EFFECT OF I.V. LOW-DOSE ADRENALINE AND PHENYLEPHRINE INFUSIONS ON PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER LUMBAR EXTRADURAL ANAESTHESIA IN ELDERLY PATIENTS†

N. E. SHARROCK, G. GO AND R. MINEO

SUMMARY
Thirty patients undergoing primary total hip replacement under lumbar extradural anaesthesia with 0.75% bupivacaine 25 ml were allocated randomly to receive either low-dose adrenaline or phenylephrine infusions i.v. throughout surgery. Haemodynamic measurements and arterial blood samples were obtained before the extradural injection and at 10, 20, 30, 40, 50, 60 and 90 min thereafter. Peak arterial plasma concentrations of bupivacaine were observed 10 min after extradural anaesthesia and were significantly lower in patients receiving adrenaline infusions. Cardiac output was significantly greater in patients receiving adrenaline infusions (P < 0.01). It is postulated that the smaller circulating concentrations of bupivacaine observed in patients receiving adrenaline were caused by increased cardiac output and a greater volume of distribution than in patients receiving phenylephrine.

KEY WORDS

Pharmacokinetic studies have demonstrated increased plasma concentrations of lignocaine after i.v. infusions of lignocaine in low flow states [1–3]. Increased plasma concentrations of local anaesthetic may contribute to circulatory depression by either myocardial or peripheral vascular effects [4]. Cardiac output may decrease after extradural anaesthesia, particularly in elderly patients who develop hypotension [5, 6]. It is important, therefore, to know the influence of low cardiac output states on the peak circulating concentrations of local anaesthetic, as this may contribute to further circulatory depression.

Adrenaline and phenylephrine are often used to maintain arterial pressure after extradural anaesthesia and are known to have different circulatory effects [7]. Adrenaline increases cardiac output secondary to its inotropic action [7–9], whereas phenylephrine is associated with a reduction in cardiac output [7]. We have compared these agents as a means of assessing the influence of cardiac output on peak local anaesthetic concentrations after extradural anaesthesia.

PATIENTS AND METHODS
After Institutional Review Board approval, 30 patients undergoing total hip replacement under lumbar extradural anaesthesia were allocated randomly to receive i.v. infusions of either low-dose adrenaline or phenylephrine to maintain mean arterial pressure at 50–60 mm Hg throughout surgery.

Patients received no premedication until arrival in the operating room, where they were sedated with midazolam 1–3 mg and fentanyl 25–50 μg i.v. Patients received Ringer's lactate 70 ml h⁻¹ overnight, but were not fluid loaded before the extradural anaesthetic. A 20-gauge radial artery
BUPIVACAINE CONCENTRATIONS AFTER EXTRADURAL ANAESTHESIA

TABLE I. Patient data, intraoperative fluid requirements and dose of vasopressors (mean (range or SD)) in patients in whom plasma bupivacaine concentrations were measured (n = 30). No significant differences between groups

<table>
<thead>
<tr>
<th></th>
<th>Adrenaline (n = 15)</th>
<th>Phenylephrine (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>3/12</td>
<td>3/12</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>69.9 (57-85)</td>
<td>71.6 (63-77)</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>166.8 (8.0)</td>
<td>161.9 (7.5)</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>78.3 (19.9)</td>
<td>71.8 (13.3)</td>
</tr>
<tr>
<td>Intra-op. fluid (ml)</td>
<td>1225.0 (352)</td>
<td>1132.0 (270.0)</td>
</tr>
<tr>
<td>Dose (µg min⁻¹)</td>
<td>2.6 (1.02)</td>
<td>10.6 (6.2)</td>
</tr>
</tbody>
</table>

cannula was inserted percutaneously. In the first 15 patients studied, thermodilution pulmonary artery catheters were inserted via the right internal jugular vein.

All extradural anaesthetics were performed with the patient in the lateral position and the operative side uppermost. Injections were performed at the L1–2 interspace as follows: 0.75% bupivacaine 5 ml was infiltrated in the paravertebral muscle and a 17-gauge Tuohy needle passed into the extradural space at L1–2 using the paramedian approach. Plain 0.75% bupivacaine 25 ml was injected via the 17-gauge Tuohy needle in 5-ml aliquots with 15 s between each 5-ml injectate. This resulted in a sensory level to pinprick of T4 or above.

In the first 15 patients, serial haemodynamic measurements were made with the subject in the lateral decubitus position before the extradural injection and at 10, 20, 30, 40, 50, 60 and 90 min thereafter. Heart rate, mean arterial and pulmonary artery pressures were recorded. Cardiac outputs were measured in triplicate using a thermodilution technique (Spectramed) by injecting 10 ml of saline at room temperature. The shape of the temperature decay curves was assessed and the mean of the two best curves was used. In all patients, mean arterial pressure decreased to between 50 and 60 mm Hg and was maintained within this range throughout surgery, to minimize intraoperative blood loss and facilitate surgical conditions.

Interim analysis was performed after the first 15 patients, resulting in a modification of the procedure for the subsequent 15 patients, in whom thermodilution cardiac output was not measured.

Blood samples were drawn from the arterial line before the extradural injection and at 10, 20, 30, 40, 50, 60 and 90 min thereafter. Samples were obtained also at 5 and 15 min after extradural injection in the last 15 of the 30 patients, to define the time to peak blood concentration. All blood samples were collected in heparinized tubes and centrifuged immediately at 4 °C. Plasma samples were stored at −70 °C until required for assay.

Measurement of plasma bupivacaine concentration was by capillary gas chromatography with nitrogen selective detection (performed at the National Medical Services, Inc. Willow Grove, PA 19090, U.S.A.) The limit of quantitation was 0.02 µg ml⁻¹ and inter-assay coefficient of variation at 0.1 µg ml⁻¹ was 7.5%.

**Analysis**

Differences in plasma bupivacaine concentrations and cardiac outputs were assessed by one-way analysis of variance (ANOVA) for repeated measures and the Scheffé F test. Differences in patient data and intraoperative fluid between groups were assessed using Student's t test. The relationship between cardiac output and arterial plasma concentration of bupivacaine was assessed using simple linear regression analysis. Significance was accepted at the 0.05 level.

**RESULTS**

There were no significant differences between patient groups regarding patient data or i.v. fluid administered during operation (table I). The arterial plasma concentrations of bupivacaine after
TABLE II. Patient data and intraoperative fluid requirements (mean (range or SD)) in patients in whom serial cardiac outputs were measured (n = 15). No significant differences between groups.

<table>
<thead>
<tr>
<th>Adrenaline (n = 6)</th>
<th>Phenylephrine (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
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<tr>
<td>Age (yr)</td>
<td>77.0 (67-85)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.0 (8.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.9 (25.8)</td>
</tr>
<tr>
<td>Intra-op. fluid (ml)</td>
<td>1237.5 (103)</td>
</tr>
<tr>
<td></td>
<td>1/8</td>
</tr>
<tr>
<td></td>
<td>71.9 (68-77)</td>
</tr>
<tr>
<td></td>
<td>161.8 (8.7)</td>
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<tr>
<td></td>
<td>68.4 (15.4)</td>
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<tr>
<td></td>
<td>1077.8 (98.3)</td>
</tr>
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</table>

extradural anaesthesia in patients who received either i.v. infusions of low-dose adrenaline or phenylephrine are shown in figure 1. Significantly smaller arterial values of bupivacaine were observed in patients receiving adrenaline at 5, 10, 20, 30 and 40 min after injection. Peak local anaesthetic concentrations occurred 5 min after extradural injection with phenylephrine, whereas the peak value did not occur until 10 min after extradural injection in patients receiving low-dose adrenaline infusions. By 20 min the arterial concentrations of bupivacaine had declined significantly from their respective peak values in both groups (P < 0.0001).

Cardiac output, heart rate, mean arterial pressure and pulmonary artery diastolic pressure of the initial 15 patients (table II) receiving adrenaline or phenylephrine are shown in figure 2. There was a significantly greater cardiac output at all times in patients receiving adrenaline. Similar responses in heart rate and mean arterial pressure were observed in the remaining 15 patients receiving either adrenaline or phenylephrine.

The peak circulating concentrations of local anaesthetic showed only a weak correlation with cardiac output 10 min after extradural injection (r = 0.39).

DISCUSSION

We have demonstrated that peak arterial concentrations of bupivacaine were evident within 10 min of extradural injection and were significantly greater in patients who received phenylephrine than those who received low-dose adrenaline infusions. In previous studies, peak concentrations were shown to occur 15-30 min after extradural anaesthesia when blood was sampled from the antecubital vein [10, 11]. Our observations suggest that toxic reactions to injection of local anaesthetic are more likely to occur within 5-10 min after extradural injection rather than later. Although relatively large doses of bupivacaine were used and peak arterial concentrations exceeded 4 µg ml⁻¹ in several patients who received phenylephrine, no toxic reactions were noted. However, it is possible that these high values might contribute to additional circulatory depression immediately after extradural anaesthesia, particularly in patients with heart failure or low cardiac output.

Cardiac output was measured only in the first 15 patients as a significant haemodynamic difference between agents was already apparent. Furthermore, the haemodynamic effects of extradural anaesthesia with or without inotropic support have been reported previously [5-7, 12]. Thereafter, we were more interested in obtaining a large number of patients to define the timing of the peak concentrations of local anaesthetic, which occurred as early as 5 min after extradural injection in patients receiving systemic phenylephrine; this was unexpected.

The mechanism whereby i.v. adrenaline reduced peak plasma concentrations of bupivacaine was not assessed in this study, but there are several possible explanations. Adrenaline may increase clearance of bupivacaine by increasing hepatic blood flow. Although this has been shown to occur with lignocaine (extraction ratio 0.9), uptake of bupivacaine by the liver is less sensitive to changes in liver blood flow (extraction ratio 0.2) [13]. Furthermore, adrenaline added to extradural bupivacaine has been shown to have no effect on the clearance of bupivacaine [14]. For these reasons, enhanced hepatic clearance is unlikely to affect peak plasma concentrations in the first 10 min after extradural injection.

Adrenaline and phenylephrine may have different vasoconstrictor effects on the extradural vasculature which could potentially influence absorption of bupivacaine from the extradural space [7]. However, this seems unlikely in the dosage used. A more plausible explanation is that the systemic effects of adrenaline which maintain cardiac output and increase skeletal muscle blood flow [8, 9] would tend to enhance redistribution of the absorbed bupivacaine to the periphery [10]. In contrast, the patients who received phenylephrine had a reduction in cardiac output. This is associated usually with vasoconstriction in the periphery and a reduction of blood flow in the vessel-rich group, reducing the volume of distribution [1-3, 15]. That we were unable to
demonstrate a strong correlation between cardiac output and circulating concentrations of bupivacaine suggests that other factors such as the effects of adrenaline on skeletal muscle blood flow also contribute to the reduction in plasma concentrations of local anaesthetic.

Peak circulating concentrations of local anaesthetic after extradural anaesthesia are reduced when adrenaline-containing local anaesthetics are used [10, 11]. A reduction in uptake from the site of injection secondary to vasoconstriction has been demonstrated [16]. However, Tucker suggested that systemic effects of adrenaline could also reduce concentrations of local anaesthetic after extradural block by increasing the volume of distribution and hepatic blood flow [10]. Our observations would tend to support this, as increased cardiac output with i.v. adrenaline was associated with reduced circulating concentrations of bupivacaine. It would appear, therefore, that the reduction in circulating concentrations of local anaesthetic after injection of adrenaline-containing anaesthetic was caused by both local and systemic effects of the adrenaline.

Although 25 ml of the 30 ml of bupivacaine was injected into the extradural space, 5 ml was infiltrated into the paravertebral muscles. The arterial concentrations of bupivacaine reported therefore do not reflect only reabsorption from the extradural space. In all likelihood, the effect of different vasopressors on peak circulatory concentrations of local anaesthetic applies to other regional anaesthetic techniques.

Therapeutic benefits of i.v. adrenaline infusions after extradural anaesthesia include a reduction in circulating concentration of local anaesthetic, a reduction in the frequency of reflex bradycardia [17, 18] and preservation of cardiac output even...
when mean arterial pressure decreases [6, 7, 18]. These effects have been observed also with adrenaline injected into the extradural space, but they tend to last for only 30–40 min [7, 18]. For this reason, we recommend that, if large doses of local anaesthetic are used to achieve extensive neural block to provide intraoperative hypotension, i.v. infusions of adrenaline are used to provide circulatory support throughout the anaesthetic.

REFERENCES


