·68), respectively, which were not significantly different at the 95% confidence level.

Model development

The best hybrid model of the heart was a single flow-limited compartment (MSC = 5·04) with an apparent volume of 0·418 L (Figure 2). For the baseline value of myocardial blood flow of 0·122 L min^{-1}, this distribution volume gave a half-time of myocardium : blood equilibration of 2·37 min. The flow-limited-with-a-loss model was a good fit of the coronary sinus concentrations, but the permeability term (PS) tended to a small non-identifiable value (0·009 ± 0·0012 L min^{-1}) and the model had a lower MSC (4·93). The membrane-limited model was also a good fit, but tended to a very large value for the volume of the second compartment, which was constrained to 10^5 L. The permeability term (PS) also tended to a small non-identifiable value (0·009 ± 0·0017 L min^{-1}) and the model had a lower MSC (4·81).

The best hybrid model of the lung was a single flow-limited model with an apparent first-order loss (MSC = 4·78) with an apparent volume of 5·40 L and a permeability term of 1·02 L min^{-1} (Figure 3). The flow-limited model was simply a poor fit of the data (MSC = 2·54); while the membrane-limited model was a good fit of the arterial concentrations, it tended to a very large value for the volume of the second compartment and was constrained to 10^5 L. The overall MSC was lower (4·67).

Initial fits of the systemic kinetics with models with both the 1 and 2 tissue pools using a venous mixing volume of 0·255 L showed a systematic overestimation of the early intra-infusion pulmonary artery concentrations. This volume was changed to a fitted parameter, whereby both systemic models were able to provide good descriptions of the systemic data (MSC values of 4·90 each) with an estimated mixing volume of 1·56 L. This suggests greater dispersion between the injection site and the pulmonary artery when comparing the present study with earlier studies of venous mixing based on intravascular markers (Upton 1996). This may be due to a more peripheral venous injection site in the present study, or may be due to some other factor enhancing dispersion when lignocaine mixes with blood in the venous vasculature.

The two-pool model was characterised by a large, uncertain value for the volume of the second pool (481 ± 471 L). In the one-pool model, this deep distribution was manifested as a high apparent clearance (4·76 ± 0·47 L min^{-1}) and this was chosen as the final systemic model. This observation agrees with earlier findings that the deep distribution of lignocaine can

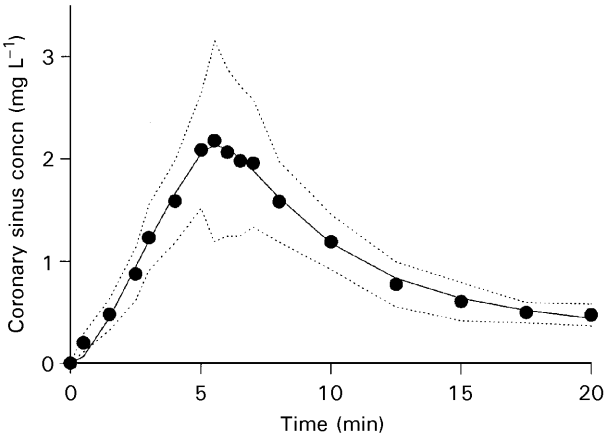

Figure 2. The observed time-course of the mean coronary sinus concentrations in 5 sheep achieved during and after an infusion of 100 mg of lignocaine over five minutes (●) and their upper and lower 95% confidence intervals (· · · · · ·). The line of best fit for the single flow-limited compartment hybrid model of the heart is also shown (——).

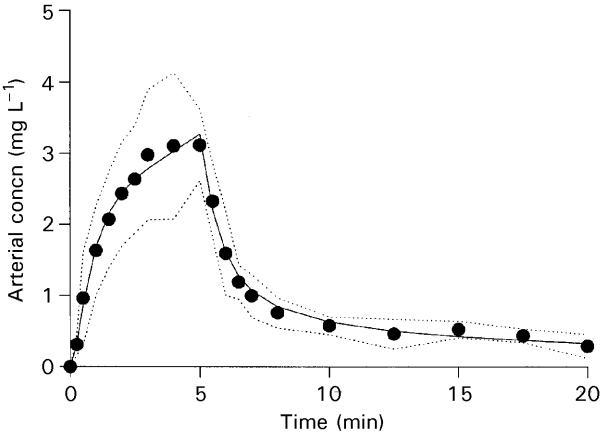

Figure 3. The observed time-course of the mean arterial concentrations in 5 sheep achieved during and after an infusion of 100 mg of lignocaine over five minutes (●) and their upper and lower 95% confidence intervals (· · · · · ·). The line of best fit for the single flow-limited compartment with a first-order loss hybrid model of the lungs is also shown (——).

be indistinguishable from a high systemic clearance in some pharmacokinetic studies (Upton et al 1988). The fit of the final systemic model incorporating the hybrid models of the lungs and heart to the observed concentrations of lignocaine in pulmonary artery, aortic and coronary sinus blood for the 5-min infusion studies are shown in Figure 4. The values of the parameters of the model estimated from these data are shown in Table 1, and were all estimated with good precision. The detailed equations of the models are given in Appendix 1.

Model validation

The observed concentrations of lignocaine in pulmonary artery, aortic and coronary sinus blood for the complex infusion studies are shown in Figure 5. The predicted values are also shown and were within the 95% confidence intervals of the observed data, except for the pulmonary artery concentrations at 0·5 and 17·5 min, and the arterial concentrations at 0·25 and 1 min. While the prediction performance of the model was generally good, it is apparent from Figure 4 that the greatest deficiency of the model was its inability to account for the early peak in the pulmonary arterial and arterial concentrations.

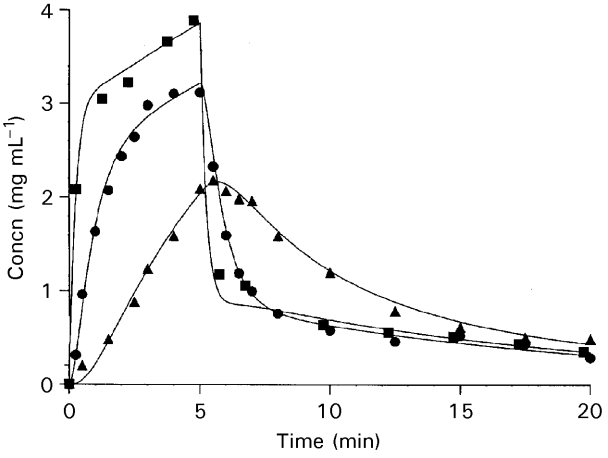

Figure 4. The observed mean pulmonary artery (■), aortic (●) and coronary sinus (▲) concentrations of lignocaine in 5 sheep achieved during and after an infusion of 100 mg of lignocaine over five minutes. The lines of best fit of the final model after defining heart, lung and systemic kinetics separately are also shown.

Pharmacodynamic measurements

Although both the 5-min or complex infusion regimens produced statistically significant reductions in LV dP/dt_{max} (Table 2), the changes were not of sufficient magnitude to be related to the coronary sinus concentrations of lignocaine in a reliable manner. This contrasted with injection of 100 mg of lignocaine as a rapid intravenous bolus (Table 2).

Neither dose regimen produced biologically significant changes in myocardial blood flow. The mean flow for the duration of the 5-min and complex regimens were $104 \pm 9\%$ and $99 \pm 6\%$ of baseline, respectively. Mean arterial pressure also varied little throughout the studies, with mean values of 103 ± 1 and 106 ± 2 mmHg for the duration of the 5-min and complex regimens, respectively.

Discussion

There is increasing evidence that the uptake of cardioactive drugs into the myocardium can be a major determinant of their efficacy and potential toxicity. For some drugs, including lignocaine, important pharmacodynamic effects are directly related to the myocardial concentrations of the drug (Mazoit et al 1990, 1993; Huang et al 1993a, 1998; Upton et al 1996, 1999). For other drugs or patient groups, or both, effects appear to be related to a slower equilibrating site within the myocardium (Ritchie et al 1998).

Table 1. The parameters of the model estimated from the 5-min infusion data following intravenous lignocaine administration to sheep.

Parameter	Description	Parameter value	Fixed or fitted
Q_{co}	Baseline cardiac output	6·36 L min^{-1}	Fixed
V_{mix}	Volume of venous mixing compartment	1·56 ± 0·08 L	Fitted
V_{lung1}	Volume of the lung	5·40 ± 0·23 L	Fitted
PS_{lung}	Lung permeability	1·02 ± 0·09 L min^{-1}	Fitted
V_{heart}	Apparent volume of heart	0·42 ± 0·009 L	Fitted
Q_h	Baseline myocardial blood flow	0·122 L min^{-1}	Fixed
V_1	Peripheral volume	76·5 ± 4·0 L	Fitted
Cl_{tot}	Total systemic clearance	4·76 ± 0·47 L min^{-1}	Fitted

The last column indicates whether the parameter was fixed (i.e. derived from direct measurements or earlier work) or determined by curve-fitting the present data. The standard deviations of the estimates returned by the curve-fitting program are shown for the fitted parameters.

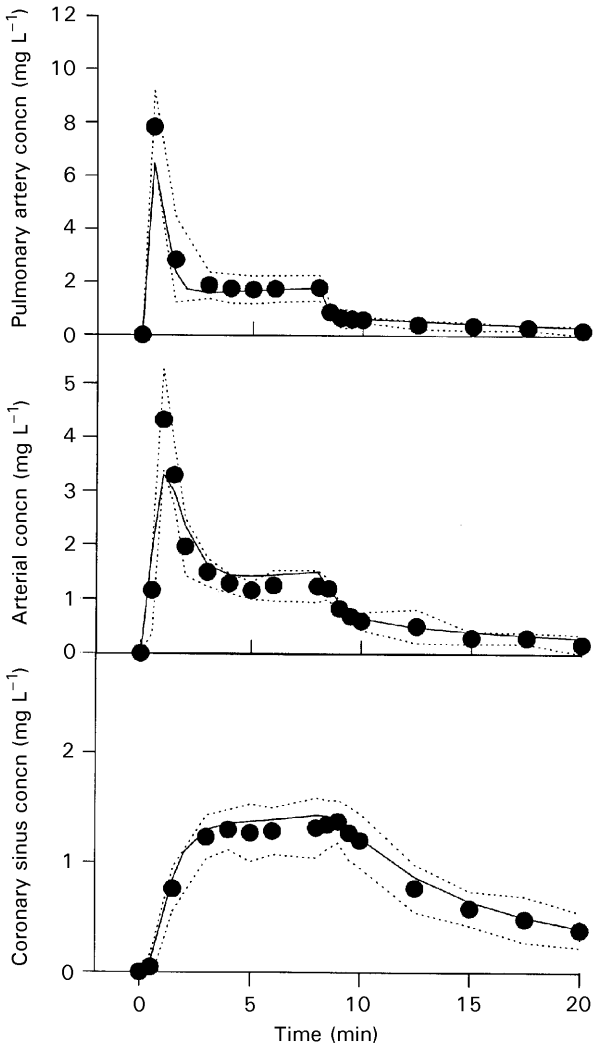

Figure 5. The mean pulmonary artery, aortic and coronary sinus concentrations of lignocaine for 5 sheep observed for the complex infusion regimen (●) comprising of an initial infusion rate of 39·1 mg min^{-1} that declined exponentially over 8 min to a basal rate of 7·02 mg min^{-1}. Observed values are shown with their upper and lower confidence intervals (·····) and values expected when the final model was used to predict the outcome of the complex infusion regimen (——).

The principal therapeutic effect of lignocaine on the heart is prevention of arrhythmias, but after bolus administration it can be associated with transient myocardial depression (Huang et al 1992). Our previous studies have shown that there is a peak in the myocardial concentration of lignocaine after bolus administration in chronically instrumented sheep (Huang et al 1993a) which is temporally correlated with this period of myocardial depression. The present data show that this myocardial depression can be reduced by administering lignocaine more slowly – both the 5-min and complex infusion regimens were associated with less myocardial depression at similar doses to those given by bolus administration (Table 2). On theoretical grounds it would be desirable to achieve a constant therapeutic concentration of lignocaine in the myocardium rapidly, but with minimal depression of myocardial contractility. It is apparent from Figure 5 and Table 2 that the complex dose regimen used in the present study is of a form that achieved this goal, and it has a conceptual counterpart in "bolus-elimination-transfer" regimens used to achieve a constant blood concentration of a drug rapidly (Vaughan & Tucker 1976). However, given the relatively rapid rate of equilibration of lignocaine with arterial blood, this complex type of regimen may not have sufficient merits for it to replace a short constant-rate infusion in clinical practice.

Several observations can be made on comparison of the present model with previously published models of lignocaine kinetics. The theoretical shortcomings of traditional compartmental kinetic models have been discussed by Krejcie et al (1997), who described a systemic model of lignocaine kinetics in dogs incorporating a detailed submodel of the pulmonary kinetics which accounted for the distribution of intravascular transit times within the lungs. A similar process was also required in a model of the kinetics of lignocaine in the isolated perfused rabbit lungs (Audi et al 1998). Both of these studies used "impulse" or instantaneous administration of lignocaine, and it is interesting that the present model could describe the pulmonary kinetics of lignocaine with a simpler compartment model. This suggests that once the duration

Table 2. Pharmacodynamic measurements following intravenous administration of lignocaine to sheep.

Lignocaine dose regimen	Minimum LV dP/dt_{max} (% baseline)	Lower 95% confidence interval	Upper 95% confidence interval	Time of minimum (min)
5 min	88·6*	81·6	95·6	6
complex	87·7*	77·5	98·0	2
1 s	67·6*	63·7	71·5	0·83

The mean minimum LV dP/dt_{max} (rise of left ventricular pressure) following lignocaine expressed as a percentage of the baseline value for the 5-min (100 mg) and complex infusion (89 mg) studies is shown with lower and upper 95% confidence intervals. The time of the minimum is shown. Previously published data for 100 mg of lignocaine administered over 1 s in similar sheep is also shown (Huang et al 1992). *Statistically significant reduction from baseline by confidence-interval analysis.

of dose regimens exceeds that of "impulse" drug administration, intravascular transit times can be neglected in lung kinetic models of lignocaine.

In agreement with previous lungs models (Krejcie et al 1997; Audi et al 1998) and the experimental work of others (Bertler et al 1978), the present data were characterised by an apparent first-order loss from the lungs consistent with sequestration of lignocaine into deep, slowly equilibrating tissue pools within the lungs. Although such sequestration can be kinetically indistinguishable from metabolism in bolus and short infusion studies (Upton & Doolette 1999), there is no evidence for lignocaine metabolism in the lungs (Audi et al 1998). Like many drugs, the transit time of unsequestered lignocaine through the lungs was rapid, with a mean transit time from our data (V_{lung1}/Q_{co}) of less than one minute.

The uptake of lignocaine into the heart occurred rapidly in the present study. Although the kinetic model of the heart describing this uptake was deceptively simple (a single flow-limited compartment), it was a good fit of the observed data. The same type of model was used by Benowitz et al (1974), who reported a directly measured heart-to-plasma partition coefficient of 0·96 in monkeys. In sheep, the apparent distribution volume of lignocaine in the heart was 0·412 L and the mass of myocardium drained by the coronary sinus catheter has previously been determined as 0·179 kg (Huang et al 1993b). This equates to an approximate heart : blood partition coefficient of 2·30 — higher than that reported by Benowitz et al (1974), but both are consistent with relatively rapid equilibration between the myocardial and blood lignocaine concentrations. Mazoit et al (1990, 1993) reported that a two-compartment model was necessary to describe lignocaine kinetics in an isolated perfused rabbit heart preparation, although their use of buffer rather than blood as a perfusate means that distribution volumes and partition coefficients can not be compared directly with the present in-vivo data. It may be that studies of myocardial uptake of longer duration than in our sheep preparation may also reveal a slower equilibrating pool within the myocardium. Horowitz et al (1986) studied the myocardial uptake of lignocaine in patients with ischaemic heart disease, and relatively rapid uptake was evident from the rapid peak in the myocardial concentration of lignocaine which occurred 2·4 min after bolus administration. Subsequently, these data were modelled as the second compartment of a three-compartment mamillary model (Morgan et al 1989), and the half-life of the second compartment can be calculated to be 3·3 min — comparable with the present data.

Our present work attempted to define a model that is relatively simple but that incorporates the essential physiological processes determining the initial target organ (myocardial) concentrations of lignocaine. The model was shown to be sufficient to account for the effect of altered dose regimens on the time-course of the myocardial concentrations of lignocaine. It remains to be determined whether the model is sufficient to account for the influence of physiological and pathophysiological states on these concentrations. Using analogous models of the disposition of intravenous anaesthetics with the brain as the target organ, is has been predicted that cardiac output and target-organ blood flow are significant determinants of initial target-organ drug concentrations (Upton & Ludbrook 1999). In future work, we propose to examine whether changes in these parameters of the model can account for the effect of pathophysiological perturbations such hypoxia and tachycardia on the initial kinetics of myocardial uptake of lignocaine. This may provide insight into how the dose and dose regimen of lignocaine should be modified in various disease states.

The equations of the final model

The equations of the model are presented as series of equations suitable for a differential-equation-solving program such as Scientist for Windows. Note that "doserate" is a time-dependent function defining the intravenous infusion rate of the drug, and will be of the form shown in equations 5 to 7 for the complex model. Comments are preceded by / /; an apostrophe (e.g. Cpa') indicates a derivative with respect to time. The parameters of the model are described in more detail in Table 1. Cinj, Cpa, Cart, Ccs and C1 are the concentrations in the hypothetical injection site, the pulmonary artery, the aorta, the coronary sinus and the tissue pool, respectively.

//Venous mixing compartment — including addition of recirculation

$$C_{inj} = \text{doserate}/Q_{co}$$

$$V_{mix}*C_{pa}' = Q_{co}*(C_{inj}-C_{pa}) + Q_1*C_1 + Q_h*C_{cs}$$

//Lungs

$$V_{lung1}*C_{art}' = Q_{co}*(C_{pa}-C_{art}) - PS_{lung}*C_{art}$$

//Heart

$$V_{heart}*C_{cs}' = Q_h*(C_{art} - C_{cs})$$

// Recirculation calculations

// Tissue pool flows

$$Q_1 = (Q_{co}-Q_h)$$

// Tissue pool kinetics

$$V_1*C_1' = Q_1*(C_{art}-C_1) - C_{ltot}*C_1$$

Acknowledgements

This work was funded by the Research Review Committee of the Royal Adelaide Hospital and the Research Committee of the Faculty of Health, University of Adelaide.

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