BUPIVACAINE CARBONATE AND BUPIVACAINE HYDROCHLORIDE: A COMPARISON OF BLOOD CONCENTRATIONS DURING EPIDURAL BLOCKADE FOR VAGINAL SURGERY

T. N. APPLEYARD, ANNE WITT, R. E. ATKINSON, A. D. G. NICHOLAS

SUMMARY
Carbonated bupivacaine, plain bupivacaine hydrochloride, and bupivacaine hydrochloride with adrenaline were used to provide epidural analgesia for patients undergoing vaginal hysterectomy. Following injection the blood concentrations of bupivacaine were measured at intervals over a period of 30 minutes. All three preparations produced satisfactory analgesia at a bupivacaine dose of 1.5 mg/kg body weight. The highest group mean blood concentrations were just outside the toxic dose range. Carbonated bupivacaine was absorbed most rapidly producing significantly higher blood concentrations up to 12 minutes after injection.

Following the studies of Condouris and Shakalis (1964), Bromage (1965), Bromage et al. (1967), and Schulte-Steinberg, Hartmuth and Shutt (1970), on carbonated salts of lignocaine and prilocaine, it seemed that the place of bupivacaine as the drug of choice for obstetric epidural analgesia, as described by Noble et al. (1971), might be superseded by carbonated bupivacaine, since the rapid release of base with consequent rapid onset of action and completeness of block would be advantageous (Lofstrom, 1970). Where midwives are helping to run epidural analgesia services it is preferable to avoid the inclusion of adrenaline in analgesic solutions.

These advantages might be outweighed by excessively high blood concentrations of bupivacaine (Reynolds and Taylor, 1970, 1971). Our initial experiences with carbonated bupivacaine for epidural analgesia were favourable and this study was designed to determine the blood concentrations associated with the technique. A comparison has been made between the carbonated salt, and the hydrochloride salt of bupivacaine both with and without adrenaline. The likelihood of an adverse concentration gradient across the placenta occurring when smaller doses were used for obstetrical analgesia could also be determined.

THE TRIAL
Twenty-four patients undergoing elective vaginal hysterectomy with no intercurrent disease were included in the trial and their informed consent to the study was obtained. The patients were between 20 and 65 years of age and their weight was in the range 45–74 kg.

Each patient was randomly allocated to one of the bupivacaine groups. There were eight in each group (table I). The bupivacaine dose was 1.5 mg/kg in 0.5% concentration. Diazepam 10–20 mg was given i.v. for premedication and sedation, small increments being given as required. It is an effective tranquillizer and does not interfere with the chromatographic estimation of bupivacaine. Occasionally a nitrous oxide and oxygen mixture was used as a supplement. An intravenous infusion was commenced, the cannula being positioned in a large vein in the forearm or antecubital fossa to enable blood samples to be taken through a three-way tap.

After insertion of an epidural cannula to 2 cm in the L2/L3 or L3/L4 interspace, the measured dose of bupivacaine was injected over a period of 1 min; the end of this period was taken as zero time. Blood samples were then taken at the times shown in figure 1. After discarding the first 2 ml of blood, 3 ml samples were taken for analysis. All the epidural blocks were clinically satisfactory. Using intravenous 4.3% dextrose/saline, arterial systolic pressure was maintained at a value greater than 80 mm Hg. No adverse reactions were encountered during the operative procedure and no sequelae were noted in the postoperative period.
BLOOD BUPIVACAINE CONCENTRATION IN EPIDURAL BLOCKADE

MEASUREMENT OF BUPIVACAINE CONCENTRATION

The extraction of bupivacaine from whole blood was performed using a method similar to that described by Reynolds and Beckett (1968). Two ml of distilled water, 0.5 ml of 5N NaOH, 1.0 ml of methadone marker (1.5 μg/ml), and 2.5 ml of diethyl ether were mixed with 2 ml of whole blood in a 10-ml glass test tube and shaken for 5 min. After centrifuging for a further 5 min at 2,500 r.p.m., the supernatant fluid was drawn off. A further 2.5 ml of ether was added and the extraction repeated for a total of three times. To the extract 5 ml of 0.1 N HCl was added and shaken for 5 min. After centrifuging the ether was discarded. A further 2.5 ml of ether was added and, after further shaking and centrifuging, discarded.

To the residue 0.5 ml of 5N NaOH was added followed by 2.5 ml of ether: after shaking for 5 min and centrifuging for a further 5 min the ether was drawn off. Extraction was repeated three times. The resultant residue in a 10-ml centrifuge tube (approximately 7 ml) was evaporated to dryness in a water bath at 40° C under a stream of nitrogen. To the residue 0.02 ml of chloroform was added and 1 microlitre of this injected into the column of a gas chromatograph. Chloroform was used because less evaporation occurred while the solution was in the injection syringe than with ether; therefore, more consistent injections were obtained. Measurements were made using a Pye-Unicam 104 gas liquid chromatograph. A flame ionization detector was used, the output of which was recorded on a Servoscribe RE511-20 potentiometric recorder, running at 600 mm/hour. The column used was glass 6 mm outside diameter, 4 mm inside diameter, 2.1 metres in length: support material diatomite CQ 80/100 mesh, DMCS treated. The stationary phase used was 2.5% methyl silicone (E301).

The peak heights were compared with a standard preparation. Two standard samples were extracted with each batch of unknowns and the mean of the two used as the standard for that estimation. The detector output was checked for linearity up to 3.0 ml concentration. It was found to be linear up to this level (r=0.98).

To ensure that the amount of base in each type of solution used was the same, concentrations of 1, 2, 3 μg/ml solutions of each were prepared and a linearity curve plotted for each and compared. The amount of base present in each was found to be the same.

Fig. 1. Bupivacaine carbonate and bupivacaine hydrochloride. A comparison of blood levels during epidural blockade for vaginal surgery.
RESULTS

Figure 1 shows the blood concentration in µg/ml for the three bupivacaine groups at the various time intervals after injection.

A significant difference was found between all the groups (table I) up to 4 min after injection. Beyond this time there was no significant difference between the adrenaline group and the plain hydrochloride groups. At 12 and 28 min there was only a small difference between the concentrations obtained with the plain hydrochloride and carbonated salts. The greatest difference was between the groups who received the carbonated salt and the hydrochloride salt with adrenaline at all times after injection except at 28 min.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Adrenaline v. Carbonate</th>
<th>Adrenaline v. Plain</th>
<th>Plain v. Carbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>P&lt;0.0005</td>
<td>P&lt;0.05</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>4</td>
<td>P&lt;0.0005</td>
<td>P&lt;0.05</td>
<td>P&lt;0.0005</td>
</tr>
<tr>
<td>12</td>
<td>P&lt;0.0005</td>
<td>P&lt;0.10</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>16</td>
<td>P&lt;0.0005</td>
<td>P&lt;0.05</td>
<td>P&lt;0.04</td>
</tr>
<tr>
<td>20</td>
<td>P&lt;0.005</td>
<td>P&lt;0.10</td>
<td>P&lt;0.15</td>
</tr>
<tr>
<td>28</td>
<td>P&lt;0.10</td>
<td>P&lt;0.20</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>36</td>
<td>P&lt;0.025</td>
<td>P&lt;0.30</td>
<td>P&lt;0.15</td>
</tr>
</tbody>
</table>

The rate of increase in concentration was compared during the first 4 min after injection (table III). There were significant differences between all three groups. The rate of increase in the carbonated solution group was approximately twice that of the other two groups. Peak blood concentrations occurred at 12 min in the carbonated solution group, 16 min in the plain solution group and 28 min for the adrenaline group. The highest individual blood concentration was 1.16 µg/ml, (1.94 µg/ml in plasma), and the highest mean blood concentration 0.58 µg/ml (0.94 µg/ml plasma level); both of these occurred when the carbonated salt was used. A concentration of 1.16 µg/ml is almost in the range known to produce toxicity (Hollmen, Kohunen and Ojala, 1969).

DISCUSSION

The mode of action of the carbonated salts of local anaesthetics has been described fully (Condouris and Shakalis, 1964; Bromage et al., 1967; Loftstrom, 1970; Schulte-Steinberg, Hartmuth and Shutt, 1970; Catchlove, 1973). Their rapid onset of action is probably the result of a rapid release of free base at the injection site. When the free base has penetrated the cell the low intracellular pH caused by the carbon dioxide causes it to recombine with cation before acting on the receptors on the cell membrane. Furthermore, carbon dioxide itself may have a stabilizing effect on the cell membrane. Our results show that in equivalent doses carbonated bupivacaine causes a significantly increased initial blood concentration of bupivacaine as compared with plain bupivacaine and bupivacaine with adrenaline and the rate of increase in concentration is also greater.

A number of factors can be expected to influence the rate of absorption of bupivacaine (Braid and Scott, 1965). These include the speed of injection, the concentration of the solution, the total dose of the drug, the type of tissue into which injection is made, the blood flow in the area of injection, and the rate of release of free base. In our patients the speed of injection was reasonably constant, as were the concentration of the drug, the site of injection, and the drug dosage on a dose per unit body mass basis. However, blood flow in the site of injection will be affected by the addition of a vasoconstrictor to the solution which could explain the low blood concentrations in the patients in the adrenaline group, and also by the drug itself as well as by the action of carbon dioxide on the blood vessels. Bupivacaine, unlike procaine, has little significant action in producing vasodilatation (Dhuner and Lewis, 1966). However, carbon dioxide does produce vasodilatation and as a result will increase local blood flow and hence the speed of absorption. Furthermore, rapid release of free base will increase absorption in that free base penetrates tissue more readily.

BRITISH JOURNAL OF ANAESTHESIA
than when it is combined with cation. So it is possible that a combination of the effect of carbon dioxide on local blood flow with the rapid release of free base would account for the high initial blood concentrations of the drug when the carbonated salt is used. In theory the addition of adrenaline to the carbonated salt should reduce the rapid initial increase in blood concentration. This warrants further investigation.

ACKNOWLEDGEMENTS
The authors would like to thank the Board of Governors of the United Sheffield Hospitals for their Research Grants for the chromatographic equipment; British Drug Houses for kindly providing supplies of carbonated bupivacaine; Professor J. A. Thornton and the University Department of Anaesthetics for their help and encouragement; and Dr R. A. Dixon for his help with the statistical analysis.

REFERENCES


