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Case Report

Convulsions after ropivacaine 300 mg for brachial plexus block

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A healthy 18-yr-old male (weight 60 kg, height 167 cm), with a history of febrile convulsions in childhood, developed a grand mal convulsion 10 min after the second of two injections of ropivacaine 150 mg, both given incrementally 15 min apart (total 300 mg), for combined axillary/interscalene brachial plexus block. Treatment was with oxygen, lung ventilation, and i.v. midazolam, and the patient made a complete recovery. Arterial plasma ropivacaine concentration 2 min after the onset of convulsions was only 2.13 mg litre^{-1}, suggesting that this patient was particularly susceptible to local anaesthetic toxicity. Whether sub-clinical EEG changes identified after operation were related to this sensitivity cannot be determined, but review illustrates wide variation in both the dose and the plasma concentration of local anaesthetics associated with systemic toxicity. The UK recommended dose of ropivacaine for brachial plexus block is 225–300 mg according to stature.

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Although ropivacaine is considered less likely to produce systemic toxicity than bupivacaine,[1 2] convulsions have been reported after its inadvertent intravascular injection[3] or the administration of a large dose.[4–7] In this report, we describe grand mal convulsions occurring after administration of ropivacaine 300 mg for brachial plexus block in a healthy, young individual whose only significant medical history was a febrile convulsion during childhood.

Case report

An 18-yr-old male (ASA I, 60 kg, and 167 cm) presented for elective open reduction and internal fixation of a fracture of the right navicular bone under brachial plexus block. The only medical history of note was a single febrile convulsion at 3 yr, and both preoperative physical and laboratory examinations were unremarkable. He did not smoke tobacco or drink alcohol regularly.

Premedication was with i.m. hydroxyzine 25 mg and atropine 0.5 mg 30 min before surgery. On arrival in the operating theatre, monitoring of arterial pressure, ECG, and Sp_{O_2} was instituted, and venous access was secured. A 22 gauge, short bevel needle with an injection line attached was inserted parallel and close to the axillary artery, and the sheath identified by a fascial 'click'. After a negative aspiration test, 20 ml of ropivacaine 7.5 mg ml^{-1} was injected over 1 min in 3–4 ml increments with repeated negative aspiration. Fifteen minutes later, a 22 gauge, short bevel needle was inserted into the interscalene groove and paraesthesia radiating to the arm obtained before a second dose of 20 ml of ropivacaine 7.5 mg ml^{-1} was injected in exactly the same manner. Thus, the total dose of ropivacaine injected was 300 mg (5 mg kg^{-1}), and it produced complete analgesia to pin-prick (C5∼Th1) in the right arm.

Twenty-five minutes after the first ropivacaine injection, therefore 10 min after the second, the patient suddenly developed a grand mal convulsion, and became apnoeic and unconscious. Heart rate increased from a baseline of 72 beats min^{-1} to 89 (sinus rhythm), whereas arterial pressure remained unchanged at about 126/70 mm Hg. Lung ventilation by face mask with 100% oxygen was started and midazolam 5 mg given i.v. Approximately 1 min after administration of midazolam, the seizure stopped and regular spontaneous respiration returned. Two minutes after the seizure started, arterial blood gas analysis

figures were pH 7.17; Pa_{O_2} 497 mm Hg; Pa_{CO_2} 55.7 mm Hg; and base excess −9.4. Because the patient's circulation remained stable, and a patent airway was maintained with regular breathing, the surgery was performed as scheduled. Oxygen 3 litre min^{-1} was administered through a face mask and Sp_{O_2} remained at 100% throughout. The patient made an uneventful postoperative recovery.

Arterial blood was sampled 2, 35, and 246 min after the onset of convulsions, that is, 27, 60, and 271 min after the first ropivacaine injection. Total plasma ropivacaine concentrations (determined by liquid chromatography and mass spectrometry) were 2.13, 2.10, and 0.91 mg $litre^{-1}$, respectively. Neurological examination and magnetic resonance imaging performed the day after surgery did not reveal any abnormality. However, an EEG recording 2 days later showed mild, localized sharp waves at both temporal lobes and these findings were diagnosed as mild epilepsy not requiring treatment. Six months after surgery, he was well and had not had any more convulsions.

Table 1 Previously published cases of ropivacaine-induced seizures due to an overdose for brachial plexus block. *Symptoms of cardiovascular toxicity were not described. †Plasma ropivacaine concentration was not determined

Reference no.	Dose of ropivacaine injected (mg kg^{-1})	Total plasma concentration (mg $litre^{-1}$)	Sampling time (min after seizure)	Cardiovascular toxicity
4	6.15	2.09	40	(−)*
5	5.36	5.22	0	Tachycardia
6	8.00	—†	—†	Cardiac arrest
7	6.25	3.65	15	Tachycardia, hypertension
Our case	5.00	2.13	2	Tachycardia

Discussion

Ropivacaine is reported to have a higher threshold for producing systemic toxicity than bupivacaine.[1 2] Therefore, it seems particularly suitable for techniques such as brachial plexus block which require large doses of drug. However, systemic toxicity has occurred after accidental intravascular injection,[3] and there are also reports of it after systemic absorption.[4–7] The patient described here developed a complete brachial plexus block and the convulsion started 10 min after the second ropivacaine dose, so intravascular injection is unlikely to have been the cause. It is possible that the dose of ropivacaine was larger than necessary, although the same amount (300 mg) was used uneventfully (unless accidental intravascular injection occurred) in a large clinical trial of brachial plexus block.[8] Similar doses, used uneventfully in an admittedly small Japanese study of brachial plexus block,[9] resulted in a mean (SD) peak plasma concentration of 2.70 (1.01) mg $litre^{-1}$, yet the highest concentration measured in the patient described here was only 2.13 mg $litre^{-1}$.

The threshold plasma concentration for severe ropivacaine toxicity is usually considered to be >3 mg $litre^{-1}$, but the symptoms of systemic toxicity correlate poorly with plasma concentration and the figures at which overt effects occur are quite variable. For instance, Scott and colleagues[1] demonstrated, in volunteers, that the early central nervous system (CNS) symptoms, such as peri-oral numbness, appeared between 1 and 2 mg $litre^{-1}$. Further, there is a significant variation in the figures reported in association with CNS toxicity after intended brachial plexus block (Table 1), although it is possible that, with only a small number of samples being obtained, the peak concentration was missed. However, the plasma concentration here had only decreased from 2.13 mg $litre^{-1}$ at 2 min to 2.10 mg $litre^{-1}$ at 35 min, making it unlikely that the figure was much above 2.13 mg $litre^{-1}$ when the convulsion started. Therefore, 300 mg ropivacaine may simply have been excessive in this (60 kg) patient. The dose recommendation in the UK for brachial plexus block is 225–300 mg 'according to the patient's physical status' (www.bnf.org).

This leaves the question of why a healthy young patient was so sensitive to the toxic effects of local anaesthetics, and whether this might be related to his history of febrile convulsion in childhood and the sub-clinical EEG abnormalities found after operation. Mardirosoff and Dumont[4] described an overtly epileptic patient who suffered generalized convulsions after receiving ropivacaine 400 mg (6.15 mg kg^{-1}) for interscalene block. The plasma ropivacaine concentration measured 40 min after injection (and 20 min after the convulsion) was 2.09 mg $litre^{-1}$, again lower than might be expected, although there was more time for a decrease after the reaction than was the case here. However, to the best of our knowledge, there is no report describing decreased threshold for local anaesthetic-induced CNS toxicity in patients vulnerable to convulsive disorders. Although Post and colleagues[10] have reported that lidocaine induces convulsions more easily in a rat model of epilepsy, lidocaine has actually been used in the clinical management of status epilepticus.[11] However, there may be a parallel with propofol, which has anticonvulsant properties,[12] but can also produce epileptiform changes more easily in epileptic patients.[13] Further studies may be needed to establish whether there is an increased risk of CNS toxicity in epileptic patients.

Liver metabolism does not play a large part in the initial disposition of local anaesthetics, but it could have contributed to the patient's greater sensitivity to ropivacaine toxicity, especially as he neither drank alcohol nor smokes regularly, habits which augment hepatic activity. In man, ropivacaine is metabolized to 2,6-pipecoloxylidide by cytochrome P450 (CYP) 3A4 and 3-hydroxyropivacaine by CYP1A2,[14] systems which mature during infancy, with both $t_{1/2}$ and clearance of plasma ropivacaine becoming equivalent to those of the young adult. Further, the activity of CYP1A2 is maximum during adolescence (<19 yr),[15] so it seems unlikely that immaturity of enzyme systems contributed to this reaction.

In conclusion, an 18-yr-old patient, weighing 60 kg received two doses of ropivacaine 150 mg, 15 min apart, for combined axillary/interscalene brachial plexus block. Ten minutes after the second injection, he developed a grand mal convulsion which was treated effectively with oxygen, lung ventilation, and midazolam. No definitive reason for this extreme reaction was identified other than the use of a large dose of drug in a patient somewhat oversensitive to its effects. Whether his latent epilepsy was relevant cannot be determined.

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