Ropivacaine pharmacokinetics after caudal block in 1–8 year old children

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We studied the pharmacokinetics of ropivacaine (2 mg ml⁻¹, 1 ml kg⁻¹) performed in 20 children aged 1–8 yr undergoing subumbilical surgery, in this open, non-comparative, multicentre study. Venous blood samples were collected up to 12–36 h. The mean (SD) peak plasma concentration, 0.47 (0.16) mg litre⁻¹, was achieved after 12–249 min. The free fraction was 5% and the highest individual peak plasma concentration of free ropivacaine was 0.04 mg litre⁻¹. Clearance was 7.4 (1.9) ml min⁻¹ kg⁻¹ and the terminal half-life 3.2 (0.8) h. Thus, the free plasma concentrations of ropivacaine were well below those associated with toxic symptoms in adults and the capacity to eliminate ropivacaine seems to be well developed in this age group. In this open study of 20 patients, ropivacaine was well tolerated and provided satisfactory postoperative pain relief without observable motor block.

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Ropivacaine, a local anaesthetic recently approved for use in adults, is less toxic to the central nervous system and heart1 and interferes less with motor function2 than bupivacaine. These characteristics of ropivacaine could potentially be of greater benefit in the paediatric population, and preliminary results in children have shown ropivacaine to be as efficacious as bupivacaine.3–5

The primary aim of the present study was to investigate the pharmacokinetics of ropivacaine after caudal administration in children. A dose of 2 mg kg⁻¹ was chosen on the basis of the experience of ropivacaine in adults and the doses of bupivacaine used in this age group. Secondary aims were to assess postoperative analgesia and motor block and to document any adverse reactions.

Materials and methods
The study was approved by local ethics committees. After obtaining written parental informed consent, 20 ASA I–II patients, aged 1–8 yr, weighing ≤25 kg and scheduled for elective surgery below the umbilicus, were enrolled in the study between October 1997 and September 1998. The patients were stratified into three age groups (1–2, 3–4 and 5–8 yr) with a minimum of five patients in each group. The study was performed according to Good Clinical Practice.

Anaesthesia
Patients were premedicated with midazolam rectally (0.3–0.45 mg kg⁻¹) or i.v. (0.1 mg kg⁻¹). Eutectic mixture of local anaesthetics (EMLA®, Astra Zeneca, Södertälje, Sweden) was used to prevent pain from the insertion of an intravenous catheter. Anaesthesia was induced by thiopentone 5–10 mg kg⁻¹ i.v. and maintained by sevoflurane, nitrous oxide and oxygen. Airway management consisted of a face mask, laryngeal mask airway or endotracheal intubation, depending on the type of surgery and the expected duration of surgical intervention. For endotracheal
intubation, adequate muscle relaxation was achieved by administration of atracurium 0.5 mg kg\(^{-1}\) i.v. or suxamethonium 2.0 mg kg\(^{-1}\) i.v. After induction of anaesthesia, a second intravenous cannula was inserted, for use for blood sampling only. The patient was then placed on their side and a caudal block with ropivacaine 2 mg ml\(^{-1}\), 1 ml kg\(^{-1}\), was performed. Ropivacaine was injected in fractions over \(\leq 2\) min. During anaesthesia, patients were monitored by ECG, pulse oximetry, capnography and non-invasive measurements of arterial pressure and inhalational agents. Opioids were avoided before or during surgery. However, according to our routine practice, all patients received paracetamol (total daily dose \(\leq 100\) mg kg\(^{-1}\)).

**Blood and urine sampling**

Peripheral venous blood samples (1 ml) for analysis of total plasma ropivacaine concentrations were collected from indwelling intravenous catheters immediately before and 15, 30, 60 min and 2, 4, 8 and 12–36 h after administration of caudal ropivacaine. Free ropivacaine and \(\alpha_1\)-acid glycoprotein (AAG) concentrations were determined in the 30 min and 8 h samples, when larger volumes of blood (5 ml) were collected. The blood samples were centrifuged within 60 min of collection and the plasma was frozen at \(-20^\circ\text{C}\) until assay.

In patients requiring urinary catheterization as a routine part of the surgical procedure, urine was collected for the determination of ropivacaine and its main metabolites, 3-hydroxyropivacaine and 2',6'-piperidinoxylylide (PPX). Urine was collected every 6 h for \(\leq 36\) h postoperatively or until the urinary catheter was removed. The volume of urine collected at each occasion was recorded and 5 ml samples were frozen at \(-20^\circ\text{C}\) until assay.

**Bioanalytical methods**

The total concentration of ropivacaine base (relative molecular mass 274) in plasma was determined by a gas-chromatographic method with nitrogen-sensitive detection.\(^6\) The limit of quantification was optimized to 0.003 mg litre\(^{-1}\) using 100 \(\mu\)l of plasma. The between-day coefficients of variation (CV) were <10% at concentrations in the range 0.0055–2.19 mg litre\(^{-1}\). The accuracy was 99–101%. The free concentration of ropivacaine base in plasma was determined using a coupled-column, liquid-chromatographic system with UV detection after ultraltrification of plasma at pH 7.4 and 37°C.\(^7\) The limit of quantification was 0.003 mg litre\(^{-1}\) using 1.0 ml of plasma. The between-day CV was 8.2% at a free ropivacaine concentration of 0.055 mg litre\(^{-1}\). The concentration of AAG in plasma was determined by an immunoturbidimetric method from Boehringer Mannheim. The limit of quantification was 0.12 g litre\(^{-1}\) using 50 \(\mu\)l of plasma. The method was linear up to 5.33 g litre\(^{-1}\). The between-day CV was 7% at 0.8 g litre\(^{-1}\).

A new method was introduced for quantifying ropivacaine, 3-hydroxyropivacaine and PPX in urine. In previous studies, the concentration of ropivacaine and its main metabolites has been determined by a method based on liquid chromatography and UV detection.\(^8\) In the present study, some patients were treated with trimethoprim, which was co-determined with 3-hydroxyropivacaine using unselective UV detection. A new method based on a selective detection technique, tandem mass spectrometry, was used in the present study. As before, the concentrations of ropivacaine, 3-hydroxyropivacaine (relative molecular mass 290) and PPX (relative molecular mass 232) in urine were determined after acid hydrolysis with 6 M hydrochloric acid. This gives the sum of the conjugated and the unconjugated 3-hydroxyropivacaine, while ropivacaine and PPX exist only in the unconjugated form. A urine volume of 1.0 ml was used. Solid-phase extraction was used for sample preparation. The new selective liquid-chromatographic method with gradient elution and electrospray tandem mass spectrometry was used for the determination of ropivacaine, 3-hydroxyropivacaine and PPX in urine. The gradient system contained acetonitrile and ammonium formate buffer, pH 4. The scan mode was multiple reaction monitoring using the precursor ions at \(m/z\), \(M+1\), 275.2 for ropivacaine, 291.1 for 3-hydroxyropivacaine and 233.2 for PPX. After collisional dissociation the product ions were used for quantification, \(m/z\), 126.0 for ropivacaine and 3-hydroxyropivacaine and 84.0 for PPX. The limit of quantification was 0.08 mg litre\(^{-1}\) for ropivacaine, 0.49 mg litre\(^{-1}\) for 3-hydroxyropivacaine and 0.18 mg litre\(^{-1}\) for PPX. The between-day CVs were <5% at ropivacaine concentrations of 0.15–4.6 mg litre\(^{-1}\). For 3-hydroxyropivacaine, the between-day CVs were <8% at concentrations of 0.99–30 mg litre\(^{-1}\) and for PPX they were <6% at concentrations of 0.42–11 mg litre\(^{-1}\). The accuracy was 97–101%.

**Pharmacokinetic calculations**

The plasma concentration–time data were analysed by non-compartmental methods using the pharmacokinetic program WinNonlin Professional version 2.0 (Pharsight Co., Mountain View, CA, USA). Peak plasma concentration (\(C_{\text{max}}\)) and the time to \(C_{\text{max}}\) (\(t_{\text{max}}\)) were obtained directly from the observed data. The free fraction of ropivacaine (\(f_d\)) in a sample was calculated as free concentration divided by total concentration and the free ropivacaine concentration at \(t_{\text{max}}\) (\(C_{d\,\text{max}}\)) was estimated from \(C_{\text{max}}\) and \(f_d\) 30 min, assuming the protein binding to be equal at 30 min and at \(t_{\text{max}}\). The terminal half-life (\(t_{1/2}\)) was calculated by linear regression of the data points in the declining and linear part of the log-linear plasma concentration–time curve. The area under the plasma concentration–time profile up to infinity (AUC) was calculated using the linear trapezoidal rule up to the last blood sample and extrapolated to infinity by multiplying the concentration in the last measurable plasma concentration by \(t_{1/2}/\ln 2\). The volume of distribution at steady
state ($V_{ss}$) was calculated as dose $\times$ (AUMC)/AUC$^2$, where AUMC is the area under the first moment–time curve. Plasma clearance (Cl) was calculated as dose/AUC. Since the absorption of ropivacaine can be assumed to be complete after caudal administration, $V_{ss}$ and Cl are not been presented as apparent parameters. $Cl$ for the unbound concentration ($Cl_{fu}$) was calculated as $Cl/f_{fu}$ 30 min and volume of distribution at steady state for the unbound fraction ($V_{ss u}$) was calculated as $V_{ss u}/f_{fu}$ 30 min. The hepatic extraction ratio ($E_{H}$) of ropivacaine was calculated as blood clearance divided by the liver blood flow ($Q_{H}$). The blood:plasma concentration ratio of ropivacaine was assumed to be similar to adult values (0.7), since the plasma protein binding of ropivacaine and the haematocrit have reached adult values in the age group studied.$^9$ $Q_{H}$ was estimated from the adult value of liver blood flow, 1350 ml min$^{-1}$, adjusted to the individual body-surface area calculated as (weight (kg)/70 kg)$^{0.7} \times 1.8$. The half-lives of 3-hydroxyropivacaine and PPX were estimated by linear regression of the linear and declining part of the log-linear plot of the excretion rate–time curve.

Clinical assessments

Postoperative analgesia and lower-limb motor function were assessed by the research staff at regular intervals, every hour during the first 8 h and then once within the interval 12–36 h. Postoperative pain was assessed using a four-point behaviour observer scale (no pain, mild pain, moderate pain, severe pain).$^{12}$ Supplemental opioid analgesia was administered if the pain was judged to be moderate or severe or the effect was considered insufficient by the research staff. The time to the first administration of opioid was recorded. Motor function was assessed as motor block present (inability to move the legs with slight stimulation allowed) or absent. Adverse events were recorded during the study period up to a telephone follow-up 2 weeks after surgery.

Statistical methods

The data were analysed using descriptive methods such as summary statistics and graphs. Possible relationships between variables were investigated using parametric linear regression. The results are presented as mean (SD) unless otherwise stated.

Results

Patient characteristics are shown in Table 1. There were five patients in the youngest age group, nine in the middle one and six in the oldest one. The main surgical diagnoses were hypospadias ($n=7$), undescended testis ($n=6$) and vesicoureteral reflux ($n=2$). The duration of surgery varied from 0.3 to 3.6 h. Two cases of protocol deviations (of minor importance) occurred: in one patient morphine 0.07 mg kg$^{-1}$ i.v. was given as premedication and in another fentanyl 2×25 µg i.v. was given in connection with surgery.

Table 1 Summary of patient characteristics (median (range) or frequency)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range) or Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>4.0 (1.3–7.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>16.5 (11–25)</td>
</tr>
<tr>
<td>ASAI/ASAII</td>
<td>19/1</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>18/2</td>
</tr>
</tbody>
</table>

![Fig 1 Individual and mean plasma concentration–time profiles of ropivacaine after caudal administration of ropivacaine 2 mg kg$^{-1}$ to 1–8 yr old children ($n=20$).](image.png)

Pharmacokinetics

The individual and mean plasma concentration–time curves are shown in Fig. 1. The pharmacokinetic parameters are reported for each age group and the entire population in Table 2. $C_{max}$ and the estimated free plasma concentration of ropivacaine at $t_{max}$ ($C_{u max}$) were similar in the age groups studied, whereas $t_{max}$, reached within 12 min to 4 h, tended to be shorter in older children. The highest individual $C_{max}$, 1.02 mg litre$^{-1}$, was observed 12 min after caudal block in a 2 yr old boy and the highest individual $C_{u max}$ was 0.043 mg litre$^{-1}$ in a 3-yr-old girl. $f_{fu}$ was similar at 30 min and 8 h after the caudal block and in the three age groups. AAG concentrations at 30 min and 8 h were 10–22 and 11–24 µmol litre$^{-1}$, respectively. Half-life was in the range 2.3–5.5 h, with similar values in the three age groups. There was no apparent age-dependency in bodyweight-adjusted Cl.
Table 2 Pharmacokinetics of ropivacaine after caudal administration at 2 mg kg\(^{-1}\) to 1–8 yr old children. The results are presented as mean (sd) (range) for all parameters, except \(t_{\text{max}}\), which is expressed as median (range). \(^{a}\)Estimated from \(C_{\text{max}}\) and \(f_{\text{u}, 30 \text{ min}}^{b}\); \(^{b}\)n=3, \(^{c}\)n=2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1–2 yr (n=5)</th>
<th>3–4 yr (n=9)</th>
<th>5–8 yr (n=6)</th>
<th>Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) (mg litre(^{-1}))</td>
<td>0.52 (0.28) (0.34–1.02)</td>
<td>0.47 (0.13) (0.32–0.75)</td>
<td>0.42 (0.07) (0.35–0.53)</td>
<td>0.47 (0.16) (0.32–1.02)</td>
</tr>
<tr>
<td>(t_{\text{max}}) (min)</td>
<td>115 (12–249)</td>
<td>62 (16–125)</td>
<td>30 (29–242)</td>
<td>60 (12–249)</td>
</tr>
<tr>
<td>(C_{\text{u, max}}) (mg litre(^{-1})) (^{a})</td>
<td>0.026 (0.013) (0.014–0.039)</td>
<td>0.024 (0.008) (0.015–0.043)</td>
<td>0.023 (0.005) (0.014–0.029)</td>
<td>0.024 (0.006) (0.014–0.043)</td>
</tr>
<tr>
<td>(f_{\text{u}}) (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>30 min</td>
<td>4.7 (2.2) (3.0–7.3)</td>
<td>5.2 (1.1) (3.0–7.1)</td>
<td>5.5 (1.3) (3.3–7.1)</td>
<td>5.2 (1.3) (3.0–7.3)</td>
</tr>
<tr>
<td>8 h</td>
<td>4.3 (1.3) (3.3–5.2)</td>
<td>4.9 (1.5) (2.9–7.8)</td>
<td>5.4 (2.9) (3.3–10.9)</td>
<td>5.0 (2.0) (2.9–10.9)</td>
</tr>
<tr>
<td>(C_{\text{F}}) (ml min(^{-1}) kg(^{-1}))</td>
<td>6.4 (1.6) (4.6–8.0)</td>
<td>7.1 (1.6) (4.6–10.0)</td>
<td>8.8 (2.0) (5.9–11.8)</td>
<td>7.4 (1.9) (4.6–11.8)</td>
</tr>
<tr>
<td>(V_{\text{u}}) (litr(^{-1}) kg(^{-1}))</td>
<td>146 (33) (109–167)</td>
<td>140 (34) (78–189)</td>
<td>170 (67) (105–292)</td>
<td>151 (46) (78–292)</td>
</tr>
<tr>
<td>(E_{\text{u}}) (%)</td>
<td>0.29 (0.08) (0.21–0.37)</td>
<td>0.34 (0.08) (0.21–0.40)</td>
<td>0.45 (0.10) (0.30–0.57)</td>
<td>0.33 (0.12) (0.21–0.57)</td>
</tr>
<tr>
<td>(V_{\text{u, u}}) (litr(^{-1}) kg(^{-1}))</td>
<td>46.5 (11.4) (35.2–58.0)</td>
<td>48.8 (18.4) (23.3–90.0)</td>
<td>49.7 (15.1) (37.2–77.4)</td>
<td>45.5 (17.2) (23.3–90.0)</td>
</tr>
<tr>
<td>(t_{1/2}) (h)</td>
<td>3.1 (0.8) (2.4–4.1)</td>
<td>3.4 (1.0) (2.3–5.5)</td>
<td>2.9 (0.5) (2.4–3.7)</td>
<td>3.2 (0.8) (2.3–5.5)</td>
</tr>
</tbody>
</table>

![Graph](image)

**Fig 2** (a) Clearance/weight versus age and (b) \(V_{\text{u, u}}\)/weight versus age after caudal administration of ropivacaine 2 mg kg\(^{-1}\) to 20 children aged 1–8 yr.

![Graph](image)

**Fig 3** Mean (sd) fraction of dose excreted in urine as ropivacaine (ROPI) and its metabolites 3-hydroxyropivacaine (3-OH-R) and PPX after caudal administration of ropivacaine 2 mg kg\(^{-1}\) to 10 children aged 1–8 yr.

Ropivacaine and PPX was 30%, with individual values between 12% and 48%. 3-Hydroxyropivacaine dominated with a mean recovery of 25%, range 10–44%. Between 1% and 12% of the dose was excreted as PPX (mean 5%), while no more than 1% of the dose was recovered in the urine as ropivacaine. In all infants the greatest amount of 3-hydroxyropivacaine was excreted within 0–12 h after the dose, whereas the greatest amount of PPX was excreted between 6 and 18 h. The half-life of 3-hydroxyropivacaine was in the range 4.0–6.3 h calculated on three to five data points (n=7); the half-life of PPX was 4.2–15.7 h as determined on the last two to four data points in six individuals.

**Clinical assessments**

The median time to supplemental analgesics (morphine) was 12.6 h after the block (Fig. 4). With the analgesic regime used, postoperative pain relief was satisfactory (i.e. no pain, mild pain or patient asleep) in ≥90% of the patients.
at all assessment times. No signs of motor block were observed in any of the patients during the postoperative period, and all children were able to move their legs when emerging from the anaesthesia. The most common adverse events were vomiting (50% of patients), nausea (15%) and pruritus (15%). No serious adverse reactions occurred and no signs or symptoms of other systemic toxic reactions were reported. Vital signs (arterial pressure, pulse rate and peripheral oxygen saturation) were measured and showed only minor variations from baseline.

### Discussion

The major finding of the present study was that caudal block with ropivacaine 2 mg kg\(^{-1}\) (2 mg ml\(^{-1}\)) in children aged 1–8 yr results in plasma concentrations of unbound ropivacaine well below toxic concentrations in adults. The dose studied was associated with adequate postoperative analgesia and no signs of motor block or serious adverse reactions related to the use of ropivacaine were noted.

Since the registration of ropivacaine for use in adults, a limited number of clinical studies have been published regarding the use of this new local anaesthetic in children.\(^3\)\(^-\)\(^5\) Caudal or epidural administration of ropivacaine 2 mg kg\(^{-1}\) has been reported to be comparable to bupivacaine 2.0–2.5 mg kg\(^{-1}\).\(^3\) Analgesia is significantly longer when using ropivacaine 5 mg ml\(^{-1}\) (3.75 mg kg\(^{-1}\)) than with either ropivacaine or bupivacaine 2.5 mg ml\(^{-1}\) (1.875 mg kg\(^{-1}\)).\(^13\) Where 2.5–3.75 mg ml\(^{-1}\) solutions of bupivacaine and ropivacaine were used, ropivacaine administration was associated with a shorter duration of motor block.\(^14\)\(^15\)

In the present study, the highest estimated individual peak plasma concentration of unbound ropivacaine was 0.043 mg litre\(^{-1}\) (mean 0.024 mg litre\(^{-1}\)) and the mean \(C_{\text{max}}\) of total ropivacaine was 0.47 mg litre\(^{-1}\), which corresponds with previous data where single caudal doses of 1.875 mg kg\(^{-1}\) produced a \(C_{\text{max}}\) of c.0.6 mg litre\(^{-1}\) in 5 yr old children.\(^13\)

\(t_{\text{max}}\), which tended to be shorter in older children, was within the range normally observed in adults.\(^16\) The acute tolerability of ropivacaine has been studied in healthy adult subjects. A threshold for central nervous system toxicity was apparent at mean (minimum–maximum) unbound arterial plasma concentrations of ropivacaine of the order of 0.6 (0.3–0.9) mg litre\(^{-1}\).\(^1\) Consequently, in the present study, the plasma concentrations of unbound ropivacaine were well below the threshold levels for toxicity in adults. AAG concentrations were similar 30 min and 8 h after caudal block and within ranges normally observed in healthy adult subjects\(^17\) and in 1–5 yr old (ASA I–II) patients.\(^18\) The free fraction of ropivacaine was in the range 3–11%, which is similar to the free fraction (6±1%) in adult patients 7–9 h after the start of an epidural infusion.\(^19\) There was no apparent age-dependency in bodyweight-adjusted volume of distribution (mean 2.4 litres kg\(^{-1}\)). However, it was larger than the corresponding value in adults (0.7 litres kg\(^{-1}\)).\(^20\)

Bodyweight-adjusted clearance was the same as in adults (5 ml min\(^{-1}\) kg\(^{-1}\)), without any apparent age-dependency. When estimating the hepatic extraction ratio in the present study, the hepatic blood flow was adjusted for body surface area, since hepatic blood flow in children correlates better with body surface area than with bodyweight.\(^11\) The hepatic blood flows found in the present study correspond to values obtained by duplex Doppler ultrasound measurements in this age group.\(^21\) Even if the estimation of the hepatic extraction ratio is based on assumptions, these are reasonable, and the extraction ratio value indicates that ropivacaine is handled as a drug with low to intermediate extraction characteristics by the liver, as in adults.\(^9\) Consequently, ropivacaine clearance is expected to depend on the unbound fraction of ropivacaine rather than on the liver blood flow.

In the present study, the metabolic pattern of the main metabolites, 3-hydroxyropivacaine (25%) and PPX (5%), was similar to that found in adults, where 37% and 3% were excreted in the urine as 3-hydroxyropivacaine and PPX, respectively, with the remainder of the dose excreted as a number of quantitatively minor metabolites.\(^9\) In vitro, cytochrome isoenzyme subclass CYP1A2 is responsible for the metabolism of ropivacaine to 3-hydroxyropivacaine and cytochrome isoenzyme subclass CYP3A4 is responsible for the metabolism of ropivacaine to PPX,\(^22\) with CYP1A2 being the most important isozyme for the metabolism of ropivacaine \textit{in vivo}.\(^23\) The activity of CYP1A2 reaches adult levels in children above the age of 7 yr\(^24\) and CYP3A4 reaches 30–40% of adult activity as early as 1 month after birth.\(^25\) It is not surprising, therefore, that children above the age of 1 yr have a well developed capacity to eliminate ropivacaine.

Since neither the unbound volume of distribution nor the unbound clearance showed any apparent age-dependency when adjusted to bodyweight, dosing per kilogram of bodyweight is supported in this age group from a pharmacokinetic point of view.
There was no evidence of motor block in the lower limbs of any of the patients as they woke up. This finding is consistent with previous publications using ropivacaine 2 mg ml⁻¹ in children.³⁴

As a result of the variation in the dermatomal level of the surgical intervention and the duration of the surgical procedure, it is difficult to assess postoperative analgesia adequately. Although analgesia was not a primary end-point and a simple pain-scoring system was used, postoperative analgesia was assessed as satisfactory in ≥90% of the patients during the study period.

The most common adverse events (vomiting, nausea and pruritus) may have been associated with the surgical procedure, the general anaesthetic and postoperative opioid treatment and are commonly seen during the postoperative period.

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