THE EFFECTS OF ADDING ADRENALINE TO ETIDOCAINE AND LIGNOCAINE IN EXTRADURAL ANAESTHESIA II: PHARMACOKINETICS

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SUMMARY

The addition of adrenaline to solutions of etidocaine or lignocaine for extradural administration resulted in significantly lower plasma concentrations in both the arterial blood (14% decrease for etidocaine and 43% decrease for lignocaine) and venous blood (35% and 60% decreases for etidocaine and lignocaine respectively). The net absorption over the first 4 h after administration, measured from the area under the plasma concentration-time curve, was decreased by the addition of adrenaline (18% and 30% decreases for etidocaine and lignocaine respectively). Both drugs were absorbed in a biexponential manner, having similar fast absorption rates but with etidocaine having a longer absorption half-life in the slow absorption phase. It is concluded that the addition of adrenaline reduces the fraction of the dose being absorbed during the first (fast) phase rather than influencing the absorption rate constants.

There is little doubt that the addition of adrenaline to solutions of the shorter-acting local anaesthetic agents causes well-defined benefits with respect to clinical block characteristics (Bromage, 1965), experimental block characteristics (Albert and Löfström, 1965) and decreased drug absorption into the systemic circulation (Braid and Scott, 1965, 1966; Lund, 1965; Tucker et al., 1972). Additionally, adrenaline tends to counteract the depressant effects of the regional anaesthetic procedure or local anaesthetic drug, or both, on the cardiovascular system. However, the effects of adrenaline in regional anaesthetic procedures, in which the long-acting local anaesthetic agents (notably bupivacaine) are used, would seem to be more closely related to functions of route and drug concentration (Nishimura, 1965; Szappanyos, 1969; Löfström et al., 1970; Swerdlow and Jones, 1970; Waters, Rosen and Perkins, 1970; Reynolds and Taylor, 1971; Telivuo, Svinhufvud and Nuuttila, 1972; Bridenbaugh et al., 1974).

With the availability of an alternative long-acting local anaesthetic agent, such as etidocaine (Duranest), it seemed desirable to make comparisons between the plain and adrenaline-containing solutions of this drug. In a companion paper (Murphy et al., 1976) we showed that adrenaline exerted a beneficial action on the block characteristics and counteracted the cardiovascular depression following extradural administration in unpremedicated volunteer subjects. We now report the effects of adrenaline on the pharmacokinetic profile of etidocaine and make some comparisons with lignocaine.

METHODS

Details of subject characteristics and preparation for study were described previously (Murphy et al., 1976). For the pharmacokinetic analysis, blood samples were drawn simultaneously from the brachial artery and from a cephalic vein of the contralateral arm. In one case, additional samples were drawn from an accessible vein on the anterior surface of the leg. Sampling times were: pre-injection, 2, 5, 10, 15, 20, 30, 45, 60, 120, 180, 240 and 360 min after etidocaine injection, and pre-injection, 2, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 180 and 240 min after lignocaine injection. For etidocaine injections, 20 ml of 1% etidocaine hydrochloride plain or containing 1 : 200 000 adrenaline (5 μg/ml) was injected over a 2-min period. Comparisons were made with solutions...
containing 2% lignocaine hydrochloride. Plasma concentrations of the local anaesthetics were determined by the gas chromatographic method of Mather and Tucker (1974).

For each patient, plots of drug concentration in plasma vs. time were prepared. From these the following variables were determined: \( C_{p,\text{max}} \) (maximum arterial plasma concentration), \( t_{\text{max}} \) (time at which \( C_{p,\text{max}} \) occurred), \( C_{v,\text{max}} \) (maximum venous plasma concentration) and \( t_{v,\text{max}} \) (the time at which \( C_{v,\text{max}} \) occurred). In addition, the relative absorption of these drugs was assessed from the area under the plasma concentration-time curve, arterial and venous (AUC\(_a\) and AUC\(_v\)) respectively, measured as appropriate to 240 and 360 min.

An assessment of the absorption rate of each drug was made using the method of Loo and Riegelman (1968). This technique makes use of previously determined systemic disposition constants for the drug after i.v. administration. These constants were available for each subject in the etidocaine series having been determined previously in another study (G. T. Tucker, unpublished data). For lignocaine, however, the constants for each individual subject were not available and average constants, which have been determined under the same circumstances but in a different group of subjects (Tucker and Boas, 1971), were used. Therefore, we were able to include comparative data indicating the trend of lignocaine absorption both with and without adrenaline.

Biexponential equations of the form \( U = Xe^{-\lambda t} + (100 - X)e^{-\mu t} \) were fitted to estimates of per cent dose unabsorbed vs. time using a non-linear least squares

**TABLE I. Plasma concentration and relative absorption data for etidocaine and lignocaine following extradural injection of 20 ml of 1% etidocaine HCl or 20 ml of 2% lignocaine HCl with or without the addition of 5 \( \mu \)g/ml adrenaline (Mean ± SD)**

<table>
<thead>
<tr>
<th>Units</th>
<th>Etidocaine + adrenaline</th>
<th>Etidocaine plain</th>
<th>Lignocaine + adrenaline</th>
<th>Lignocaine plain</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{p,\text{max}} ) ( \mu )g/ml</td>
<td>0.92 ± 0.19</td>
<td>1.07 ± 0.16</td>
<td>2.1 ± 0.4</td>
<td>3.7 ± 0.5</td>
</tr>
<tr>
<td>( t_{\text{max}} ) min</td>
<td>16 ± 9</td>
<td>15 ± 5</td>
<td>25 ± 4</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>( C_{v,\text{max}} ) ( \mu )g/ml</td>
<td>0.50 ± 0.18</td>
<td>0.77 ± 0.07</td>
<td>0.95 ± 0.12</td>
<td>2.40 ± 0.60</td>
</tr>
<tr>
<td>( t_{v,\text{max}} ) min</td>
<td>26 ± 12</td>
<td>36 ± 8</td>
<td>102 ± 84</td>
<td>11 ± 6</td>
</tr>
</tbody>
</table>

**Relative absorption**

| AUC\(_{240}\) \( \mu \)g.min/ml | 100 ± 18 | 119 ± 17 | 221 ± 71 | 274 ± 19 |
| AUC\(_{360}\) \( \mu \)g.min/ml | 121 ± 27 | 144 ± 17 |
| AUC\(_{v,240}\) \( \mu \)g.min/ml | 79 ± 24 | 109 ± 13 | 102 ± 43 | 235 ± 21 |
| AUC\(_{v,360}\) \( \mu \)g.min/ml | 100 ± 36 | 132 ± 16 |
program (BMDX85R) and a digital computer (where χ and ψ are fast and slow absorption rate constants and X is the percentage of the dose proceeding through the fast absorption pathway, and U is the percentage of the dose unabsorbed at time, t).

RESULTS

Plasma concentrations of etidocaine (fig. 1A, table I)

Following extradural injection, arterial plasma concentrations of etidocaine increased to a well-defined maximum of 1.07 ± SD 0.16 μg/ml occurring at 15 ± 5 min. When adrenaline was included, the plasma concentrations of etidocaine reached a maximum of 0.92 ± 0.19 μg/ml (P<0.05) at 16 ± 2 min. Compared with the well-defined maxima of the arterial plasma concentration, the maxima in the venous blood were more variable and reached values averaging 75% and 55% of the arterial maxima for plain and adrenaline-containing solutions respectively.

The magnitude of the difference between these concentrations is significant (P<0.05) and these occurred at significantly later times than the maxima in the arterial blood. There were differences, also, between the rates of decrease in plasma concentrations of etidocaine and lignocaine for the plain solutions (P<0.01).

Plasma concentrations of lignocaine (fig. 1B, table I)

Mean arterial plasma concentrations of lignocaine resulting from injection of plain solutions were significantly greater than from the injection of adrenaline-containing solutions (P<0.01). Additionally, the maximum plasma concentrations occurred sooner with plain solutions than with adrenaline-containing solutions (P<0.01). Similar differences were noted in maximum venous plasma concentrations and the time in which they were achieved. Arterial plasma concentrations decreased at a faster rate with the plain solutions compared with the adrenaline-containing solutions.

Systemic absorption (table I)

For both drugs, the addition of adrenaline decreased the values of AUC<sub>n</sub> and AUC<sub>r</sub> (P<0.05). Additionally, AUC<sub>n</sub> and AUC<sub>r</sub> etidocaine, respectively, tended to be less than AUC<sub>n</sub> and AUC<sub>r</sub> lignocaine, but the difference was not statistically significant.

Fraction of dose unabsorbed (fig. 2, table II)

Using the mean data for both drugs and the individual data for etidocaine, a trend emerged for both drugs—a higher fraction of the dose remained unabsorbed for the adrenaline-containing solutions compared with the plain. However, these differences were not statistically significant. At the time of

TABLE II. Pharmacokinetic constants describing the systemic absorption of etidocaine and lignocaine following extradural administration with and without added adrenaline. (Etidocaine data are mean ± SD, whereas lignocaine data are trends derived from average constants.)

<table>
<thead>
<tr>
<th></th>
<th>Etidocaine + adrenaline</th>
<th>Etidocaine plain</th>
<th>Lignocaine + adrenaline</th>
<th>Lignocaine plain</th>
</tr>
</thead>
<tbody>
<tr>
<td>χ(h⁻¹)</td>
<td>2.2 ± 2.7</td>
<td>36 ± 8</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>χ(4h⁻¹)</td>
<td>0.3 ± 2.2</td>
<td>2.0 ± 1.1</td>
<td>2.3</td>
<td>3.3</td>
</tr>
<tr>
<td>χ(8h⁻¹)</td>
<td>0.09 ± 0.05</td>
<td>0.11 ± 0.05</td>
<td>0.26</td>
<td>0.11</td>
</tr>
<tr>
<td>T/2₇ (h)</td>
<td>7.7 ± 4.3</td>
<td>6.5 ± 3.5</td>
<td>2.7</td>
<td>6.6</td>
</tr>
</tbody>
</table>

* Half-life of fast (χ) phase; ** half-life of slow (ψ) phase.
$C_{P_{\text{amax}}}$, there were no differences in the fraction of dose unabsorbed between etidocaine and lignocaine. However, at all times after this, more of the dose of etidocaine remained unabsorbed compared with lignocaine. The etidocaine data represent the means and standard deviations of the actual values for each individual, whereas the lignocaine values are representative of the trend based on mean systemic disposition constants for a group of comparable subjects different from those examined in the extradural study.

**DISCUSSION**

The data reported in this study show that adrenaline decreases the plasma concentrations of etidocaine in both venous and arterial blood. We have confirmed also the results of others (Braid and Scott, 1965, 1966) in demonstrating the same effect for lignocaine. The results for etidocaine resemble those of Bridenbaugh and others (1974), who noted a difference, which was not statistically significant, between maximum concentrations obtained with plain and adrenaline-containing solutions of etidocaine in patients. However, these authors did not observe a significant difference between maxima in arterial and venous plasma concentrations, whereas we did. Although the shape of the arterial plasma concentration–time curve for etidocaine found in this study was similar to arterial curves reported by Bridenbaugh and others (1974), the shape of the venous curve was not (Lund, Cwik and Gannon, 1974). This difference may be related to the fact that, in our study, unpremedicated volunteers were used as subjects, whereas the other studies have been made on surgical patients who were premedicated at the time. Similar comparisons may be made with the lignocaine data obtained in the present study and those data reported by Braid and Scott (1965, 1966) who also studied patients. It is possible that these differences in venous plasma concentrations are related to relaxed sympatetec motone in the patients as a result of premedication. This causes the venous plasma concentration v. time curves to resemble more closely the curves from arterial plasma concentrations. The likelihood of this concept is strengthened by the data described in the inset of figure 1B. In the presence of extradural vaso-motor anaesthesia, the lignocaine concentrations in plasma obtained from the leg vein of a volunteer subject were considerably greater (approaching arterial concentration) than those in plasma drawn simultaneously from an arm vein. Further studies are in progress to clarify this point.

The differences between arterial and venous concentration may be important. Moore and others (1971) pointed out that the concentration of the drug in the arterial system is more directly related to the systemic effects of the drug. It also appears to be less sensitive to effects caused by changes in the local circulation.

Both etidocaine and lignocaine are absorbed initially at approximately the same rate (2 h$^{-1}$ corresponding to a half-life of approximately 0.693/2 = 0.35 h = 20 min), but significantly less etidocaine than lignocaine is absorbed during this phase. The similarity to the fast absorption rate constant for both drugs is responsible for the similarities in $C_{P_{\text{amax}}}$ irrespective of the use of adrenaline. The difference in $X$ reflects the differences in magnitude of $C_{P_{\text{amax}}}$ which are especially obvious in the case of lignocaine without adrenaline. However, the major differences in absorption rate are reflected in the differences in $t_p$ for etidocaine and lignocaine–adrenaline studies. In these cases, the half-life of the slow phase of etidocaine is about 2–3 times that of lignocaine. In the case of plain lignocaine, the half-life of the slow phase is nearly as long as that of etidocaine, but only one-third as much of the dose is absorbed by this slow route. It is probable that slower etidocaine absorption is a result of slower release of this more lipid-soluble drug from storage in extradural fat (Lebax and Tucker, personal communication).

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**REFERENCES**


La absorción neta durante las primeras 4 h tras la administración, medida en la zona bajo la gráfica tiempo-concentración plasmática, se vio disminuida por la adición de adrenalina (descensos del 18% y 30% para etidocaina y lignocaina, respectivamente). Ambos fármacos fueron absorbidos en forma bi-exponencial, poseyendo índices similares de rápida absorción, pero con la etidocaina mostrando una media vida de absorción más prolongada en la fase de absorción lenta. Se concluye que la adición de adrenalina disminuye la fracción de la dosis que es absorbida durante la primera fase (rápida) más bien que influye las constantes de los índices de absorción.