CASE REPORT

Lipid rescue for treatment of delayed systemic ropivacaine toxicity from a continuous thoracic paravertebral block

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SUMMARY

A 66-year-old man underwent a left minithoracotomy for pleural biopsies and thoracentesis. A left T3 paravertebral catheter was placed prior to induction of general anaesthesia, and a total of 20 mL of bupivacaine 0.25% administered. Postoperatively, ropivacaine 0.2% infusion was commenced at 10 mL/hour. Thirty-seven hours after the initial block, the patient developed convulsions without loss of consciousness. The ropivacaine infusion rate was unchanged and no further boluses had been given. He reported of perioral tingling, a burning sensation in his legs and penis and agitation. Ropivacaine infusion was ceased and a bolus of lipid emulsion (Intralipid 20%) administered, followed by an infusion. His symptoms (aside from mild agitation) resolved within an hour of cessation of the local anaesthetic and commencement of lipid rescue. The total serum concentration of ropivacaine during the event was 2.1 mg/L compared with a published toxic level of 2.2 mg/L in healthy human volunteers.

BACKGROUND

Continuous paravertebral blocks are often used for thoracotomy analgesia. The uncommon occurrence of local anaesthetic systemic toxicity (LAST) has previously been reported in this setting following a bolus of bupivacaine.^{1 2} There has also been a case report of lipid rescue for ropivacaine-induced asystole during placement of an axillary plexus block.³ Our case is unique as it demonstrates an episode of delayed LAST occurring with ropivacaine use during a continuous paravertebral block in the absence of bolus dosing.

CASE PRESENTATION

A 66-year-old man initially presented with a left T4 radiculopathy and underwent open biopsy of a left-sided lesion, involving the T3 and T4 vertebral bodies and pedicles. The lesion was subsequently identified, unusually, as a schwannoma. Four months later, he underwent a left minithoracotomy for adjacent pleural biopsy and drainage of effusion. His medical history included chronic left chest and shoulder pain, which was managed with oxycodone/naloxone and amitriptyline. He had a history of asbestos exposure. In addition, he took esomeprazole for gastro-oesophageal reflux disease, and atorvastatin for hypercholesterolaemia. He had no known drug allergies, and was otherwise well preoperatively.

The patient weighed 98 kg and was 178 cm tall (body mass index, 31 kg/m²).

As routine work up for the thoracotomy, he was reviewed in the preadmissions clinic, where it was decided that thoracic epidural analgesia was contraindicated due to likely changes in the epidural space following open vertebral biopsy.

On the day of surgery, ultrasound was used to identify the left T3 transverse process. Tissue overlying this structure was infiltrated with lidocaine 1% (5 mL), and a paravertebral block was inserted using an 18G Tuohy needle. The transverse process was contacted at 4 cm, and the needle walked off caudally and advanced 1 cm where there was a subtle loss of resistance. A catheter was easily inserted 3.5 cm beyond the tip of the Tuohy needle. Aspiration was negative for blood, air and cerebrospinal fluid. A test dose of 5 mL of bupivacaine 0.25% was injected via the catheter, with no immediate effect. Three further 5 mL boluses were given, producing unilateral reduced temperature sensation to ice from T2 to T6 on the left side. A total of 50 mg of bupivacaine was used (1.96 mg/kg).

Prophylactic cefazolin was administered, and general anaesthesia induced using fentanyl, lidocaine, propofol and rocuronium. A double lumen tracheal tube was inserted without difficulty, and anaesthesia was maintained with sevoflurane. Paracetamol, parecoxib and methadone were administered intraoperatively. A left minithoracotomy was performed with the patient in the right lateral position. Diffuse nodular pleural thickening was noted and multiple biopsies were taken. Pleural fluid (1.2 L) was aspirated and a sample sent to cytology.

Emergence and tracheal extubation were uneventful. An infusion of ropivacaine 0.2% was started via the paravertebral catheter at 10 mL/hour (20 mg/hour, 0.2 mg/kg/hour), and was supplemented with intravenous fentanyl boluses. Intravenous fentanyl patient-controlled analgesia was started (20 µg bolus, 5 min lockout). The patient was transferred to a cardiothoracic high dependency unit (HDU) for monitoring and discharged to the ward within 24 hours.

On the evening of the second postoperative day, 37 hours after the initiation of the block, he started feeling agitated and developed a burning sensation in his penis and legs. After returning from the toilet, he developed violent convulsions mainly affecting the limbs. On examination, he was fully conscious (Glasgow Coma Scale 15) with no focal

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neurological deficits; the blood glucose level was 6.9 mmol/L. There was hypertension to 181/109 mm Hg and tachycardia to 107/min. Oxygen saturation was 96% on Hudson mask oxygen, with a respiratory rate of 28/min.

The patient denied having experienced symptoms like this before, and had no history of seizures.

LAST was presumed and the paravertebral infusion was ceased. Ondansetron was given sublingually and midazolam 2.5 mg was given intramuscularly. Intravenous access was established; blood was drawn to send to pathology and then treatment with a lipid emulsion started as a 150 mL intravenous bolus and a 1500 mL/hour infusion (total dose 1000 mL; 10.2 mL/kg). The symptoms of burning resolved within an hour of lipid rescue administration. Limb movements decreased. Further doses of benzodiazepines were given for the patient's feeling of agitation. The tachycardia, hypertension and tachypnoea resolved within 7 hours.

The patient had no recurrence of these symptoms during his stay in hospital, and was discharged home several days later. The biopsy specimens were consistent with desmoplastic (sarcomatoid) mesothelioma. He died a year later from progression of his malignancy.

INVESTIGATIONS

Venous serum ropivacaine levels at 2.1 mg/L.

DIFFERENTIAL DIAGNOSIS

Seizure.

TREATMENT

Lipid rescue (Intralipid 20%).

OUTCOME AND FOLLOW-UP

The patient had complete resolution of symptoms and was discharged home with no further postoperative complications.

However, he died 1 year later from progression of his malignancy.

DISCUSSION

LAST remains a relatively rare event despite the widespread use of local anaesthetic agents.⁴ Continuous regional nerve blocks are employed as opioid sparing techniques for intraoperative and postoperative use. Paravertebral blocks are an option for thoracotomy analgesia, which provide analgesia that is as effective as a thoracic epidural but with fewer complications.⁵

The use of lipid rescue as an antidote for LAST has been reported in multiple case studies.⁶ The dose recommended by the American Society of Regional Anesthesia is 1.5 mL/kg as an initial bolus, followed by an infusion of 0.25 mL/kg/min.⁷ The bolus is to be repeated once or twice for persistent cardiovascular collapse and the infusion doubled to 0.5 mL/kg/min if the blood pressure remains low. The infusion is to continue for at least 10 min after achieving circulatory stability. The proposed mechanism of the action of lipid rescue is that it provides a lipid sink: a medium into which the local anaesthetic will diffuse from tissue via the aqueous plasma phase.⁸ This results in less local anaesthetic available to affect sites such as the central nervous system and the cardiovascular system.

Although treatment with lipid rescue has been suggested for cardiovascular collapse, the severity of neurological symptoms and distress in our patient coupled with worsening tachycardia warranted intervention. There was a concern that without starting the infusion the patient could have progressed to cardiotoxicity. The doses of lipid rescue for resuscitation are not known to

cause complications as there have been no reports of complications following lipid emulsion therapy for LAST.⁶ Weinberg *et al*⁶ suggested a safety margin of 10–12 mL/kg over 30 min.

Ropivacaine is an amide local anaesthetic that has a longer duration of action, similar to bupivacaine but with less cardiotoxicity. It is 94% protein bound in plasma.⁹

The unbound fraction is free to interact with receptors and is pharmacologically active. In our patient, the total ropivacaine level, which is a measure of the free and protein bound levels of ropivacaine, was 2.1 mg/L. This was measured ~5 min after onset of symptoms and prior to the start of lipid rescue. Free ropivacaine levels were not measured. The maximum tolerated total plasma venous concentration for ropivacaine has been quoted as 2.2 mg/L by Knudsen *et al*.¹ This was determined by infusing ropivacaine into healthy volunteers until symptoms of central nervous system toxicity manifested. The investigators included symptoms such as oral numbness, light-headedness and tinnitus. All these symptoms resolved within 13 min of cessation of ropivacaine infusion.

The actual cause of the accumulation of the local anaesthetic to toxic levels in our patient is unclear although a number of plausible scenarios have been considered.

We used bupivacaine to establish the initial block, however, we do not think it contributed to the toxicity, due to the long duration of time from bupivacaine use to onset of toxicity.

Intravascular migration of the paravertebral catheter could have occurred. This would account for an increased rate of ropivacaine delivery into the plasma, leading to toxicity.

We think it is more likely that systemic local anaesthetic uptake may have been increased by the proximity of the block to areas with more vascularity, such as the tumour and pleural biopsy sites.

Our infusion rate of ropivacaine was reasonable based on pharmacokinetics.

The elimination half-life of ropivacaine has been quoted as 111 ± 62 min and clearance as 0.82 ± 0.16 L/min.⁹ Our dose of 20 mg/hour of ropivacaine (0.2 mg/kg/hour) would not normally be expected to cause toxicity. It has been found that the addition of epinephrine to ropivacaine in thoracic paravertebral blocks did result in lower peak plasma concentration and delayed systemic absorption. Use of epinephrine with ropivacaine in our institution could be considered in the future to broaden the safety margin of continuous blocks in our practice.¹⁰

The patient's albumin level was found to be 27 g/L at the time of the event, compared to 35 g/L preoperatively. That could have accounted for an increase in the free fraction of ropivacaine in the serum potentiating the observed toxicity.

Ropivacaine is metabolised extensively in the liver by cytochrome P450 1A2 (CYP1A2) and to a lesser extent cytochrome P450 3A4 (CYP3A4).¹¹ Ropivacaine's metabolism to 3-hydroxyropivacaine was impaired when CYP1A2 was inhibited by administration of fluvoxamine, a selective serotonin reuptake inhibitor.

Inhibition of CYP3A4 by fluconazole decreased the metabolism of ropivacaine to (S)-2',6'-pipecoloxylidide. The plasma clearance of ropivacaine with CYP1A2 inhibition was reduced from 354 mL/min to 112 mL/min (68%) versus CYP3A4 inhibition, which reduced plasma clearance to 302 mL/min (15%). Our patient was on amitriptyline, which is a known inhibitor of CYP1A2.¹² This could have decreased the metabolism of ropivacaine thereby increasing our patient's susceptibility to LAST.

It is also possible that the cessation of the ropivacaine infusion alone would have ameliorated the patient's symptoms.

However, our patient's symptoms did not completely subside after we ceased the ropivacaine infusion. This, coupled with a persistent tachycardia, prompted transfer to the intensive care unit and start of lipid rescue therapy to prevent progression of CNS symptoms and possible cardiovascular collapse.

Learning points

- ▶ There is a potential association between ropivacaine infusion and the occurrence of delayed local anaesthetic systemic toxicity (LAST). Vigilance is therefore called for to monitor for its development in patients undergoing a ropivacaine infusion.
- ▶ Lipid rescue treatment for LAST appeared to be effective in this situation.
- ▶ We recommend caution in selecting the location of a block as proximity to a tumour could conceivably accelerate systemic uptake of local anaesthetic.
- ▶ The association between amitriptyline and the development of LAST deserves further investigation.

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REFERENCES

- 1 Knudsen K, Beckman SM, Blomberg S, *et al.* Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;78:507–14.
- 2 Fagenholz PJ, Bowler GMR, Carnochan FM, *et al.* Systemic local anaesthetic toxicity from continuous thoracic paravertebral block. *Br J Anaesth* 2012;109:260–2.
- 3 Litz RJ, Popp M, Stehr SN, *et al.* Successful resuscitation of a patient with ropivacaine-induced asystole after axillary plexus block using lipid infusion. *Anaesthesia* 2006;61:800–1.
- 4 Liu SS, Ortolan S, Sandoval MV, *et al.* Cardiac arrest and seizures due to local anesthetic systemic toxicity after peripheral nerve blocks: should we still fear the reaper? *Reg Anesth Pain Med* 2016;41:5–21.
- 5 Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. *Br J Anaesth* 2006;96:418–26.
- 6 Weinberg GL. Lipid emulsion infusion: resuscitation for local anesthetic and other drug overdose. *Anesthesiology* 2012;117:180–7.
- 7 Neal JM, Mulroy MF, Weinberg GL. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity 2012 version. *Reg Anesth Pain Med* 2012;37:16–18.
- 8 Weinberg GL, VadeBoncouer T, Ramaraju GA, *et al.* Pretreatment or resuscitation with a lipid infusion shifts the dose-response to bupivacaine-induced asystole in rats. *Anesthesiology* 1998;88:1071–5.
- 9 McClure JH. Ropivacaine. *Br J Anaesth* 1996;76:300–7.
- 10 Karmakar MK, Ho AM, Law BK, *et al.* Arterial and venous pharmacokinetics of ropivacaine with and without epinephrine after thoracic paravertebral block. *Anesthesiology* 2005;103:704–11.
- 11 Arlander E, Ekström G, Alm C, *et al.* Metabolism of ropivacaine in humans is mediated by CYP1A2 and to a minor extent by CYP3A4: an interaction study with fluvoxamine and ketoconazole as in vivo inhibitors. *Clin Pharmacol Ther* 1998;64:484–91.
- 12 Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 2007;151:737–48.

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