EFFECT OF ADRENALINE ON VENOUS PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER INTERPLEURAL ADMINISTRATION


SUMMARY

Bupivacaine 2.5 mg kg\(^{-1}\) (0.5 ml kg\(^{-1}\) of 0.5% solution), with or without adrenaline 5 \(\mu g\) ml\(^{-1}\), was administered by interpleural injection to 12 patients after elective cholecystectomy. Non-compartmental analysis indicated that the addition of adrenaline had no effect on total body clearance, apparent volume of distribution at steady state or elimination half-life of bupivacaine. However, peak plasma concentrations were lower in the adrenaline group (mean (so) [range]: 2.57 (0.61) [1.52-3.11] vs 3.22 (0.27) [2.84-3.53] \(\mu g\) ml\(^{-1}\), \(P < 0.05\)) and the time to maximum concentration was delayed (median [range]: 25 [15-30] vs 15 [10-20] min, \(P < 0.05\)). Analgesia was variable and no differences were detected between the two groups. The addition of adrenaline appears prudent to minimize possible bupivacaine toxicity.

KEY WORDS


Interpleural analgesia is a recent technique which was used initially for postoperative pain relief for unilateral abdominal or breast surgery [1]. The position of interpleural analgesia in modern anaesthetic practice is under review and many questions remain to be answered [2]. The successful dose of bupivacaine has varied from 0.5% bupivacaine 8 ml [3] for pancreatic cancer pain, to 0.5% bupivacaine 30 ml [4] for cholecystectomy and even 0.75% bupivacaine 60 ml has been used in a bilateral block [5].

As with intercostal block [6], interpleural bupivacaine is absorbed rapidly [4, 7-9] and concern regarding toxic concentrations of bupivacaine led to the routine addition of adrenaline to the local anaesthetic solution. However, there have been no controlled studies to confirm that this decreased the absorption of bupivacaine. The use of adrenaline has been criticized because significant cardiovascular side effects have been reported when infusions have been used [10]. A recent study of interpleural bupivacaine, with and without adrenaline, administered a fixed volume and dose of local anaesthetic but did not analyse the effect of patients' body weight and size on the peak concentrations of bupivacaine [11]. The time to peak absorption was much later in their adrenaline group compared with previous reports while, in the plain group, results were skewed by one patient who had peak values three times that of the other patients.

The aim of this study was to determine the effects of added adrenaline 1:200000 (5 \(\mu g\) ml\(^{-1}\)) on the absorption of interpleural bupivacaine.

PATIENTS AND METHODS

After approval from the Research Ethics Committee of the Chinese University Faculty of Medicine, 12 ASA I or II Chinese patients for...
elective cholecystectomy gave informed consent for this study. Patients were not taking any medications and had no history of pulmonary disease or allergy to local anaesthetics. No patient admitted to regular alcohol intake or smoking history. All patients had normal routine haematology and biochemistry, including liver function tests.

Anaesthesia was induced with thiopentone 4 mg kg\(^{-1}\), fentanyl 2 \(\mu\)g kg\(^{-1}\) and atracurium 0.5 mg kg\(^{-1}\). Further increments of atracurium were given as required and anaesthesia was maintained with 70% nitrous oxide with 0.5–1.0% isoflurane in oxygen. An interpleural catheter (16-gauge extradural) was inserted at the end of the operation, before antagonism of neuromuscular block with neostigmine 2.5 mg and atropine 1.2 mg.

The patient was turned to the left lateral position and the sixth intercostal space located in the posterior axillary line. A disposable 16-gauge Tuohy needle was walked off the superior border of the seventh rib with the shaft parallel to the posterior path of the rib. As one hand of the anaesthetist guided the advance, the other hand attempted to pass the extradural catheter through the needle. When the parietal pleura was pierced, the catheter could be threaded without resistance, enabling the Tuohy needle to be withdrawn slightly and the catheter inserted to 5 cm.

In the recovery area, patients were requested to complete a visual analogue pain score (VAS) which had been explained before operation. They were also questioned directly about severity of pain on a simple scale from 0 to 3, with 0 representing no pain, 1 slight pain, 2 moderate pain and 3 severe pain.

Patients were allocated randomly to receive 0.5 % bupivacaine 0.5 ml kg\(^{-1}\) with or without the addition of 1:200 000 adrenaline as available commercially from Astra Pharmaceuticals. This was injected over 2 min with the patient lying supine. Assessment of pain score and VAS were repeated at 5, 10, 15, 20, 30, 60, 120, 240, 360 and 480 min after bupivacaine was administered. Plasma concentrations were determined by a gas–liquid chromatographic procedure with a nitrogen-sensitive detector as described previously [12]. This technique is based on a single extraction of bupivacaine and internal standard etidocaine from alkalized plasma samples into n-hexane. The calibration curve was linear over the range 0.1–4.0 \(\mu\)g ml\(^{-1}\) and the mean (sd) recovery from plasma at 2.0 \(\mu\)g ml\(^{-1}\) was 91.9 (4.2) %. The intra-assay and inter-assay coefficients of variation were 2.9 % and 6.9 %, respectively, at 2.0 \(\mu\)g ml\(^{-1}\) using a 1-ml sample. Plasma concentration data were analysed by a model-independent method based on statistical moment theory [13]. The analysis was carried out using a microcomputer program PKCALC and the augmented ESTRIP [14] which determined the elimination half-life according to the terminal linear position (usually the last four to five points) of the plasma concentration–time curve. The computer calculated the linear least squares regression line associated with the data subset. Area under the plasma concentration–time curve, apparent volume of distribution and total body clearance were computed by PKCALC.

The Mann–Whitney \(U\) test or Fisher's exact test was used for comparisons where appropriate. \(P \leq 0.05\) was accepted as significant.

**RESULTS**

There were no differences in age, weight, sex or total anaesthetic time between the groups (table I).

<table>
<thead>
<tr>
<th>TABLE I. Patient data (mean (sd))</th>
<th>Plain</th>
<th>Adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.0 (14.8)</td>
<td>46.3 (11.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.2 (11.7)</td>
<td>58.3 (9.4)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/3</td>
<td>6/0</td>
</tr>
<tr>
<td>Anaesthetic time (min)</td>
<td>92.5 (23.0)</td>
<td>90.0 (24.9)</td>
</tr>
</tbody>
</table>
Derived pharmacokinetic variables are presented in table II. The addition of adrenaline did not alter the total body clearance, apparent volume of distribution or elimination half-life of bupivacaine. Peak plasma concentrations (Cmax) were significantly lower in the adrenaline group (mean (SD) [range]): 2.57 (0.61) [1.52–3.11] µg ml⁻¹ and the time to maximum concentration (tmax) delayed (median [range]: 25 [15–30] min) compared with the plain group (3.22 (0.27) [2.84–3.53] µg ml⁻¹ and 15 [10–20] min) (fig. 1). The difference in Cmax was still significant when adjusted for the initial dose of bupivacaine.

Fifty percent of the patients could not complete the VAS immediately after surgery. Some patients had not recovered eye-hand co-ordination sufficiently to mark the chart accurately. As these

<table>
<thead>
<tr>
<th></th>
<th>Plain</th>
<th>Adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀⁻∞ (µg min ml⁻¹)</td>
<td>595.3 (144.8)</td>
<td>592.7 (181.9)</td>
</tr>
<tr>
<td>Cl (ml min⁻¹ kg⁻¹)</td>
<td>4.60 (1.92)</td>
<td>4.67 (1.83)</td>
</tr>
<tr>
<td>Vₚ (litre kg⁻¹)</td>
<td>1.70 (0.91)</td>
<td>2.05 (0.93)</td>
</tr>
<tr>
<td>Tf (min)</td>
<td>234.8 (42.6)</td>
<td>278.8 (50.4)</td>
</tr>
<tr>
<td>Cmax (µg ml⁻¹)</td>
<td>3.22 (0.27)</td>
<td>* 2.57 (0.61)</td>
</tr>
<tr>
<td>tmax (min)</td>
<td>15 (10–20)</td>
<td>* 25 (15–30)</td>
</tr>
</tbody>
</table>

patients requested analgesia, we felt obliged ethically to administer the interpleural local anaesthetic solution. The VAS were thus partially incomplete and analysis abandoned.

There were no differences in the pain scores between the two groups and duration of analgesia was variable. Two patients in the plain group required i.v. morphine 5 mg at 30 min, although one subsequently required no more opioid analgesia throughout her hospital stay; one patient had excellent analgesia requiring no pethidine, and analgesia lasted 1.5, 7.5 and 12.8 h in the remaining three patients. Duration of analgesia was more consistent in the adrenaline group (range 3.3–10.8 h, median 9.2 h). Two patients in the adrenaline group requested no further pethidine after the first dose.

There were no signs of local anaesthetic toxicity after interpleural injection. Two patients complained of transient retrosternal chest discomfort, but clinical examination and chest radiographs failed to reveal any abnormality. No air was aspirated from the catheters, all of which were removed intact.

**DISCUSSION**

The addition of adrenaline delayed and decreased peak concentrations of bupivacaine after interpleural injection. Absorption of interpleural bupivacaine appeared to be as rapid as that following intercostal block [15] with tmax usually between 10 and 20 min after both routes.

![Fig. 1. Mean (SEM) venous plasma concentrations after interpleural administration of bupivacaine 2.5 mg kg⁻¹ plain (---) or with 1:200000 adrenaline (----).](image-url)
Peak venous plasma concentrations of bupivacaine were high compared with other studies; the potential range for CNS toxicity is estimated to be 2–4 \( \mu g \) ml\(^{-1} \) [15]. \( C_{max} \) varies widely between studies, partly because of different doses, long intervals in blood sampling and interpatient variability. In thoracic surgery, there is variable damage to lung tissue, dilution of local anaesthetic by blood and loss from chest drains. Greater concentrations than ours have been reported in adults [5], and peak arterial concentrations of 4–7 \( \mu g \) ml\(^{-1} \) after interpleural infusions in children caused no complications [16]. There is continued debate on the optimal dosage, volume and concentration of local anaesthetic solution, although the minimum effective dose should be used. Animal studies demonstrate that the mechanism of interpleural analgesia is multiple intercostal block [17] and an increased volume causes a more extensive block [18]. Quality of analgesia after 0.25% and 0.5% bupivacaine may be similar [9].

We calculated the interpleural dose and volume of bupivacaine from the patient’s weight. Weight has not been shown to affect the pharmacokinetics of local anaesthetics [15], but it is logical that weight should have some effect on \( C_{max} \). If the same dose is given to two patients with markedly different body weight, we would expect the peak concentration to be comparatively smaller in the heavier patient if the rate of absorption is similar. The drug would distribute through a greater volume of distribution in the heavier patient before achieving a peak concentration. Weight in this study ranged from 46 to 80 kg and we did not wish to give the same dose to the patients at each extreme.

Pharmacokinetic variables for interpleural bupivacaine with adrenaline have been estimated in Caucasian patients [4]. \( C_{max} \) and volume of distribution at steady state were similar, but clearance and elimination half-life greater (Student’s \( t \) test, \( P < 0.05 \)) compared with our patients. \( C_{max} \) was not significantly different (\( P = 0.12 \)). The patients were much younger than our patients and no weight data were given. Details of the general anaesthetic technique were not provided and all patients were given bupivacaine 150 mg with a greater concentration of adrenaline (1 : 100000). However, ethnic race, age and weight are not usually significant factors affecting the pharmacokinetics of local anaesthetics [15]. We have no other explanation for the differences in clearance and elimination half-life, and a further comparative study would be required to clarify this.

Efficacy of analgesia has been variable and this is apparent even in series from proponents of interpleural analgesia. Effective pain relief in 78 of 81 patients, with a mean duration of 10 h, was reported initially [1], but subsequent papers by the same group were less consistent. There was unsatisfactory analgesia in two of 30 patients, with a further six requiring additional analgesia within 4 h [9]. Total postoperative analgesic requirements were not decreased by interpleural bupivacaine [19], although reduced morphine usage has been shown in the first 4 h after operation [20]. After cholecystectomy, three of 11 patients required additional opioid analgesia [4] and there was no pain relief in five of 24 patients after thoracotomy [11]. Inadequate analgesia [8, 10, 21], pneumothorax and lung trauma [22] have been common problems in other studies.

The addition of adrenaline has been postulated to improve the quality of analgesia: by decreasing the absorption of bupivacaine, it might provide increased time for the local anaesthetic to diffuse through the pleura to the intercostal nerves. This has not been apparent in the present study or in previous work [11].

The original authors identified the interpleural space by movement of the plunger of a glass syringe attached to the Tuohy needle. Variations of this method have been criticized as the cause of increased complications [23]. However, with the equipment available in our institution, we agree with other researchers that movement of the plunger is not always a definite endpoint [4, 24].

We feel that the method we have described is a useful alternative, with some advantages. The Tuohy needle is withdrawn slightly as soon as the catheter is passed. This may decrease the chance of damage to lung by the tip of the needle. It is not necessary to remove any syringe and so no inadvertent movement of the Tuohy needle or entrainment of air occurs. It is important not to withdraw the catheter after it has been passed a few centimetres as the catheter may shear. With practice, the operator rapidly discerns the appropriate time to thread the catheter, as there is slight resistance until the Tuohy needle has pierced the pleura. In four separate patients, this procedure was performed before elective thoracotomy; the catheter was placed correctly, with no visual evidence of damage or bleeding from the pleura or lung surface.
There was no clinically detectable pneumothorax in our small series. Interpleural analgesia may improve postoperative respiratory function \[7, 20\] and opioid drugs are avoided. However, we are concerned that the patients who may benefit the most, for example those with chronic obstructive airways disease, are individuals in whom a pneumothorax would be most dangerous.

For those workers and situations where interpleural analgesia with bupivacaine is found to be a useful technique, we recommend the addition of adrenaline 5 μg ml\(^{-1}\) to delay absorption and decrease peak drug concentrations.

REFERENCES