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Ropivacaine-induced toxicity with overdose suspected after axillary brachial plexus block

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Abstract
Ropivacaine has a high threshold for systemic toxicity. We report and highlight a rare case in which an overdose of ropivacaine was suspected of leading to a generalized convulsion following the injection of this agent for axillary brachial plexus block (ABPB). A 25-year-old woman (height, 153 cm; weight, 48 kg; American Society of Anesthesiologists physical status I) was scheduled for finger surgery with ABPB. The perivascular sheath was identified by fascial clicks. We administered 300 mg (6.25 mg·kg^{-1}) ropivacaine, while confirming that no blood flow was observed in the injection line by repeated negative aspiration tests. Ten minutes after the injection, most sensory and motor nerves were blocked effectively. Thirteen minutes after the administration, the patient lost consciousness and convulsed suddenly. No severe symptoms of cardiovascular toxicity occurred. The concentration of ropivacaine in a venous blood sample taken 28 min after the ropivacaine injection was 3.65 μg·ml^{-1}. She recovered with no sequelae. Limited cases have indicated high efficacy and sufficient safety for the use of 300 mg ropivacaine for ABPB. However, the toxic threshold of ropivacaine remains unclear, and the dose should be calculated in relation to the weight of the patient to prevent severe toxic complications.

Key words Ropivacaine · Local anesthetic toxicity · Axillary brachial plexus block · Overdose

Introduction

Axillary brachial plexus block (ABPB) requires large amounts of local anesthetic to establish complete anesthesia, so the safety of the anesthetic is critical. Ropivacaine, a relatively new amide local anesthetic agent, is considered safer than bupivacaine on the basis of experimental and clinical reports indicating lower systemic toxicity [1–4]. Clinical trials were performed, and it was concluded that ABPB induced by 40 ml 0.75% ropivacaine (total dose, 300 mg) achieved excellent anesthesia without severe complications [4–6]. Some toxic cases secondary to presumed inadvertent intravascular injection were reported, but overdose cases were rare. We report a case in which an overdose of ropivacaine was suspected of leading to a generalized convulsion following the injection of 300 mg (6.25 mg·kg^{-1}) ropivacaine for ABPB.

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Case report

A 25-year-old woman (height, 153 cm; weight, 48 kg; American Society of Anesthesiologists physical status I) was scheduled for the removal of a metal plate from the left ring finger and lysis of adhesions with ABPB. She had previously undergone pancreatic duodenectomy and fixation of the finger with a plate because of a traffic accident 6 months earlier. She had no history of neurological or cardiac disease. She was taking no medication. Before surgery, all routine laboratory test results were normal and an electrocardiogram (ECG) showed normal sinus rhythm. The patient did not receive any sedation before surgery. In the operating room, monitoring (ECG, pulse oximetry, and noninvasive arterial blood pressure) was placed 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 1% lidocaine 10 mg after sterile preparation, and a 22-gauge 32-mm intravenous catheter (SARFLO Flash; Terumo, Tokyo, Japan) was inserted parallel to and close to the artery and directed towards the apex of the axilla. The perivascular sheath was identified with fascial clicks. The outer catheter alone was advanced over the inner needle until it was fully inserted. After the inner needle was withdrawn, the catheter, to which a 50-cm-long intravenous extension tube was connected, was fixed to

be immobile. We confirmed that the catheter was not bent, with 2 ml normal saline solution injected smoothly. No blood flow was observed in the connected injection line, by negative aspiration tests. After firm digital compression of the neurovascular sheath at the level of the catheter hub, 40 ml of 7.5 mg·ml^{-1} ropivacaine (total dose, 300 mg) was injected, with negative aspirations every 5 ml. Verbal communication was made during injection and no early signs of systemic toxicity were noted. Five minutes after the injection of ropivacaine, sensory block was seen in the ulnar and the median nerves. Ten minutes after the injection, sensory block was seen in the radial and musculocutaneous nerves, and complete motor block was seen in the ulnar, the median, and the musculocutaneous nerves. There were no changes on the ECG monitor. Thirteen minutes after the injection, she said she began to feel numbness in her lip, and at that time she lost consciousness and convulsed suddenly. During the convulsion, her heart rate increased from 85 to 140 beats·min^{-1} and systolic blood pressure rose from 104 to 160 mmHg. The lungs were ventilated immediately with 100% oxygen, using a mask. General anesthesia was induced with propofol 60 mg. The convulsion stopped after about 20 s. After 5 min, spontaneous respiration gradually appeared and this changed to hyperventilation (tidal volume, 12–15 ml·kg^{-1}; respiratory rate, 22–28 times·min^{-1}), which allowed the insertion of a laryngeal mask airway (LMA). There were no other arrhythmias or changes in PQ or QT intervals or QRS width. After an observation period, the scheduled surgery was performed with the patient under general anesthesia. Her heart rate began to decrease gradually, and at the end of the surgery, it had returned to a normal level (85 beats·min^{-1}). General anesthesia was terminated 72 min after the convulsion, and the LMA was removed after confirming her clear consciousness. She had neither sequelae nor awareness of the incident. A venous blood sample was taken 28 min after the injection of ropivacaine, immediately placed on ice, centrifuged, and frozen. The total plasma concentration of ropivacaine in the sample was 3.65 μg·ml^{-1} of blood.

Discussion

In clinical trials, a 300-mg dose of ropivacaine for ABPB showed high efficacy and sufficient safety, but these studies were in a limited number of patients [4–6]. Because repeated negative aspirations do not preclude the possibility of inadvertent intravascular injection [7–10], we used an intravenous catheter. Though a plastic catheter has a risk of collapse, we think such a catheter is better for moving the tips in the axillary sheath to avoid nerve injuries. This catheter also gives us the fascial click twice, penetrating the sheath with the inner needle and the outer catheter. In the patient reported here, 300 mg ropivacaine (6.25 mg·kg^{-1}) was administered in 5 min with the catheter fixed, and a generalized convulsion appeared 13 min after the ABPB. Though failed ABPB techniques result in high plasma concentrations of local anesthetic [11], the late onset of the symptoms, the high concentration of ropivacaine, and the almost complete local anesthetic block are suggestive of a nonintravascular, nonextrasheath injection. These situations imply that the symptoms were due to an overdose of ropivacaine, though no direct proof of this exists.

In this patient, we induced general anesthesia with 60 mg propofol. Early treatment of seizure activity is particularly important, because seizures produce acidosis and hypoxia that exacerbate local anesthetic toxicity. It has been said that a lipid emulsion such as propofol is an effective antidote to the cardiovascular collapse caused by bupivacaine overdose in animals [12]. It has been reported that even in ropivacaine-induced asystole in which conventional cardiopulmonary resuscitation was unsuccessful, the use of a lipid emulsion enabled complete recovery [13]. But neither the precise mechanism of the collapse caused by the local anesthetic nor how the lipid emulsion reverses the toxicity of the local anesthetic' are clear. Further studies and refinements are needed.

An LMA was used in our patient because it was deemed unnecessary to suppress the patient's strong spontaneous respiration after her convulsion, however, in general, intubation and appropriate hyperventilation are needed to prevent patients from developing acidosis.

Toxic symptoms of ropivacaine, including inadvertent intravascular injections, present mainly as central nervous system (CNS) symptoms and less often as cardiovascular symptoms [1,2,7,14], although recent reports have stated that a large amount of ropivacaine may cause severe cardiovascular symptoms [9,13,15]. Additionally, caution is advised in patients in whom toxicity is suspected and who have no convulsions, if premedication such as midazolam has been administered, because this medication may have a protective anticonvulsant effect [15,16].

According to several previous reports of ropivacaine overdose toxicity (see Table 1), the total dose of ropivacaine administered for brachial plexus block was 4.28–8.00 mg·kg^{-1} [13,17–20]. These cases all occurred between 10 and 20 min after the brachial plexus block. The difference in the venous total plasma concentrations of ropivacaine between those reported by Mardirosoff and Dumont [17] and Ala-Kokko et al. [18] may be due to the patient reported by Mardirosoff and Dumont [17] having higher levels of alpha-1-acid glyco-

Table 1. Previously reported cases of overdose induced by ropivacaine used for brachial plexus block

Method	Dose of injected ropivacaine ($mg \cdot kg^{-1}$)	Adverse effects	Time interval after injection (min)	Total plasma concentration ($\mu g \cdot ml^{-1}$)	Time blood sample was measured (min)[a]
Axillary [13]	8.0	Convulsions cardiac arrest	15	Unknown	Unknown
Interscalene [17]	6.15	Convulsions	20	2.09	60
Interscalene [18]	6.0	Convulsions sinus tachycardia	15	6.0, 5.4, 4.6, 4.0	40, 60, 80, 98
Midhumeral [19]	4.28	Convulsions	15	2.27	120
Midhumeral [20]	5.35	Convulsions sinus tachycardia	10	5.22, 3.79	0, 15

[a] Time interval after first symptom was observed

protein, because of chronic renal failure, and a modified seizure threshold for local anesthetics, owing to epilepsy.

It has been stated that 300 mg ropivacaine injected within the axillary sheath could reach the systemic circulation via the capillary network, or by transarterial absorption, and lead to a maximum plasma concentration at 0.57 ± 0.26 h after injection [5]; another similar study reported the period to be 0.90 ± 0.37 h [6]. According to a report on the continuous intravenous administration of ropivacaine in volunteers [14], venous plasma concentrations, obtained when the first symptoms occurred, were 2.2 (range, 0.5–3.2) $\mu g \cdot ml^{-1}$ and 0.15 (range, 0.01–0.24) $\mu g \cdot ml^{-1}$ for the total and unbound venous plasma concentrations, respectively. It is the unbound drug that is available for distribution, crossing biological membranes and binding to the receptor sites where the pharmacological effects are initiated. But this interindividual variability makes the toxic threshold of ropivacaine unclear and this prevents the use of a 300-mg standard dose, of ropivacaine for all patients, particularly in the elderly or in patients whose physiques are small. In cases of interscalene brachial plexus block with a local anesthetic, there is an inverse correlation between the patient's body weight and the maximum venous concentration of the anesthetic [21], and reports have stated that it would be unsafe to use one standard dose for all patients; thus, the dosage requires calculation. Although it is difficult to recommend a safe maximum dose, ropivacaine, at a mean dose range of 3.0–5.0 $mg \cdot kg^{-1}$, has been reported to show effective brachial plexus block without evidence of central nervous system or cardiovascular toxicity [3,6,22–24].

There have been no clinical trials in which the dose of ropivacaine to employ for brachial plexus block has been calculated; more reports and studies are required to determine the maximum dose of ropivacaine.

Conclusion

Though 300-mg ropivacaine was accurately administered in a normal adult, a serious drug reaction involving generalized convulsion was noted. Rather than a vague limit, a specific numerical value for the dose is required to avoid toxic events. We conclude that dose calculations must be made according to the patient's weight and physical status, and that caution should be maintained at 10–20 min after ropivacaine injection if a large dose of ropivacaine is required.

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