

Case report: Ropivacaine neurotoxicity at clinical doses in interscalene brachial plexus block

[Présentation de cas : neurotoxicité de la ropivacaine à des doses cliniques lors du bloc du plexus brachial par approche interscalénique]

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Purpose: To describe a case of ropivacaine toxicity following an ultrasound guided interscalene block and discuss the possible mechanisms involved.

Clinical features: A 76-yr-old woman with multiple myeloma was scheduled for open reduction and internal fixation following a pathological fracture of her left upper humerus. She developed central nervous system toxicity with ropivacaine 15 min after a carefully placed ultrasound-guided interscalene catheter. The dose of ropivacaine was within recommended limits and there was no evidence that the catheter was intravascular. Surgery proceeded uneventfully under general anesthesia. The interscalene catheter was left *in situ* for postoperative evaluation and intravascular injection was ruled out with a colour Doppler study. The total ropivacaine plasma concentration was $3.68 \mu\text{g}\cdot\text{mL}^{-1}$. Neurological evaluation, contrast computerized tomography and electroencephalogram were normal. The patient was discharged home with no sequelae. Advanced age, malnutrition, epinephrine and possible elevation of α_1 -acid glycoprotein levels could have altered the pharmacokinetics of plasma ropivacaine and possibly contributed to delayed neurotoxicity.

Conclusions: Local anesthetic toxicity is an uncommon but well documented complication of regional anesthesia. Careful monitoring and preparedness for managing complications during the conduct of regional anesthesia cannot be overemphasized. Experience from this case suggests that local anesthesia toxicity can happen within safe dose limits and without intravascular placement despite careful attention to needle and catheter placement, fractionated dosing and frequent aspirations.

Objectif: Décrire un cas de toxicité à la ropivacaine suite à un bloc interscalénique écho-guidé et examiner les mécanismes possibles impliqués.

Éléments cliniques: Une réduction ouverte et une fixation interne ont été prévues chez une patiente âgée de 76 ans souffrant de myélome multiple, à la suite d'une fracture pathologique de son humérus supérieur gauche. Elle a développé une toxicité impliquant le système nerveux central avec de la ropivacaine 15 min après le positionnement d'un cathéter interscalénique placé avec soin grâce à un écho-guidage. La dose de ropivacaine se situait dans les limites recommandées et il n'y avait aucune indication que le cathéter était intravasculaire. La chirurgie a eu lieu sans incident sous anesthésie générale. Le cathéter interscalénique a été laissé *in situ* à des fins d'évaluation postopératoire, et la possibilité d'une perfusion intravasculaire a été écartée par une étude Doppler couleur. La concentration plasmatique de ropivacaine totale était de $3,68 \mu\text{g}\cdot\text{mL}^{-1}$. L'évaluation neurologique, la tomographie de contraste par ordinateur et l'électroencéphalogramme étaient normaux. La patiente est rentrée chez elle sans séquelles. L'âge avancé, la malnutrition, l'épinéphrine et une élévation possible des niveaux de glycoprotéine acide α_1 ont pu modifier la pharmacocinétique de la ropivacaine et possiblement contribuer à une neurotoxicité retardée.

Conclusion: La toxicité d'un anesthésique local est une complication peu commune mais bien documentée de l'anesthésie régionale. Une surveillance soignée et une capacité de réaction pour la prise en charge de complications pendant l'anesthésie régionale ne peuvent être suffisamment recommandées. Ce cas suggère que la toxicité d'une anesthésie locale peut survenir même dans les limites sécuritaires de dosage et sans positionnement intravasculaire, malgré une attention particulière au positionnement de l'aiguille et du cathéter, un dosage fractionné et des aspirations fréquentes.

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RECENT modifications of various block techniques include the use of ultrasonography to improve the quality of blocks and to avoid complications.¹ Ropivacaine has been documented to be less cardiotoxic and neurotoxic² when compared to other local anesthetics (LA). To date, while there have been few reports of toxicity associated with ropivacaine, most have involved inadvertent intravascular injection or higher doses of the drug. We report a case of central nervous system (CNS) toxicity that occurred without intravascular injection, while using recommended dosing guidelines. The patient gave written consent for photography and publication of case.

Case description

After sustaining a pathological fracture of her left proximal humerus, a 76-yr-old female patient (body mass index 18.3 kg·m⁻²) was scheduled for open reduction and internal fixation followed by postoperative radiation. She had been diagnosed with multiple myeloma six years previously. She had received radiation therapy for the involved bony lesions. Other medical history included occasional sinusitis and a recent episode of pneumonia. She also reported an isolated seizure at age 21. However, the details were unknown. She presented with no cardiac, neurological symptoms or signs. Medications at the time of admission included thalidomide, pamidronate, dexamethasone aspirin, ibuprofen, paroxetine and docusate. On physical examination, the patient's vital signs were stable. Of note was a large 4 × 4 cm metastatic lesion, superior to the medial end of left clavicle (Figure 1).

Continuous interscalene brachial plexus block for intra- and postoperative analgesia was discussed with her and informed consent was obtained. With intravenous access, 2 L·min⁻¹ oxygen by facemask and routine hemodynamic monitoring (pulse oximetry, non-invasive blood pressure five-minute cycling and 3-lead electrocardiography), the patient received conscious sedation with fentanyl and midazolam. Lidocaine, 3 mL of 10 mg·mL⁻¹ (30 mg, < 0.8 mg·kg⁻¹) was used for local infiltration and superficial cervical plexus block. An ultrasound-guided and peripheral nerve stimulator assisted interscalene brachial plexus catheter was placed using standard technique. Twenty-five millilitres of ropivacaine (75 mg, 0.3% with epinephrine 2.5 µg·mL⁻¹, 1.97 mg·kg⁻¹) were administered in aliquots through the catheter after negative aspiration. Verbal contact was maintained with the patient throughout the procedure and there were no signs of early toxicity. Approximately 15 min after the injection of ropivacaine, the patient suddenly



FIGURE 1 Tumour present at the medial end of left clavicle

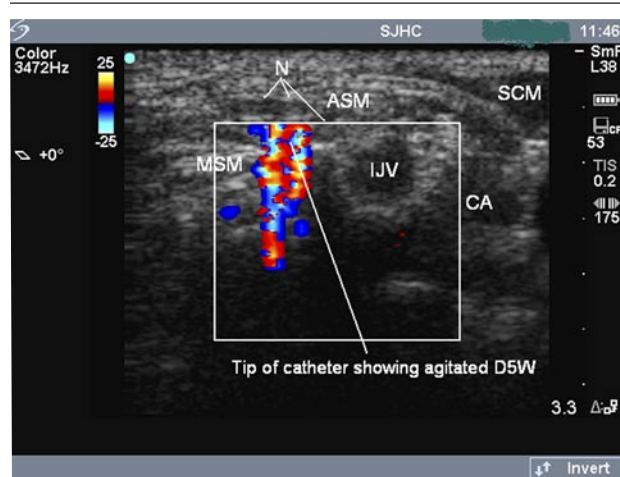


FIGURE 2 Ultrasound examination of the interscalene area with colour Doppler flow assessment
N = nerves; SCM = sternocleidomastoid muscle; ASM = anterior scalene muscle; MSM = middle scalene muscle; IJV = internal jugular vein; CA = carotid artery; D5W = 5% dextrose in water.

became unresponsive and experienced a generalized grand mal seizure. Propofol and suxamethonium were administered, her trachea was intubated, and she was ventilated with 100% oxygen. A venous blood sample was sent for ropivacaine levels. Aspiration of the catheter did not reveal any blood. As the seizure did not recur following recovery from succinylcholine, a decision was made to proceed with surgery, which was uneventful.

Postoperatively, the patient had complete motor and sensory block of the brachial plexus of the operative limb and she had no recollection of the seizure. She was informed of the event. The motor and sensory block resolved over the ensuing 24 hr, but we chose not to use the interscalene catheter for postoperative analgesia. It was left for diagnostic imaging, later.

On postoperative day one, ultrasound evaluation of the interscalene area excluded intravascular catheter placement. Injection of 5 mL of hand agitated 5% dextrose (D5W) through the catheter with colour Doppler flow assessment could be seen around the plexus and away from the vessels (Figure 2). Aspiration of the catheter again did not reveal any blood. It was subsequently removed. The total ropivacaine plasma concentration (liquid gas chromatography mass spectrometry with nitrogen-sensitive detection) was 3.68 $\mu\text{g}\cdot\text{mL}^{-1}$, 20 min after the block. Free ropivacaine levels were not available in our hospital. A neurological examination, contrast computerized tomography scan of brain and electroencephalogram were within normal limits. The patient was discharged home and reported no sequelae from the seizure at the three-month follow-up.

Discussion

The S-enantiomer of ropivacaine is associated with lower lipid solubility and provides a better neurological and cardiac toxicity profile as compared to an equal dose of bupivacaine.³ The incidence of ropivacaine-induced toxic events has been estimated as six to eight cases per 1,000,000 patients.^A

Chazalon *et al.*⁴ cited cases of severe toxicity associated with ropivacaine after regional anesthesia. As an update to the worldwide cumulative experience, the Table summarizes cases of ropivacaine toxicity during peripheral nerve blocks in adults reported since 2002. Only those cases are included in which ropivacaine blood levels were measured. All incidents were the consequence of direct intravascular injection or secondary plasma absorption of a large volume of LA. In our case, a seizure occurred despite the fact that recommended dosing guidelines were followed and potential intravascular injection was excluded. The time profile and the onset of symptoms strongly suggest a LA-induced etiology. The total dose of lidocaine was 30 mg ($< 0.8\text{mg}\cdot\text{kg}^{-1}$) though additive effects of LA cannot be entirely ruled out.

Plasma concentrations of ropivacaine exceeding 5 $\mu\text{g}\cdot\text{mL}^{-1}$ have been detected without any clinical signs of neurological or cardiac toxicity.⁵ Knudsen *et al.*⁶ noted the threshold for early neurological toxicity symptoms to be 2.2 $\mu\text{g}\cdot\text{mL}^{-1}$ in healthy volunteers. However, the threshold plasma concentration at which CNS toxicity occurs may be related more to the rate of increase of the serum concentration rather than to the total amount of drug injected.⁷ The temporal association of symptoms with the timing of injection and resulting ropivacaine serum concentration suggest that a portion of the 75 mg dose may have entered the circulation rapidly via the tumour present in the vicinity (Figure 1). Malnutrition and/or lack of fat in the area may have contributed to the seizure. The total ropivacaine plasma concentration measured 20 min after the injection of ropivacaine was 3.68 $\mu\text{g}\cdot\text{mL}^{-1}$.

The addition of epinephrine may explain the delayed onset of seizure as it decreases peak plasma concentration (C-max), delays the time to peak plasma concentration (T-max) and decrease the bioavailability of the rapid absorption phase thereby reducing systemic ropivacaine toxicity.⁸ The vasoconstrictive action of ropivacaine also could have contributed to the delay of initial absorption.

Ropivacaine is highly bound to α_1 -acid glycoprotein (AAG), which entails that the concentration of AAG in plasma may markedly affect the pharmacokinetics of ropivacaine. Increased levels of AAG can buffer the unbound fraction of the LA.⁹ Alpha₁-acid glycoprotein in turn is known to be an independent prognostic factor in multiple myeloma and is significantly raised when compared to healthy subjects.¹⁰ Clearance of ropivacaine in conditions where AAG is increased (e.g., multiple myeloma) has not been studied. Alpha₁-acid glycoprotein levels were not measured in this case.

Age may have influenced the absorption kinetics of ropivacaine in this case although it has not been studied in peripheral nerve blockade. Simon *et al.*¹¹ reported total plasma ropivacaine concentrations reached a maximum at approximately 16 min and decreased continuously thereafter in older subjects. This may explain the seizure in our patient at 15 min and the absence of further toxicity.

Careful and continuous monitoring as well as preparedness for managing complications including airway and circulatory support is imperative for the safe conduct of regional anesthesia. An increase in blood pressure and tachycardia are considered reliable markers of epinephrine injection but in our case they may have been missed due to a slow rate of injection, the five-minute interval between blood pressure cycling, as well sedation.

A Periodic Safety Update Report: Naropin, AstraZeneca, May 17, 2000.

TABLE Reported cases of severe neurological or cardiac adverse effects induced by ropivacaine after peripheral nerve blockade (since 2002)

Year ^{ref}	Block	Dose of Ropivacaine (mg)	Effects seen	Total (free) plasma concentration $\mu\text{g}\cdot\text{mL}^{-1}$	Time (min)	Proposed mechanism
2002 ¹⁵	Lumbar plexus + sciatic	187.5 + (300 Mepi)	Bradycardia, seizure	3.2, 0.5	10	Possibly intravascular
2003 ⁴	Sciatic + tibial + saphenous	300	Confusion, convulsions, arrest	1.88	60	Over dosage, 6.6 mg·kg ⁻¹
2003 ¹⁴	Sciatic	160 + (300 Mepi)	Unresponsive, seizure, V. fib	3.2 (.05)	5	Intravascular, 2.3 mg·kg ⁻¹
2003 ¹⁶	Interscalene	150 + (360 Lido)	Arrest	1.24 (1.5), 0.93 (1.05)	110, 200	Intravascular, 1.5 mg·kg ⁻¹
2003 ¹⁷	Lumbar plexus	187.5	Convulsions, arrest	5.61, 2.69, 1.16	55, 125, 420	Intravascular, 1.9 mg·kg ⁻¹
2005 ¹⁸	Obturator	150	Convulsions	4.5, 3.5, 2.9	15, 32, 52	Intravascular

*Total ropivacaine plasma concentrations (venous samples). Lido = lidocaine; Mepi = mepivacaine; V. fib = ventricular fibrillation; Ref: = references.

Tsui and colleagues¹² have reported on the use of D5W to distend the perineural space without losing neurostimulation. Hand agitation of D5W is an easy and inexpensive way of using contrast enhancement with colour Doppler evaluation and has been used successfully for plexus and catheter tip localization.¹³ Incorporating all these principles, we were able to precisely locate the site of the tip of catheter.

In conclusion, LA toxicity is an uncommon but well documented complication of regional anesthesia. Experience from this case suggests that LA toxicity may occur despite careful attention to needle and catheter placement, fractionated dosing, and frequent aspirations, within safe dose limits and without intravascular placement. Careful monitoring and preparedness for managing complications during the conduct of regional anesthesia cannot be overemphasized.

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