Comparison of mepivacaine and lidocaine for intravenous regional anaesthesia: pharmacokinetic study and clinical correlation

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Background. Limitations to the use of lidocaine for intravenous regional anaesthesia (IVRA) include lack of optimal intraoperative analgesia and systemic toxic reactions. This randomized double-blind study was conducted to compare intraoperative and postoperative analgesia, adverse effects, and plasma concentrations of mepivacaine or lidocaine, on release of the tourniquet in patients undergoing IVRA for distal upper limb surgery.

Methods. Forty-two adult patients were randomly allocated to receive either a 0.5% lidocaine solution 3 mg kg⁻¹ (n=20) or mepivacaine 5 mg kg⁻¹ (n=22). Plasma concentrations of both anaesthetic agents were measured at 5, 10, 20, 30, 45, and 60 min after deflation of the tourniquet by gas chromatography.

Results. Although plasma concentrations of mepivacaine and lidocaine were comparable 5 min after deflation, concentrations of lidocaine decreased significantly thereafter, whereas plasma concentrations of mepivacaine were similar over the 60-min study period. Supplementary analgesia during the intraoperative period was required by 45% of patients in the lidocaine group compared with 9% in the mepivacaine group (P=0.02). No adverse effects were observed in patients given mepivacaine. In the lidocaine group, adverse effects were observed in 10% of the patients. The total ischaemia time, volume of the local anaesthetic, and duration of the surgical procedure were not significantly different between the two groups.

Conclusions. Mepivacaine 5 mg kg⁻¹ ensured better intraoperative analgesia than lidocaine 3 mg kg⁻¹ when used for IVRA. Plasma concentrations of lidocaine decreased significantly between 5 and 60 min following tourniquet deflation, whereas blood concentrations of mepivacaine remained below the toxic concentration.

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Intravenous regional anaesthesia (IVRA) is a simple and effective technique for distal upper limb surgery of less than 1 h duration.¹ Some clinical studies have recently shown that the addition of a non-steroidal anti-inflammatory agent,² an opioid,³ neuromuscular blocking agents,⁴ clonidine,⁵ and even ketamine⁶ to lidocaine can improve the quality of the regional anaesthesia. Although lidocaine is one of the least toxic local anaesthetics, in our experience, limitations to its use include lack of optimal intraoperative analgesia and systemic toxic reactions. In our clinical experience of more than 10 yr, we found that the use of mepivacaine 5 mg kg⁻¹ for IVRA was a satisfactory alternative to the classical IVRA technique and that systemic reactions after tourniquet deflation did not occur. Therefore, a randomized double-blind study was designed to compare IVRA using lidocaine or mepivacaine in
forearm and hand surgery. Plasma concentrations of the drugs on release of the tourniquet, intraoperative and postoperative analgesia and adverse effects were determined.

Methods

The procedure for this study was approved by the Ethics Committee of the hospital. Informed consent was obtained. Forty-two adult ASA physical status I or III patients of both sexes undergoing elective minor forearm and hand surgery gave written informed consent to participate in this prospective double-blind study. Patients with liver disorders, history of allergic reaction to local anaesthetics, those not wishing the IVRA technique, or in whom venipuncture was difficult were excluded. Patients were allocated to one of two groups according to a table of random numbers. Patients in one group \((n=22)\) received 0.5–1% mepivacaine 5 mg kg\(^{-1}\) up to a maximal dose of 400 mg and maximal volume of 40 ml, whereas those in the other group \((n=20)\) received 0.5% lidocaine 3 mg kg\(^{-1}\) up to a maximal dose of 400 mg and maximal volume of 40 ml.

Patients ≤50 kg and/or with respiratory disease were premedicated with diazepam 5 mg, whereas patients weighing greater than 50 kg were given diazepam 10 mg. A 20-gauge catheter was introduced into a vein on the dorsum of the hand to be operated upon and another 16-gauge catheter was inserted into a vein of the arm not requiring surgery for fluid infusion and blood sampling. The operative arm was exsanguinated by elevating it and wrapping it with a rubber Esmarch bandage. The proximal cuff of a double tourniquet was then inflated to 350 mm Hg and 20 ml min\(^{-1}\) of either mepivacaine or lidocaine was injected in a double-blind fashion into the indwelling cannula. After approximately 15 min, the distal cuff was inflated to the same pressure. A minimum total ischaemia time of 40 min was established for safety reasons because of the use of mepivacaine in doses much larger than those reported in the literature. Midazolam 1 mg every 10 min up to a maximum of 5 mg was used for intraoperative sedation trying to maintain the patient at level 2–3 on the Ramsay sedation scale. Supplementary intraoperative analgesia consisted of intravenous boluses of fentanyl 50 μg every 10 min up to a total dose of 150 μg. Boluses of fentanyl were provided whenever there was a 20% increase in baseline values of arterial pressure and/or heart rate or when analgesia was graded as poor by the patient. Patient’s vital signs (arterial pressure, ventilatory frequency, pulse oximeter), analgesic request, and presence of adverse events related to unexpected deflation of the tourniquet were assessed intraoperatively.

Venous blood samples were obtained from the opposite arm at 5, 10, 20, 30, 45, and 60 min after release of the tourniquet. The samples were centrifuged and the plasma frozen at −20°C and stored. Plasma concentrations of local anaesthetics were analysed by gas chromatography/mass spectrometry.

After tourniquet release and at the end of surgery, patients were asked to report any adverse effects. Symptoms of dizziness, nystagmus, tinnitus, facial dysaesthesia, convulsions, depression of the central nervous system, bradypnoea (ventilatory frequency ≤10 breaths min\(^{-1}\)), bradycardia (heart rate ≤50 beats min\(^{-1}\)), and cardiovascular depression (≤25% decrease in baseline arterial pressure) were noted, if present. Patient’s vital signs and time to the first analgesic request after cuff release (time of residual analgesia) were recorded in the postanaesthesia care unit.

The sample size was calculated according to the main objective of the study, that is adequate intraoperative analgesia with mepivacaine for IVRA, which was determined by the need for supplementary medication intraoperatively, for a sensitivity of 20%, beta error of 0.10 and an alpha error of 0.05. Patient characteristics and data related to the anaesthetic technique and the surgical procedure were recorded in both groups. Comparison of categorical variables was carried out with the Pearson’s chi-squared test. All quantitative variables with the exception of time of residual analgesia were normally distributed and were analysed using the Student’s \(t\)-test if variances were comparable or with the Mann–Whitney \(U\) test if variances were not comparable. Paired data were analysed with the paired \(t\)-test. Kaplan–Meier survival analysis was performed for time of residual analgesia. Statistical analysis was performed with the SPSS/PC+ (version 8.0, SPSS Inc., Chicago, IL) software programme. Data are expressed as mean (SD) unless indicated otherwise.
Table 2 Plasma concentrations of mepivacaine and lidocaine (µg ml⁻¹) during the observation period at the of surgery. *P<0.05

<table>
<thead>
<tr>
<th>Blood sampling after surgery</th>
<th>Mepivacaine (n=22)</th>
<th>Lidocaine (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>1.60 (0.52)</td>
<td>1.68 (0.73)*</td>
</tr>
<tr>
<td>10 min</td>
<td>1.70 (0.51)</td>
<td>1.37 (0.48)</td>
</tr>
<tr>
<td>20 min</td>
<td>1.77 (0.47)</td>
<td>1.11 (0.30)</td>
</tr>
<tr>
<td>30 min</td>
<td>1.69 (0.42)</td>
<td>0.98 (0.26)</td>
</tr>
<tr>
<td>45 min</td>
<td>1.72 (0.48)</td>
<td>0.86 (0.23)</td>
</tr>
<tr>
<td>60 min</td>
<td>1.68 (0.41)</td>
<td>0.81 (0.21)*</td>
</tr>
</tbody>
</table>

Results

Patients characteristics and data of the anaesthetic and surgical techniques in both study groups are shown in Table 1. There were no statistically significant differences in relation to weight, height, gender, volume of local anaesthetic agent used, time of ischaemia, duration of operation, and type of surgical procedure. However, patients in the mepivacaine group were significantly younger (47.4 (22–78) yr) than those in the lidocaine group (57.9 (31–85) yr) (P=0.04).

Intraoperative analgesia was significantly better amongst mepivacaine-treated patients because supplementary analgesia with fentanyl was required by 9% of patients in the mepivacaine group as compared with 45% in the lidocaine group (P=0.02). Median times required for supplementary analgesia were 35 min (95% confidence interval (CI) 18–52 min) in the mepivacaine group and 30 min (95% CI 19–41 min) in the lidocaine group. With regard to the frequency of adverse events on release of the tourniquet, no adverse effects were observed in patients given mepivacaine, whereas in the lidocaine group, transient bradycardia, and dizziness were experienced by one patient each within 5 min after tourniquet deflation.

Plasma concentrations of both local anaesthetic agents are shown in Table 2. Five minutes after cuff deflation, plasma concentrations of mepivacaine and lidocaine were comparable. However, plasma concentrations of lidocaine decreased significantly between 5 and 60 min following tourniquet deflation (P<0.001), whereas blood concentrations of mepivacaine did not change during the observation period. At 60 min, plasma concentrations of mepivacaine were significantly higher than those of lidocaine (P<0.001).

Discussion

Different anaesthetic agents including procaine, lidocaine, and prilocaine have been used for IVRA since the initial description of this technique by Bier in 1908. Research in this field has been focused on the search for the ideal agent for IVRA that would be the one with which adequate intraoperative analgesia is attained, but without the systemic toxicity in the event of tourniquet release. The inadvisability of using bupivacaine for IVRA is related to the sudden occurrence of dangerous cardiotoxicity, whereas the use of chlorprocaine in IVRA ceased after reports of hypersensitivity reactions and postanaesthetic thrombophlebitis. The ideal anaesthetic agent for IVRA would be the one that had the requisite degree of local anaesthetic activity, but with low cardiovascular and central nervous system toxicity. Lidocaine is probably the local anaesthetic most commonly chosen for this technique, although prilocaine is better tolerated in terms of systemic toxicity than lidocaine.

The dose of lidocaine recommended for classical IVRA technique (3 mg kg⁻¹ as a 0.5% lidocaine solution) was used. With respect to mepivacaine, we used a dose of 5 mg kg⁻¹ with which consistent satisfactory results had been obtained by our group as well as by others. According to the study of Rawal and co-workers in which plasma concentrations of mepivacaine, lidocaine, and prilocaine when given at the 3 mg kg⁻¹ dose peaked within 5 min after tourniquet release, we decided to start measurements of plasma drug concentrations at 5 min following tourniquet deflation, with the last measurement at 60 min because in the pharmacokinetic study of Simon and associates in which toxic plasma concentrations of lidocaine were measured from that time. Although in the case of mepivacaine for IVRA, no previous studies have evaluated plasma concentrations of this agent at 60 min after deflation, a pharmacokinetic behaviour similar to that of lidocaine was assumed as in the study of Rawal and co-workers, mepivacaine and lidocaine showed similar pharmacokinetics 5 min after tourniquet release.

As compared with lidocaine, mepivacaine 5 mg kg⁻¹ provided better intraoperative analgesia with no adverse effects on release of the tourniquet. Moreover this finding is supported by plasma concentrations of the drugs that were comparable 5 min after deflation (1.68 (0.73) µg ml⁻¹ for lidocaine and 1.62 (0.52) µg ml⁻¹ for mepivacaine), whilst plasma concentrations of lidocaine decreased significantly (0.81 (0.21) µg ml⁻¹) at 60 min as opposed to plasma concentrations of mepivacaine that did not vary (1.68 (0.41) µg ml⁻¹). The observation of similar plasma concentrations of both anaesthetic agents despite the use of almost double concentrations of mepivacaine may be explained by the vascular effects of mepivacaine (vasoconstriction) in IVRA and a much more sustained release to the systemic circulation as compared with the predominantly vasodilatory effects of lidocaine. Therefore, toxic plasma concentrations of mepivacaine are not reached rapidly as opposed to lidocaine 3 mg kg⁻¹ when adverse events may appear within the first minute after tourniquet release as reported by Simon and associates. On the other hand, the relatively prolonged nature of the increase in systemic mepivacaine concentrations might produce longer term psychometric effects. However, we did not examine this in our study.

Up to the present time, toxic plasma concentrations of local anaesthetics greater than 4 µg ml⁻¹ for lidocaine and between 5 and 6 µg ml⁻¹ for mepivacaine have been quoted. In our study, however, plasma drug concentrations
within the first 5 min after tourniquet release were not measured but in that interval a case of dizziness and a case of bradycardia occurred. No patient in the lidocaine group showed plasma concentrations greater than 3 μg ml⁻¹, although there was a greater dispersion of lidocaine values at 5 min (predominately 2–3 μg ml⁻¹). In our study, there were no statistically significant differences in the occurrence of adverse events, probably because of the small sample size. In the study of Simon and co-workers,⁸ five of the 10 patients showed plasma concentrations of lidocaine greater than 4 μg ml⁻¹ during the first minute after release of the tourniquet. This is in contrast to findings of Rawal and associates¹⁸ who reported plasma concentrations of lidocaine less than 1 μg ml⁻¹ at this time. It should be noted, however, that in the first study⁸ high-performance liquid chromatography was used for the assessment of plasma drug concentrations in 10 patients, whereas in the second study¹⁸ gas chromatography in 20 patients. In the study of Simon and co-workers,⁸ although toxic plasma concentrations were obtained in half of the patients, none of them experienced any adverse effect. In contrast, in the study of Rawal and colleagues,¹⁸ four patients in the lidocaine group experienced dizziness as compared with none in the mepivacaine group.

This preliminary study in a small number of patients indicates that mepivacaine 5 mg kg⁻¹ has a closer profile of the ideal local anaesthetic agent for IVRA than lidocaine 3 mg kg⁻¹. Mepivacaine offered adequate intraoperative analgesia with no incidence of adverse effects on release of the tourniquet despite persistence of plasma drug concentrations during the 60-min study period.

Acknowledgement

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