PLASMA CONCENTRATIONS OF BUPIVACAINE AND ITS ENANTIOMERS DURING CONTINUOUS EXTRAPLEURAL INTERCOSTAL NERVE BLOCK

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SUMMARY

Plasma concentrations of bupivacaine have been measured in 12 patients given bupivacaine through a paravertebral catheter placed under direct vision at thoracotomy. After an initial bolus of 0.5% bupivacaine 20 ml, mean (SEM) C_p,max was 1.45 (0.32) µg ml⁻¹ and median (range) tC_p,max was 25 (10–60) min. A concentration of 4.43 µg ml⁻¹ measured in one patient was not associated with toxic signs. During continuous infusion of bupivacaine for 120 h, C_p,max was 4.9 (0.7) µg ml⁻¹ and tC_p,max 48 (5–96) h. No symptoms or signs of toxicity occurred. Separate measurement of R- and S-bupivacaine concentrations demonstrated significantly different concentration–time profiles. (Br. J. Anaesth. 1993; 70: 201–204)

KEY WORDS


Continuous extrapleural intercostal nerve block is an effective method of analgesia for patients undergoing thoracotomy [1]. It has been shown to reduce pain scores, minimize reduction in lung volumes [2] and reduce the incidence of pulmonary complications after lung resection [3]. While the rate at which bupivacaine is infused does not exceed the maximum recommended dose (2 mg kg⁻¹/4 h), there remains the potential for bupivacaine toxicity.

Bupivacaine is a synthetic chiral compound comprising two optically active enantiomers, R-bupivacaine and S-bupivacaine. It is administered as a racemic mixture of these two enantiomers (RS-bupivacaine). As enantiomers may differ in their pharmacokinetics, pharmacological effects and toxicity, full evaluation of the potential toxicity of bupivacaine requires separate measurement of R- and S-enantiomers [4–6].

This study was undertaken to measure plasma bupivacaine concentrations achieved during continuous extrapleural intercostal nerve block.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and all patients gave informed consent. Twelve consecutive patients (ASA I) undergoing thoracotomy for anti-reflux procedures were investigated. Patients were excluded if they received a peroperative blood transfusion, lost more than 1 litre of blood, or were taking histamine antagonists which may affect bupivacaine metabolism [7]. Hepatic and renal disease was excluded on the basis of preoperative blood tests.

All patients received a sleep dose of thiopentone, vecuronium 0.1 mg kg⁻¹ and phenoperidine (1 mg if weight less than 50 kg, 2 mg if weight greater than 50 kg). Intermittent positive pressure ventilation was used with 66% nitrous oxide in oxygen supplemented with 0–1% isoflurane or 0–1.5% enflurane. Mean end-tidal carbon dioxide concentration was maintained at 4–5% and pulse oximetry saturation greater than 90%.

Towards the end of the operation, a 16-gauge extradural catheter was placed against the paravertebral space after the posterior parietal pleura had been raised as described previously [1, 2]. The tip of the catheter was inserted into the paravertebral space through a defect made in the extrapleural fascia [8].

A bolus of 0.5% plain bupivacaine 20 ml was given through the catheter when it had been secured in place (t = 0). The continuous infusion of bupivacaine was started 1 h later (t = 60 min). To remain within the guideline dosage of 2 mg kg⁻¹/4 h, the rate of infusion was set according to body weight and continued until the morning of the fifth day after operation: 50–59 kg—5 ml h⁻¹ (25 µg h⁻¹); 60–69 kg—6 ml h⁻¹ (30 µg h⁻¹); 70–79 kg—7 ml h⁻¹ (35 µg h⁻¹); 80–89 kg—8 ml h⁻¹ (40 µg h⁻¹); 90–99 kg—9 ml h⁻¹ (45 µg h⁻¹); more than 100 kg—10 ml h⁻¹ (50 µg h⁻¹).

Blood samples were collected from a central venous catheter into pre-cooled polypropylene tubes, centrifuged and stored at −20°C until required for analysis. Samples were collected at 10, 20, 30, 45 and 60 min after initial bolus injection, 5, 20, 60, 120, 180, 240, 360 and 480 min after the infusion began and at 24, 48, 72, 96 and 120 h after operation.
Results

Patient characteristics were: age range 27–64 yr, mean (SEM) weight 75.2 (3.9) kg, sex ratio 6:6. No patient reported symptoms of bupivacaine toxicity, neither were any signs of toxicity observed.

Bupivacaine assay

For the concentration range 1–20 µg ml⁻¹ of aqueous standards, the regression equation was \( y = 8.14x + 1.06 \) (\( r = 0.999, n = 12 \)). Repeatability for a standard at 10 µg ml⁻¹ was 0.58% (\( n = 8 \)). The limit of detection for bupivacaine in pooled serum was 13 ng on column for a 50-µl injection [9].

Bupivacaine concentrations after bolus injection

RS-bupivacaine concentrations measured during the first 60 min after injection are shown for individual patients in figure 1; mean values are shown in figure 2. Values for \( C_{p\text{max}} \) are shown in table I. One patient exhibited greater concentrations compared with the remainder, although they were not associated with symptoms or signs of toxicity.

Mean (SEM) \( C_{p\text{max}} \) was 1.45 (0.32) µg ml⁻¹ and median \( t_{C_{p\text{max}}} \) 25 min (range 10–60 min), although there was wide variation between individual patients.

Bupivacaine concentrations during infusion

After the initial peak after the bolus injection, there was a gradual increase to a mean (SEM) peak RS-bupivacaine concentration of 4.92 (0.7) µg ml⁻¹ at 48 (5–96) h (fig. 3, table II). Subsequent concentrations were smaller, although this decrease was not significant. The greatest concentration of RS-bupivacaine measured in any patient was 7.48 µg ml⁻¹. However, there were no symptoms or signs of bupivacaine toxicity.

Plasma concentrations of R- and s-bupivacaine are shown in figure 4. Concentrations differed significantly at 30, 45, 210, 300 and 420 min and at 24, 48 and 96 h.

Discussion

There is an extensive literature on plasma bupivacaine concentrations after injection for regional anaesthetic techniques [10]. However, to our knowl-
pleural infusion, mean venous concentrations of bupivacaine, 2.29 µg ml⁻¹ (range 0.72—4.24 µg ml⁻¹) were measured after 48 h of infusion by any route. Increasing concentrations, in some cases greater than 4 µg ml⁻¹, have been measured after 48 h of extradural infusion [14]. After continuous interpleural infusion, mean venous concentrations of bupivacaine 2.29 µg ml⁻¹ (range 0.72—4.24 µg ml⁻¹) at 48 h [10] and 4.25 µg ml⁻¹ and 2.5 µg ml⁻¹ at 24 h [15] have been measured. None of these authors reported associated toxicity. We are not aware of any study which has documented bupivacaine concentrations after 120 h of infusion by any route.

Systemic accumulation may be explained in terms of plasma protein binding. Bupivacaine is 92% bound to plasma proteins in man (at 1.0 µg ml⁻¹) [16] and only free drug concentration determines biological action and therefore toxicity. Thus total drug concentration measured in most studies does not reflect active (potentially toxic) drug concentrations. A marked increase in plasma alpha₁-acid glycoprotein occurs after surgery and is associated with increased plasma drug binding [17]. Therefore, although total drug concentration may exceed "minimal toxic concentration", free drug concentration may remain within acceptable limits after operation [18]. This has been confirmed by a study in patients undergoing cholecystectomy given i.v. bupivacaine; total plasma drug concentrations doubled after operation, whilst unbound (active) drug concentrations were similar to those measured before operation [19].

TABLE II. Maximum bupivacaine concentrations after continuous paravertebral infusion of 0.5% bupivacaine (dose according to body weight)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>C_max (µg ml⁻¹)</th>
<th>t_Cmax (min)</th>
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<tr>
<td>1</td>
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<td>Mean (SEM)</td>
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<tr>
<td>Median (range)</td>
<td>—</td>
<td>48 (5—96)</td>
</tr>
</tbody>
</table>

Fig. 4. Plasma R- and S-bupivacaine concentrations during continuous paravertebral infusion of S-enantiomer. Although mean concentration appeared different at times (arrows), differences were not statistically significant.

REFERENCES


