Serum Ropivacaine Concentrations and Systemic Local Anesthetic Toxicity in Trauma Patients Receiving Long-Term Continuous Peripheral Nerve Block Catheters

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BACKGROUND: Ropivacaine is a long-acting local anesthetic used frequently for peripheral nerve blocks and continuous peripheral nerve block catheters. Combat trauma patients at Walter Reed Army Medical Center often receive continuous peripheral nerve block catheters as part of their pain regimen. These catheters remain *in situ* for several days to weeks. In this study, we evaluated the free ropivacaine drug levels over time in trauma patients by measuring the serum concentration of bound and unbound local anesthetic. The corresponding α_1-acid glycoprotein concentration in patients with prolonged ropivacaine infusions was also measured.

METHODS: Fifteen patients were enrolled in the study; 2 patients were excluded because only a single ropivacaine level was obtained. Of the remaining 13 patients in the study, 2 had peripheral nerve catheters placed at the time of enrollment; the remaining 11 patients had catheters placed before enrollment. These patients were already receiving 0.2% ropivacaine infusions for a period of 18–126 h before the first assessment of local anesthetic level. Catheters infused 0.2% ropivacaine at a rate of 6–14 mL/h; catheter boluses were administered with 0.5% ropivacaine. Local anesthetic blood concentrations were scheduled to be measured on Days 1, 3, 5, 7, and 10 and every 3 days thereafter until all catheters were removed, although not all patients underwent each assessment. Specimens were assayed using high-performance liquid chromatography for total and free serum ropivacaine concentrations. α_1-Acid glycoprotein was also measured.

RESULTS: Thirteen patients remained in the study, for a total of 59 blood samples. The median number of days catheters remained *in situ* for the duration of acute pain therapy was 7 days (range: 6–27 days). The median number of days catheters remained *in situ* after enrollment into the study was 7 days (range: 4–25 days). The median number of blood samples collected per patient was 4 (range: 2–10 samples). Two patients had isolated increased concentrations of free ropivacaine into a previously identified toxic range with no obvious mitigating factors; both patients had received a 300-mg bolus of 0.5% ropivacaine approximately 24 h before that blood collection. The median ropivacaine concentration over the length of the study was 0.11 mg/L (range: undetectable to 0.63 mg/L). During the first week of the study, the median change in ropivacaine concentration per patient was 0.00 mg/L (range: −0.35 to 0.47 mg/L).

CONCLUSION: Although 2 patients demonstrated isolated serum ropivacaine concentration spikes into a previously identified toxic range, continuous peripheral nerve block catheter management and local anesthetic doses as practiced at Walter Reed Army Medical Center did not result in clinically evident systemic ropivacaine toxicity. There was no correlation between free ropivacaine concentration and α_1-acid glycoprotein concentration except in patients who had already been receiving ropivacaine infusions before entering the study. Despite this lack of correlation, the total duration of local anesthetic infusion did not seem to influence the free concentration of the drug.

(Anesth Analg 2010;110:630–4)

Ropivacaine is a long-acting amide local anesthetic with a structure and clinical profile similar to bupivacaine but with less associated toxicity at comparable doses.[1,2] For this reason, ropivacaine is the preferred local anesthetic for peripheral nerve blocks and continuous peripheral nerve infusions at many institutions. Because of an anticipated extended hospital admission associated with challenges involving pain control, continuous peripheral nerve block catheters have become a mainstay of therapy for the acute pain

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Accepted for publication October 5, 2009.

Supported by John P. Murtha Neuroscience and Pain Institute, Henry M. Jackson Foundation, and departmental funds.

Reprints will not be available from the author.

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DOI: 10.1213/ANE.0b013e3181c76a33

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCT 2009		**00-00-2009 to 00-00-2009**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Serum Ropivacaine Concentrations and Systemic Local Anesthetic Toxicity in Trauma Patients Receiving Long-Term Continuous Peripheral Nerve Block Catheters	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Walter Reed Army Medical Center,Department of Surgery, Anesthesia and Operative Service,Washington,DC,20307**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**Same as Report (SAR)**	**5**	

service at Walter Reed Army Medical Center. The polytrauma and severe acute pain associated with combat injury have necessitated the use of continuous peripheral nerve block catheters from several days to longer than a month in select cases, with the average residence time of catheters being 9 ± 5 days.[3] Information regarding ropivacaine blood concentrations during long-term infusions of this local anesthetic is limited.

This pilot study determined the concentration of bound and unbound ropivacaine circulating in the blood of acute trauma patients who had a prolonged indwelling peripheral nerve catheter(s). The concentration of α_1-acid glycoprotein, an acute-phase reactant that binds free ropivacaine,[4,5] was also assayed to determine whether there was a correlation between glycoprotein blood concentrations and free drug blood concentrations.

Table 1. Patient Demographics

Patient[a]	Age	Height (cm)	Weight (kg)
1	27	178	83
2	30	178	90
3	26	178	77
4	23	173	65
5	31	163	107
6	28	173	97
7	25	180	83
8	29	188	109
9	24	173	63
10	27	189	91
11	24	183	86
12	34	180	75
13	24	183	70
14	22	178	81
15	22	183	98

[a] All patients are male.

METHODS

Patients

After obtaining Walter Reed Army Medical Center human use committee approval, written informed consent was obtained from 15 patients injured during the Afghanistan or Iraq wars. Patient demographics are provided in Table 1. The patients had varying degrees of orthopedic trauma, and all had either a preexisting peripheral nerve catheter placed in Iraq, Afghanistan, Germany, or Walter Reed Army Medical Center ($n = 13$) or were scheduled to receive a catheter in conjunction with their next surgical procedure at Walter Reed Army Medical Center ($n = 2$) (Table 2). All catheters were infused with 0.2% ropivacaine solution, and boluses were achieved with 0.5% ropivacaine for pain control on the ward or before a surgical procedure. Patients were excluded from the study because of refusal to have >2 serial ropivacaine levels; any contraindication to a continuous peripheral nerve catheter including allergy to local anesthetic, infection or trauma at the site of catheter placement, increased coagulation times, therapeutic dosing (≥1 mg/kg) of Lovenox® (Sanofi-Aventis, Paris, France), moderate to severe traumatic brain injury; hematocrit <20, or severe liver or renal disease.

Table 2. Local Anesthetic Administration

Patient	Catheter type	Hours on 0.2% ropivacaine before study	Infusion rate (mL/h)[a]	Surgical boluses (0.5% ropivacaine)[b]	Analgesic boluses (0.5% ropivacaine)[c]	Total ropivacaine samples obtained	Highest measured free ropivacaine concentration (mg/L)[d]	Ropivacaine bolus (mg) preceding highest ropivacaine blood level[e]	Hours between ropivacaine bolus and blood draw[f]
1	F	53	10	3	1	5	0.32	None	N/A
2	F	32	10	3	0	2	0.045	400	27
	SC		8	3	0				
3	SC	1	10	0	0	3	0.084	None	N/A
4	SP	18	8	0	0	1	0.11	None	N/A
5	PC	18	8	1	0	4	0.391	300	28
	SC		8	1	0				
6	SP	3	8	1	2	6	0.351	250	24
7	F	24	10	2	0	6	0.077	200	30
8	SC	31	14	0	0	1	0.0215	300	31
9	SP	28	8	1	0	3	Undetected[g]	200	26
10	IC	122	8	2	2	6	0.021	250	28
11	F	126	8	1	0	5	0.096	None	N/A
	SC		10	1	0			None	N/A
12	PC	78	8	4	2	3	0.2765	300	6
	SC		8	4	2				
13	PC	79	10	5	1	10	0.585	300	23
	SC		6	5	1				
14	SC	32	8	2	0	2	0.627	300	29
15	PC	50	10	1	1	3	0.115	125	40

F = femoral; SC = sciatic; SP = supraclavicular; IC = infraclavicular; PC = psoas compartment; N/A = not applicable.

[a] All infusions maintained with 0.2% ropivacaine.

[b] All upper extremity catheters bolused with 40 mL ropivacaine and all lower extremity catheters bolused with 30 mL ropivacaine.

[c] All analgesic boluses achieved with 10 mL ropivacaine.

[d] Highest free ropivacaine concentration obtained during study period.

[e] Surgical bolus preceding peak free ropivacaine level.

[f] Hours elapsed between surgical bolus and peak free ropivacaine level.

[g] Undetected by high-performance liquid chromatography.

Data Collection

Serum ropivacaine concentrations were scheduled to be obtained on Days 1, 3, 5, 7, and 10, and every 3 days thereafter until the continuous peripheral nerve block catheter was removed. A daily diary was maintained on each patient to include date and time of each ropivacaine blood level, catheter infusion rates, extra boluses of local anesthetic administered via the continuous peripheral nerve catheter, catheter(s) location, signs or symptoms of systemic local anesthetic toxicity (tinnitus, circumoral numbness, and restlessness), weight, daily hematocrit, notation of blood transfusions, and medication list. Infectious complications were minimized by adhering to institutional guidelines for sterile technique during infusion bag replacement. All patients were receiving broad spectrum antibiotics because of the nature of combat injury.

Blood Collection

The study was designed as a prospective longitudinal case series and was based on venous blood analysis to determine serum ropivacaine concentrations. The local anesthetic blood sample was obtained from any available extremity that did not host a peripheral nerve catheter. Ten milliliters of venous blood was collected and divided; 7 mL was placed into a sodium heparin tube (Becton, Dickinson and Company, Franklin Lakes, NJ) for the ropivacaine measurement and 3 mL was placed into a Corvac tube (Becton, Dickinson and Company) containing no anticoagulant for the α_1-acid glycoprotein measurement.

Blood Preparation

The ropivacaine samples were taken to the blood bank within 1 h of collection and centrifuged at room temperature at 3590 rpm for 10 min. The plasma was collected by pipette and transferred to a polypropylene tube (Nalgene cryogenic vial, Nalge Company, Rochester, NY) and was immediately placed into a locked freezer and stored at −20°C until the sample could be transferred to a Uniformed Services University of the Health Sciences (Bethesda, MD) laboratory for analysis. Upon preparation for plasma sample transfer to Uniformed Services University of the Health Sciences for analysis, the specimens were placed on dry ice for the duration of the 30-min excursion. The samples to be measured for α_1-acid glycoprotein were sent to the chemistry laboratory within 5 min of obtainment and analyzed via a turbidimetric method on an Olympus AU640 using Olympus reagent (Olympus, Hamburg, Germany).

Drug Analysis

Assay of Total Serum Ropivacaine Concentration

The high-performance liquid chromatography method and purification of samples were modified from a previously reported method by Hansen et al.[6]

Assay of Free Serum Ropivacaine Concentration

Free ropivacaine in serum samples was assayed after ultrafiltration of samples (0.5–1 mL) using Amicon Centricon YM-30 centrifugal filtration devices (Millipore, Billerica, MA). Aliquots of the ultra filtrate (0.3–0.5 mL) were then extracted and analyzed as described for the determination of total serum ropivacaine concentration. A high-performance liquid chromatography (Separation Module Model 2695) equipped with Empower-2 software and photodiode array detector (Waters, Milford, MA) was used. The limit of instrument detection was 10 ng/mL and the limit of quantitation of the assay was the same. Serum ropivacaine concentrations were calculated from the following 2 methods:

1. Using peak area ratio of ropivacaine/bupivacaine of samples versus peak area ratio of ropivacaine/bupivacaine of standards (0–3000 ng/mL) using the following formula:

$$[\text{Rop}]_S = [(\text{PA of Rop})/(\text{PA of Bup})_S] \\ /[(\text{PA of Rop})/(\text{PA of Bup})_{STD}] \\ \times [\text{Bup}]\ (1/\text{mL serum used})$$

where Rop = ropivacaine, Bup = bupivacaine, PA = peak area, S = sample, and STD = standard.

2. Samples of ropivacaine concentrations interpolated from plotted standard curve of ropivacaine concentrations (0–3000 ng/mL) versus peak area. The average of the data obtained from these 2 methods was reported.

Data Analysis

Data are reported as median (range). The association of α_1-acid glycoprotein, free ropivacaine, and length of time receiving ropivacaine before enrolling in the study was examined using Spearman correlation coefficient. Data were analyzed using SPSS for Windows (version 14.0, SPSS, Chicago, IL).

RESULTS

Fifteen patients were enrolled in the study (Table 1). Two patients were eliminated because of refusal to have repeated ropivacaine levels obtained. Of the remaining 13 patients in the study, only 2 had peripheral nerve catheters placed at the time of enrollment (Patients 3 and 6). The remaining 11 patients had catheters placed before enrollment and were receiving 0.2% ropivacaine infusions for a period of 18–126 h before the first assessment of local anesthetic level (Table 2). Of the 13 patients in the study, 12 received boluses to provide anesthesia for surgery. These surgical boluses consisted of 30–60 mL 0.5% ropivacaine, depending on location and number of catheters. To supplement analgesia while on the ward, 10-mL boluses of 0.5% ropivacaine were administered (Table 2).

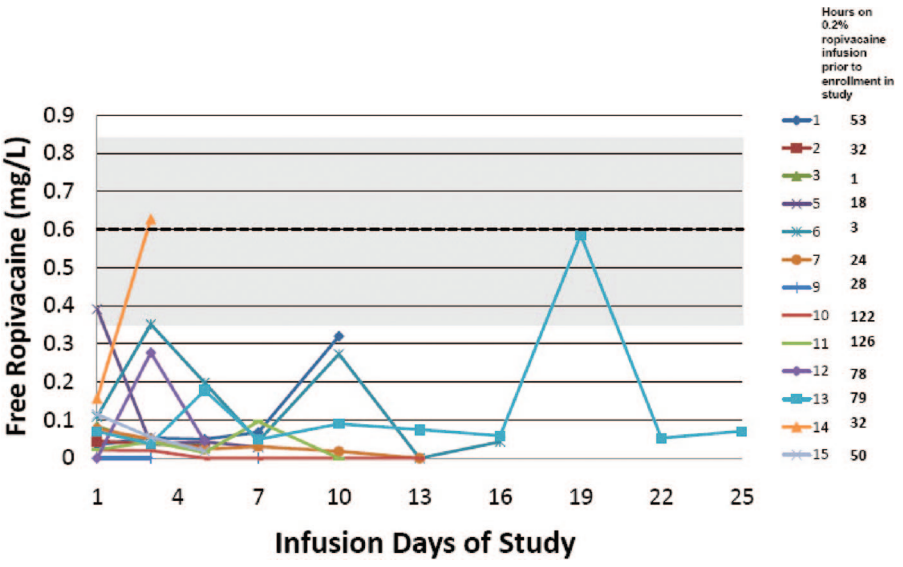

Figure 1. Free ropivacaine concentrations (mg/L) for each study participant for the duration of their enrollment in the study. The shaded area represents the upper and lower limits of toxic free ropivacaine blood levels as demonstrated by Knudsen et al.[2] (0.34–0.85 mg/L; mean value of 0.6 mg/L) on healthy volunteers.

The median free ropivacaine concentration on the first assessment was 0.07 mg/L (range: undetectable to 0.39 mg/L) (n = 13). For the length of the study period, the median highest free ropivacaine concentration was 0.11 mg/L (range: undetectable to 0.63 mg/L). Two study patients had measured free ropivacaine values that entered into a previously identified toxic range.[2] One patient had a concentration of 0.63 mg/L on Day 3 (Fig. 1). This patient had only 2 ropivacaine concentrations obtained during the study; the first free ropivacaine concentration was 0.156 mg/L and the second was 0.63 mg/L. Associated events included a surgical procedure the previous day with a total of 60 mL of 0.5% ropivacaine bolused via femoral and sciatic catheters. A second patient had a ropivacaine concentration of 0.59 mg/L on Day 19 (Fig. 1). This patient had multiple local anesthetic concentrations obtained throughout the study with an isolated free ropivacaine spike of 0.59 mg/L. Associated events included a 60-mL bolus of 0.5% ropivacaine via a lumbar plexus and sciatic nerve catheter; again, the bolus was administered on the day before the free drug spike. The median maximum change for the group was 0.10 mg/L (range: 0.00–0.55 mg/L). The assay recovery was 88% ± 4%.

Examination of the change in ropivacaine concentration during the first week of enrollment in the study (maximum ropivacaine concentrations on Days 3, 5, and 7 and subtracting the value from Day 1) showed that 5 of the patients had a decrease in free ropivacaine, 6 patients had an increase, and 2 patients had no change. The median change was 0.00 mg/L (range: −0.35 to 0.47 mg/L).

There was no significant correlation in the duration the patient had been taking the drug (before enrollment) and the concentration of free ropivacaine (r_s = −0.51, P = 0.053). There was a significant increase in α_1-acid glycoprotein concentration (r_s = 0.68, P = 0.008) for those patients already with indwelling continuous peripheral nerve block catheters receiving ropivacaine. There was no correlation between α_1-acid glycoprotein concentration and free ropivacaine concentration (r_s = 0.34, P = 0.24) for that patient population.

DISCUSSION

A single study in healthy volunteers has defined the toxic plasma concentration of free ropivacaine to have a range between 0.34 and 0.85 mg/L with a mean value of 0.6 mg/L.[2] In this study, 2 patients had an isolated single free ropivacaine concentration that either approached or surpassed these mean toxic values with no reported signs or symptoms of systemic local anesthetic toxicity. These 2 isolated incidences cannot be explained by any immediate preceding events such as surgical or analgesic boluses. Of note, the median change in free ropivacaine levels between Days 1 and 7 was 0.00 mg/L suggesting that the drug levels were remaining relatively stable.

Approximately 94% of the ropivacaine in plasma is bound to α_1-acid glycoprotein,[4] an acute-phase reactant that increases postoperatively[7] and after trauma.[8] This relationship accounts for the fact that a constant infusion of drug will result in a linear relationship of drug-protein binding. Several studies have demonstrated that there is a consistent and steady increase in α_1-acid glycoprotein during continuous ropivacaine infusions.[9–11] In our study, there was no correlation between free ropivacaine and α_1-acid glycoprotein concentrations. However, the longer a patient had been receiving ropivacaine, the more likely the α_1-acid glycoprotein level was increased at the time of the first assessment of free ropivacaine concentration.

Walter Reed Army Medical Center is a tertiary care facility that receives many soldiers who have been injured in combat. At the outbreak of Operation Enduring Freedom (Afghanistan), and soon followed

by Operation Iraqi Freedom, there was a large increase in the number of polytrauma casualties treated at the facility with a subsequent need for comprehensive acute pain control. Peripheral nerve catheters quickly emerged as a key component for managing pain in this complex patient population.

Because of extensive traumatic injury, catheters remain *in vivo* for a prolonged period.[12] The mean catheter infusion time was 9 days in a series of 287 combat trauma patients at Walter Reed Army Medical Center[3]; however, many of these catheters were used for >1 mo. Complications within this series of patients (myotoxicity, infection, and hematoma), many of whom were anticoagulated during continuous peripheral nerve block therapy, were rare. During these infusions, patients were receiving up to 20 mL/h of 0.2% ropivacaine with the potential for another 6–10 mL/h from patient-controlled bolus infusions of local anesthetic. Despite lack of overt clinical toxicity, we were curious about the free ropivacaine drug concentrations that were being reached. This study was undertaken as a pilot study to evaluate serum ropivacaine concentrations in acute trauma patients with long-term continuous peripheral nerve block catheters.

Ropivacaine has been implicated in both central nervous system and cardiovascular complications resulting from inadvertent IV injection.[13,14] Systemic uptake is another mode of ropivacaine entry into a patient's circulating blood with absorption being greatest via intercostal injection, followed by caudal, epidural, and brachial plexus administration.[15] Plasma concentrations of the drug have been studied with prolonged epidural infusions of 24 h[9] up to 120 h[16] with findings of a plateau and eventual decrease of free drug despite a progressive increase in total concentrations.[17] This study presents the first information of this type in long-term continuous peripheral nerve block infusions in trauma patients.

Despite our efforts with data collection, there are significant limitations to this study. The inability to obtain ropivacaine levels at each designated period because of patient refusal was a major obstacle that resulted in an incomplete data set. This is evidenced by only 6 of the 15 patients (40%) having data through Day 7. Additionally, it is impossible to standardize doses among this patient population and therefore no comparisons among patients can be made. Each patient received a unique amount of drug over the duration of catheter(s) insertion based on the acute pain service's individualized plan.

We are unable to form definitive conclusions concerning the relationship among ropivacaine continuous peripheral nerve block catheter infusions, blood ropivacaine concentrations, and α_1-acid glycoprotein concentrations. This study provides the first information on ropivacaine blood concentrations in trauma patients receiving long-term continuous peripheral nerve block infusions. Free ropivacaine concentrations in this case series tended to remain at nontoxic levels, as defined by a previous volunteer study,[2] although measured blood concentrations occasionally exceeded toxic thresholds. Despite this finding, clinical manifestations of systemic local anesthetic toxicity were not observed.

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