PHARMACOKINETIC STUDY OF THE LOCAL ANAESTHETICS
BUPIVACAINE (MARCAIN) AND ETIDOCAINE (DURANEON) IN MAN

D. B. Scott, P. J. R. Jebson and R. N. Boyes

SUMMARY

Fifty mg and 25 mg of bupivacaine and etidocaine were injected intravenously into six volunteers and serial plasma levels were determined. Etidocaine gave significantly lower plasma levels than bupivacaine. Kinetic analyses of the data indicate that etidocaine has a larger volume of distribution than bupivacaine which may account for the more rapid rate of tissue redistribution.

A new local anaesthetic, etidocaine, has been shown in animals to have a duration of action similar to that of bupivacaine (Adams, Kronberg and Takman, 1972). The structural formulae of the two drugs are shown in figure 1. As animal experiments indicated advantages for the new compound over bupivacaine in respect of toxicity when administered subcutaneously (Adams, Kronberg and Takman, 1972), it was decided to perform a pharmacokinetic study to compare the distribution and elimination of the drugs in man.

![Structural formulae](image)

**FIG. 1. Structural formulae.**

METHOD

Six healthy volunteers (all medically qualified), aged 26–46 years, took part. Their body weights varied from 75 to 108 kg. Each subject received, on four separate occasions, intravenous bupivacaine 50 mg and 25 mg, and etidocaine 50 mg and 25 mg. The injected drugs were all in the form of the hydrochloride salt. The drugs were injected into a peripheral vein by means of a constant infusion pump at a rate of 5 mg/min. Venous blood from the opposite arm was withdrawn 7, 12, 15, 20, 25, 30, 40, 50, 60, 70, 90, 110 and 130 minutes after the start of the infusion. Plasma levels of the drugs were measured by means of gas chromatography. All measurements were in terms of local anaesthetic base.

Continuous recordings of the electroencephalogram and electrocardiogram were made during and for 20 minutes after the infusion of the 50-mg doses. In addition, the arterial blood pressure and the heart rate were measured every 2 minutes. Any signs or symptoms of toxicity were noted.

Using a model previously described for the distribution and elimination of lignocaine (Boyse et al., 1971), the plasma level data for bupivacaine and etidocaine were analysed to determine the volumes of distribution and half-lives of these drugs.

RESULTS

Plasma levels.

The plasma levels of bupivacaine and etidocaine after injection of 50 mg are shown in figure 2. It will be seen that the levels of etidocaine are consistently lower than those of bupivacaine. Using a paired t-test the difference is statistically significant at each time interval from 20 to 130 min.

A similar situation was seen with the 25-mg infusions (fig. 3). In this case, statistical significance was seen from 12 to 60 min inclusive.

Volumes of distribution and half-lives.

The data were analysed using the two-compartment model of Boyes and associates (1971). The
central or rapidly equilibrating space was approximately 16 l. with bupivacaine and 26 l. with etidocaine. The total volume of distribution was approximately 34 l. with bupivacaine and 62 l. with etidocaine (table I).

Two half-lives for the plasma level curves can be determined. The first represents the distribution of the drug as it leaves the plasma and enters the tissues. The second is more related to the elimination of the drug from the body. In the case of bupivacaine, the average half-lives were 7 min and 76 min. With etidocaine, the respective figures were 6 min and 57 min (table I).

The figures presented here are based on rather small doses of each agent and there must be some reservations regarding them on this account. More accurate assessments must await experiments using higher dosage.

|                    | Etidocaine | Bupivacaine | Lignocaine*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapidly equilibrating space (L.) (Vc)</td>
<td>26.2 ± 13.2†</td>
<td>16.3 ± 4.4</td>
<td>62.4 ± 30.1</td>
</tr>
<tr>
<td>Total vol. of distribution (L.) (Vd)</td>
<td>62.1 ± 44.7</td>
<td>33.5 ± 9.4</td>
<td>157.4 ± 34.9</td>
</tr>
<tr>
<td>Distribution half-life (min) (T₁/₂d)</td>
<td>6.0 ± 2.8</td>
<td>7.0 ± 2.4</td>
<td>5.4 ± 2.8</td>
</tr>
<tr>
<td>Elimination half-life (min) (T½β)</td>
<td>57.0 ± 15.8</td>
<td>76.4 ± 55.6</td>
<td>88.1 ± 12.2</td>
</tr>
</tbody>
</table>

*Data from Boyes et al., 1971. †±SD.

Toxicity.

One subject experienced mild side effects which occurred during an infusion of bupivacaine. They consisted of lightheadedness and were accompanied by a change in the electroencephalographic pattern with the appearance of slow waves (fig. 4).

---

**TABLE I. Rapidly equilibrating space volume, distribution volume, distribution half-life and elimination half-life of etidocaine and bupivacaine calculated from the pharmacokinetic data. The figures for lignocaine are given for comparison.**
No changes were observed in any of the electrocardiographic records. Minor variations in the heart rate and arterial pressure occurred but were consistent with those expected in subjects undergoing acute experiments. No subject developed hypotension.

**DISCUSSION**

The most interesting findings in these experiments were the differences between bupivacaine and etidocaine in their pharmacokinetic behaviour. Etidocaine disappeared much more quickly from the plasma and gave plasma levels 40–50% lower at all time intervals.

As can be seen in figures 2 and 3, the plasma levels of etidocaine and bupivacaine exhibit a biphasic character after intravenous injection. For the purposes of kinetic analysis, this type of plasma level behaviour is considered to represent the equilibration of the drug within a two-compartment open system. The drug is assumed to distribute rapidly in the blood and highly perfused tissues such as the brain, myocardium, lungs, kidneys, and liver. The initial rapid decline in the plasma levels between 7 and 30 min is believed to result from slower equilibration of the drug with the poorly perfused tissues such as muscle and fat.

After this interval, the decline of the plasma levels more closely represents the overall clearance of the drug from the body. The kinetic parameters shown in table I were estimated from the plasma level data for etidocaine and bupivacaine making the assumption of this type of distribution model. For comparative purposes, the respective values previously calculated for lignocaine have also been included in table I. Because of the variables involved in the estimation of the kinetic parameters and the small number of subjects, meaningful statistical comparisons between the values cannot be made, but certain trends are apparent. The fact that at equivalent intravenous doses etidocaine produces lower plasma levels than bupivacaine may be explained by the larger volume of the rapidly equilibrating compartment (Vc) for etidocaine. It should also be noted that the Vc values for both etidocaine and bupivacaine are considerably smaller than the equivalent value for lignocaine. It has been observed that at equal concentrations, the plasma binding of etidocaine and bupivacaine is considerably greater than that of lignocaine (G. T. Tucker, personal communication). Thus, at equivalent plasma levels, a greater proportion of lignocaine would be present in a freely diffusible form, which may explain the considerably larger Vc value for this drug.

It also has been noted that etidocaine has a considerably higher partition coefficient than bupivacaine. The apparently larger volume of distribution for etidocaine, when compared with bupivacaine, may be related to this difference in partition coefficient.

The smaller Vd values for etidocaine and bupivacaine as compared to lignocaine may be implicated in the observation that both former drugs appear to be eliminated at more rapid rates than the latter compound. It has been found that in a closed system, such as the isolated perfused guinea pig liver, where volumes are kept constant, the rates of metabolism of all three compounds were very similar (Boyce, unpublished data). In the in-vivo situation, liver metabolism is dependent on hepatic blood flow, which in normal volunteers may be assumed to be constant. Thus, if the intrinsic metabolic rates of various compounds are similar and hepatic blood flow is constant, the overall elimination will be inversely related to the volume of distribution (Vd), since a greater amount of the agent with the smaller Vd will be supplied to the liver per unit time by the hepatic circulation.

It is possible to speculate that the difference between bupivacaine and etidocaine represents an advantage for the latter drug in terms of systemic toxicity. The situation is similar in many respects to the difference observed between lignocaine and prilocaine (Braid and Scott, 1965). However, such conclusions must await further acute tolerance studies and additional clinical experience with this new agent, etidocaine.

**REFERENCES**

