Ropivacaine Pharmacokinetics After Local Infiltration Analgesia in Hip Arthroplasty

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In this study, we determined the plasma concentration of ropivacaine by liquid chromatography-mass spectrometry for 30 hours after local infiltration analgesia in 15 patients with elective hip arthroplasty. The 95% upper prediction bound of maximal unbound plasma concentration of ropivacaine was 0.032 mg/L. Side effects sufficient to stop an IV infusion have been reported at arterial concentrations of 0.34 to 0.85 mg/L. Alpha-1-acid glycoprotein did not correlate with the fraction of unbound ropivacaine during the first 24 hours after local infiltration analgesia. No signs or symptoms of systemic local anesthetic toxicity were observed. The Clopper-Pearson 95% upper confidence limit for adverse signs was 0.218. (Anesth Analg 2014;XXX:00–00)

Local infiltration analgesia with ropivacaine, ketorolac, and epinephrine is a technically simple method for postoperative pain management after knee and hip replacement,[1] which has gained popularity in many countries.[2] Local infiltration analgesia not only improves postoperative pain but also reduces the need for opioid analgesic drugs and leads to faster rehabilitation and earlier discharge from hospital.[3–7] Information regarding the pharmacokinetics and safety margin of ropivacaine and area under the curve after local infiltration analgesia is still sparse. Ropivacaine binds mainly to alpha-1-acid glycoprotein (AAG),[8] a plasma protein, which increases during trauma.[8–14]

A generalized grand mal seizure has been reported at an IV concentration of 3.68 mg/L of ropivacaine, 15 minutes after an ultrasound-guided and peripheral nerve stimulator–assisted interscalene brachial plexus blockade, with no sign of intravascular placement, with 75 mg of ropivacaine, a dose considered to be safe.[15] Large surgical incisions and soft-tissue dissection, typical of major orthopedic surgery, may lead to peak plasma levels of local anesthetics[16] with increased risk for central nervous system and cardiovascular toxicity.[17]

The aim of this study was to determine the maximal plasma concentration of unbound ropivacaine for 30 hours after elective primary total hip arthroplasty using local infiltration analgesia for postoperative analgesia. In addition, we assessed whether the level of AAG during the first postoperative day after local infiltration analgesia correlates with the fraction of unbound ropivacaine.

METHODS

This study, conducted between 2010 and 2011, was approved by the IRB and the medical product agency of Sweden. This study was conducted with written informed consent from the study subjects. We included 15 adult patients, ASA grade I to III, without allergies to any of the study drugs, creatinine plasma concentration <100 mmol/L, and QT-interval <450 milliseconds. Access to research staff limited inclusion of patients. No eligible patient refused participation.

All patients had spinal anesthesia at L2-L3 or L3-L4 with isobaric bupivacaine (Marcain Spinal®, AstraZeneca, Stockholm, Sweden). Local infiltration analgesia consisted of peri- and intra-articular infiltration with a mixture of 100 mL ropivacaine (2 mg/mL; Narop®, AstraZeneca), 1 mL ketorolac (30 mg/mL; Toradol®, Roche), and 5 mL epinephrine (0.1 mg/mL; Adrenalin®, NM Pharma): 20 mL was injected subcutaneously at the start of the operation and the remaining 86 mL in the capsula, the resutured short outward rotators and the gluteus maximus.

Quantification of Total and Unbound Ropivacaine

Sampling started 10 minutes after completing local infiltration analgesia at 10, 20, 30, 45 minutes and 1, 2, 3, 4, 6, 8, 12, 24, and 30 hours, respectively. Liquid chromatography-mass spectrometry (Agilent 1100 MSD; Agilent Technologies, CA) was used. The limits of quantification were 0.0053 to 2.66 mg/L. The internal standard was doxepine (Sigma-Aldrich, St. Louis, MD). The unbound ropivacaine concentration was determined after centrifugation at 5500*g* for 10 minutes at 37°C using an Amicon ULTRA centrifugal filter.

Quantification of AAG

Plasma AAG, collected before moving the patient to the operating room and 1, 4, 12, and 24 hours after surgery, was analyzed with nephelometry (IMMAGE by Beckman Coulter, Stockholm, Sweden).

Safety Monitoring

Electrocardiograph changes and neurological symptoms of local anesthetic toxicity were monitored according to clinical routine.

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Statistics

This pilot study without prior power calculation used a sample size of 15 based on previous experience.[18] Prism 6.0 software (GraphPad Software, San Diego, CA) was used to calculate area under the curve. The upper prediction bound for maximal unbound ropivacaine was 2.22 SD based on normal distribution. Since zero adverse events were observed, we calculated the Clopper-Pearson exact value.[19] Statistica 12 (StatSoft, Tulsa, OK) was used to calculate linear correlation and estimate the statistical power. $P < 0.05$ and a power of at least 80% were required to draw any conclusion on correlation.

RESULTS

All patients completed the study. Demographic data and individual results are presented in Table 1, the pharmacokinetic profile for ropivacaine in Figure 1, the AAG profile over time in Figure 2, and percentage of unbound ropivacaine versus AAG in Figure 3, respectively. The 95% upper prediction bound for unbound ropivacaine was 0.032 mg/L. The statistical power of the linear correlation of maximal concentration versus age or creatinine clearance was 53% and 50%, respectively. Neither tachycardia, nor arrhythmias on electrocardiogram, nor neurological signs of local anesthetic toxicity (circumoral paresthesia, tinnitus, muscle twitch, or seizure) were detected. The Clopper-Pearson 95% upper confidence limit for adverse signs was 0.218.

Two hours after surgery, no prolongation of QT-interval >450 milliseconds was observed in any patient.

DISCUSSION

The 95% upper prediction bound for maximal unbound plasma concentration after injection of 200 mg ropivacaine in local infiltration analgesia was 0.032 mg/L. This level is comparable with levels observed after local infiltration analgesia without epinephrine[20] and half as high as after 400 mg.[21] Plasma concentrations within the same range,[22–27] or considerably higher,[28,29] without adverse reactions have been reported during epidural infusion or peripheral nerve block with ropivacaine. Side effects sufficient to stop an IV infusion were reported at arterial concentrations of 0.34 to 0.85 mg/L.[30] This range has been considered a relevant safety limit in studies reporting the venous plasma concentration of unbound ropivacaine.[26,29]

With increasing age, total body water, peripheral circulation, and renal function decrease.[31] These changes may affect the pharmacokinetics of ropivacaine after local infiltration analgesia. Using a 2-sided test based on our data, at least 29 individuals are needed to get a power of 80% to test the hypotheses that the maximal unbound ropivacaine concentration correlates with age and creatinine clearance. Thus, our sample size of 15 individuals was insufficient to test this hypothesis.

Ropivacaine binds mainly to AAG,[12,14] but previous studies on ropivacaine after local infiltration analgesia[16,21,32] have not reported the plasma level of AAG. We detected AAG levels similar to those in young healthy adults.[33] After 24 hours, AAG had increased by <40%. However, we did not find any correlation between the plasma concentration of AAG and the percentage of unbound plasma concentration of ropivacaine during the first 24 hours after local infiltration analgesia. AAG levels may double approximately 4 days postoperatively and seem to reach a maximal concentration at postoperative days 6 to 12.[11,13] An increase of AAG sufficient to decrease the unbound concentration of ropivacaine has been observed later than 24 hours after surgical trauma.[8,22,28,34] Not only the unbound plasma concentration but also physiological, anatomical, and pharmacokinetic factors contribute to toxicity of local anesthetic.[35]

CONCLUSIONS

The unbound ropivacaine concentration after 200 mg of ropivacaine administered during local infiltration analgesia seems to be below plasma concentrations linked to adverse cardiac or neurological reactions in the patient population included in this study. Inclusion of more elderly patients with decreased renal function is needed to determine cutoff levels for decreased doses of ropivacaine in local infiltration analgesia required for safety concerns. AAG levels are of minor importance for unbound ropivacaine plasma concentration during the first 24 hours after total hip arthroplasty

Table 1. Patient Demographics and Results

Patient number and sex	ASA	Age (y)	Weight (kg)	BMI (kg/m²)	CC (mL/min)	C_{max} unbound (mg/L)	C_{max} total (mg/L)	AUC unbound for 0–30 h (h × mg/L)	T_{max} unbound (h)
1 M	I	65	89	29	82	0.016	0.578	—	4
2 F	I	58	63	24	106	0.013	0.769	0.180	2
3 M	II	54	90	28	134	0.022	0.672	0.317	4
4 M	II	85	75	27	58	0.018	0.995	0.229	4
5 F	I	32	62	24	143	0.015	0.443	0.268	8
6 F	I	35	74	26	150	0.005	0.505	0.075	1
7 F	III	75	100	32	75	0.018	0.872	0.328	12
8 M	III	61	105	36	140	0.023	0.877	0.316	6
9 M	III	79	90	28	62	0.018	1.356	0.290	4
10 M	II	72	83	25	108	0.021	0.754	0.327	4
11 F	III	76	106	40	69	0.026	0.686	0.272	8
12 F	III	71	107	35	98	0.018	0.576	0.313	6
13 F	III	58	106	38	101	0.016	0.548	0.320	6
14 M	III	70	71	24	66	0.031	1.333	0.335	6
15 M	II	65	95	24	159	0.012	0.448	—	4

CC = creatinine clearance was calculated according to Cockroft-Gould; C_{max} = maximum concentration; T_{max} = time to maximum concentration; BMI = body mass index; AUC = area under the curve; M = male; F = female.

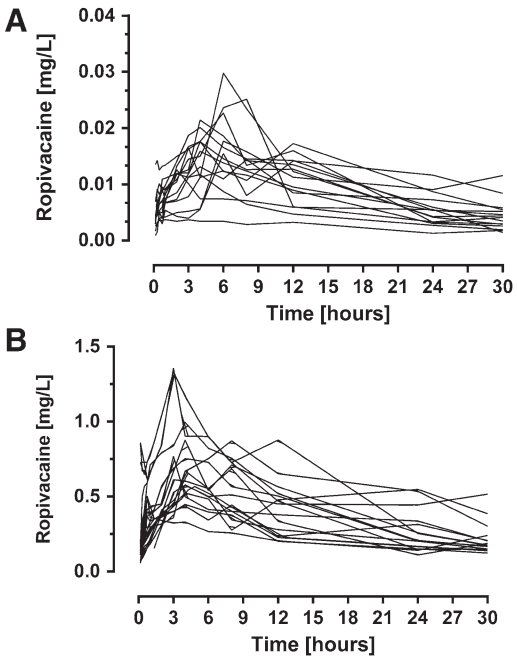

Figure 1. Individual data of unbound (A) and total (bound and unbound) (B) plasma concentrations versus time for 30 hours after local infiltration analgesia. The lower limit of the maximal tolerated arterial concentration of ropivacaine at the end of an infusion of 10 mg/min in healthy volunteers is 0.34 mg/L.[33]

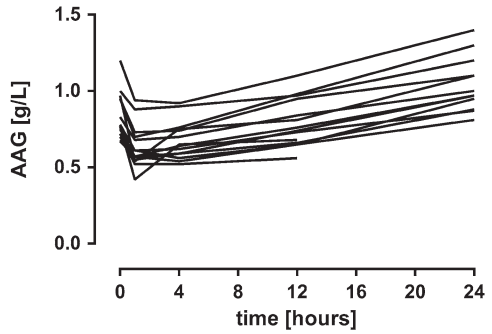

Figure 2. Individual plasma concentrations of alpha-1-acid glycoprotein (AAG) versus time profile (24 hours) in 14 patients. Time zero "0" indicates a baseline sample before surgery.

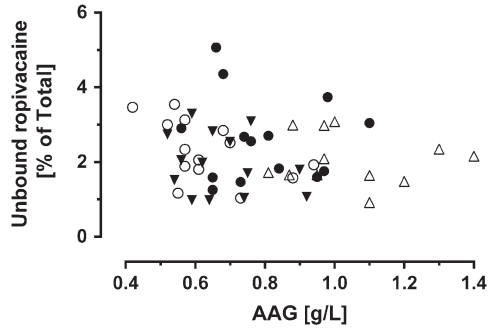

Figure 3. Unbound fraction of ropivacaine at different concentrations of alpha-1-acid glycoprotein (AAG) at 1 hour after surgery (open circle), at 4 hours after surgery (filled circle), at 12 hours (filled triangle), and 24 hours (open triangle) in 14 patients.

with local infiltration analgesia. Larger studies are needed to test the hypothesis that the unbound ropivacaine concentration correlates with age and creatinine clearance.

DISCLOSURES

Name: Fatin Affas, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Fatin Affas has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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REFERENCES

1. Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. Acta Orthop 2008;79:174–83
2. Kehlet H, Andersen LØ. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. Acta Anaesthesiol Scand 2011;55:778–84
3. Tanaka N, Sakahashi H, Sato E, Hirose K, Ishii S. The efficacy of intra-articular analgesia after total knee arthroplasty in patients with rheumatoid arthritis and in patients with osteoarthritis. J Arthroplasty 2001;16:306–11
4. Busch CA, Shore BJ, Bhandari R, Ganapathy S, MacDonald SJ, Bourne RB, Rorabeck CH, McCalden RW. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. J Bone Joint Surg Am 2006;88:959–63
5. Vendittoli PA, Makinen P, Drolet P, Lavigne M, Fallaha M, Guertin MC, Varin F. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. J Bone Joint Surg Am 2006;88:282–9
6. Husted H, Solgaard S, Hansen TB, Søballe K, Kehlet H. Care principles at four fast-track arthroplasty departments in Denmark. Dan Med Bull 2010;57:A4166
7. Liu W, Cong R, Li X, Wu Y, Wu H. Reduced opioid consumption and improved early rehabilitation with local and intraarticular

cocktail analgesic injection in total hip arthroplasty: a randomized controlled clinical trial. Pain Med 2011;12:387–93
8. Erichsen CJ, Sjövall J, Kehlet H, Hedlund C, Arvidsson T. Pharmacokinetics and analgesic effect of ropivacaine during continuous epidural infusion for postoperative pain relief. Anesthesiology 1996;84:834–42
9. Aronsen KF, Ekelund G, Kindmark CO, Laurell CB. Sequential changes of plasma proteins after surgical trauma. Scand J Clin Lab Invest Suppl 1972;124:127–36
10. Tucker GT. Pharmacokinetics of local anaesthetics. Br J Anaesth 1986;58:717–31
11. Edwards DJ, Lalka D, Cerra F, Slaughter RL. Alpha1-acid glycoprotein concentration and protein binding in trauma. Clin Pharmacol Ther 1982;31:62–7
12. Lee A, Fagan D, Lamont M, Tucker GT, Halldin M, Scott DB. Disposition kinetics of ropivacaine in humans. Anesth Analg 1989;69:736–8
13. Wulf H, Worthmann F, Behnke H, Böhle AS. Pharmacokinetics and pharmacodynamics of ropivacaine 2 mg/mL, 5 mg/mL, or 7.5 mg/mL after ilioinguinal blockade for inguinal hernia repair in adults. Anesth Analg 1999;89:1471–4
14. Yokogawa K, Shimomura S, Ishizaki J, Shimada T, Fukuwa C, Kawada M, Tsubokawa T, Yamamoto K, Miyamoto K. Involvement of alpha1-acid glycoprotein in inter-individual variation of disposition kinetics of ropivacaine following epidural infusion in off-pump coronary artery bypass grafting. J Pharm Pharmacol 2007;59:67–73
15. Dhir S, Ganapathy S, Lindsay P, Athwal GS. Case report: ropivacaine neurotoxicity at clinical doses in interscalene brachial plexus block. Can J Anaesth 2007;54:912–6
16. Bianconi M, Ferraro L, Traina GC, Zanoli G, Antonelli T, Guberti A, Ricci R, Massari L. Pharmacokinetics and efficacy of ropivacaine continuous wound instillation after joint replacement surgery. Br J Anaesth 2003;91:830–5
17. Shipton EA. New formulations of local anaesthetics-part I. Anesthesiol Res Pract 2012;2012:546409
18. Affas F, Stiller C-O, Nygårds E-B, Stephanson N, Wretenberg P, Olofsson C. A randomized study comparing plasma concentration of ropivacaine after local infiltration analgesia and femoral block in primary total knee arthroplasty. Scand J Pain 2012;3:46–51
19. McCracken CE, Looney SW. A comparison of methods for finding the upper confidence limit for a binomial proportion when zero successes are observed. Proceedings of the American Statistical Association; 2011:2876–90
20. Breindahl T, Simonsen O, Hindersson P, Brødsgaard Dencker B, Brouw Jørgensen M, Rasmussen S. Autologous blood transfusion after local infiltration analgesia with ropivacaine in total knee and hip arthroplasty. Anesthesiol Res Pract 2012;2012:458795
21. Busch CA, Whitehouse MR, Shore BJ, MacDonald SJ, McCalden RW, Bourne RB. The efficacy of periarticular multimodal drug infiltration in total hip arthroplasty. Clin Orthop Relat Res 2010;468:2152–9
22. Burm AG, Stienstra R, Brouwer RP, Emanuelsson BM, van Kleef JW. Epidural infusion of ropivacaine for postoperative analgesia after major orthopedic surgery: pharmacokinetic evaluation. Anesthesiology 2000;93:395–403
23. Ekatodramis G, Borgeat A, Huledal G, Jeppsson L, Westman L, Sjövall J. Continuous interscalene analgesia with ropivacaine 2 mg/ml after major shoulder surgery. Anesthesiology 2003;98:143–50
24. Meyer M, Siauw PT, Scholz G, Frey DJ. Plasma concentrations and analgesic effects of ropivacaine 3.75 mg/ml during long-term extrapleural analgesia after thoracotomy. Reg Anesth Pain Med 2005;30:356–62
25. Corso OH, Morris RG, Hewett PJ, Karatassas A. Safety of 96-hour incision-site continuous infusion of ropivacaine for postoperative analgesia after bowel cancer resection. Ther Drug Monit 2007;29:57–63
26. Schoenmakers KP, Vree TB, Jack NT, van den Bemt B, van Limbeek J, Stienstra R. Pharmacokinetics of 450 mg ropivacaine with and without epinephrine for combined femoral and sciatic nerve block in lower extremity surgery. A pilot study. Br J Clin Pharmacol 2013;75:1321–7
27. Pettersson N, Emanuelsson BM, Reventlid H, Hahn RG. High-dose ropivacaine wound infiltration for pain relief after inguinal hernia repair: a clinical and pharmacokinetic evaluation. Reg Anesth Pain Med 1998;23:189–96
28. Wiedemann D, Mühlnickel B, Staroske E, Neumann W, Röse W. Ropivacaine plasma concentrations during 120-hour epidural infusion. Br J Anaesth 2000;85:830–5
29. Bleckner LL, Bina S, Kwon KH, McKnight G, Dragovich A, Buckenmaier CC 3rd. Serum ropivacaine concentrations and systemic local anesthetic toxicity in trauma patients receiving long-term continuous peripheral nerve block catheters. Anesth Analg 2010;110:630–4
30. Knudsen K, Beckman Suurküla M, Blomberg S, Sjövall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997;78:507–14
31. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 2009;41:67–76
32. Stringer BW, Singhania AK, Sudhakar JE, Brink RB. Serum and wound drain ropivacaine concentrations after wound infiltration in joint arthroplasty. J Arthroplasty 2007;22:884–92
33. Kremer JM, Wilting J, Janssen LH. Drug binding to human alpha-1-acid glycoprotein in health and disease. Pharmacol Rev 1988;40:1–47
34. Scott DA, Emanuelsson BM, Mooney PH, Cook RJ, Junestrand C. Pharmacokinetics and efficacy of long-term epidural ropivacaine infusion for postoperative analgesia. Anesth Analg 1997;85:1322–30
35. Rosenberg PH, Veering BT, Urmey WF. Maximum recommended doses of local anesthetics: a multifactorial concept. Reg Anesth Pain Med 2004;29:564–75