Efficacy and uptake of ropivacaine and bupivacaine after single intra-articular injection in the knee joint

P. N. Convery1*, K. R. Milligan1, P. Quinn1, J. Sjövall2 and U. Gustafsson2

1Musgrave Park Hospital, Belfast, UK. 2AstraZeneca R & D, Södertälje, Sweden.
*Corresponding author: Department of Anaesthetics, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB, UK
**Present address, Belfast City Hospital, Belfast, UK

The efficacy of ropivacaine 100 mg (5 mg ml⁻¹), 150 mg (7.5 mg ml⁻¹) and 200 mg (10 mg ml⁻¹) and bupivacaine 100 mg (5 mg ml⁻¹) given by intra-articular injection into the knee after the end of surgery was studied in 72 ASA I–II patients scheduled for elective knee arthroscopy under general anaesthesia in a randomized, double-blind study. Kapake (paracetamol 1 g and codeine 60 mg) was given as a supplementary analgesic. Pain scores were assessed 1–4 h after surgery and a verbal rating scale of overall pain severity was assessed on second postoperative day. Ropivacaine or bupivacaine concentrations were determined in peripheral venous plasma up to 3 h after injection in eight patients in each group. Verbal rating pain scores were lower with ropivacaine 150 mg compared with bupivacaine 100 mg (P<0.05). There was a tendency for lower analgesic consumption and pain scores with all doses of ropivacaine (not significant). The mean (SD) maximum total plasma concentrations of ropivacaine were 0.64 (0.25), 0.78 (0.43) and 1.29 (0.46) mg litre⁻¹ after 100, 150 and 200 mg. The corresponding unbound concentrations were 0.018 (0.009), 0.024 (0.020) and 0.047 (0.022) mg litre⁻¹. Both were proportional to the dose. The maximum total concentration after bupivacaine 100 mg was 0.57 (0.36) mg litre⁻¹. The time to reach maximum plasma concentration was similar for all doses and varied between 20 and 180 min. All concentrations were well below the threshold for systemic toxicity.

Keywords: anaesthetics local, bupivacaine; anaesthetics local, ropivacaine; anaesthetic techniques, regional, intra-articular; equipment, arthrooscope

Accepted for publication: June 12, 2001

The intra-articular administration of a local anaesthetic agent after arthroscopic surgery of the knee has been shown by the majority of studies to provide superior early postoperative analgesia compared with placebo,1–5 though this has been called into question by several investigators.6–8 A systematic review of 20 studies showed evidence for a reduction in postoperative pain after intra-articular local anaesthesia following arthroscopic knee surgery, which, although being slight to moderate and of short duration, may be of clinical significance in day-case surgery.9 No adverse effects or toxicity attributable to the intra-articular administration of local anaesthetics were reported in this review. Synovial procedures have been reported to lead to increased absorption of bupivacaine as a result of the creation of extensive raw surfaces within the joint,10 but a dose of bupivacaine 225 mg (7.5 mg ml⁻¹, 30 ml) was well tolerated. Peak concentrations have been reported to be minimized with shorter tourniquet inflation times and longer intervals between injection and tourniquet release.11 Ropivacaine is an aminoamide local anaesthetic with similar clinical efficacy to12 and lower cardiotoxicity than racemic bupivacaine.11,13 It is a long-acting local anaesthetic that is chemically homologous to bupivacaine and mepivacaine. Ropivacaine is in the form of the S-enantiomer, making it the first enantiomerically pure local anaesthetic.12 In contrast to bupivacaine, it has shown fewer inherent vasodilator properties after intradermal administration.14 The purpose of this study was to compare the analgesic efficacy and systemic uptake of three different doses of ropivacaine administered as single intra-articular injections after arthroscopic knee surgery, with bupivacaine as a control.
Methods
After local ethics committee approval and written informed consent, 72 ASA I or II patients scheduled for elective arthroscopy of the knee were recruited into the study. Patients were not recruited if they had a history of sensitivity to local anaesthetics or had received preoperative opioids or any other analgesics in the preceding 48 h. Patients with known osteoarthritis of the knee or the same discovered at surgery were excluded, as were those on whom synovial surgery was planned or had been performed. All patients were visited before surgery and instructed in the use of an Abbott Laboratory 10 cm visual analogue scale (VAS) for pain, with 0 cm as ‘no pain’ and 10 cm as ‘worst pain imaginable’. A preoperative pain score on active flexion of the knee was recorded by the enrolling investigator.

Patients were unpremedicated and on arrival in the operating theatre all received a standardized general anaesthetic. This consisted of a sleep dose of propofol and alfentanil 10 µg kg⁻¹, after which a laryngeal mask was inserted. Anaesthesia was maintained using isoflurane (1–2%) with nitrous oxide (66%) in oxygen. Non-invasive monitoring was undertaken, consisting of ECG, arterial blood pressure, peripheral oxygen saturation, $F_{\text{CO}_2}$ and $P_{\text{Fr}}$.

Patients were allocated to one of four groups of 18 patients in a double-blind, randomized manner using randomly selected sealed envelopes. They received ropivacaine 100 mg (5 mg ml⁻¹, group R100), ropivacaine 150 mg (7.5 mg ml⁻¹, group R150), ropivacaine 200 mg (10 mg ml⁻¹, group R200) or bupivacaine 100 mg (5 mg ml⁻¹, group B100) in a 20 ml intra-articular injection at the end of surgery. A syringe of the corresponding local anaesthetic was prepared by an assistant who took no further part in the study. The anaesthetist, surgeon, observer and patient were all unaware of the nature of the contents of each syringe. These drugs were administered by intra-articular injection by the surgeon on completion of surgery, 5 min before deflation of the tourniquet, which had been inflated to a pressure of 300 mm Hg. All patients had 2% lidocaine 2 ml with epinephrine infiltrated into each skin wound at the end of surgery. In eight patients in each group, blood (5 ml) was drawn from a dedicated, unheparinized cannula sited in the non-injection antecubital fossa before (time 0) and 10, 20, 30, 45, 60, 90, 120 and 180 min after completion of the local anaesthetic injection. These samples were centrifuged as soon as possible after collection and the separated plasma was frozen at −80°C until assay. The total plasma concentrations of ropivacaine and bupivacaine base were determined by high-performance liquid chromatography with ultraviolet detection at 210 nm using bupivacaine as the internal standard. The limit of quantitation of the method was 50 ng ml⁻¹. The unbound (free) plasma concentration of ropivacaine base was determined by coupled column liquid chromatography with ultraviolet detection at 210 nm after ultrafiltration of the plasma samples.\(^{15}\) The limit of quantitation was 3 ng ml⁻¹. The unbound concentration was determined in peak plasma samples of ropivacaine or in samples taken at an adjacent sampling time.

Postoperative pain scores (VAS, 0–100 mm) on active flexion of the knee were recorded by a blinded observer 1, 2 and 4 h after the intra-articular injection. Postoperative pain was treated by the ward nursing staff with paracetamol 1 g + codeine phosphate 60 mg (Kapake) and, if this did not provide adequate analgesia, as judged by recovery nursing staff, morphine 0.15 mg kg⁻¹ was administered i.v. Patients were discharged 4 h after surgery if comfortable, with analgesic packs and instructions to take the above dose of Kapake up to every 4 h if needed. The time to the first request for analgesia and the total analgesic requirements were recorded. Patients were telephoned at home on the second postoperative day and their post-discharge analgesic use and a subjective verbal rating of overall pain severity were recorded. Ratings were ‘no pain’, ‘mild pain’, ‘moderate pain’ and ‘severe pain’ and were identified as such for reference purposes on the record chart given to the patient on discharge from hospital.

Physical characteristics, operation type and duration were analysed by analysis of variance (ANOVA) and the $\chi^2$ test when appropriate, and their relationships to pain scores tested with Spearman’s rank correlation. Pain scores were analysed by ANOVA and time to first analgesia by survival analysis. Analgesic tablet consumption and verbal rating scale scores were analysed with the Mann–Whitney U-test. Results were considered statistically significant when $P<0.05$. To achieve an 80% power of detecting a 15 mm difference in VAS score, the study required 18 patients in each group if the common standard deviation of pain scores in all groups is 5 mm.

The total ($C_{\text{max}}$) and unbound ($C_{u,\text{max}}$) peak plasma concentrations were estimated from the observed values. The area under the plasma concentration-time curve during the 3 h of observation (AUC$_{0,3}$) was calculated using the trapezoidal rule. The fraction of unbound drug in plasma ($f_u$) was calculated as the unbound divided by the total plasma concentration. Dose proportionality for $C_{\text{max}}$, $C_{u,\text{max}}$ and AUC$_{0,3}$ were analysed with the power model $y=\alpha d^{\beta}$, where $\alpha$ depends on subject, period and error.\(^{16}\) This model assumes a linear relationship between log $y$ and log dose. Dose proportionality requires that $\beta=1$ for dose-dependent parameters. In terms of this model, a doubling of the dose is reflected in the ratio $R=2^\beta$ of corresponding effects, i.e. $(y_2/y_1)=2^\beta$. If dose proportionality holds, the effect ratio $R$ equals 2. A simple linear regression was also used to study the relationships of dose with $C_{\text{max}}$, $C_{u,\text{max}}$ and AUC$_{0,3}$. Ninety per cent confidence intervals for the intercepts were calculated.

Results
Patient characteristics were similar in all groups. Neither the nature of the procedure (whether diagnostic or therapeutic)
nor the duration of tourniquet inflation were different between the groups (Table 1). All 72 patients completed the study. The median postoperative pain score varied between 6 and 28 mm, and there were no statistically significant differences between the groups in pre- and postoperative pain scores or in the postoperative change from preoperative pain scores (Fig. 1). The median analgesic consumption in the first and second postoperative 24 h periods were lower in all three ropivacaine groups than in the bupivacaine group; these differences did not achieve statistical significance (Table 2). Both the number of patients who did not consume postoperative analgesics and the time to first analgesic request tended to be highest in group R150, but there was no statistically significant difference. The median verbal rating scale scores of the overall pain experienced by the patient were significantly lower ($P<0.05$) in group R150 (Fig. 2). One patient only, in group R150, required the administration of morphine for breakthrough pain. Increased pain scores at 1 h were correlated with an increased tourniquet time ($P<0.05$) and with preoperative pain scores ($P<0.01$). Preoperative and postoperative pain scores were strongly and positively related to analgesic consumption and negatively to the time to first analgesic request ($P<0.001$).

The total plasma concentration–time curves over the 3 h after local anaesthetic administration for each patient in all groups are shown in Fig. 3. The highest individual peak plasma concentration measured was in group R200 (2.2 mg litre$^{-1}$ at 30 min) and was associated with an

---

### Table 1
Patient characteristics, type of surgery and tourniquet time in the groups receiving ropivacaine 100 mg (R100), ropivacaine 150 mg (R150), ropivacaine 200 mg (R200) and bupivacaine 100 mg (B100). Mean (SD) or number of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>R100 (n=18)</th>
<th>R150 (n=18)</th>
<th>R200 (n=18)</th>
<th>B100 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33 (12.1)</td>
<td>36 (9.9)</td>
<td>33 (9.4)</td>
<td>34 (7.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82 (14.5)</td>
<td>85 (15.8)</td>
<td>83 (11.8)</td>
<td>84 (9.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (15.1)</td>
<td>176 (12.0)</td>
<td>172 (8.8)</td>
<td>175 (15)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/2</td>
<td>14/4</td>
<td>17/1</td>
<td>17/1</td>
</tr>
<tr>
<td>Type of surgery (diagnostic/therapeutic)</td>
<td>5/13</td>
<td>6/12</td>
<td>3/15</td>
<td>3/15</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>27.9 (7.6)</td>
<td>27.2 (6.5)</td>
<td>28.1 (8.7)</td>
<td>26.7 (4.9)</td>
</tr>
</tbody>
</table>

### Table 2
Median analgesic consumption (number of tablets per patient) and mean (SD) time to first request of analgesia in the groups receiving ropivacaine 100 mg (R100), ropivacaine 150 mg (R150), ropivacaine 200 mg (R200) and bupivacaine 100 mg (B100)

<table>
<thead>
<tr>
<th>Group</th>
<th>R100 (n=18)</th>
<th>R150 (n=18)</th>
<th>R200 (n=18)</th>
<th>B100 (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of analgesics 0–24 h</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No. of analgesics 24–48 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>No. of patients requiring no analgesics</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Time to first analgesia (min)</td>
<td>1002 (1070)</td>
<td>1383 (1269)</td>
<td>938 (953)</td>
<td>719 (703)</td>
</tr>
</tbody>
</table>
unbound concentration of 0.061 mg litre⁻¹. Time to $C_{\text{max}}$ ($t_{\text{max}}$) was similar for all doses and occurred at the last sampling time in one patient in each ropivacaine group and in two patients in the bupivacaine group, indicating slow uptake. Mean $C_{\text{max}}$ and $t_{\text{max}}$ were similar after R100 and B100 (Table 3). In common with all study patients, neither of these patients showed any sign of systemic local anaesthetic toxicity.

$C_{\text{max}}$ (Fig. 4), $C_{u,\text{max}}$ (Fig. 5) and $\text{AUC}_{0-3}$ (Fig. 6) were proportional to the dose after intra-articular administration of ropivacaine, as the intercepts of the linear regression lines were close to zero. The 90% confidence limits for the intercepts were −0.59 and 0.46 for $C_{\text{max}}$, −0.037 and 0.010 for $C_{u,\text{max}}$ and −1.12 and 1.35 for $\text{AUC}_{0-3}$. The point estimates for $C_{\text{max}}$, $C_{u,\text{max}}$ and $\text{AUC}_{0-3}$ in the power model further support dose proportionality, with a point estimate of β close to 1 and an $R$ value close to 2 (Table 4). Based on the $R$ values, the increase in $C_{\text{max}}$, $C_{u,\text{max}}$ and $\text{AUC}_{0-3}$ with a doubling of the dose was 96, 143 and 78% respectively. The mean (SD) $f_u$ estimated at $C_{\text{max}}$ was 3.1 (1.1)%. The concentration of $\alpha_1$-acid glycoprotein was similar between the ropivacaine groups and was in the normal range.

### Table 3 Mean (SD) pharmacokinetic parameters after single intra-articular injections of ropivacaine 100, 150 and 200 mg and bupivacaine 100 mg in patients scheduled for elective arthroscopy of the knee. *Median (minimum/maximum); ‡$n=7$. AAG, $\alpha_1$-acid glycoprotein

<table>
<thead>
<tr>
<th>Group</th>
<th>R100 ($n=8$)</th>
<th>R150 ($n=8$)</th>
<th>R200 ($n=8$)</th>
<th>B100 ($n=8$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (min)*</td>
<td>60 (20/180)</td>
<td>75 (30/180)</td>
<td>75 (30/180)</td>
<td>53 (20/180)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (mg litre⁻¹)</td>
<td>0.64 (0.25)</td>
<td>0.78 (0.43)</td>
<td>1.29 (0.46)</td>
<td>0.57 (0.36)</td>
</tr>
<tr>
<td>$\text{AUC}_{180}$ (mg min litre⁻¹)</td>
<td>91 (32)</td>
<td>114 (64)</td>
<td>170 (66)</td>
<td>68 (50)</td>
</tr>
<tr>
<td>$f_u$ at $C_{\text{max}}$ (%)</td>
<td>2.8 (0.9)</td>
<td>2.8 (1.2)</td>
<td>3.5 (1.1)</td>
<td>2.8 (1.2)</td>
</tr>
<tr>
<td>$C_{u,\text{max}}$ (mg litre⁻¹)</td>
<td>0.018 (0.009)</td>
<td>0.024 (0.020)</td>
<td>0.047 (0.022)</td>
<td>0.044 (0.022)</td>
</tr>
<tr>
<td>AAG (µmol litre⁻¹)</td>
<td>18.2 (4.1) ‡</td>
<td>17.9 (2.0) ‡</td>
<td>19.1 (3.2)</td>
<td>17.9 (2.0) ‡</td>
</tr>
</tbody>
</table>

Fig 3 Individual total plasma concentrations after single intra-articular injection of ropivacaine 100, 150 and 200 mg and bupivacaine 100 mg in patients scheduled for elective arthroscopy of the knee ($n=8$ in each group).
Discussion

Intra-articular long-acting local anaesthetics are the standard for postarthroscopy analgesia in our institution. Our experience is supported by a recent review of 20 studies based on 900 patients for whom there is evidence of a definite reduction in postoperative pain associated with the use of intra-articular local anaesthetics, suggesting a clinical benefit in day-case surgery. More studies detected differences in analgesic consumption than in pain scores. Previous authors have suggested that post arthroscopy discomfort is a poor model of pain because a high percentage of patients had minimal pain scores and required no supplementary analgesics. Our finding that 78% of patients took postoperative analgesics is consistent with a previous study. The relationship observed between postoperative pain scores and analgesic consumption in the present study suggests variable rather than insignificant postoperative pain.

In this study pain scores demonstrated similar variability to that in work reported previously. As a result, there were non-significant consistent differences between groups in VAS pain scores in the first 4 h after surgery and in analgesic consumption in the first 48 h after surgery. However, for the verbal rating pain score, a significant improvement was seen with ropivacaine 150 mg compared with bupivacaine. In ethical clinical trials, pain scores should tend towards convergence with the free availability of analgesics, and serve to emphasize the adequacy of the rescue analgesic in placebo or control groups. In situations such as this, it may well be that analgesic consumption and overall patient satisfaction would be more reliable and appropriate measures than pain scores.

All patients had their skin entry wounds (two or three wounds) injected with a uniform dose of lidocaine and epinephrine in an attempt to standardize the effect of postoperative pain from these sites for at least the early VAS pain scores. This may have had the effect of removing a large component of the early postoperative pain, perhaps reducing early differences between the groups. Postoperative pain may have been further reduced across all groups by the interval of 5 min between injection and tourniquet deflation and the consequent increase in tissue uptake of the local anaesthetics. Furthermore, ropivacaine has anti-inflammatory effects in human mucosal cells, which may contribute to the observed difference in analgesic effect on the second postoperative day.

The systemic uptake of the two local anaesthetics from the knee joint appears similar, as reflected by their corresponding \( C_{\text{max}} \) and \( t_{\text{max}} \) values. The similarity of these times in this study suggests that there was little difference in the vasomotor activities of the agents at the studied doses at this site. \( C_{\text{max}} \) was considerably higher than previously described for intra-articular bupivacaine, probably as a result of the extended tourniquet inflation time and the hyperaemia resulting from post-ischaemic reperfu-
Efficacy and uptake of ropivacaine and bupivacaine after knee arthroscopy

Table 4 Results of power model analysis in the evaluation of dose proportionality based on single intra-articular injections of ropivacaine 100, 150 and 200 mg in patients scheduled for elective arthroscopy of the knee (n=8 in each group)

<table>
<thead>
<tr>
<th>Pharmacokinetic variable</th>
<th>n</th>
<th>β</th>
<th>90% confidence limits</th>
<th>R</th>
<th>90% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td>AUC0-3</td>
<td>24</td>
<td>0.83</td>
<td>0.24</td>
<td>1.42</td>
<td>1.78</td>
</tr>
<tr>
<td>Cmax</td>
<td>24</td>
<td>0.97</td>
<td>0.40</td>
<td>1.54</td>
<td>1.96</td>
</tr>
<tr>
<td>Cu,max</td>
<td>24</td>
<td>1.28</td>
<td>0.50</td>
<td>2.06</td>
<td>2.43</td>
</tr>
</tbody>
</table>

Plasma drug concentrations were still slowly rising in five patients (two receiving bupivacaine and three receiving ropivacaine) in the 180 min sample, although the curves were similarly shaped across the groups. The sustained plasma drug concentrations observed over the sampling period may be consistent with prolonged absorption exceeding the true elimination rate (i.e. the absorption/elimination rate that would be seen after i.v. administration of ropivacaine or bupivacaine, which have terminal half-lives of 1.9 and 2.7 h respectively). Prolonged absorption has also been described after infiltration of the hernia wound with ropivacaine, the plasma concentration being elevated for the entire 2 h sampling period.

In this study, the peak concentrations of both total and unbound ropivacaine were proportional to the dose administered, which is important in allowing predictability in analgesia and in the risk of systemic effects in clinical practice. Intersubject variability, however, is the largest unpredictable factor in this regard, and our curves appear to confirm this. Nevertheless, all total and unbound individual peak plasma concentrations for each drug and dose were well below the recognized toxic threshold. Bupivacaine administered intra-articularly to the knee has been associated with cardiovascular toxicity despite the use of accepted doses. This was probably as a result of an accidental intravascular injection in this relatively vascular joint, and in such a situation the lower cardiotoxicity of ropivacaine would be beneficial.

In conclusion, we have demonstrated that ropivacaine and bupivacaine 100 mg provide similar and effective post-arthroscopy analgesia and that ropivacaine at the higher dose of 150 mg appears to further reduce patients’ pain ratings in the 48 h period after surgery. A higher ropivacaine dose does not seem to improve efficacy. Plasma concentrations for all patients and all doses fell below the estimated toxic thresholds, and therefore it seems that these drugs can be safely administered by intra-articular injection.

Acknowledgements
We are grateful to Margareta Bielenstein of AstraZeneca, Sweden for bioassay of unbound ropivacaine and to William J. Leahey of the Department of Therapeutics, Queen’s University Belfast for the bioassay of total ropivacaine and bupivacaine.

References
1 Chirwa SS, MacLeod BA, Day B. Intra-articular bupivacaine (Marcaine) after arthroscopic meniscectomy: a randomized double-blind controlled study. Anesthesiology 1989; 5: 352–3
5 Morrow BC, Milligan KR, Murthy BV. Analgesia following day-case knee arthroscopy—the effect of piroxicam with or without bupivacaine infiltration. Anaesthesia 1995; 50: 461–3
23 Mulroy M, Burgess F, Emanuelsson BM. Ropivacaine 0.25% and 0.5%, but not 0.125% provide effective wound infiltration analgesia after outpatient hernia repair, but with sustained plasma drug levels. Reg Anesth Pain Med 1999; 24: 136–41