LIGNOCAINE KINETICS DURING CARDIOPULMONARY BYPASS
Optimum Dosage and the Effects of Haemodilution

D. F. Morrell and G. G. Harrison

SUMMARY
Lignocaine was administered to patients undergoing cardiopulmonary bypass at 28–29°C in bolus doses of 1.5, 2.5 and 3.5 mg kg⁻¹. Plasma concentrations greater than 1.5 µg ml⁻¹ were found briefly and inconsistently in patients receiving the usually recommended dose (1.5 mg kg⁻¹), but reliably for 14 min in those receiving 2.5 mg kg⁻¹. The 3.5 mg kg⁻¹ dose produced statistically and clinically significant decreases in mean arterial pressure. Examination of calculated kinetic parameters showed a two-fold decrease in $T_1^a$, two-fold increases in $T_1^b$ and $V$ and unaltered $C_p$ and $V_p$ when compared with those of unanaesthetized, normothermic patients. The alteration in pharmacokinetics may be attributed largely to decreased binding to albumin following haemodilution.

With the use of present methods of myocardial preservation during cardiopulmonary bypass (CPB), ventricular arrhythmias at the end of the procedure pose less of a problem than previously. Antiarrhythmic agents are seldom indicated, but on those occasions when they are required, lignocaine is selected most frequently. In normal subjects the effective plasma concentration of the drug against ventricular arrhythmias is greater than 1.5 µg ml⁻¹ (Grossman, Cooper and Frieden, 1969). This study was undertaken to determine the dose required to achieve this concentration during CPB.

PATIENTS AND METHODS
Twenty-four patients undergoing surgery for valve replacement or coronary artery bypass grafts were studied.

Anaesthesia included the use of morphine, halothane and nitrous oxide in oxygen, following the induction of anaesthesia with sufficient thiopentone to abolish the eyelash reflex. Neuromuscular blockade was produced (pancuronium) and ventilation controlled mechanically. The extracorporeal circulation was powered by Sarns Modular roller pumps and used bubble oxygenators (Polystan Venotherm VT 5000). The bypass technique included haemodilution and cardioplegia with moderate hypothermia (28–29°C). The pump priming volume was 3 litre of balanced salt solution (Plasmalyte B), and pump flow was calculated on the basis of 2.4 litre/m² body surface area.

Blood-gas tensions, pH and plasma potassium concentration were kept constant throughout CPB.

Once cardiovascular conditions had stabilized on CPB at 28–29°C, lignocaine was injected over 30 s to a port immediately below the bubble oxygenator. The bolus doses of lignocaine administered were (1) 1.5 mg kg⁻¹ in 10 patients, (2) 2.5 mg kg⁻¹ in nine patients, and (3) 3.5 mg kg⁻¹ in five patients. The mean (± SD) doses for the three groups were 105.5 (± 28.9), 163 (± 40.6), and 218.5 (± 50) mg, respectively. The largest dose was abandoned after use in five patients because of unacceptable decreases in mean arterial pressure (MAP).

Blood samples were aspirated from the oxygenator debubbler at 2, 4, 6, 8, 10, 15, 20 and 30 min after injection. Although we recognize the sampling period to be shorter than ideal for a pharmacokinetic study, this limitation was required because of the duration of CPB. Plasma concentrations of lignocaine were assayed by gas–liquid chromatography (Morrell, Chappell and White, 1982). Other biochemical measurements included total protein and albumin concentrations.

From the plasma lignocaine assay data, coefficients and exponents for the concentration curve for each patient were calculated using the Fortran IV program CSTRIP (Sedman and Wagner, 1976), and pharmacokinetic parameters (table I) were calculated using formulae described by Wagner (1976). The $R^2$ value obtained from CSTRIP was always better than 0.98.

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TABLE I. Pharmacokinetic symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tbody>
<tr>
<td>( T_{1}^{a} )</td>
<td>( \alpha ) phase half-life (min)</td>
</tr>
<tr>
<td>( T_{1}^{b} )</td>
<td>( \beta ) phase half-life (min)</td>
</tr>
<tr>
<td>( C_{p} )</td>
<td>Plasma clearance (ml min(^{-1}) kg(^{-1}))</td>
</tr>
<tr>
<td>( V_{p} )</td>
<td>Volume of plasma compartment (ml kg(^{-1}))</td>
</tr>
<tr>
<td>( V_{m} )</td>
<td>Apparent steady state distribution volume (ml kg(^{-1}))</td>
</tr>
<tr>
<td>( V_{b} )</td>
<td>Apparent volume of distribution during ( \beta ) phase (ml kg(^{-1}))</td>
</tr>
</tbody>
</table>

RESULTS

The mean plasma lignocaine decay curves following the three different doses are shown in figure 1. A decrease to \( 1.5 \mu g\) ml\(^{-1}\) occurred within 3, 14 and more than 30 min following bolus injections of 1.5, 2.5 and 3.5 mg kg\(^{-1}\), respectively. Only 60% of patients receiving the usually recommended dose of 1.5 mg kg\(^{-1}\) were found to have plasma concentrations above \( 1.5 \mu g\) ml\(^{-1}\) at 2 min, declining to 10% at 4 min. While the concentration of \( 1.5 \mu g\) ml\(^{-1}\) was achieved for 4 min in all patients receiving the intermediate-sized dose of 2.5 mg kg\(^{-1}\), it was maintained at 30 min in 10% of this group. Following the 3.5-mg kg\(^{-1}\) bolus, lignocaine concentrations were greater than \( 1.5 \mu g\) ml\(^{-1}\) in all patients for up to 20 min, and in 60% of patients remained so at 30 min.

MAP did not change significantly in those patients receiving the two smaller doses but decreased on average by 20.5% from the pre-injection pressure of 66 mm Hg in those receiving 3.5 mg kg\(^{-1}\). The maximum individual decrease was 45% of the pre-injection pressure.

Haemodilution resulted in a decrease in mean serum albumin concentration to 65% of its pre-bypass value, which was itself at the lower limit of the normal range (table II). Serum protein concentrations did not alter during the experimental period.

Pharmacokinetic parameters are recorded in table III. These represent the means of the values as calculated for each patient. The clinically stable sampling period was limited to 30 min and, as a result, our calculated coefficients and exponents are liable to error since a limited number of data points was obtained in the metabolic phase. Therefore, for the purpose of comparison with published work, we recalculated the data of Rowland and colleagues (1971) as if their sampling was discontinued at 30 min. The method used was to calculate from their data expected plasma concentrations at our sampling times using the coefficients and exponents provided, and then to recalculate (using CSTRIP) the exponents and coefficients for the initial 30-min period. From these, pharmacokinetic parameters were derived. The original and recalculated data are provided in table III, rows A and B. Comparison of the data from our 1.5-mg kg\(^{-1}\) bolus group (mean dose = 105.5 mg) with theirs (dose = 100 mg) reveals a halving in \( T_{1}^{b} \) and a doubling in \( T_{1}^{a} \), \( V_{m} \) and \( V_{b} \) in our data relative to theirs. \( C_{p} \) and \( V_{p} \) were the same.

The extent of the error induced by the shortened sampling period is evident when the original data from Rowland's work are compared with the recalculated data (table III, row A v. row B), incurring an underestimate of half-lives and volumes of distribution and overestimate of clearance.

DISCUSSION

Although the pharmacokinetic behaviour of lignocaine and its relevance to the development of effective dosage schedules have been well reviewed in patients with normal haemodynamics, heart failure and liver or renal disease (Benowitz and Meister, 1978), we are not aware of similar studies having been undertaken during CPB. Many factors which would influence pharmacokinetics are introduced such as anaesthetic and vasoactive drugs,
**TABLE III. Pharmacokinetic parameters. Mean ± SD of parameters as calculated for each individual.**

A = Original data from Rowland and colleagues (1971) for 100-mg bolus; B = A recalculated for a 30-min sampling period. 1 = Parameter in 1.5-mg kg⁻¹ bolus group differs significantly from that in 3.5-mg kg⁻¹ bolus group (P < 0.05; Student's t test); 2 = Parameter in 2.5-mg kg⁻¹ bolus group differs significantly from that in 3.5-mg kg⁻¹ bolus group (P < 0.005; Student's t test)

<table>
<thead>
<tr>
<th>Dose (mg kg⁻¹)</th>
<th>T₇f</th>
<th>T₁β</th>
<th>Cl₁p</th>
<th>V₁p</th>
<th>V₁m</th>
<th>V₁β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>1.74 ± 0.78</td>
<td>44.4 ± 21</td>
<td>21.7 ± 7.2</td>
<td>535 ± 221</td>
<td>1158 ± 279</td>
<td>1231 ± 263</td>
</tr>
<tr>
<td>2.5</td>
<td>1.38 ± 0.6</td>
<td>31.8 ± 12</td>
<td>26.7 ± 8.1</td>
<td>371 ± 220</td>
<td>945 ± 219</td>
<td>1063 ± 208</td>
</tr>
<tr>
<td>3.5</td>
<td>1.02 ± 0.3</td>
<td>21.4 ± 6.6</td>
<td>25.1 ± 5.3</td>
<td>243 ± 61</td>
<td>666 ± 114</td>
<td>740 ± 124</td>
</tr>
<tr>
<td>A</td>
<td>8.8</td>
<td>92</td>
<td>9.94</td>
<td>480</td>
<td>1080</td>
<td>1447</td>
</tr>
<tr>
<td>B</td>
<td>3.7</td>
<td>22.6</td>
<td>20.5</td>
<td>493</td>
<td>629</td>
<td>667</td>
</tr>
</tbody>
</table>

Statistics: 1, 1, 2, 1, 2

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Hypothermia, dilution of red cell and protein concentrations, non-pulsatile flow, decreased blood viscosity and exclusion of the lung as a first-pass organ. Furthermore, whereas a total drug concentration of 1.5 μg ml⁻¹ has been established as necessary for antiarrhythmic activity in the unanaesthetized patient, it is not axiomatic that this concentration applies following CPB.

The main results of this study were the low initial and rapid decrease in plasma concentrations of lignocaine during CPB. This is in keeping with the finding of altered distribution kinetics which were the two-fold decrease in T₇f and two-fold increase in V₁m and V₁β. The metabolic handling of lignocaine as reflected by Cl₁p is unaltered, the increased T₁β caused by the increased volumes of distribution (Hull, 1981). The addition of an oxygenator prime on a volume basis would not significantly increase volume of distribution as it would form part of V₁p, which, for a 70-kg man receiving a 1.5-mg kg⁻¹ bolus, is of the order of 37.5 litre. The additional 3 litre prime volume is thus less than 10% of V₁p and would require only an additional 4.5 mg of lignocaine over and above the 105-mg bolus to achieve a concentration of 1.5 μg ml⁻¹.

We feel that the explanation for the altered distribution kinetics can be attributed largely to an increase in the unbound pharmacodynamic fraction.

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**Fig. 2.** Curve A = Total lignocaine plasma concentration following 2.5-mg kg⁻¹ bolus. Curves B and C = Calculated unbound lignocaine concentrations at albumin concentrations of 23 (B) and 35 g litre⁻¹ (C). x = mean value for the group at each sampling time.
of lignocaine caused by the decrease in concentration of binding sites resulting from dilution of plasma albumin. Actual measurements of this unbound fraction were not performed in our study, but estimates may be made using published information. Drug binding to macromolecules (Koch-Weser and Sellers, 1976) is dependent on the total drug concentration, the macromolecular concentration, the number of binding sites per macromolecule and the dissociation constant for the drug–macromolecule complex. Applying the constants derived by Tucker and co-workers (1970) for lignocaine–albumin binding, the calculated change in bound drug concentration following the injection of a 2.5 mg kg⁻¹ bolus of lignocaine in our patients is shown in figure 2. This records the decay curves for total and unbound drug at albumin concentrations of 35 and 23 g litre⁻¹, representing the pre-CPB and CPB concentrations in our patients. The 35% decrease in albumin concentration following haemodilution produced an almost constant 37% increase in unbound drug concentration over the whole range of total lignocaine concentrations encountered. Furthermore, an anti-arrhythmic total drug concentration of 1.5 µg ml⁻¹ corresponds to an unbound drug concentration of 0.45 µg ml⁻¹ at an albumin concentration of 35 g litre⁻¹. Figure 2 demonstrates also that haemodilution to the extent of decreasing albumin concentration to 23 g litre⁻¹ extends the time for which the unbound drug fraction is greater than 0.45 µg ml⁻¹ from 14 to 26 min.

Our results indicate that, during CPB with haemodilution, the bolus loading dose of lignocaine with which to precede a continuous infusion is 2.5 mg kg⁻¹ rather than the more usually recommended 1.5 mg kg⁻¹. The larger dose produces greater and more sustained plasma concentrations without incurring clinical changes in vascular resistance and MAP.

ACKNOWLEDGEMENTS

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REFERENCES


Wagner, J. G. (1976). Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of exponential equations which have been fitted to the data. J. Pharmacokinet. Biopharm., 4, 443.
LIGNOCAINE KINETICS

korisierten, normothermischen Patienten. Die veränderte Phar-
makokinetik ist wahrscheinlich zum Großteil auf die verringernte
Albuminbindung durch Hämodilution zurückzuführen.

CINETICAS DE LA LIGNOCAINA DURANTE
LA DESVIAción CARDIOPULMONAR

Dosis óptima y efectos de la hmodilución

SUMARIO

Se administró lignocaína a pacientes sometidos a desviación
cardiopulmonar, a temperaturas de 28 a 29 ºC y en dosis de 1,5,
2,5 y 3,5 mg kg⁻¹. Se encontraron concentraciones de plasma
superiores a 1,5 µg ml⁻¹ muy brevemente y de forma irregular
en pacientes que recibieron la dosis de 1,5 mg kg⁻¹ normalmente
recomendada, pero de forma fiable por espacio de 14 min en
aquellos que recibieron 2,5 mg kg⁻¹. La dosis de 3,5 mg kg⁻¹
produjo disminuciones de la presión arterial media que fueron
significativas tanto desde el punto de vista estadístico como desde
el clínico. El examen de los parámetros cinéticos calculados
mostró una doble disminución del Tt₁, un doble incremento del
T₁₂ y Vₐ, y C₁ y V₉ sin alteración alguna cuando se compararon
con los de los pacientes normotérmicos anestesiados. La variación
de los aspectos farmacocinéticos pueden atribuirse en gran medi-
da a la disminución de la ligazón a la albúmina a raíz de la
hemodilución.