SUMMARY

We have studied relationships between the time-courses of lignocaine concentrations in arterial and coronary sinus blood and myocardial tissue, and negative inotropic effects on the myocardium, after i.v. bolus administration of 50-, 75- or 100-mg doses of lignocaine to conscious, chronically instrumented sheep. Peak arterial and coronary sinus blood lignocaine concentrations occurred 26-38 s before and 29-78 s after the maximum decreases in myocardial contractility, respectively. Peak myocardial concentrations occurred simultaneously with the maximum decreases in myocardial contractility, except for the 100-mg doses. Anti-clockwise hysteresis occurred only between arterial blood lignocaine concentrations and the negative inotropic effect. It was concluded that, after short-term i.v. administration, only the myocardial concentrations of lignocaine were in pseudoequilibrium with the negative inotropic effects of the lignocaine on the myocardium.

KEY WORDS


An assumption in many pharmacokinetic studies is that the drug concentrations in the "biophase" are proportional to, or in pseudoequilibrium with, blood drug concentrations, and that there is a simple relationship between this biophase concentration and the magnitude of the effects of the drug. While this may be true after the long-term use of drugs, in the first few minutes after short-term (i.v. bolus) drug administration (a frequent occurrence during anaesthesia) there may be a substantial lack of pseudoequilibrium between drug concentrations in blood and drug effects in the vital organs such as the heart and brain. For example, there is often an "antclockwise hysteresis" apparent on plots of the time-course of myocardial drug effects against the time-course of the systemic (arterial or peripheral venous) blood drug concentrations after short-term drug administration, which has often been attributed to a lack of pseudoequilibrium between the drug concentrations in blood and at the receptor sites responsible for drug action in the myocardium [1-3].

It has been suggested that arterial blood drug concentration should be better indicators of the duration and potency of drug effects because arterial blood carries drug to the sites of effect [4, 5]. Alternatively, the use of local venous blood drug concentrations has been proposed because these should be in pseudoequilibrium with tissue concentrations [4, 5]. It has also been proposed that drug concentrations at the receptor sites of a tissue should be in continuous equilibrium with drug concentrations in that tissue [6], and the magnitudes of drug effects on the myocardium therefore should be a function of the myocardial drug concentrations [7]. However, these relationships between drug concentrations in arterial or venous blood or the myocardium and drug effects on the heart after short-term i.v. drug administration are still uncertain.

This study compared the time-courses of the depression of myocardial contractility caused by i.v. bolus doses of lignocaine [8] with the simultaneously measured time-courses of its concentrations in arterial and coronary sinus blood, and in the myocardium determined using mass balance principles [9], in a chronically instrumented sheep preparation. The aim was therefore to determine which, if any, of these concentrations is related directly to the myocardial contractility depression induced by lignocaine. When this concentration has been identified, a knowledge of the determinants of its time-course may be used to explore avenues for optimizing the initial time-course of the myocardial effects of lignocaine.

MATERIALS AND METHODS

In this paper, aspects of the pharmacodynamic [8] and pharmacokinetic [9] data arising from a series of studies in five chronically instrumented adult female merino sheep are analysed and compared in detail.
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Data and statistical analysis

Relevant details of methods used in those studies [8, 9] are summarized here.

Sheep preparation

Sheep were prepared under anaesthesia (thiopentone for induction, 1.5% halothane for maintenance) with catheters in the ascending aorta, coronary sinus and inferior vena cava (IVC) via the carotid artery or jugular vein [8, 9]. An ultrasonic Doppler flow probe was placed on the left main coronary artery for measuring blood flow in this vessel [9]. A gas-powered system kept the intra-catheter vessels flushed with heparinized saline. Studies were conducted 1 week after the surgical preparations and at 2-day intervals thereafter while the sheep remained in their cages with free access to food and water.

Study design

Lignocaine hydrochloride in doses of 50, 75 or 100 mg was diluted to 10 ml with 0.9% saline immediately before each experiment. After a period of baseline haemodynamic measurements, a randomly selected dose was injected i.v. via the IVC catheter over 1 s [8, 9]. Pharmacodynamic and pharmacokinetic measurements were made for the next 15 min. The 50-, 75- and 100-mg doses of lignocaine were studied in five, four and five sheep, respectively.

Pharmacodynamic measurements. Left coronary artery blood flow velocity was measured continuously using an ultrasonic Doppler flowmeter and the Doppler flow probe placed on the left main coronary artery [9]. The maximum rate of increase in left ventricular pressure (LV dP/dt\text{max}), used as an index of myocardial contractility, was obtained from the differentiated left ventricular pressure, which was measured continuously using a Millar Mikro-Tip pressure transducer catheter (Millar Instruments Inc., Houston, Texas, U.S.A.) placed in the left ventricle via one of the arterial catheters before each experiment [9].

Pharmacokinetic measurements. Paired blood samples were collected from the ascending aorta and the coronary sinus at up to 5-s intervals for 15 min after drug administration, using the sampling methods described previously [8, 10]. All samples were stored at −20 °C and the whole blood concentrations of lignocaine were assayed using a single extraction gas chromatographic method [11]. These concentrations and left coronary blood flow were used to calculate the time-courses of lignocaine concentrations in the myocardium perfused by the left coronary artery using mass balance principles. This method calculates the time-course of the myocardial drug concentrations from the net difference in flux of drug in the afferent (arterial) and efferent (coronary sinus) blood; its application to the myocardium has been described in detail previously [9, 12].

Data and statistical analysis

The following comparisons were made between the time-courses of the concentrations of lignocaine in arterial and coronary sinus blood and the myocardium, and the time-courses of the depression of myocardial contractility.

(1) The times of the peak arterial blood, coronary sinus blood or calculated myocardial lignocaine concentrations were compared with the times of the maximum depression of myocardial contractility.

Note that the maximum depression of myocardial contractility described here refers to the observed maximum decrease in LV dP/dt\text{max} under conditions of non-steady-state blood drug concentration (fig. 1).

(2) Lignocaine concentrations in the arterial blood, coronary sinus blood or the myocardium were plotted in time order against the percent decreases in myocardial contractility induced by lignocaine to examine for hysteresis and non-linearity in the concentration–effect relationships. If there was a time lag between concentration and effect (e.g. hysteresis), the plots were not superimposable and showed a clockwise or anticlockwise loop. To quantify the magnitude of hysteresis, each plot was divided into two sections at the point of the peak lignocaine concentration so that one section represented concentration–effect relationships when lignocaine concentrations were increasing, and the other represented the relationships when the lignocaine concentrations were decreasing. The area under each section of the curve (AUC) was calculated using the trapezoidal rule. Hysteresis was considered to be present when the differences between the AUC of these two sections of the hysteresis loop were statistically significant.

Two-sample t tests were used for the analysis of the AUC of the two sections of the hysteresis loops and the differences between the times of peak lignocaine concentrations and the times of maximum drug effect. Linear regression was used to correlate myocardial lignocaine concentrations and the percent decreases in myocardial contractility (LV dP/dt\text{max}). P < 0.05 was considered statistically significant.

RESULTS

These subconvulsive doses of lignocaine induced significant and dose-dependent negative inotropic effects on the myocardium, as indicated by the decreases in LV dP/dt\text{max}, in the absence of significant changes in heart rate or mean arterial pressure [8]. During the 15 min period after lignocaine administration, there was substantial lack of pseudoequilibrium between the myocardial lignocaine concentrations calculated using mass balance principles and lignocaine concentrations measured in arterial or coronary sinus blood [9]. The raw data for all the three dose groups are summarized in figure 1.

The times of the peak lignocaine concentrations in arterial blood, coronary sinus blood and myocardium are listed in table 1. For all the doses, the times of the peak arterial blood lignocaine concentrations were approximately 26–38 s earlier than the times of maximum decreases in myocardial contractility. The times of the peak coronary sinus blood lignocaine concentrations were approximately 29–78 s later than the times of maximum decreases of myocardial contractility. With the exception of the 100-mg
doses of lignocaine, the times of the calculated peak myocardial lignocaine concentrations did not differ from the times of the maximum decreases in myocardial contractility (table I). For the 100-mg doses, the mean time of the peak lignocaine myocardial concentrations was 17 s later than the mean time of maximum myocardial contractility depression.

Examples of the percent decreases in LV $dP/dt_{\text{max}}$ plotted against lignocaine concentrations in the arterial and coronary sinus blood and the myocardium after i.v. injection of 100-mg doses are shown in figure 2. The differences between the AUC under the sections when lignocaine concentrations were increasing and the sections when lignocaine concentrations were decreasing in the concentration–effect curves for the three doses are shown in table II. Significant anticlockwise hysteresis was present between the arterial lignocaine concentrations and the decreases of myocardial contractility in each dose group. No significant hysteresis was found between the coronary sinus blood lignocaine concentrations or the calculated myocardial lignocaine concentrations and the decreases of myocardial contractility.

A linear pharmacodynamic model [2, 13] was used to describe the myocardial lignocaine concentration–effect relationships. The data for the three doses were pooled together for this analysis. Linear regression between the myocardial lignocaine concentrations and the percent decreases of LV $dP/dt_{\text{max}}$ were performed (fig. 3). The correlation coefficient ($r$) between myocardial lignocaine concentrations and the percent decreases in LV $dP/dt_{\text{max}}$.
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TABLE I. Times of peak arterial blood, coronary sinus blood and myocardial concentrations of lignocaine and times of maximum depression of myocardial contractility (LV \( \frac{dP}{dT_{\max}} \)) after the i.v. bolus injection of lignocaine in conscious, chronically instrumented sheep (mean (s.d.)). *Time significantly earlier or later than time of maximum depression (P < 0.05)

<table>
<thead>
<tr>
<th>Lignocaine dose</th>
<th>Arterial</th>
<th>Coronary sinus</th>
<th>Myocardium</th>
</tr>
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<tbody>
<tr>
<td>50 mg (n = 5)</td>
<td>16 (2)*</td>
<td>83 (7)*</td>
<td>66 (23)</td>
</tr>
<tr>
<td>75 mg (n = 4)</td>
<td>15 (0)*</td>
<td>129 (43)*</td>
<td>55 (9)</td>
</tr>
<tr>
<td>100 mg (n = 5)</td>
<td>16 (4)*</td>
<td>85 (38)*</td>
<td>59 (14)*</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>54 (11)</td>
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<td></td>
<td></td>
<td></td>
<td>51 (5)</td>
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<td></td>
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<td>42 (4)</td>
</tr>
</tbody>
</table>

Fig. 2. Relationships between mean concentrations of lignocaine in arterial blood, coronary sinus blood and myocardium, and the mean percent decreases (Dec.) in myocardial contractility (LV \( \frac{dP}{dT_{\max}} \)) after 100-mg doses (n = 5). Arrows show the time sequences of the concentration-effect relationships. Significant anticlockwise hystereses were found in arterial lignocaine concentration-effect relationships.

was 0.92. The slope of this correlation was 4.4 and the intercept −4.5. Linear regression between myocardial lignocaine concentrations and the percent decreases in LV \( \frac{dP}{dT_{\max}} \) also was performed for each dose group. The mean (s.d.) of the slopes of the 50-, 75- and 100-mg groups were 4.5 (2.7), 6.0 (2.4) and 5.7 (2.7), respectively. There was no significant difference among the individual slopes.

DISCUSSION

The technical difficulties of measuring myocardial drug concentrations in conscious animals without perturbing myocardial function have presumably contributed to the use of compartmental pharmaco-
kinetic and pharmacodynamic models to describe and predict the relationship between myocardial drug kinetics and dynamics, because these models can be developed on the basis of blood drug concentration data [14]. Alternatively, the theoretical receptor site drug concentrations can be modelled using "effect compartment" pharmacokinetic and pharmacodynamic models such as those reported in the study of tubocurarine and thiopentone [15, 16]. In these models, the "receptor site" drug kinetics were linked to the central compartment by a first-order rate constant which was adjusted empirically so that hysteresis between drug concentrations at the receptor sites and drug effect disappeared. Although these models offer some resolution to the problem of hysteresis, their significance is limited by their lack of physiological reality [17]. In this study, lignocaine concentrations were measured or calculated at three sites relevant to myocardial drug kinetics and dynamics: arterial blood, coronary sinus blood and myocardium. Their usefulness in predicting drug effect is discussed in turn.

A poor relationship between the arterial blood concentrations of lignocaine and the decreases in myocardial contractility was shown by the differences between the times of the maximum decreases in myocardial contractility and the times of peak arterial blood concentrations of lignocaine (table 1), and the anticlockwise hysteresis of the concentration–contractility relationships (fig. 2, table 11), which suggests that these effects lag behind the arterial drug concentrations. Similar hysteresis between the arterial plasma concentrations of propofol, procainamide, lignocaine and their depressant effects on myocardial contractility after short term i.v. administration have also been reported [3, 18, 19]. The myocardial effects of some general anaesthetics were found to be poorly correlated with blood drug concentrations [20]. The lack of pseudoequilibrium between arterial blood and myocardial lignocaine concentrations reported in previous studies is the most likely explanation for these observations [9].

From the argument of Horowitz and Powell [21], it would be anticipated that the lignocaine concentrations in the myocardium would be better indices of the myocardial effects than its arterial concentrations. However, it should be remembered that methods based on mass balance principles determine the mean myocardial drug concentration, which may in itself be inadequate if the drug acts on specific sites of the myocardial cells that are not in pseudoequilibrium with the mean tissue concentration shortly after an i.v. bolus. Nevertheless, for all the doses used, good correlations were found between the myocardial lignocaine concentrations and the depression of myocardial contractility, with no significant hysteresis in the concentration–effect plots (table II, fig. 2). This provides evidence that lignocaine concentrations at the receptor sites responsible for the decrease of myocardial contractility were in pseudoequilibrium with the measured myocardial lignocaine concentrations [6].

A saturable concentration–effect curve was not observed in this study. However, during the first 20–30 s after lignocaine injection (represented by the first four points on the curve in figure 3), the myocardial lignocaine concentration–effect plots appear to curve upwards. After this period, the concentration–effect relationship was essentially linear. Because neither the concentrations nor the effects of lignocaine reached steady-state or their maximum values in this study, a linear pharmacodynamic model was used to describe the myocardial lignocaine concentration–effect relationship (fig. 3). Myocardial drug concentrations are relatively difficult to monitor in patients [7]. As a simpler alternative, the effluent regional venous blood from the tissue or organ in which a drug exerts its effects could be used for the study of regional pharmacodynamics [4, 5]. This is an extension of the concept of venous equilibrium used in many physiological pharmacokinetic models in which the tissue and the effluent venous drug concentrations were related by a constant ratio—the partition coefficient. In this study, the coronary sinus blood concentrations of lignocaine were related relatively closely to the myocardial depressant effects (fig. 2, table II). However, the times of peak coronary sinus blood lignocaine concentrations were significantly later than the times of the maximum depression of myocardial contractility induced by lignocaine (table I). In this sense, the coronary sinus blood concentrations of lignocaine were not in equilibrium with the negative inotropic effects on the myocardium and therefore were not equivalent to the calculated myocardial concentrations of lignocaine, at least after such rapid i.v. drug administration. It would be expected that, in situations in which the blood drug concentration changes are slower than those which occur after i.v. bolus administration, the use of regional venous blood concentrations as indices of drug effect may have some merit, although a thorough knowledge of the relationships between regional venous and tissue drug concentrations would be an important prerequisite [22].

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**REFERENCES**

4. Chiou WL. The phenomenon and rationale of marked dependence of drug concentration on blood sampling site. *Implications in pharmacokinetics, pharmacodynamics, tox-


17. Hull CJ. How far can we go with compartmental models? Anesthesiology 1990; 72: 399-402.


