Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal–iliohypogastric nerve block in children†

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Background. Blockade of the ilioinguinal and iliohypogastric nerves is a useful procedure in paediatric patients undergoing inguinal surgery. Bupivacaine 2 mg kg−1 has been recommended for this block. We compared the plasma concentrations of ropivacaine and bupivacaine following an ilioinguinal–iliohypogastric block.

Methods. Forty children scheduled for elective inguinal surgery were randomized to receive 2 mg kg−1 of either 0.75% ropivacaine or 0.5% bupivacaine. Surgical anaesthesia was maintained with mask inhalation of oxygen, nitrous oxide and sevoflurane. Venous blood samples were drawn at regular intervals for up to 2 h and plasma was separated. Total venous plasma concentrations were determined by gas chromatography.

Results. The groups were similar with respect to age, weight and dose of local anaesthetic. The peak plasma concentration achieved was significantly higher in the bupivacaine group compared with the ropivacaine group (2.2 vs 1.2 µg ml−1, P=0.025). The time to peak plasma concentration was significantly shorter in the bupivacaine group (24 vs 35 min, P=0.024). The initial distribution half time of bupivacaine was significantly shorter (3.6 vs 6.5 min, P=0.020) compared with that of ropivacaine.

Conclusions. Bupivacaine is more rapidly absorbed from the injection site and leads to higher plasma concentrations than ropivacaine.

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Ropivacaine is the first S-enantiomer aminoamide local anaesthetic in clinical use. It has been found to cause less cardiac and central nervous system toxicity than bupivacaine.1–3 Blockade of the ilioinguinal and iliohypogastric nerves with bupivacaine is a useful procedure that provides postoperative analgesia in paediatric patients undergoing inguinal surgery.4 Bupivacaine 2 mg kg−1 has been recommended for this block. Ropivacaine has been previously used in paediatric patients for caudal block.5–11

There are some physicochemical differences between ropivacaine and bupivacaine. They have almost identical dissociation constants, but ropivacaine is marginally less tightly bound to plasma proteins and its apparent lipid solubility is approximately half of that of bupivacaine.12–14 Plasma levels of bupivacaine and ropivacaine in children have been previously compared following caudal administration.5–8 There are no comparative data available on their plasma levels following an ilioinguinal–iliohypogastric block. This study was undertaken to compare the total venous plasma concentrations of similar doses of ropivacaine and bupivacaine following ilioinguinal–iliohypogastric blockade in children.

Methods

After written informed parental consent and approval by the Oulu University Hospital Ethics Committee, 40 ASA I children, aged 2–16 yr and scheduled for elective inguinal surgery, were enrolled to receive 2 mg kg−1 of either ropivacaine or bupivacaine. The children were premed-
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Table 1 Patient characteristics in the two treatment groups. The data are expressed as mean (SD or range). The volume of local anaesthetic per kg of body weight was significantly higher in the bupivacaine group. *P = 0.006 ropivacaine vs bupivacaine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bupivacaine (n=20)</th>
<th>Ropivacaine (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>5.9 (2.9–12.6)</td>
<td>7.6 (2.3–12.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>23.7 (2.4)</td>
<td>27.5 (9.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>117.0 (17.0)</td>
<td>124.1 (16.9)</td>
</tr>
<tr>
<td>Volume of local anaesthetic per patient weight (ml kg⁻¹)</td>
<td>0.39 (0.005)</td>
<td>0.29 (0.06)*</td>
</tr>
</tbody>
</table>

Table 2 Pharmacokinetic parameters following ilioinguinal–iliohypogastric blockade with bupivacaine or ropivacaine. The data are expressed as mean (SD). Cmax = the maximum measured plasma concentration; Tmax = time to the maximum measured concentration. TA = initial distribution half time, AUC = area under the concentration–time curve from 0–120 min, calculated from the individual concentration–time curves according to the trapezoid rule. Differences between the groups were compared by the Mann–Whitney test, with a P-value of <0.05 considered statistically significant. The SPSS for Windows statistical package was used.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bupivacaine</th>
<th>Ropivacaine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg ml⁻¹)</td>
<td>2.2 (1.0)</td>
<td>1.5 (0.8)</td>
<td>0.025</td>
</tr>
<tr>
<td>Tmax (min)</td>
<td>24 (11.9)</td>
<td>35.0 (15.4)</td>
<td>0.024</td>
</tr>
<tr>
<td>T1/2 (min)</td>
<td>3.6 (1.8)</td>
<td>6.5 (4.4)</td>
<td>0.020</td>
</tr>
<tr>
<td>AUC (µm 120 min)</td>
<td>189.6 (89.5)</td>
<td>115.3 (68.1)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Intravenously administered and randomly allocated to receive either 0.75% ropivacaine (Naropin, Astra, Finland) or 0.5% bupivacaine (Marcain, Astra, Finland). The administration of the local anaesthetic was not blinded. The treatment allocation codes were placed in sealed envelopes, and for each consecutive patient, the anaesthetist opened the next envelope in order.

The patients underwent ECG, end-tidal CO₂ concentration (ECO₂) monitoring, non-invasive arterial pressure measurements and pulse oximetry. In all cases, anaesthesia was maintained with sevoflurane and nitrous oxide in oxygen by facemask inhalation, with spontaneous ventilation.

After induction of anaesthesia, ilioinguinal–iliohypogastric nerve blockade was performed with a 22-gauge short bevelled needle. The local anaesthetic was injected at a point that was 1–2 cm medial and inferior to the superior anterior iliac spine under the fascia of the external oblique muscle. If the calculated volume of local anaesthetic was <4 ml, it was diluted with saline up to 4 ml. All blocks were performed by experienced paediatric anaesthetists (J.K., K.K.).

Venous blood samples of 5 ml were drawn for the determination of total drug concentrations at 2, 5, 10, 20, 30, 40, 50, 60 and 120 min after the dose. Care was taken not to exceed 5% of the estimated blood volume of the patient. The blood samples were immediately centrifuged at room temperature, and the plasma was separated and stored at −20°C until analysis.

The total concentrations of ropivacaine and bupivacaine bases in 1 ml of plasma were measured by gas chromatography. All samples were measured in duplicates with intra-pair variations (SD) of 4.0 (3.0)% and 3.4 (3.5)% for ropivacaine and bupivacaine, respectively.

The peak measured plasma concentration (Cmax) and the time to reach Cmax (Tmax) were estimated from the individual observed plasma concentration time profiles. The initial distribution and elimination half-lives were calculated from the linear phases of the semilogarithmic concentration–time curves. The area under the concentration–time curve (AUC) was calculated from the individual concentration–time curves according to the trapezoid rule. Differences between the groups were compared by the Mann–Whitney test, with a P-value of <0.05 considered statistically significant. The SPSS for Windows statistical package was used.

Results

Patient characteristics were similar in the two groups (Table 1). By chance, children in the ropivacaine group were slightly taller than those in the bupivacaine group. The volume of local anaesthetic used per kg of body weight was higher in the bupivacaine group (0.39 vs 0.29 ml kg⁻¹, P=0.006). Dilution was required for only one patient in the ropivacaine group. The peak plasma concentration achieved was significantly higher in the bupivacaine group (2.2 vs 1.5 µg ml⁻¹, P=0.025) (Table 2). The time to the peak plasma concentration was significantly shorter in the bupivacaine than in the ropivacaine group (24 vs 35 min, P=0.024). The initial distribution half time of bupivacaine was also significantly shorter (3.6 vs 6.5 min, P=0.020) compared with that of ropivacaine. The mean AUC from 0–120 min for bupivacaine was larger than that for ropivacaine (189.6 vs 115.4 min µg ml⁻¹, P=0.025). At all time points, the plasma concentrations of bupivacaine were higher than those of ropivacaine (Fig. 1). No opioid analgesics were needed during the anaesthesia in either group.

Discussion

The concentrations of local anaesthetics used in this study were those used in routine clinical practice in our hospital. Ilioinguinal–iliohypogastric nerve blockade with similar doses of 0.75% ropivacaine and 0.5% bupivacaine resulted in higher peak plasma concentrations and more rapid absorption of bupivacaine than ropivacaine. The volume of bupivacaine injected per kg of body weight was 1.5 times higher than that of ropivacaine. In addition to the total dose of local anaesthetic injected, the rate of absorption is related to the vascularity of the injected area, the concentration of local anaesthetic used and the volume of the space into which the injection is made. The higher volumes of bupivacaine injected into the inter-fascial space partly...
explain the higher bupivacaine concentrations obtained. Although the concentration of ropivacaine administered was higher, the plasma concentrations observed were lower than those of bupivacaine at the higher absorption rate of bupivacaine. This may be further explained by the higher lipid solubility of bupivacaine.

Maximum total venous plasma concentrations of $>2 \mu g/ml^{-1}$ were achieved in 60% of the children in the bupivacaine group and 30% in the ropivacaine group. These concentrations of bupivacaine and ropivacaine are close to the reported maximum tolerated venous plasma concentrations of 2.1 $\mu g/ml^{-1}$ and 2.2 $\mu g/ml^{-1}$, respectively, as evaluated from i.v. administration to healthy volunteers. 3 A ‘full dose’ of 2 mg kg$^{-1}$ is probably not necessary for an ilioinguinal–iliohypogastric block, and further studies with efficacy data are required to determine the minimum dose required. Although the mean peak plasma concentration in the bupivacaine group was lower than the generally accepted safe maximum total plasma concentration of 4 $\mu g/ml^{-1}$, a peak concentration of 4.9 $\mu g/ml^{-1}$ of bupivacaine was observed in one child.17 Such a high concentration may suggest that at least part of the injection might have inadvertently been administered intravascularly. However, no adverse effects were noted in any of the children in this study. It should be pointed out, however, that possible seizure activity may have been masked by the general anaesthesia, which is known to increase the threshold for seizures.

There are only limited data available on bupivacaine concentrations following ilioinguinal–iliohypogastric blockade. In previous studies, lower mean peak plasma bupivacaine concentrations of 0.79 $\mu g/ml^{-1}$ and 1.35 $\mu g/ml^{-1}$ have been reported. 18,19 In the study by Stow and colleagues, 18 however, a lower dose of bupivacaine (1.25 mg kg$^{-1}$) was used. In the study by Epstein and coworkers, 19 a dose of 2 mg kg$^{-1}$ of 0.25–0.5% bupivacaine was used, and their study series included younger and smaller children than those in our study. Furthermore, both unilateral and bilateral blocks were induced in their study. There were only eight patients who received unilateral blocks induced with 0.5% bupivacaine similar to those used in our study. Although the volume of local anaesthetic per kg of body weight was similar to ours, the mean peak plasma concentration of bupivacaine was lower (1.45 $\mu g/ml^{-1}$) than that measured in our study. They observed a peak plasma concentration of 2.3 $\mu g/ml^{-1}$ in one patient. This could be explained by the fact that there is generally wide interindividual variation between the plasma concentrations of local anaesthetics as well as their pharmacokinetic variables. 20 Our series of 20 patients included eight patients with a peak plasma concentration of bupivacaine lower than 2 $\mu g/ml^{-1}$. In these patients, the mean peak plasma concentration was 1.3 $\mu g/ml^{-1}$, which is similar to that found in the study of Epstein and colleagues. 19 In contrast to ilioinguinal–iliohypogastric blockade, equal peak plasma concentrations of bupivacaine and ropivacaine have been measured following a caudal block. 8 This has been explained by the lower rate of systemic absorption of bupivacaine from the caudal space. Furthermore, the concentrations of bupivacaine and ropivacaine measured in the present study were three times and twice as high, respectively, than those following caudal block. 8 In addition, the times to the peak plasma concentration were shorter for both bupivacaine and ropivacaine than those following a caudal block. 19 It has been shown with bupivacaine that absorption from the caudal space is slower and results in lower plasma concentrations than following ilioinguinal–iliohypogastric blockade. 18 The absorption rates at different sites of injection are known to be directly related to local blood flow and inversely related to local
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tissue binding. The intrinsic vasoconstrictive effect of ropivacaine may slow down its absorption from the injection site while, in contrast, the vasodilative effect of bupivacaine enhances absorption. It has been shown that plasma uptake is faster from more vascular areas, such as the intercostal space or the axilla, compared with the caudal space. A previous study showed that, due to its higher lipid solubility, bupivacaine is more intensively absorbed locally into the caudal space, preventing its systemic absorption. Injection into the narrow inter-fascial space may enhance systemic absorption and partly explain the higher plasma concentrations of both ropivacaine and bupivacaine compared with those following injection into the caudal space.

In conclusion, ilioinguinal–iliohypogastric blockade with 2 mg kg⁻¹ of 0.5% bupivacaine led to a more rapid absorption and higher plasma concentrations than a similar dose of 0.75% ropivacaine. Furthermore, the rate of absorption and the peak plasma concentrations of both drugs were higher than those reported following caudal block.

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