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A Safety and Pharmacokinetic Study of Ropivacaine Concentrations During Continuous Erector Spinae Plane Block for Thoracic Surgery

Scott Witzeling, Eric Schwenk, Eugene Viscusi, Jaime Baratta, Mark Torjman, Febina Padiyath, Rohan Sarna, Akshay Roy, Dalmar Mohammed, Joy Zhao, Gagan Kaushal, Ankit Rochani, Edwin Lam, Nathaniel Evans, Tyler Grenda, Olugbenga Okusanya

Thomas Jefferson University Hospital

Introduction

The erector spinae plane (ESP) block has emerged as a popular alternative to thoracic epidurals for thoracic surgery.1 However, local anesthetic systemic toxicity (LAST) risk is unknown and safety studies are lacking. Many dosing strategies have been used, including intermittent bolus with large volumes of local anesthetic.1 Additionally, there is evidence of intercostal spread with ESP blocks, potentially increasing plasma levels and associated risks.2 The ESP block has been touted as "safer" than neuraxial or paravertebral blockade, but without studies of LAST this is premature. Knudsen et al established that 4.3 mg/L is the arterial concentration at which patients begin to experience LAST symptoms.3
Our objectives were to evaluate the safety, tolerability, and pharmacokinetics of ropivacaine in patients receiving an ESP block.

Materials and Methods

IRB approval was obtained prior to patient enrollment and all patients signed written informed consent. This was a prospective, observational pharmacokinetic study of patients undergoing robotic or video-assisted thoracic surgery for a cancer or non-cancer diagnosis. Inclusion criteria: age ≥ 18 years, ASA physical status 1-4, and English speaking. Exclusion criteria: allergy to ropivacaine, coagulopathy (INR > 1.5, PTT > 1.5 times normal), platelet count < 100,000, local infection/bacteremia, abnormal liver function tests, renal disease (acute kidney injury or chronic kidney disease), or sensory deficit in thoracic region.
A timeout was performed prior to block procedure and midazolam was given as needed. A T5 or T7 ESP block was performed, depending on the expected location of chest tube placement. Patients were seated and the ESP was identified using ultrasound guidance with a curvilinear probe in the sagittal oblique position. The primary block consisted of ropivacaine 0.375% 40 mL through an 18-g Tuohy needle, followed by 20-g multi-orifice catheter being inserted 4-5 cm beyond the needle tip. Sensory assessment was performed with ice on the lateral chest at 15 minutes after block placement. General anesthesia was then administered and managed at the discretion of the intraoperative team. No additional local anesthetics were given intraoperatively. The next ropivacaine dose was at T=6 hours, at

which time the infusion of ropivacaine 0.2% was started at 1 mL/hour and remained for the duration of the catheter being in place. All patients were in the recovery room and extubated at that time.
Drug dosing followed standard institutional practice of 40 mL of ropivacaine 0.375% preoperatively at T=0, followed by 20 mL of ropivacaine 0.2% every 6 hours thereafter via continuous catheter along with a basal infusion of 1 mL/hour beginning at T=6 hours, modified from a previously published report.4 A total of 19 blood samples were collected for each patient according to a time schedule based on expected Cmax time and clustered around subsequent bolus doses. Samples were all arterial except for patients #8 and #9, who had 2 and 11 venous samples each, respectively, after their arterial lines stopped drawing back. Levels were not adjusted in those two patients. Samples were immediately placed on ice and stored in a freezer. Plasma levels were determined using liquid chromatography-mass spectrometry.
Data collected included demographics, past medical history, medications, baseline laboratory values, smoking status, postoperative QoR-15 scores, pain levels (0-10 NRS) during the first 12 postoperative hours, opioid consumption for 24 h, ropivacaine dosing, timing, and plasma levels, and presence of LAST symptoms.
The primary outcome was the mean Cmax of ropivacaine. Secondary outcomes included opioid consumption at 24 hours and Quality of Recovery (QoR)-15 scores assessed on postoperative day 1. Non-compartmental and compartmental analyses were performed on Phoenix WinNonlin (Certara, Princeton, NJ) version 8.3. Student t test was used to compare pre- and post-bolus pain scores using GraphPad.

Results/Case Report

A total of 25 patients were screened and 5 were excluded (3 declined, 1 had kidney disease, and surgeon refused block for 1). Initially 15 patients were enrolled but a freezer failure led to the damage of samples from the first 5 patients so 5 more patients were enrolled. Data presented here are from patients #6-20. Demographic data are shown in Figure 1.
A two-compartment model with first-order input and elimination was selected to model the observed data following the initial bolus dose. Individual plasma concentrations are shown in Figure 2. The mean (SD) Cmax for ropivacaine was 2.5 ± 1.1 mg/L with concentrations ranging from 0.8 - 4.6 mg/L. The median Tmax was 10 minutes. The median half-life following a bolus dose was 146 minutes (Table 1). One patient had an observed concentration above the 4.3 mg/L threshold shortly after primary block but denied any LAST symptoms throughout admission. Patient #11 experienced a mild LAST symptom (metallic taste) but this was determined to be unlikely related to the block. No other patients reported symptoms of LAST.
The mean oral MMEs during the first 24 hours was 91.4 ± 62.9. The mean QoR-15 score was 113 ± 32 on postoperative day 1. Prior to bolus 2 at T=6 hours mean pain was 6.8 ± 3.5, which remained unchanged at 6.9 ± 2.7 at 15 minutes after bolus 2 (p=0.95). Before bolus 3 at T=12 hours the mean pain score was 6.7 ± 2.8, which decreased to 4.8 ± 2.5 at 15 minutes after the bolus (p=0.06) but was not statistically significant.
Eight patients experienced decreased sensation along the T4-T8 dermatomes 15 minutes after initial block, bolus 2, and bolus 3. The remaining 7 patients did not have any sensory changes.

Discussion

The ESP block has exploded in popularity but LAST risk has not been studied. Our results show that pharmacokinetics of ropivacaine administered via ESP blocks are similar to previous reports.5 While most patients achieved Cmax values below the established LAST threshold of 4.3 mg/L, one patient did not. This patient denied LAST symptoms, weighed 61.2 kg and had CrCl of 56 mL/min, potentially indicating

a relatively low clearance rate for ropivacaine. This finding suggests the need to proceed cautiously when dosing local anesthetics in ESP blocks, particularly after large primary bolus doses. Ropivacaine concentrations were well under the toxicity threshold after subsequent catheter bolus doses with a low basal infusion rate.

References

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Disclosures

No

Tables / Images

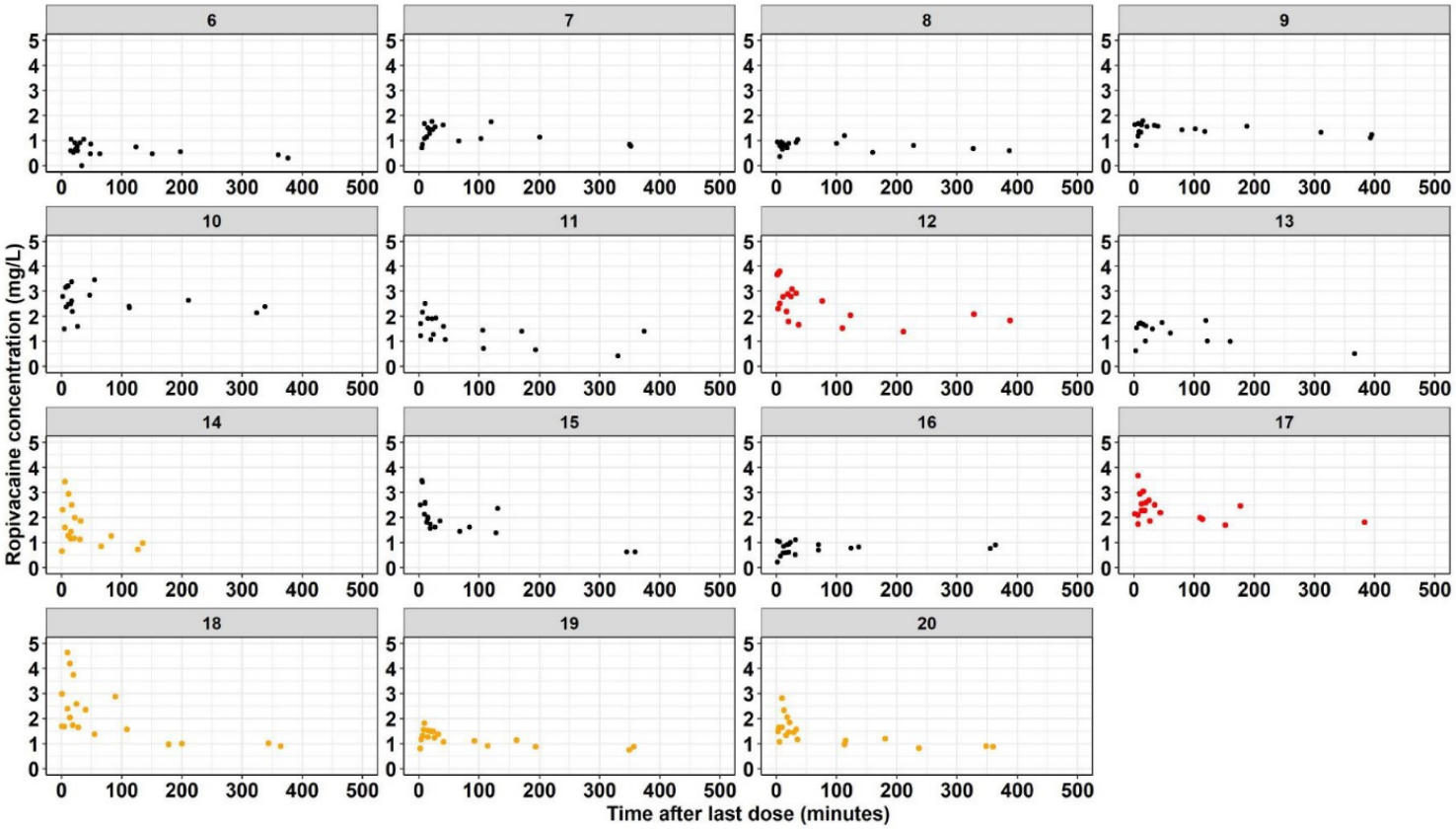

Table 1. Non-compartmental and two-compartment pharmacokinetic estimates

Variable	N	Mean	SD	Minimum	Maximum	Median	Range
Non-Compartmental Analysis							
Cmax (mg/L)	15	2.5	1.1	0.8	4.6	2.5	3.8
Tmax (minutes)	15	36.9	46.6	5	137	10	132
$AUC_{infusion}$ (min* mg/L)	11	1277.9	1112.4	366.1	3663.5	806.7	3297.4
2-Compartment Analysis							
K01 (1/min)	8	0.46	0.28	0.13	0.88	0.34	0.75
$T_{1/2}$ (minutes)	8	135.9	130.9	-	-	145.5	43.7

Patient #	Age	Sex	Height (cm)	Weight (kg)	BMI	Procedure	Smoking History	CrCl (mL/min)	Opioids in Month Prior to Surgery
6	64	M	168	68.5	24.3	Robotic Right upper lobectomy, mediastinal lymph node dissection, partial decortication, flexible bronchoscopy	Former Smoker	74	No
7	71	F	175	63.5	20.7	Robotic Xi assisted left upper lobectomy, mediastinal lymph node dissection, flexible bronchoscopy	Non-Smoker	65	No
8	63	M	180	106	37.2	Robotic right upper lobe wedge resection, middle lobectomy, mediastinal lymph node dissection, flexible bronchoscopy	Current Smoker	126	No
9	52	M	173	112	37.4	Right video-assisted thoracoscopic total decortication, flexible bronchoscopy	Non-Smoker	102	No
10	64	M	183	74.4	22.2	Robotic right upper lobectomy, micro direct laryngoscopy with biopsy	Former Smoker	101	No
11	65	F	165	72.1	26.5	Robotic right upper lobe wedge resection, upper lobe segmentectomy, mediastinal lymph node dissection, flexible bronchoscopy	Current Smoker	90	No
12	80	F	152	85.4	37.0	Robotic Xi left lower lobe wedge resection/basilar segmentectomy, mediastinal lymph node dissection, flexible bronchoscopy	Non-Smoker	49	No
13	66	M	183	81.6	24.4	Robotic video assisted thoracoscopic left lower lobe superior segmentectomy	Non-Smoker	88	No
14	65	F	155	72.4	30.1	Robotic right upper lobe lung wedge resection, middle lobe wedge resection, mediastinal lymph node dissection, diagnostic laparoscopy, coagulation of liver bleeding	Current Smoker	62	No
15	69	F	160	52.2	20.4	Robotic Xi left upper lobe segmentectomy, lymph node dissection	Current Smoker	68	No
16	66	F	165	116	42.6	Robotic XI left upper lobectomy, mediastinal lymph node dissection, flexible bronchoscopy	Current Smoker	122	Yes
17	67	F	155	53.5	22.3	Left robotic left upper lobe segmentectomy, mediastinal lymph node dissection, flexible bronchoscopy	Former Smoker	45	No
18	64	F	160	61.2	23.9	Robotic Xi resection right lung lobe, thoracoscopy, flexible bronchoscopy	Former Smoker	56	No
19	76	F	158	77.1	30.9	Video-assisted thoracoscopic surgery right lobectomy and bronchoscopy	Non-Smoker	63	No
20	62	F	165	66.7	24.5	Xi robotic left upper lobectomy, lymph node dissection, flexible bronchoscopy	Current Smoker	78	Yes