EFFECT OF ADRENALINE ON PLASMA CONCENTRATIONS OF BUPIVACAINE FOLLOWING LOWER LIMB NERVE BLOCK

C. ROBISON, D. C. RAY, D. W. McKEOWN AND A. S. BUCHAN

SUMMARY
Twenty-two patients undergoing total knee arthroplasty received combined sciatic plus femoral “3 in 1” blocks as adjuncts to general anaesthesia. Eleven patients received 0.375% bupivacaine 45 ml (168.75 mg) with adrenaline 1 in 200000 and the remaining 11 received plain solution according to a previously prepared, randomized list. The mean maximum plasma bupivacaine concentration was significantly greater with plain solution than when adrenaline was added (1.66 μg ml⁻¹ compared with 0.98 μg ml⁻¹) (P < 0.05). Bupivacaine concentrations were greater at all times in the plain group compared with the group receiving adrenaline. These differences were statistically significant at 10, 15 and 20 min (P < 0.05). The greatest peak concentration recorded was 3.13 μg ml⁻¹ in one patient receiving plain bupivacaine. No patient developed signs of systemic toxic effects. Peak plasma concentrations were related inversely to body weight in patients receiving solution containing adrenaline (P < 0.005), but no relationship existed in patients who received plain solution.

KEY WORDS

Local analgesia of the lower limb using combined sciatic plus “3 in 1” femoral blocks is an established technique used at our hospital. The blocks are an adjunct to light general anaesthesia, and this balanced technique is used for major surgery to the lower limbs. It provides 12–36 h of postoperative pain relief, much longer than that provided by a single-shot spinal or extradural technique, and we have found this is of particular value in patients who are placed in the passive knee mobilizer after joint replacement and who would otherwise require frequent large doses of opioid analgesics. However, a large volume of solution (40–45 ml) of moderately high concentration of local anaesthetic is required for the technique to be effective. Therefore it was decided to study the plasma concentrations of bupivacaine after combined sciatic and femoral “3 in 1” block with and without adrenaline.

MATERIALS AND METHODS
Patients and samples
Patients undergoing prosthetic knee arthroplasty, aged 18–75 yr, gave informed consent to the study. The local Area Ethics Committee approved the study. Patients with evidence of significant cardiorespiratory disease, or impaired hepatic or renal function were excluded. Patients were allocated to one of two groups according to a previously prepared, randomized list to receive either a total volume of 45 ml of 0.375 % bupivacaine, or the same volume of solution prepared freshly with adrenaline 1 in 200000.

Premedication was with oral diazepam 10 mg 90 min before operation. Anaesthesia was induced with either methohexitone 1–1.5 mg kg⁻¹ or thiopentone 4–6 mg kg⁻¹; suxamethonium 1 mg kg⁻¹ was given to facilitate tracheal intubation if this was considered necessary. Anaesthesia was maintained with nitrous oxide, oxygen and enflurane.
PLASMA CONCENTRATIONS OF BUPIVACAINE

TABLE I. Patient and anaesthetic characteristics for the groups receiving plain and adrenaline-containing solution (median (range) or mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Plain</th>
<th>Adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65 (25–71)</td>
<td>65 (38–75)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62 (12)</td>
<td>66 (14)</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>127 (36)</td>
<td>117 (19)</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>98 (32)</td>
<td>101 (29)</td>
</tr>
<tr>
<td>Block to tourniquet inflation (min)</td>
<td>32 (24)</td>
<td>36 (31)</td>
</tr>
</tbody>
</table>

Ventilation was spontaneous in all patients. The ECG was monitored continuously and systemic arterial pressure was recorded at 5-min intervals for the duration of anaesthesia.

After induction of anaesthesia, a cannula was inserted into a vein at the antecubital fossa for blood sampling. The sciatic block was performed first using the supine technique described by Raj and colleagues [1]. Fifteen millilitre of solution was injected through a 22-gauge Whitacre spinal needle, the start of the injection being designated time 0. Following this, 30 ml of solution was injected into the femoral sheath via a 22-gauge beaded regional block needle to perform the “3 in 1” block [2]. Accurate localization of the peripheral nerves was facilitated using a peripheral nerve stimulator (Bard 750 digital). The blocks were performed in all patients by one of two authors (D.W.McK. or A.S.B.). Surgery was performed under tourniquet on the thigh, inflated to a pressure of 400 mm Hg immediately before skin incision.

Ten millilitre of venous blood was withdrawn into lithium–heparin tubes at times 0, 5, 10, 15, 20, 25, 30, 45, 60 and 120 min for measurement of plasma concentration of bupivacaine. Plasma was separated by centrifugation and stored at –20 °C. The sample was prepared by solvent extraction at pH 13 before analysis was performed by high pressure liquid chromatography on reverse phase with ultraviolet detection at 205 nm (limit of detection 0.05 μg ml⁻¹).

Statistical analysis

Differences between the groups in age, weight, duration of anaesthesia, duration of tourniquet inflation and the time from performing the blocks to initial tourniquet inflation were assessed by Student’s t test. Comparison of plasma concentrations of bupivacaine was by analysis of variance. Correlation of peak plasma concentration of bupivacaine and age and weight of the patient was by Spearman’s rank coefficient.

RESULTS

We studied 22 patients; in 11 (five male) plain local anaesthetic solution was used, while the other 11 (four male) received local anaesthetic with adrenaline. The blocks were considered satisfactory in 19 patients; in three the sciatic block was incomplete. No significant differences between the groups were observed with regard to age, weight, duration of anaesthesia, duration of tourniquet inflation and time from performing the blocks to initial tourniquet inflation (table I).

The plasma concentration in the group receiving adrenaline was significantly smaller at 10, 15 and 20 min than in the plain group (P < 0.05 for each time) (table II). The mean peak plasma concentration was significantly greater in

TABLE II. Mean (sd) and maximum plasma concentrations of bupivacaine (μg ml⁻¹) following sciatic plus femoral “3 in 1” blocks with and without adrenaline. *P < 0.05 compared with mean plasma concentration of bupivacaine in plain group

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.14</td>
<td>0.76</td>
<td>0.72</td>
<td>0.79</td>
<td>0.79</td>
<td>0.86</td>
<td>0.88</td>
<td>0.80</td>
<td>0.72</td>
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<tr>
<td>sd</td>
<td>0.21</td>
<td>0.76</td>
<td>0.79</td>
<td>0.79</td>
<td>0.86</td>
<td>0.88</td>
<td>0.80</td>
<td>0.72</td>
<td>0.70</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.67</td>
<td>2.15</td>
<td>2.62</td>
<td>2.76</td>
<td>3.13</td>
<td>2.99</td>
<td>2.35</td>
<td>2.71</td>
<td>2.07</td>
</tr>
<tr>
<td>Adrenaline</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.04</td>
<td>0.21</td>
<td>0.48</td>
<td>0.60</td>
<td>0.60</td>
<td>0.65</td>
<td>0.74</td>
<td>0.82</td>
<td>0.84</td>
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<tr>
<td>sd</td>
<td>0.08</td>
<td>0.21</td>
<td>0.27</td>
<td>0.39</td>
<td>0.54</td>
<td>0.62</td>
<td>0.63</td>
<td>0.59</td>
<td>0.72</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.28</td>
<td>0.53</td>
<td>1.01</td>
<td>1.46</td>
<td>1.96</td>
<td>2.30</td>
<td>2.32</td>
<td>2.08</td>
<td>2.06</td>
</tr>
</tbody>
</table>
the plain group than that in the adrenaline group (1.66 µg ml⁻¹ compared with 0.98 µg ml⁻¹) (P < 0.05). The addition of adrenaline delayed the attainment of peak concentrations from about 30 min with plain solution to between 60 and 120 min. The plasma concentration of bupivacaine did not exceed 4 µg ml⁻¹ in any patient.

The maximum plasma concentration of bupivacaine irrespective of time was related inversely to body weight in patients receiving solution containing adrenaline (P < 0.005). No significant relationship existed between weight and peak plasma concentration of bupivacaine in the group receiving plain solution. There was no correlation between the peak plasma concentration and the ages of the patients in each group. None of the patients demonstrated any adverse reaction attributable to the blocks and no patient showed appreciable alterations in heart rate, arterial pressure or cardiac rhythm.

**DISCUSSION**

Astra Pharmaceuticals Limited, the U.K. manufacturer of bupivacaine, recommend a maximum single dose of bupivacaine 150 mg, based on experience to date. We administered 168.75 mg to all patients in the present study. This did not result in plasma concentrations greater than the predicted toxic concentration of 4 µg ml⁻¹ [3], the greatest recorded plasma concentration being 3.13 µg ml⁻¹, and no patient showed signs of toxic effects. All patients received general anaesthesia throughout the period of blood sampling for plasma bupivacaine concentrations and it is possible that this would conceal signs of overt CNS toxicity. The average peak plasma concentration in the group receiving plain bupivacaine was 1.66 µg ml⁻¹, and 0.98 µg ml⁻¹ when adrenaline was added. These concentrations compare favourably with those of a previous study [4] in which a mean peak plasma concentration of 1.6 µg ml⁻¹ was found in patients given 0.5% bupivacaine 80 ml with 1 in 320000 adrenaline in similar combined sciatic plus femoral “3 in 1” blocks. The implication is that the dose of bupivacaine that we used is acceptable for this combined local anaesthetic technique.

In the present study, peak plasma concentrations of bupivacaine occurred after 30–45 min for plain solution and 60–120 min for the solution containing adrenaline. Indeed, four of the 11 patients receiving solution containing adrenaline may not have developed peak concentrations even by 120 min. This is at variance with an earlier study in which peak concentrations were attained within 15 min [4]. There are at least two possible explanations for this difference. First, the much greater total dose and volume administered in that study may have led to a larger bolus of local anaesthetic being delivered systemically, resulting in the earlier attainment of peak concentrations. Second, the concentration of adrenaline used by Moore and colleagues [4] is less effective in reducing vascular absorption than the 1 in 200000 concentration we used [5].

It is debatable if the addition of adrenaline to the local anaesthetic solution confers any clinically relevant advantage over the use of plain solution. We did not undertake any formal assessment of analgesia in the present study and so cannot comment if adrenaline prolongs the duration of block in this combined approach. Although the mean peak plasma concentrations of bupivacaine in both groups were considerably smaller than the reported toxic concentration, five patients receiving plain solution, but only two receiving adrenaline, exhibited peak concentrations in excess of 2 µg ml⁻¹. Scott [6] has shown previously that systemic toxic effects can result with a mean peak concentration of 2.24 µg ml⁻¹ in awake volunteers. In an earlier study [3], volunteers reported slight numbness in the eyelids when infused i.v. with bupivacaine 1.25 mg kg⁻¹ over 20 min (mean plasma bupivacaine concentration 2.1 µg ml⁻¹). The often quoted [4, 7–9] toxic concentration of 4 µg ml⁻¹ in man is hypothetical, as it is predicted from studies in dogs. Because this is the concentration at which convulsions, rather than subjective feelings of toxicity, might be expected to occur, it may be that the addition of adrenaline does protect against the development of potentially toxic blood concentrations. No patient receiving adrenaline in the present study showed appreciable changes in heart rate or arterial pressure. On the basis of these findings, it is now policy in our hospital to use adrenaline-containing solution for this combined block.

The principal factor in determining local anaesthetic toxic dosage is probably the vascularity of the site of injection and the possibility of intravascular injection. It is thought that sciatic–femoral blocks represent a low risk for inadvertent intravascular injection [4]. Other factors such as age and weight have been said to influence development of systemic toxic reactions [5]. Our
results suggest that weight might be a predictor of toxicity only in patients receiving solution containing adrenaline, but confirm the previous finding that age of the patient does not correlate with peak plasma concentration of bupivacaine [10].

Several authors have described local anaesthetic techniques using a larger dose of bupivacaine than the manufacturer recommends. In a series of 11080 regional nerve blocks using doses of up to 600 mg with adrenaline, Moore and colleagues found only 15 patients with systemic toxic effects [11]. Touminen, Rosenberg and Kalso [12], studying axillary nerve block, administered bupivacaine in doses greater than 3 mg kg\(^{-1}\) and reported no toxic effects and a greatest plasma concentration of 3.3 \(\mu g\) ml\(^{-1}\). In a further study, Neill and Watson [8] demonstrated that, although a mean dose of bupivacaine 3.4 mg kg\(^{-1}\) resulted in mean peak concentrations of 4.95 \(\mu g\) ml\(^{-1}\) without adrenaline and 3.56 \(\mu g\) ml\(^{-1}\) with adrenaline, no systemic toxic effects were apparent. This reinforces the notion that the maximum safe total dose of local anaesthetic varies and depends upon the area to be anaesthetized, the vascularity of the tissues, individual tolerance and the technique of anaesthesia used.

REFERENCES


