Grand mal convulsion and plasma concentrations after intravascular injection of ropivacaine for axillary brachial plexus blockade

M. Müller*, R. J. Litz, M. Hübler and D. M. Albrecht

Department of Anaesthesiology and Intensive Care Medicine, Carl Gustav Carus University Hospital, Dresden, Germany

*Corresponding author: Department of Anaesthesiology and Intensive Care Medicine, Carl Gustav Carus University Hospital, Fetscherstrasse 74, D-01307 Dresden, Germany

We report a patient to whom ropivacaine 1.1 mg kg⁻¹ was administered for brachial plexus blockade and who developed grand mal convulsions because of inadvertent i.v. injection. No symptoms of cardiovascular toxicity occurred. Venous blood samples were taken 15, 45, 75 and 155 min after the injection. The measured total plasma concentrations of ropivacaine were 3.3, 1.6, 1.2 and 1.0 mg litre⁻¹ respectively. Initial plasma concentration after the end of the injection period was estimated at 5.75 mg litre⁻¹ using a two-compartment pharmacokinetic model.

Br J Anaesth 2001; 87: 784–7

Keywords: complications, convulsions; anaesthetics local, ropivacaine

Accepted for publication: May 18, 2001

Brachial plexus blockade is a frequently used anaesthetic technique for surgery of the upper limb. Very often, short-acting local anaesthetics, such as prilocaine and lidocaine, are chosen because of their good safety profiles. However, in some circumstances, using a longer-acting local anaesthetic is more desirable, e.g. in vascular surgery. Ropivacaine appears to have lower cardiac and central neurological toxicity than the otherwise similar long-acting local anaesthetic bupivacaine. So far, only a few cases of severe cardiac or central neurological complications after administration of ropivacaine have been reported. Plasma concentrations associated with these side-effects have been measured in healthy volunteers but the thresholds for symptoms in patients are still controversial.¹² We report a case of grand mal seizure that occurred in a patient after an inadvertent intravascular injection of ropivacaine 1.1 mg kg⁻¹ for axillary brachial plexus blockade. Blood samples were taken and the total venous plasma concentration of ropivacaine was determined.

Case report

A 65-yr-old male (ASA III, 90 kg, 175 cm) was scheduled for surgical revascularization of a thrombosed arteriovenous (Cimino) shunt. Significant medical history included insulin-dependent diabetes mellitus, terminal renal insufficiency and renal hypertension. He had no history of neurological or cardiac disease. Medication included insulin, nitrrendipin, furosemide, metoprolol, doxazosin, sodium hydrogen carbonate and calcitriol. Before operation, the following routinely tested variables were abnormal: platelet count (119 × 10⁹ litre⁻¹, normal range 150–400 × 10⁹ litre⁻¹), haemoglobin (6.7 mmol litre⁻¹, normal range 8.6–12.1 mmol litre⁻¹), haematocrit (0.30, normal range 0.40–0.54), creatinine (391 μmol litre⁻¹, normal range <124 μmol litre⁻¹) and urea (15.3 mmol litre⁻¹, normal range 3.6–8.9 mmol litre⁻¹). All other variables, including liver enzymes, electrolytes and protein concentrations, were normal. The electrocardiogram (ECG) showed normal sinus rhythm with a heart rate of 70 beats min⁻¹. The patient did not receive any sedation before surgery. In the induction room, monitoring was placed (ECG, pulse oximetry and non-invasive arterial blood pressure) and peripheral venous access was established. The left arm was abducted at a right-angle with the forearm flexed towards the head. The skin was infiltrated with 2% lidocaine 20 mg after sterile preparation, and a 23 gauge short bevel needle with an injection line was inserted parallel and close to the
artery and directed towards the apex of the axilla. The perivascular sheath was identified with the loss of resistance technique. No spontaneous blood flow was observed in the connected injection line. After careful negative aspiration, 20 ml of ropivacaine 0.5% was injected over 1 min in 5 ml increments, with intermittent negative aspiration. Verbal contact was made during the injection and no early signs of systemic toxicity occurred. The brachial artery was then palpated again in order to insert the needle for a second injection. Suddenly, the patient lost consciousness without any prodromal signs, such as perioral numbness or dizziness, and a grand mal seizure started. During the convulsion, heart rate increased from 70 to 80 beats min\(^{-1}\) and arterial blood pressure increased from 130/80 to 145/85 mmHg. The lungs were ventilated immediately with 100% oxygen using a mask. General anaesthesia was induced with thiopentone 400 mg, fentanyl 0.2 mg and succinylcholine 60 mg and the trachea was intubated. The convulsions stopped immediately after induction of general anaesthesia. For the following 30 min, anaesthesia was maintained with desflurane 2% in oxygen/nitrous oxide (30%/68%). ECG showed no signs of arrhythmia or changes in PQ or QT interval or QRS width. After this observation period, the scheduled surgery was performed under general anaesthesia. Three hours after the inadvertent intravascular injection of the local anaesthetic, the tracheal tube was removed. The patient had an incomplete sensory block of the ulnar nerve, evaluated by pinprick test, which lasted 4 h. The remaining brachial plexus showed no impairment of sensory function. The patient did not recall the seizure episode.

Venous blood samples were taken 15, 45, 75 and 155 min after the injection of ropivacaine. After immediate centrifugation, plasma samples were stored at \(-20^\circ C\). Total plasma concentrations of ropivacaine were determined using high-performance liquid chromatography (Institute of Clinical Pharmacology, Technical University, Dresden). The linear calibration curve was validated using four samples with known ropivacaine concentrations (0.5, 1.0, 2.0 and 4.5 mg litre\(^{-1}\)). The detection limit of the method was below 0.5 mg litre\(^{-1}\) and the relative standard deviation of the method was 4.2%. The measured plasma concentrations of ropivacaine at 15, 45, 75 and 155 min were 3.3, 1.6, 1.2 and 1.0 mg litre\(^{-1}\) respectively (Fig. 1).

The peak plasma concentration immediately after the end of the injection period was estimated using a two-compartment pharmacokinetic model: 

\[
C_t = C_a e^{-\alpha t} + C_b e^{-\beta t},
\]

where \(C_t\) is the plasma concentration at time point \(t\) in minutes, \(C_a\) is the concentration in the \(\alpha\)-compartment, \(C_b\) is the concentration in the \(\beta\)-compartment, and \(\alpha\) and \(\beta\) are the respective elimination constants. This analysis yielded an initial concentration of ropivacaine of 5.75 mg litre\(^{-1}\). From a pharmacokinetic point of view, the available data did not allow us to discriminate between venous and arterial injection.

![Fig 1](image-url) Total venous plasma concentration of ropivacaine. The curve was extrapolated after estimation of the initial concentration with a pharmacokinetic model.

### Table 1: Published cases of severe cardiac or neurological adverse effects after regional anaesthesia with ropivacaine

<table>
<thead>
<tr>
<th>Regional anaesthetic technique</th>
<th>Amount of ropivacaine injected</th>
<th>Plasma concentration (mg litre(^{-1}))</th>
<th>Neurological side-effect</th>
<th>Cardiovascular side-effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interscalene brachial plexus block</td>
<td>2.3 mg kg(^{-1})</td>
<td>N/A (ND)</td>
<td>ND</td>
<td>Grand mal seizure</td>
<td>None</td>
</tr>
<tr>
<td>Epidural brachial plexus block</td>
<td>2.0 mg kg(^{-1})</td>
<td>N/A (ND)</td>
<td>ND</td>
<td>Grand mal seizure</td>
<td>Sinus tachycardia</td>
</tr>
<tr>
<td>Epidural anaesthesia</td>
<td>0.5 mg kg(^{-1})</td>
<td>30–40 (1.4)</td>
<td>ND</td>
<td>Grand mal seizure</td>
<td>None</td>
</tr>
<tr>
<td>Brachial plexus block</td>
<td>300 mg</td>
<td>N/R (2.7)</td>
<td>0.5</td>
<td>Grand mal seizure</td>
<td>None</td>
</tr>
<tr>
<td>Sciatic block</td>
<td>2.5 mg kg(^{-1})</td>
<td>7 (3.6)</td>
<td>0.69</td>
<td>Grand mal seizure</td>
<td>Severe bradycardia</td>
</tr>
<tr>
<td>Interscalene brachial plexus block</td>
<td>6 mg kg(^{-1})</td>
<td>40 (6.0)</td>
<td>0.66</td>
<td>Minor</td>
<td>Arterial hypertension, sinus tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>5.4</td>
<td>0.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>4.6</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>98</td>
<td>4.0</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Brachial plexus block</td>
<td>4.5 mg kg(^{-1})</td>
<td>25 (4.0)</td>
<td>0.36</td>
<td>Minor</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37</td>
<td>2.5</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>56</td>
<td>2.0</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Data regarding the incidence of seizures after brachial plexus blockade with ropivacaine are not available, but an incidence of 1.2 per 1000 blocks has been described after the use of bupivacaine. Three studies investigated the thresholds for signs of minor central neurological toxicity in healthy, male volunteers by administering a continuous i.v. infusion of ropivacaine 10 mg min$^{-1}$. First symptoms occurred after an infusion of 0.8–2.6 mg kg$^{-1}$. The corresponding total dose ranged between 62 and 160 mg and the peak total plasma concentrations measured in the venous blood samples were between 0.5 and 3.2 mg litre$^{-1}$. No severe side-effects, such as convulsions or cardiac arrhythmias, were observed. The speed of injection has a great effect on the peak plasma concentration. In clinical practice, most regional techniques are performed with infusion rates above 10 mg min$^{-1}$, which increases the possibility of higher peak plasma concentrations when accidental intravascular injection occurs. Therefore, plasma concentrations determined after continuous infusions in volunteers might not truly represent clinical seizure thresholds. However, the data obtained from healthy males show that seizure thresholds vary between individuals.

Cardiac or central neurological complications after the administration of ropivacaine have been described after brachial plexus and sciatic blockade and after epidural anaesthesia. The wide range of administered doses of ropivacaine causing the symptoms confirms the inter-individual variation in threshold obtained in healthy volunteers (Table 1). Plowman and co-workers reported the onset of a grand mal seizure in a 13-yr-old boy after injecting ropivacaine 0.5 mg kg$^{-1}$ into the epidural space. The total plasma concentration of ropivacaine 30 min later was 1.4 mg litre$^{-1}$, suggesting a much larger value at the time of the incident. In our patient, we measured a total plasma concentration of ropivacaine of 3.3 mg litre$^{-1}$ 15 min after inadvertent intravascular injection, and extrapolated to a concentration of 5.75 mg litre$^{-1}$ immediately after the end of the injection period. This value is well above the venous plasma concentration of ropivacaine found to produce neurological symptoms in humans. Unfortunately, we did not measure the concentrations of $\alpha$-1 glycoprotein, which are known to affect the unbound concentration of local anaesthetic. Knudsen and co-workers demonstrated that the total and the unbound concentrations of ropivacaine in arterial plasma are consistently higher than the corresponding venous concentrations during and up to 20 min after an i.v. infusion. After i.v. administration, the arterial circulation carries the local anaesthetic to various parts of the body, while the peripheral venous flow also returns from poorly perfused tissues. Therefore, during rapid i.v. injection the peak venous concentration probably does not represent the concentration at the site of action until equilibrium is reached. In our patient, the first sample was taken 15 min after the injection and the difference, if any, between the arterial and the venous concentrations was probably minor.

Understanding the relationship between dose, body weight and speed of the systemic absorption is important in clinical practice because even a non-intravascular injection may lead to a high plasma concentration of local anaesthetic and signs of systemic toxicity. The time course of the symptoms in our patient suggests that a considerable amount of the local anaesthetic had been injected intravascularly and that symptoms were not caused by systemic absorption of ropivacaine. An arterial injection with a retrograde flow up to the branches of the carotid artery appears unlikely as the vascular volume of the axillary artery up to the branches exceeds the volume of local anaesthetic administered. Addition of epinephrine to local anaesthetic has been shown to identify reliably an intravenous injection if the systolic blood pressure increases more than 15 mm Hg. In the present case, no epinephrine had been added to the local anaesthetic solution because the cardiovascular response to epinephrine is reduced in patients receiving $\beta$-adrenergic-blocking drugs.

Our patient showed no signs of cardiac toxicity and the changes in heart rate and arterial pressure were probably a consequence of the seizure, although a small increase in heart rate and arterial pressure has been described at similar plasma concentrations of ropivacaine. In one published case, severe cardiac arrhythmias were reported in addition to convulsions. The venous plasma concentrations 7 min after the inadvertent i.v. injection of ropivacaine were similar (3.6 mg litre$^{-1}$). The authors extrapolated to a peak plasma concentration at the time when the arrhythmia occurred of 7–8 mg litre$^{-1}$. This confirms that the cardiovascular system is more resistant to the effects of local anaesthetics than the central nervous system.

Although brachial plexus blockade with 40 ml of ropivacaine 5 or 7.5 mg ml$^{-1}$ has been shown to be safe, administering the smallest clinically reasonable dose reduces the risk of severe toxic side-effects. Coventry and colleagues showed recently that brachial plexus blockade could be achieved with 30 ml of local anaesthetic using a nerve stimulator technique. The choice of local anaesthetic is also an important issue. The short-acting local anaesthetics prilocaine and lidocaine have been shown to be safer regarding systemic toxicity. We chose ropivacaine in the present case because of its long-lasting beneficial effects on arterial and venous blood flow after brachial plexus blockade and its better safety profile when compared with bupivacaine.

In summary, we report a case of inadvertent intravascular injection of 1.1 mg kg$^{-1}$ of ropivacaine leading to a total venous plasma concentration of 3.3 mg litre$^{-1}$. Its initial plasma concentration after the end of the injection period was estimated at 5.75 mg litre$^{-1}$ using a two-compartment model. A grand mal seizure but no symptoms of cardiovascular toxicity occurred and the patient recovered without sequelae. This case emphasizes that regional
anaesthetic techniques have to be applied very carefully and that appropriate monitoring of the patient is necessary. In the absence of contraindications, the addition of epinephrine to the local anaesthetic solution should be considered in order to detect inadvertent intravascular injection.

Acknowledgements
We thank Dr Klaus Richter (Institute of Clinical Pharmacology, University of Dresden) for performing the high-performance liquid chromatography and Dr Dobromir Dobrev (Institute of Pharmacology and Toxicology, University of Dresden) for expert technical advice regarding the extrapolation of the initial ropivacaine concentration.

References
7 Ruetsch YA, Fattinger KE, Borgetto A. Ropivacaine-induced convulsions and severe cardiac dysrhythmia after sciatic block. Anesthesiology 1999; 90: 1784–6
9 Plowman AN, Bollsin S, Mather LE. Central nervous system toxicity attributable to epidural ropivacaine hydrochloride. Anaesth Intensive Care 1998; 26: 204–6

© The Board of Management and Trustees of the British Journal of Anaesthesia 2001