PLASMA CONCENTRATIONS OF BUPIVACAINE AND TWO OF ITS METABOLITES DURING CONTINUOUS INTERSCALENE BRACHIAL PLEXUS BLOCK

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SUMMARY

An interscalene brachial plexus block was performed via a catheter with 20–28 ml of 0.75% bupivacaine plus adrenaline for surgery of the shoulder region in 12 patients. Constant infusion of 0.25% bupivacaine 0.25 mg kg\(^{-1}\) h\(^{-1}\) was continued for 24 h. During surgery light general anaesthesia, without analgesics, was maintained. Plasma concentrations of total and unbound (free fraction) bupivacaine, desbutylbupivacaine (DBB), 4-hydroxybupivacaine (4-OHB) and \(\alpha\)-acid glycoprotein (AAG) were measured at predetermined intervals during the continuous block. The greatest mean plasma concentrations of bupivacaine were measured at 30 min (1.63 (SD 0.55) \(\mu\)g ml\(^{-1}\)) and 60 min (1.38 (0.48) \(\mu\)g ml\(^{-1}\)). There was a small but statistically significant increase in the plasma concentration of bupivacaine between 12 and 24 h of infusion. The mean unbound concentration of bupivacaine in plasma decreased from 0.044 (0.015) \(\mu\)g ml\(^{-1}\) (3.6 (1.1) % of total bupivacaine concentration) at 3 h to 0.023 (0.011) \(\mu\)g ml\(^{-1}\) (2.1 (1.0) %) at 24 h. The AAG concentration in plasma increased by 38% in 24 h. The metabolites DBB and 4-OHB were detectable in plasma from 30 min. with a gradual increase during infusion. At 24 h the mean concentrations of DBB and 4-OHB were 0.33 (0.22) \(\mu\)g ml\(^{-1}\) and 0.13 (0.04) \(\mu\)g ml\(^{-1}\), respectively. There were no toxic reactions during the blocks.

KEY WORDS

PATIENTS AND METHODS

The study was approved by the institutional Ethics Committee and each patient gave informed consent for the study. We studied 12 patients undergoing orthopaedic surgery of the shoulder joint (table I). The patients were premedicated with diazepam 0.15 mg kg\(^{-1}\) orally, and oxycodone 0.15 mg kg\(^{-1}\) i.m. Needle placement for brachial plexus block surgery of the shoulder joint [1–3]. Large doses are used, in general exceeding recommended doses. There is evidence of accumulation of bupivacaine in the circulation, but toxic symptoms are rare and mild, possibly because the concentration of the free (unbound) local anaesthetic remains virtually unchanged in the postoperative period [4, 5]. Hepatic metabolism and elimination of the toxic parent compound may contribute also to the clinical safety of long-term treatment with bupivacaine. Only a small fraction (6 %) of i.v. administered bupivacaine is recovered unchanged in the urine of man [6]. The toxicity (LD\(_{50}\) i.v. in mice) of the main metabolite, desbutylbupivacaine (2,6-pipemolyxylidine (DBB)) reportedly is about 12.5 % of that of bupivacaine [7].

In the study reported here, we have assessed the extent to which the plasma concentration of unbound (active) bupivacaine changes and to what maximum value the concentrations of two bupivacaine metabolites increase during a 24-h interscalene infusion treatment in surgical patients.
Table 1. Patient characteristics. AAG = Alpha,-acid glycoprotein

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>ASA risk group</th>
<th>Concomitant diseases</th>
<th>AAG concn before op. (g litre⁻¹)</th>
<th>Duration of op. (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>43</td>
<td>162</td>
<td>78</td>
<td>I</td>
<td>None</td>
<td>0.32</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>41</td>
<td>172</td>
<td>72</td>
<td>I</td>
<td>None</td>
<td>0.30</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>53</td>
<td>168</td>
<td>77</td>
<td>III</td>
<td>Angina pectoris</td>
<td>0.12</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>48</td>
<td>180</td>
<td>74</td>
<td>I</td>
<td>None</td>
<td>0.30</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>60</td>
<td>152</td>
<td>67</td>
<td>I</td>
<td>None</td>
<td>0.46</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>44</td>
<td>183</td>
<td>103</td>
<td>I</td>
<td>None</td>
<td>0.62</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>52</td>
<td>170</td>
<td>67</td>
<td>I</td>
<td>None</td>
<td>0.49</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>56</td>
<td>174</td>
<td>97</td>
<td>I</td>
<td>None</td>
<td>1.08</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>49</td>
<td>158</td>
<td>48</td>
<td>I</td>
<td>None</td>
<td>0.24</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>60</td>
<td>163</td>
<td>83</td>
<td>II</td>
<td>Hypertension</td>
<td>0.29</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>68</td>
<td>154</td>
<td>55</td>
<td>III</td>
<td>Asthma, diabetes</td>
<td>0.94</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>48</td>
<td>172</td>
<td>98</td>
<td>II</td>
<td>Severe migraine</td>
<td>0.58</td>
<td>50</td>
</tr>
</tbody>
</table>

via the interscalene approach was aided by use of a nerve stimulator (DualStim, Life-Tech Inc., Houston, Texas) connected to the proximal end of the metal inner needle of a plastic plexus block cannula (Contiplex, B. Braun–Melsungen AG, FRG). For the interscalene brachial plexus block, 20–28 ml (according to the weight of the patient) of 0.75% bupivacaine with adrenaline 5 μg ml⁻¹ was injected. Through the plastic plexus block cannula, an interscalene catheter (o.d. 0.85 mm, Contiplex, B. Braun–Melsungen AG, FRG) was introduced and fixed to the skin with a tight suture. Then a local infiltration of the suprascapular nerve (5 ml) and the intercostobrachial nerves (5 ml) was performed with 0.5% bupivacaine. Immediately thereafter, a continuous interscalene infusion of 0.25% bupivacaine 0.25 mg kg⁻¹ h⁻¹ was continued for 24 h. When all patients had evidence of a developing block by pinprick testing, general anaesthesia was induced. Glycopyrrolate 0.2 mg followed by thiopentone 5 mg kg⁻¹ was given i.v. The patient’s lungs were ventilated with 1% enfurane in 100% oxygen and then vecuronium 0.1 mg kg⁻¹ was given i.v. to facilitate tracheal intubation. General anaesthesia was maintained with 0.2–1% enfurane and 70% nitrous oxide in oxygen. Ringer’s acetate solution 3–4 ml kg⁻¹ h⁻¹ i.v. was given during surgery, and 1–1.5 ml kg⁻¹ h⁻¹ i.v. in the postoperative period.

Non-invasive arterial systolic and diastolic pressures and heart rates were recorded at 5-min intervals. ECG was monitored continuously in the operating theatre or recovery room, and during general anaesthesia end-tidal PCO₂ and PO₂ were monitored continuously. In all patients the initial neuromuscular block reversed spontaneously during surgery and anticholinesterases were not required.

The distribution of the sensory block (pinprick) and the motor block (flexion at the elbow or wrist) was tested as soon as the patient was co-operative in the recovery room after awakening from general anaesthesia. The patients were observed in the recovery room for about 2 h before transfer to the ward. If a patient complained of postoperative pain in the region operated, oxycodone 0.15 mg kg⁻¹ i.m. (0.05–0.06 mg kg⁻¹ i.v. in the recovery room) was given. For pain in any other region (e.g. headache, backache) ketoprofen 100 mg per rectum was given. Any side effects were noted on a specifically designed form, by the nurses.

Patients were interviewed by one of the investigators at the completion of the 24-h infusion. The catheter was removed and the site of puncture inspected.

Venous blood samples from a contralateral antecubital vein were taken before and 5, 30 and 60 min and 3, 6, 12 and 24 h after induction of the block. Plasma concentrations of bupivacaine and two of its metabolites, desbutylbupivacaine (DBB) and 4-hydroxybupivacaine (4-OHB) were measured in all the samples. The concentration of unbound (free) bupivacaine from samples at 5 min and 3, 6, 12 and 24 h, and the concentration of alpha,-acid glycoprotein (AAG) from samples taken before and 12 and 24 h after induction of the block were also measured.

Bupivacaine and its metabolites were measured by high pressure liquid chromatography [8]. The assay limit for all agents was approximately 0.01 μg ml⁻¹. The coefficients of variation of the intra-assay variability (n = 12) of bupivacaine,
Unbound bupivacaine was separated from plasma using an ultrafiltration method (Amicon Micropartition System). The concentrations were corrected for the deviation in test temperature (25 °C) and sample pH (pH 7.75–7.80) from the physiological values using a mean correlation coefficient of 1.14 (SD 0.10). This coefficient was derived from control experiments in which separation of the free local anaesthetic was performed from plasma equilibrated at 37 °C and pH 7.4 (bubbling with 5% carbon dioxide) for 30 min and compared with that at 25 °C and pH 7.75 (n = 9).

AAG concentrations in plasma were measured by radial immunodiffusion on M-partigen plates [9] and by an immunoturbidometric method (Kone Process, Finland) with antiserum and standards from Orion Diagnostica (Espoo, Finland).

Statistical analyses

Values are presented as mean (SD). For analysis of differences in concentrations, paired Student's t test was used. P < 0.05 was considered statistically significant.

RESULTS

The block technique used in this study gave good regional analgesia immediately after surgery in the shoulder region of all patients, except one who had only partial analgesia at the shoulder and the elbow. This patient, however, had a detectable partial motor block of the extremity, similar to that of the other patients. One patient had a vasovagal reaction (bradycardia, hypotension and sweating) during the initial search for the nerve plexus with the nerve stimulator needle. None of the patients required analgesics or additional neuromuscular block during general anaesthesia.

After awakening from general anaesthesia, the patients had either anaesthesia or analgesia of the entire upper extremity in addition to anaesthesia of the shoulder region, except for three patients who had no pinprick analgesia in the region innervated by the ulnar nerve. The catheter was removed accidentally from one patient 9 h after the block. He was given oxycodone i.m. twice in the remaining 15 h.

None of the patients complained of discomfort related to the analgesic therapy during infusion.

DBB and 4-OHB were 3%, 5% and 3%, respectively.

Toxic symptoms were not observed and the puncture site was not inflamed after infusion. Four patients had signs of Horner's syndrome during the infusion. Another four complained of sore throat.

The measured plasma concentrations of bupivacaine, unbound bupivacaine and AAG are shown in table II. Samples up to 6 h only were obtained from the patient whose catheter was removed inadvertently after 9 h of infusion.

There was great interindividual variation in both total and unbound plasma concentrations of bupivacaine. The greatest individual concentration of bupivacaine was 3.25 ug ml⁻¹ (unbound 0.072 ug ml⁻¹) occurring in patient No. 8, 5 min after the initial interscalene injection. This particular patient had the greatest individual plasma concentrations of bupivacaine throughout the period of observation. His unbound bupivacaine concentration decreased from 0.072 ug ml⁻¹ (2.2% of total bupivacaine concentration) at 5 min to 0.019 ug ml⁻¹ (1.2% of total bupivacaine concentration) at 24 h, while his AAG concentration increased from 1.08 g litre⁻¹ to 1.22 g litre⁻¹.

In the other patients, the maximal plasma concentration of bupivacaine was measured at 30 or 60 min. There was a small but significant increase in the concentration of bupivacaine between 12 (0.92 (0.27) ug ml⁻¹) and 24 h (1.08 (0.35) ug ml⁻¹) (P < 0.01). The fraction of unbound bupivacaine, on average, was unchanged during the first 3 h of infusion, but decreased thereafter from 3.6 (1.1)% (0.044 (0.015) ug ml⁻¹) to 2.1 (1.0)% (0.023 (0.011) ug ml⁻¹) during the remaining 21 h (P < 0.001). The greatest indivi-

<table>
<thead>
<tr>
<th>Time</th>
<th>Total bupivacaine (ug ml⁻¹)</th>
<th>Unbound bupivacaine (ug ml⁻¹)</th>
<th>AAG (g litre⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>0</td>
<td>0</td>
<td>0.48 (0.29)</td>
</tr>
<tr>
<td>5 min</td>
<td>0.82 (0.84)</td>
<td>0.025 (0.020)</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>1.63 (0.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>1.38 (0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>1.28 (0.41)</td>
<td>0.044 (0.015)</td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>1.08 (0.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 h</td>
<td>0.92 (0.27)</td>
<td>0.029 (0.010)</td>
<td>0.48 (0.24)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.08 (0.35)</td>
<td>0.023 (0.011)</td>
<td>0.66 (0.24)</td>
</tr>
</tbody>
</table>
FIG. 1. Mean plasma concentrations of bupivacaine (■), desbutylbupivacaine (■) and 4-hydroxybupivacaine (□) during continuous interscalene brachial plexus block in surgical patients.

individual concentration of unbound bupivacaine at 24 h was 0.051 μg ml⁻¹ (total 1.27 μg ml⁻¹).

The mean plasma concentration of AAG increased from 0.48 (0.29) g litre⁻¹ at the beginning of the bupivacaine infusion to 0.66 (0.24) g litre⁻¹ during the 24 h (P = 0.15). Only in one patient (No. 11) was there a small decrease in AAG, from 0.94 g litre⁻¹ to 0.85 g litre⁻¹.

Measurable plasma concentrations of DBB and 4-OHB were present 30 min after the initial interscalene injection of bupivacaine. The concentrations of both metabolites increased gradually, more so in the case of DBB (fig. 1). At 24 h the mean concentrations of DBB and 4-OHB were 0.33 (0.22) μg ml⁻¹ and 0.13 (0.04) μg ml⁻¹, respectively. The greatest individual DBB concentration at 24 h was 0.86 μg ml⁻¹ (total bupivacaine 1.27 μg ml⁻¹).

DISCUSSION

This study confirms previous clinical observations that continuous interscalene infusion of bupivacaine for therapeutic relief of postoperative pain (500–800 mg 24 h⁻¹) is not likely to cause toxic complications [1, 2]. This view is shared by others who have investigated continuous extradural analgesia with bupivacaine and found no toxicity, despite relatively great concentrations of bupivacaine in plasma [10] and relatively slow accumulation of bupivacaine in blood during repeated intermittent administration [11].

The main reason for the lack of toxicity is the unchanged [4, 5], or even decreasing concentration of free bupivacaine in plasma. As predicted [2], surgery of the shoulder stimulated acute-phase protein synthesis: the AAG concentration increased by approximately 38%, on average, in 24 h. The AAG concentrations may continue to increase until 5 days after surgery [12], allowing increased binding of bupivacaine in plasma. In our patients, administration of bupivacaine by continuous infusion with the same dosage could, therefore, have been extended safely beyond 24 h. The concentrations of unbound bupivacaine in plasma at 24 h were considerably less than the estimated plasma concentration of unbound bupivacaine which may produce toxic central nervous system symptoms in cancer patients during continuous extradural infusion (0.24 μg ml⁻¹) [13].

The plasma concentrations of AAG before surgery in otherwise healthy surgical patients may be difficult to predict. Despite the lack of known AAG reducing factors, such as liver disease, nephrotic syndrome and young age, etc., or factors which increase the concentration of AAG, such as trauma and cancer [14], the concentrations of AAG before operation in our patients exhibited a wide range (0.12–1.08 g litre⁻¹).

In addition to extensive binding to plasma protein, hepatic metabolism may inhibit bupivacaine activity. In comparison with lignocaine (0.65), the hepatic extraction ratio of bupivacaine in man is relatively small (0.38) [15]. However, hepatic blood flow and splanchnic extraction (0.80) in man have been shown to increase markedly when a constant i.v. infusion of bupivacaine 2 mg min⁻¹ is given [16], resulting in a high hepatic clearance of bupivacaine at the beginning of the infusion. The splanchnic extraction ratio decreased to about 50% in 2.5 h during the infusion. In the case of amide-type local anaesthetics, hepatic clearance and metabolic clearance are virtually interchangeable terms [17] and, therefore, the hepatic metabolism of bupivacaine may offer another protective mechanism against toxicity when large doses are used in patients with normal liver function.

Only about 6% of a bolus dose of bupivacaine is excreted unchanged, and about 5% appears as desbutylbupivacaine in urine collected for 24 h in man [6]. As almost 50% of an i.v. dose of desbutylbupivacaine is excreted unchanged in urine [6], the amount of desbutylbupivacaine formed by hepatic metabolism of bupivacaine is probably relatively small. However, as shown in the present study, the urinary elimination is not...
rapid enough to prevent considerable cumulation of desbutylbupivacaine in blood when bupivacaine is administered as a continuous infusion. Further metabolic degradation of desbutylbupivacaine by amide hydrolysis may be inhibited by steric interference from the piperidine ring of the molecule [18]. Although it has been suggested that desbutylbupivacaine is pharmacologically inactive [19], its LD50 value (i.v. in mice) of 63 mg kg\(^{-1}\) [7], implies that this is not so. For comparison, the LD50 (i.v. in mice) of bupivacaine and mepivacaine are 7.8 mg kg\(^{-1}\) and 40 mg kg\(^{-1}\), respectively [20]. As the desbutylbupivacaine molecule represents the basic structure and one of the main metabolites of a series of pipecolylxilide-based local anaesthetics (mepivacaine, ropivacaine, bupivacaine), it would not be surprising to find some local anaesthetic properties in desbutylbupivacaine.

The toxicity of 4-hydroxybupivacaine is not known, but this hydrophilic metabolite is probably conjugated extensively and excreted by the kidneys. Less than 1 %, on average, of an i.m. dose of bupivacaine was recovered as 4-hydroxybupivacaine in urine over a period of 24 h [21].

The role played by each of the metabolic pathways and the pharmacological and toxicological actions of the metabolites of bupivacaine warrant further study. Because of great species variation in metabolic pathways [18, 22], animal data may probably not be applicable directly to man.

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REFERENCES
