



Ropivacaine and dexamethasone: a potentially dangerous combination for therapeutic pain injections

Trevor William Watkins,^{1,3} Simon Dupre^{2,3} and John Richard Coucher¹

1 Department of Medical Imaging, Princess Alexandra Hospital, Brisbane, Queensland, Australia

2 Department of Medical Imaging, Nambour General Hospital, Nambour, Queensland, Australia

3 University of Queensland, Brisbane, Queensland, Australia

TW Watkins BSc (Hons), MBBS, FRANZCR; **S Dupre** BSc, MBBS (Hons), FRANZCR; **JR Coucher** BSc, MBBS, MRCP, FRCR, FRANZCR.

Correspondence

Dr Trevor William Watkins, Department of Medical Imaging, Princess Alexandra Hospital, Ipswich Rd, Woolloongabba, Qld 4102, Australia.

Email: trevor.watkins@health.qld.gov.au

Conflict of Interest: The authors have none to declare.

Submitted 8 March 2015; accepted 11 May 2015.

doi:10.1111/1754-9485.12333

Abstract

Introduction: Targeted spinal steroid injections are effective in reducing back pain in selected patient populations and carry a small risk of significant adverse neurological outcomes. Recent recommendations are for the use of non-particulate steroid agents for all spinal injections to reduce the risk of neurovascular embolic adverse events. Many injections have used a combination of local anaesthetic agent with the steroid. At our institutions, we have recently observed interactions between ropivacaine and dexamethasone combinations ascribed to the incompatibility of the former with alkaline solutions, resulting in rapid crystallisation. This study has further investigated the combinations of commonly used local anaesthetic and steroid combinations to determine if such precipitation effects are more widespread.

Methods: The commonly used local anaesthetics (lignocaine, bupivacaine, ropivacaine) and the non-particulate steroid dexamethasone sodium phosphate combinations were evaluated macroscopically, microscopically, and pH values measured. Where crystallisation was observed the rate of precipitation and crystal size was measured. Contamination of ropivacaine with sodium bicarbonate solution was also evaluated. Particulate size of the particulate steroid agent betamethasone acetate was evaluated as a comparison.

Results: All mixtures of ropivacaine and the non-particulate dexamethasone sodium phosphate assessed demonstrated a pH-dependent crystallisation of the solution. No precipitation was demonstrated with the combinations of dexamethasone and lignocaine or bupivacaine. Contamination of ropivacaine with residual sodium bicarbonate in a drawing up needle following air clearing had a precipitation effect.

Conclusion: We describe the effect of crystallisation with the combination of ropivacaine and the non-particulate steroid, dexamethasone sodium phosphate, a mixture that has been used in the literature for targeted pain injections. As this may be considered a non-particulate steroid/anaesthetic injectate, this would potentially carry increased risk if inadvertent intravascular injection occurred during a targeted spinal injection, as has been described with particulate steroid agents. This is due to the elevated pH of dexamethasone and the incompatibility of ropivacaine with alkaline solutions.

Key words: anaesthetic, local; crystallisation; dexamethasone; injection, spinal; ropivacaine.

Introduction

Lumbar back pain is a common health problem affecting all age groups and increases in frequency with advancing age with a peak between ages 35 and 55. The estimated

lifetime prevalence of non-specific low back pain is 60–70% in developed countries and it carries a significant socioeconomic burden.¹ Targeted epidural, transforaminal and perineural steroid injections have been shown to be effective in reducing lumbar back pain with,

and without radiculopathy, and there is strong evidence showing the benefit of epidural steroid injection for treatment of lumbar back pain in a patient population with appropriate indications.^{2–6} Recently, there has been concern raised regarding the use of particulate steroids for spinal injections given the risk, albeit rare, of serious neurological adverse events ascribed to inadvertent neurovascular embolisation. Cases of cerebrovascular events, spinal cord injury, paralysis and death have been reported.^{7,8} In response, it has been suggested that the use of non-particulate steroids over particulate steroid agents should be considered for all targeted epidural, transforaminal and perineural spinal injections.⁹ Recent studies have demonstrated comparable efficacy between non-particulate and particulate steroids for spinal injections when appropriate dosages are utilised.^{10,11} At the authors' institutions, use of non-particulate steroids for all spinal epidural and perineural injections in combination with a local anaesthetic has commenced. A variety of anaesthetic–steroid mixtures are widely used for spinal, musculoskeletal and other pain-management procedures including targeted spinal injections and infusions. We have, however, observed that the combination of ropivacaine 0.75%, typically with 4 and 10 mg/mL concentrations of dexamethasone sodium phosphate results in rapid crystallisation in the non-particulate steroid/anaesthetic combination, even to the extent of occlusion of 22-G spinal needles. This is due to inadvertent alkalisation of ropivacaine. Furthermore, commonly used local anaesthetics (as mentioned earlier) are prepared with an acidic pH to maximise their water solubility and chemical stability,¹² and the pain associated with cutaneous/subcutaneous administration of local anaesthetics is largely ascribed to this low pH. To counter this, it is common practice to admix a small volume of sodium bicarbonate to the local anaesthetic solution to raise the pH, increase the local anaesthetic effect and lessen the discomfort,¹³ also a potential source for contamination of subsequently drawn up agents with an alkaline agent. This observation of crystallisation is concerning, given the basis of the shift from particulate to non-particulate agents for spinal injections to minimise the risk of significant neurological events. In this study, we have assessed the commonly used local anaesthetic and non-particulate steroid combinations in our centres. The authors caution readers regarding the use of such combinations for spinal perineural, transforaminal and epidural injections without thorough preliminary assessment to ensure such combinations are not precipitating, and thus negating the proposed risk reduction of significant neurological events with use of a non-particulate steroid.

Materials and methods

Routinely used particulate and non-particulate steroid and local anaesthetic agent combinations used at our

institutions were assessed macroscopically and microscopically.

Non-particulate steroid agent: dexamethasone presented as 4 and 10 mg/mL preparations (dexamethasone sodium phosphate, chemical formula $C_{22}H_{28}FNa_2O_8P$).

Particulate steroid agent: betamethasone acetate (Celestone Chronodose, MSD, Macquarie Park, NSW, Australia) presented as 5.7 mg/mL preparation (each millilitre containing 3.9 mg betamethasone sodium phosphate (in solution), chemical formula $C_{22}H_{28}FNa_2O_8P$, and 3 mg betamethasone acetate (in suspension), chemical formula $C_{24}H_{31}FO_6$).

Local anaesthetic agents: lignocaine 1% (lignocaine hydrochloride, chemical formula $C_{14}H_{22}N_2O.HCl.H_2O$); ropivacaine 0.75% (ropivacaine hydrochloride, chemical formula $C_{17}H_{26}N_2O.HCl.H_2O$); bupivacaine 0.25% (bupivacaine hydrochloride, chemical formula $C_{18}H_{28}N_2O.HCl$).

Combinations of these medications were prepared, mirroring those commonly used in clinical practice; 1 mL of each of the local anaesthetic agents was admixed with 1 mL of dexamethasone steroid (both 4 and 10 mg/mL). A preparation of 5 mL of ropivacaine 0.75% together with 0.5 mL of sodium bicarbonate 8.4% alkalising agent was also prepared. In addition, an 18-G drawing up needle that was first used to draw up sodium bicarbonate 8.4% and macroscopically 'cleaned out' by passing air through it via a syringe, was then applied to a clean syringe, which was subsequently used to draw up 1 mL of ropivacaine 0.75% local anaesthetic.

After formulating each of these preparations, several drops of each solution were placed onto a glass slide and observed under a microscope using low- and high-power fields for 15 min each. Combinations were also created directly on slides under continuous microscopic observation to monitor precipitation rate.

An electronic pH probe (Horiba Benchtop pH/Water Quality Analyzer LAQUA F-71, Horiba, Ltd., Kyoto, Japan) was used to measure the pH of ropivacaine 0.75%, dexamethasone 4 mg/mL, dexamethasone 10 mg/mL, 1 mL ropivacaine + 1 mL dexamethasone steroid (4 mg/mL) and 1 mL ropivacaine 0.75% + 1 mL dexamethasone steroid (10 mg/mL).

Betamethasone acetate (5.7 mg/mL) was examined under the same microscope to assess crystal size (microscope magnification calibrated against a ruler standard).

Results

The observation of crystals (subjectively on a 6-point ordinal scale with 0 = *no crystals*, 1(+) = *minimal crystallisation* to 5 (+++++) = *heavy crystallisation*), in each of the preparations under the microscope (up to 15 min) is documented in Table 1.

Non-particulate dexamethasone sodium phosphate when combined with ropivacaine showed prompt crystallisation at all concentration combinations tested.

Table 1. Subjective microscopic assessment of crystallisation up to 15 min

	Lignocaine 1%	Bupivacaine 0.5%	Ropivacaine 0.75%
Dexamethasone 4 mg/mL	Clear	Clear	Crystals +++
Dexamethasone 10 mg/mL	Clear	Clear	Crystals ++++
Sodium bicarbonate 8.4%	Clear	Clear	Crystals +++++
Grossly 'clean' 18-G needle used to draw up sodium bicarbonate 8.4%	Clear	Clear	Crystals +

Extent of crystallisation ranging from + (*minimal*) to +++++ (*heavy*).

Crystallisation began almost instantaneously, reaching near full size by 30 s, with minor growth observed between 1 and 3 min, without significant growth or breakdown between 3 and 15 min (Fig. 1). Macroscopically, the mixture had a slightly cloudy appearance, more pronounced with the higher concentration of dexamethasone (10 mg/mL), with a residual white film seen coating the plastic surfaces and syringe plunger (Fig. 2). With lower concentrations of dexamethasone, the macroscopic precipitation was less apparent, although discrete crystals were identifiable along the inner surfaces of the syringe. Average diameter of stellate crystals was in the range of 50–60 microns, with linear crystals measuring up to 100–120 microns. A pH-dependent relationship was observed with more pronounced crystallisation observed with the addition of the 10 mg/mL dexamethasone (pH 8.4) compared with 4 mg/mL (pH 8.2) concentrations. The size of the large particles in the particulate

steroid betamethasone was comparable with the crystal sizes observed with the ropivacaine and dexamethasone combinations (Fig. 3).

Severe precipitation of ropivacaine was observed with sodium bicarbonate 8.4% solution, forming a thick gelatinous compound virtually instantaneously, apparent both microscopically and macroscopically.

The 1 mL of ropivacaine drawn up with a grossly 'clean', but pre-used 18-G drawing up needle (previously used to draw up sodium bicarbonate 8.4%) into a fresh syringe also resulted in extensive crystal formation, with a lower number, but still apparent, both microscopically and macroscopically (Fig. 4).

Non-particulate dexamethasone sodium phosphate when combined with bupivacaine remained in solution at all concentration combinations tested.

The combination of lignocaine and sodium bicarbonate in addition to dexamethasone remained clear of crystals.

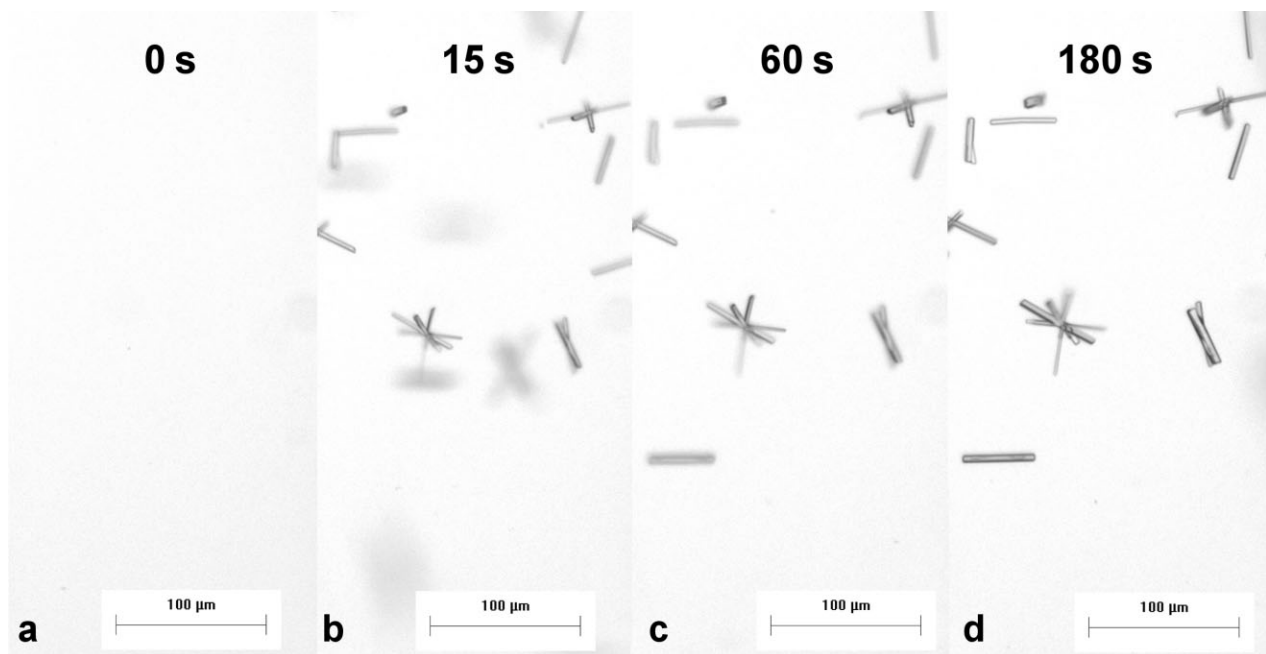


Fig. 1. Microscopic images (20x objective) demonstrating progressive crystallisation of ropivacaine 0.75% and dexamethasone 10 mg/mL combination over time: (a) $t = 0$ s; (b) $t = 15$ s; (c) $t = 60$ s; (d) $t = 180$ s.

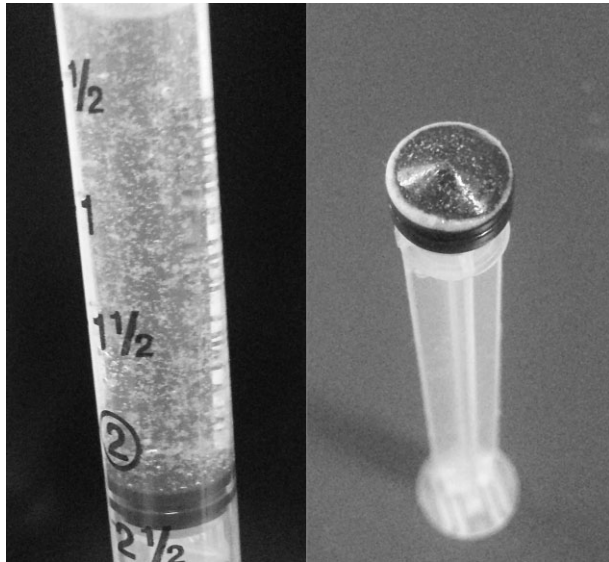


Fig. 2. Macroscopic appearance of ropivacaine 0.75% and dexamethasone 10 mg/mL combination after ~10 min showing obvious precipitation within solution and residual white film precipitate on the plunger.

The particles in betamethasone steroid (5.7 mg/mL) measured up to a maximum of 50 microns, with the majority measuring 10–30 microns.

The pH values of the mixtures were as follows: 1 mL ropivacaine 0.75% + 1 mL dexamethasone (4 mg/mL) pH = 6.8, and 1 mL ropivacaine 0.75% + 1 mL dexamethasone (10 mg/mL) pH = 7.0. The pH of ropivacaine 0.75% in isolation was pH 5.3, reflecting the product disclosure statement of all local anaesthetics which are prepared in the acidic range. Conversely, sodium bicarbonate 8.4% was alkaline, with a pH of 8.0. The measured pH of dexamethasone 4 and 10 mg/mL was 8.2 and 8.4, respectively.

Discussion

Targeted epidural, transforaminal and perineural steroid injections are commonly used for treatment of back pain in patients, and there is strong evidence supporting their efficacy when utilised in an appropriate patient population with appropriate indications.^{2–6} As with any interventional procedure, the risk profile includes, although usually uncommon, a number of potential severe adverse outcomes. Spinal cord injury, infarction, paralysis and death are a number of the serious neurological adverse effects that fall into the arena of targeted spinal injections.^{14–16} Inadvertent intravascular injection, in particular into a radiculomedullary artery, is believed to be a primary cause of a number of serious adverse effects reported with spinal injections, particularly with particulate agents; however, the overall rate of severe complications remains small. Spinal cord injury following

targeted pain injections have been documented following transforaminal epidural and perineural injections, and to the best of the authors' knowledge, there are no reports of such adverse effects with non-particulate steroid agents or when an interlaminar epidural technique is utilised in a patient without a history of spinal surgery.^{7,14,17–19} Our findings with ropivacaine and non-particulate dexamethasone combinations producing crystallisation are concerning and would theoretically carry the same intravascular injection risk as seen with particulate steroid agents. This finding further supports the pharmacological principle that a combination of drugs should be considered incompatible, until proven compatible.

Some institutions, including our own, have preferentially used ropivacaine over the previously used alternative agent bupivacaine for steroid/local anaesthetic targeted injections. This transition was based on the improved cardiovascular risk profile of ropivacaine in the setting of inadvertent intravascular injection,²⁰ and

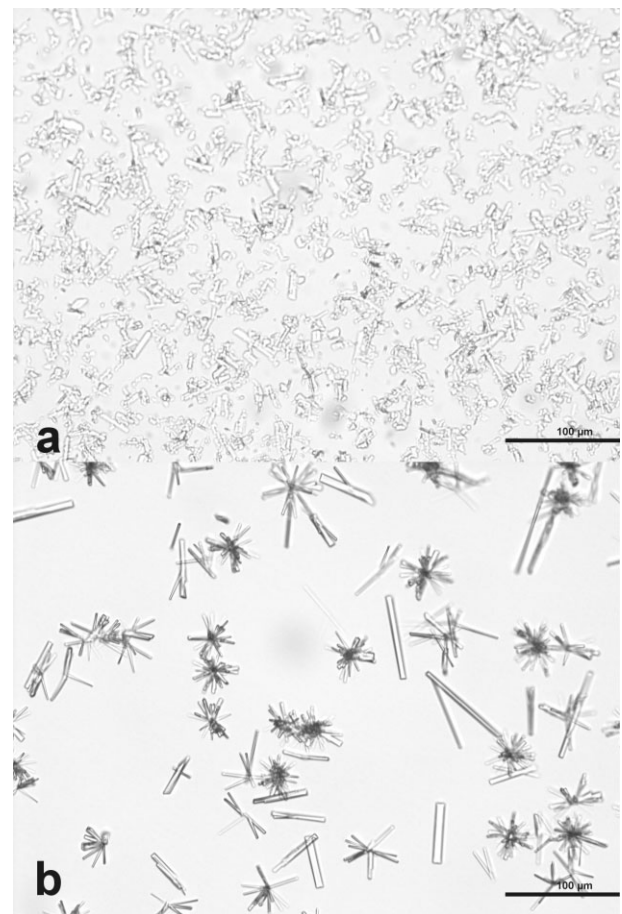


Fig. 3. Microscopic images (20x objective) showing relative particulate size between (a) betamethasone acetate and (b) dexamethasone 4 mg/mL and ropivacaine 0.75% combination.

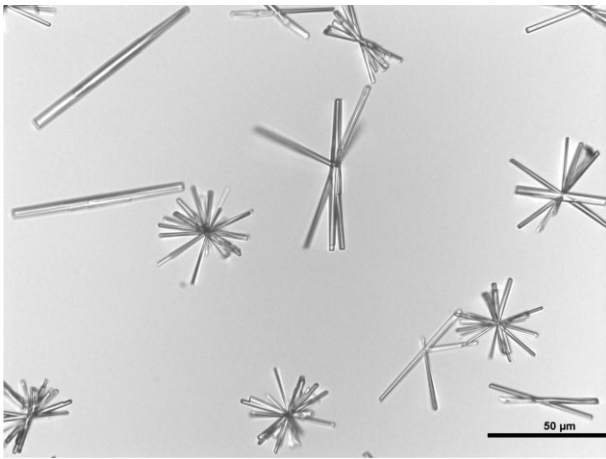


Fig. 4. Microscopic image (40× objective) of crystal formation in ropivacaine 0.75% following contamination with residual sodium bicarbonate 8.4% solution remaining in a 'grossly' clean 18-G drawing up needle.

previous reports of intraarticular injections of bupivacaine and lidocaine demonstrating increased chondrotoxicity relative to ropivacaine; however, in the latter, the clinical relationship of these findings is less well defined.^{21–24} The combination of ropivacaine and both particulate and non-particulate steroid agents, has been used for both various spinal and musculoskeletal diagnostic and therapeutic injections, with reports in the literature of such combinations being used for pain injections and infusions.^{25–30}

The combination of concern is that of ropivacaine and alkaline solutions, a category that dexamethasone sodium phosphate falls into with a pH of 8.0. This has been previously described in the literature when evaluating alkalinising local anaesthetic agents, with reports of ropivacaine precipitating at a pH of 6.0 and above.³¹ Fulling *et al.* demonstrated that the proportion of non-ionised ropivacaine increased with alkalinisation, although only achieving modest precipitation with the concentrations used in their study.³² We observed all concentration combinations used clinically at our institutions for both ropivacaine and dexamethasone, given the alkaline pH of dexamethasone showing a pronounced dose-dependent crystallisation, with higher concentrations producing obvious macroscopic precipitates in the injectate. We observed that the lower concentrations of dexamethasone with the standard ropivacaine concentration used at our institutions resulted in microscopically appreciable crystallisation, which was barely visible macroscopically, however, was still apparent. The incompatibility of ropivacaine with alkaline solutions was further confirmed with sodium bicarbonate, as has been previously been reported,^{31,32} showing a pH-dependent precipitation increasing from 0.3% to greater than 30% with pH increasing from 5.51 to 7.63. Increasing time also contributed to the extent of precipitation, and in their study,

Fulling *et al.* suggested that there was a low likelihood of substantial drug precipitation after alkalinisation of ropivacaine with low doses of bicarbonate if the mixture was administered within 5–10 min. We, however, observed rapid crystallisation occurring with the typical concentrations of dexamethasone and ropivacaine used in our clinical practice, with macroscopically apparent precipitates evident almost instantaneously with the 10 mg/mL dexamethasone and 0.75% ropivacaine 1:1 combination attributed to the alkalinisation of the resultant mixture (pH 7.0). Lower concentrations of dexamethasone (4 mg/mL) combined with 0.75% ropivacaine in a 1:1 mixture showed a slight delay, and subjectively reduced extent of precipitation, corresponding to the relatively decreased pH of the mixture (pH 6.8). Although Melton *et al.* reported stability of ropivacaine–dexamethasone admixture using nuclear magnetic resonance analysis, this was with volumes not reflective of those typically utilised in clinical practice (–9:1 ratio of ropivacaine 0.5%:dexamethasone 4 mg/mL). This likely would not have achieved the required alkalinisation to achieve crystallisation.³³ We did not observe any such crystallisation or precipitation with combinations of dexamethasone and bupivacaine or lignocaine, which remains concordant with other studies.^{34,35}

The practice of alkalinising local anaesthetics with sodium bicarbonate is known to increase the speed of onset of nerve blocks and minimise initial discomfort with cutaneous/subcutaneous local anaesthetic injection.^{11,12} Local anaesthetics are weak bases presented in an acidic solution for solubility and to prolong shelf life. The proportion of the non-ionised form of local anaesthetics increases with elevated pH, and it is believed that this form crosses neural membranes more readily, thus increasing its rate of action in addition to increasing the pH.^{11,12} Even the small volumes of sodium bicarbonate more typically used for alkalinisation of lignocaine were shown to cause rapid precipitation when mixed with ropivacaine. We further tested the possibility of residual sodium bicarbonate in an 18-G drawing up needle, should the same needle be used to aspirate ropivacaine after alkalinising another agent, and this also produced microscopic precipitation.

Interestingly, in the literature, there are reports of improved efficacy with ropivacaine and dexamethasone mixtures. This may relate to the effects of alkalinisation of local anaesthetic agents and their non-ionised proportions; however, the crystallisation may also be contributing to the observed improved efficacy, potentially acting in a similar fashion to particulate steroid agents.

Conclusion

We describe the effect of crystallisation with the combination of ropivacaine and the non-particulate steroid, dexamethasone sodium phosphate, a mixture that has

been used in the literature for targeted pain injections. As this may be considered a non-particulate steroid/anaesthetic injectate, this would potentially carry increased risk if inadvertent intravascular injection occurred during a targeted spinal injection, as has been described with particulate steroid agents. This is due to the elevated pH of dexamethasone and the incompatibility of ropivacaine with alkaline solutions. We did not observe any such crystallisation or precipitation with dexamethasone and bupivacaine or lignocaine, which would be the more appropriate choice for situations where non-particulate agents are required. Thorough assessment of any medication mixture prior to use in clinical practice is essential, particularly when precipitation of a solution, such as in spinal injections could result in severe adverse outcomes. Although, incompatibility of ropivacaine with alkaline solutions is referred to in available drug information, no specific comment is made of the relevance of this information with respect to common injectable steroid formulations, which potential users may consider using together. Clarifying this information would help improve patient safety.

Acknowledgements

We would like to acknowledge Dr Andrew Dettrick MBBS, FRCPA and Dr Joanna Perry-Keene MBBS, FRCPA from the Pathology Department at the Nambour General Hospital and Associate Professor Andrew van Eps, BVSc, PhD, MACVSc, DACVIM from the University of Queensland Equine Hospital, for their assistance with reagents, medications and laboratory equipment.

References

- Duthey B. Update on 2004 Background Paper, BP 6.24 Low Back pain. World Health Organisation. Priority Medicines for Europe and the world 'A Public Health Approach to Innovation'. 2013.
- Abdi S, Datta S, Trescot AM *et al.* Epidural steroids in the management of chronic spinal pain: a systematic review. *Pain Physician* 2007; **10**: 185–212.
- Kaufmann TJ, Geske JR, Murthy NS *et al.* Clinical effectiveness of single lumbar transforaminal epidural steroid injections. *Pain Med* 2013; **14**: 1126–33.
- MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. *Pain Med* 2013; **14**: 14–28.
- Riew KD, Park JB, Cho YS *et al.* Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006; **88**: 1722–5.
- Roberts ST, Willick SE, Rho ME, Rittenberg JD. Efficacy of lumbosacral transforaminal epidural steroid injections: a systematic review. *PM R*. 2009; **1**: 657–68.
- Kennedy DJ, Levin J, Rosenquist R *et al.* Epidural steroid injections are safe and effective: multisociety letter in support of the safety and effectiveness of epidural steroid injections. *Pain Med* 2015; **16**: 833–8.
- Racoosin J, Seymour S, Roca R, Hertz S. FDA Briefing Document. Anesthetic and Analgesic Drug Products Advisory Committee Meeting. Epidural steroid injections (ESI) and the risk of serious neurologic adverse reactions. Food and Drug Administration, Center for Drug and Evaluation and Research. [Cited 24–25 November 2014.] Available from URL: <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM422692.pdf>.
- The Royal Australian and New Zealand College of Radiologists. Australian Musculoskeletal Imaging Group. Faculty of Clinical Radiology Communiqué to All Members. Risk of Spinal Cord Injuries from Nerve Root Blocks. [Cited 3 November 2014]. Available from URL: <http://www.vision6.com.au/em/message/email/view.php?id=1145393&u=22768>.
- El-Yahchouchi C, Geske JR, Carter RE *et al.* The noninferiority of the nonparticulate steroid dexamethasone vs the particulate steroids betamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. *Pain Med* 2013; **14**: 1650–7.
- Kennedy DJ, Plastaras C, Casey E *et al.* Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. *Pain Med* 2014; **15**: 548–55.
- Brandis K. Alkalinisation of local anaesthetic solutions. *Aust Prescr*. 2011; **34**: 173–5.
- Mutalik S. How to make local anesthesia less painful. *J Cutan Aesthet Surg*. 2008; **1**: 37–8.
- Cook TM, Counsell D, Wildsmith JA, Royal College of Anaesthetists Third National Audit P. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009; **102**: 179–90.
- Somayaji HS, Saifuddin A, Casey AT, Briggs TW. Spinal cord infarction following therapeutic computed tomography-guided left L2 nerve root injection. *Spine* 2005; **30**: E106–8.
- Suresh S, Berman J, Connell DA. Cerebellar and brainstem infarction as a complication of CT-guided transforaminal cervical nerve root block. *Skeletal Radiol* 2007; **36**: 449–52.
- Abbasi A, Malhotra G, Malanga G, Elovic EP, Kahn S. Complications of interlaminar cervical epidural steroid injections: a review of the literature. *Spine* 2007; **32**: 2144–51.
- Ma DJ, Gilula LA, Riew KD. Complications of fluoroscopically guided extraforaminal cervical nerve

- blocks. An analysis of 1036 injections. *J Bone Joint Surg Am* 2005; **87**: 1025–30.
19. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Fellows B. A prospective evaluation of complications of 10,000 fluoroscopically directed epidural injections. *Pain Physician* 2012; **15**: 131–40.
 20. Kuthiala G, Chaudhary G. Ropivacaine: a review of its pharmacology and clinical use. *Indian J Anaesth* 2011; **55**: 104–10.
 21. Chu CR, Coyle CH, Chu CT *et al*. In vivo effects of single intra-articular injection of 0.5% bupivacaine on articular cartilage. *J Bone Joint Surg Am* 2010; **92**: 599–608.
 22. Chu CR, Izzo NJ, Papas NE, Fu FH. In vitro exposure to 0.5% bupivacaine is cytotoxic to bovine articular chondrocytes. *Arthroscopy* 2006; **22**: 693–9.
 23. Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. *J Bone Joint Surg Am* 2008; **90**: 986–91.
 24. Piper SL, Kramer JD, Kim HT, Feeley BT. Effects of local anesthetics on articular cartilage. *Am J Sports Med* 2011; **39**: 2245–53.
 25. Chipde S, Banjare M, Arora K, Saraswat M. Prospective randomized controlled comparison of caudal bupivacaine and ropivacaine in pediatric patients. *Ann Med Health Sci Res* 2014; **4** (Suppl. 2): S115–18.
 26. Evaristo-Mendez G, Garcia de Alba-Garcia JE, Sahagun-Flores JE *et al*. Analgesic efficacy of the incisional infiltration of ropivacaine vs ropivacaine with dexamethasone in the elective laparoscopic cholecystectomy. *Cir Cir* 2013; **81**: 383–93.
 27. Yousef GT, Ibrahim TH, Khder A, Ibrahim M. Enhancement of ropivacaine caudal analgesia using dexamethasone or magnesium in children undergoing inguinal hernia repair. *Anesth Essays Res* 2014; **8**: 13–19.
 28. Goravanchi F, Kee SS, Kowalski AM, Berger JS, French KE. A case series of thoracic paravertebral blocks using a combination of ropivacaine, clonidine, epinephrine, and dexamethasone. *J Clin Anesth* 2012; **24**: 664–7.
 29. Kim EM, Lee JR, Koo BN, Im YJ, Oh HJ, Lee JH. Analgesic efficacy of caudal dexamethasone combined with ropivacaine in children undergoing orchiopexy. *Br J Anaesth* 2014; **112**: 885–91.
 30. Rasmussen SB, Saied NN, Bowens C Jr, Mercaldo ND, Schildcrout JS, Malchow RJ. Duration of upper and lower extremity peripheral nerve blockade is prolonged with dexamethasone when added to ropivacaine: a retrospective database analysis. *Pain Med* 2013; **14**: 1239–47.
 31. Milner QJ, Guard BC, Allen JG. Alkalinization of amide local anesthetics by addition of 1% sodium bicarbonate solution. *Eur J Anaesthesiol* 2000; **17**: 38–42.
 32. Fulling PD, Peterfreund RA. Alkalinization and precipitation characteristics of 0.2% ropivacaine. *Reg Anesth Pain Med* 2000; **25**: 518–21.
 33. Melton MS, Sposito J, Riberio A, Nielsen K, Tucker M, Kein S. Determination of Compatibility and Stability of a Ropivacaine–Dexamethasone Admixture using Nuclear Magnetic Resonance Analysis [abstract]. In: *Anesthesiology 2011: Program and abstracts of American Society of Anesthesiologists Annual Meeting, October 15–19, 2011 Chicago, Illinois*. 2011.
 34. Derby R, Lee SH, Date ES, Lee JH, Lee CH. Size and aggregation of corticosteroids used for epidural injections. *Pain Med* 2008; **9**: 227–34.
 35. MacMahon PJ, Shelly MJ, Scholz D, Eustace SJ, Kavanagh EC. Injectable corticosteroid preparations: an embolic risk assessment by static and dynamic microscopic analysis. *AJNR Am J Neuroradiol* 2011; **32**: 1830–5.