Serum Free Ropivacaine Concentrations Among Patients Receiving Continuous Peripheral Nerve Block Catheters: Is It Safe for Long-Term Infusions?

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BACKGROUND: Ropivacaine is a long-acting local anesthetic used for continuous peripheral nerve catheter infusions. Catheters may remain in situ for prolonged time periods. In the present study, patients were enrolled to receive continuous peripheral nerve catheters with measurement of free serum ropivacaine concentrations.

METHODS: Peripheral nerve catheters were placed for postoperative pain management in trauma patients and infused with ropivacaine 0.2% or bolused with 0.5%. Blood samples were obtained from each subject on days 0 (preinfusion), 3, 5, 7, 10, and every third day until catheter removal. Serum free ropivacaine concentrations were measured via high-performance liquid chromatography and were compared using the Wilcoxon signed rank test.

RESULTS: One hundred thirty-three blood samples were analyzed in 35 patients; all serum free ropivacaine concentrations after infusion initiation (99 samples from 35 subjects) were below 0.34 mg/L (previously determined toxic threshold). The highest concentration achieved in a blood sample was 0.19 mg/L; all other values were <0.09 mg/L. The total amount of drug received during the study ranged from 1146 to 22,320 mg (median of 3722 mg). Catheters remained in situ for a median of 7 days (range: 3–23). From day 0 to 3 (preinfusion), 77% of the study participants had an increase in the serum free-fraction ropivacaine concentrations. The median concentration on day 3 was 0.025 mg/L (95% upper confidence limit for mean: 0.05, range: <0.01–0.19); $P < 0.001$ compared with preinfusion levels). From day 3 to 5, 68% of the participants had a decrease in the serum free ropivacaine concentrations (median level 0.016 mg/L [95% upper confidence limit for mean: 0.021] $P = 0.007$ for day 5 compared with day 3).

CONCLUSIONS: In this study, free serum ropivacaine concentrations remained well below toxic values despite large amounts of drug administration in combat-wounded patients. The administration of continuous ropivacaine infusions over prolonged time periods, coupled with multiple drug boluses, did not produce toxic or near-toxic serum concentrations. (Anesth Analg 2014;118:225–9)

Although the incidence of systemic toxicity from local anesthetics has been decreasing over the last 2 decades,[1] the possibility still remains of an accidental intravascular injection or systemic absorption occurring during a peripheral nerve block. The resulting systemic local anesthetic toxicity may lead to central nervous system toxicity,[2] cardiovascular collapse, and death.[3,4]

While there have been sufficient data published concerning local anesthetic absorption from single injection peripheral nerve blocks[5–8] and short-term peripheral nerve catheters,[9,10] there is little information regarding local anesthetic systemic absorption during long-term continuous peripheral nerve catheter analgesia. The Acute Pain Service (APS) at Walter Reed Army Medical Center (WRAMC) reported results from a pilot study examining the relationship between serum ropivacaine concentrations and long-term peripheral catheter infusions.[11] This 13-patient study reported 2 subjects with isolated serum ropivacaine concentration spikes that breached a previously identified toxic threshold (0.34–0.85 mg/L).[11] However, no overt clinical signs or symptoms of toxicity were observed.

Out of concern that our patients may be receiving excessive ropivacaine during long-term infusions, we performed this study to further clarify the relationship between serum ropivacaine concentrations and long-term peripheral nerve catheter analgesia.

METHODS

Patients

After receiving protocol approval from the WRAMC IRB, written informed consent was obtained from 49 patients; all but 2 were injured during the Afghanistan or Iraq wars. The patients had varying degrees of orthopedic trauma

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including multiple fractures and amputations. No patient had a preexisting indwelling peripheral nerve catheter or had received a peripheral nerve block within the past 72 hours as per reviewed, available medical records. All but 1 catheter was infused with 0.2% ropivacaine, and the remaining catheter was infused with ropivacaine 0.375%. Catheter boluses were achieved with 0.5% ropivacaine for surgical boluses and 0.2% ropivacaine for pain boluses on the surgical wards. Patients were excluded from the study for refusal to have >2 serial ropivacaine blood samples; 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.

Data Collection

Serum ropivacaine concentrations were obtained on days 0 (baseline value), 3, 5, 7, and 10, and every 3 days thereafter until the continuous peripheral nerve block catheter was removed, or as occurred in 1 instance, when the patient's infusion was changed to bupivacaine for clinical reasons. Blood specimen acquisition times varied throughout the day pending patient availability. A daily diary was maintained by the APS nurses on each patient to include the date and time of each ropivacaine blood sampling, catheter infusion rates, additional 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, and daily hematocrit (blood was not sampled if hematocrit was <20).

This study was designed as a longitudinal prospective investigation based on venous blood analysis to determine serum ropivacaine concentrations in trauma patients receiving long-term peripheral nerve catheters. The local anesthetic blood specimen was obtained from any extremity that did not host a peripheral nerve block catheter. Approximately, 7 mL venous blood was collected during each blood sampling and placed into a sodium heparin tube (Becton, Dickinson and Company, Franklin Lakes, NJ).

Blood Preparation

The ropivacaine samples were immediately placed on ice and taken to our institution's laboratory within 1 hour of collection where they were centrifuged at room temperature at 1500 rpm for 10 minutes. The plasma was collected by pipette and transferred to a polypropylene tube (Nalgene cryogenic vial, Nalge Company, Rochester, NY) and was then placed into a locked freezer and stored at −80°C until samples were ready for analysis.

Drug Analysis

Free serum ropivacaine was assayed after ultrafiltration of serum (0.5–1 mL) using Amicon Ultracel 30K centrifugal filter units (EMD Millipore Corporation, Billerica, MA). Aliquots of the ultrafiltrate (0.5 mL) were extracted and analyzed by high-performance liquid chromatography using the method modified from that reported by Hansen et al.[12] Free ropivacaine concentration was determined on a Waters 2695 Alliance HPLC and detected by absorbance at 220 nm. A Waters Nova-Pak C18, 4 µm, 3.9 × 300 mm Column was used with a mobile phase of 20% acetonitrile, 20% methanol, and 60% 50 mM phosphate buffer were used for analysis. Data were analyzed using Empower 2 (Waters Corporation, Milford, MA). Using the standards as controls, a coefficient variation of 2.5% to 8.2% was yielded over the range of 31.3 to 500 ng/mL, and the average of R^2 for the standard curve for all runs was 0.997. Free ropivacaine concentrations were calculated as described previously.[11]

Data Analysis

Data are reported as counts (percentage), means (standard deviation), or medians (range). Ninety-five percent upper confidence limits for the mean (95% UCL for mean) for serum ropivacaine levels were estimated using the method proposed by Chen.[13] The Wilcoxon signed rank test was used to compare ropivacaine levels on day 0 (preinfusion) to day 3 levels (first measurement after catheter placement) and day 3 to day 5 levels. Given a weak association between the day 3 level and the subsequent change in ropivacaine between days 3 and 5, as well as several tied pairs between days, concentrations at these time points were compared using both paired and unpaired nonparametric methods with significant results using either method. Data were analyzed using STATA 12.0 (StataCorp LP, College Station TX).

RESULTS

Forty-nine patients consented to study participation (mean age 26.2 years; average body mass index 27.4), and 14 patients ended participation after the first blood sample was obtained (12 declined further participation, and 2 did not undergo catheter placement); data are reported for 35 patients. Patient demographics are provided in Table 1. Catheter distribution sites are provided in Table 2 (second catheter refers to placement of a concomitant peripheral nerve catheter in addition to the initial nerve catheter).

Table 3 depicts the ropivacaine dosages over the length of the study. Analysis of the 35 patients who had >1 blood sample taken (12 patients gave 2 blood samples, and 23 patients gave 3 or more blood samples) revealed the median number of days that the catheters remained in situ was 7 (range: 3–23 days); the median total ropivacaine dose was 3722 mg (range: 1146–22,320 mg); and the median total dose per catheter day was 519 mg (range 306–1194 mg). The

Table 1. Patient Demographics

Race	
Caucasian	30
African-American	0
Hispanic	2
Asian	1
Other	2
Gender	34
Male	1
Female	
Age	
19–59	26.4 (mean)
Body Mass Index	
22–60	28.0 (mean)

Patient demographics: 49 patients were enrolled; all but 2 patients were wounded soldiers from operation enduring freedom or operation Iraqi freedom.

median number of blood samples collected per patient was 4 (range: 2–9 samples), and a total of 133 blood samples were analyzed. The total number of samples obtained per patient is depicted in Figure 1. All serum free-fraction ropivacaine concentrations were well below the previously published toxic threshold (0.34–0.85 mg/L). The highest concentration achieved in a single blood sample was 0.19 mg/L; all other values were <0.09 mg/L (Fig. 2). The patient who achieved a blood concentration of 0.19 mg/L did not receive any ropivacaine boluses before obtainment of the sample.

From day 0 to 3, 77% of the study participants had an increase in the serum free-fraction ropivacaine concentrations, with a median level on day 3 of 0.025 (95% UCL for mean: 0.05, range: <0.01–0.19; $P < 0.001$ compared with day 0 preinfusion levels). From day 3 to 5, 68% of the participants had a decrease in the serum free ropivacaine concentrations. Ropivacaine levels on day 5 (median: 0.016 mg/L, 95% UCL for mean: 0.021, range: <0.01–0.039) were lower compared with day 3, $P = 0.007$. No statistically significant changes were evident from subsequent blood sampling.

Table 2. Catheter Distribution

First catheter	
Femoral	12
Interscalene	3
Supraclavicular	7
Sciatic–lateral	8
Sciatic–posterior	5
Second catheter	
Femoral	5
Sciatic–lateral	4
Sciatic–posterior	7
Supraclavicular	1

Catheter distribution: 47 patients received peripheral nerve catheters. "First catheter" refers to the primary catheters; "Second catheter" refers to additional catheter placement.

Table 3. Ropivacaine Dosage

	Median (range)
Time with any catheter (d)	7 (3–23)
Total ropivacaine received (mg)	3722 (1146–22320)
Total ropivacaine per catheter per day (mg)	519.3 (305.5–1194.0)
Total ropivacaine per catheter per hour (mg)	21.6 (12.7–49.8)

Ropivacaine dosage: Total median doses of ropivacaine received per hour, per day, and total throughout duration of study. Catheter infusion rates of 0.2% ropivacaine range from 2 to 12 mL/h per catheter, with the ability to administer a self-bolus of 5 mL every 30 minutes or 3 mL every 20 minutes. Patients requiring analgesic boluses on the surgical ward were administered 10 mL of 0.2% ropivacaine. Catheters being bolused before surgery receive 20 to 30 mL of 0.5% ropivacaine per catheter.

Conclusions

Ropivacaine is a long-acting local anesthetic that is frequently used for peripheral nerve catheter infusions. Despite its widespread use with continuous catheters, little data have been published regarding systemic blood concentrations of the free form of drug during long-term infusions. Our previous study reported free serum ropivacaine concentrations but failed to report these drug values within the context of the total amount of ropivacaine received.[11] In the present study, we attempted to further our understanding of free ropivacaine and better assess how the drug accumulates in serum over extended time periods. By expanding our subject cohort and reporting free serum ropivacaine values in the context of total infusion doses, we more clearly defined the relationship between long-term infusions and drug accumulation.

Several studies have been conducted in an attempt to delineate minimum thresholds of intravascularly injected local anesthetic at which point healthy volunteers begin to report symptoms of central nervous system toxicity.[14,15] Knudsen et al.[14] defined a lower limit of free serum ropivacaine, 0.34 to 0.85 mg/L, at which point patients began to exhibit symptoms of local anesthetic toxicity. These levels were based on arterial blood sampling, but the authors argued that the arterial values obtained after rapid drug administration would be similar to peripheral venous free plasma concentrations after a slower systemic absorption of drug. This was supported by Denson et al.[16] who demonstrated similar toxic values of venous bupivacaine concentrations as compared with the arterial samples of Knudsen.

As previously noted from our pilot study,[11] 2 patients had breached this toxic threshold, although they did not display overt signs of toxicity. In the present study, no patient approached this lower limit threshold of toxicity. The highest drug concentration achieved (0.19 mg/L) was

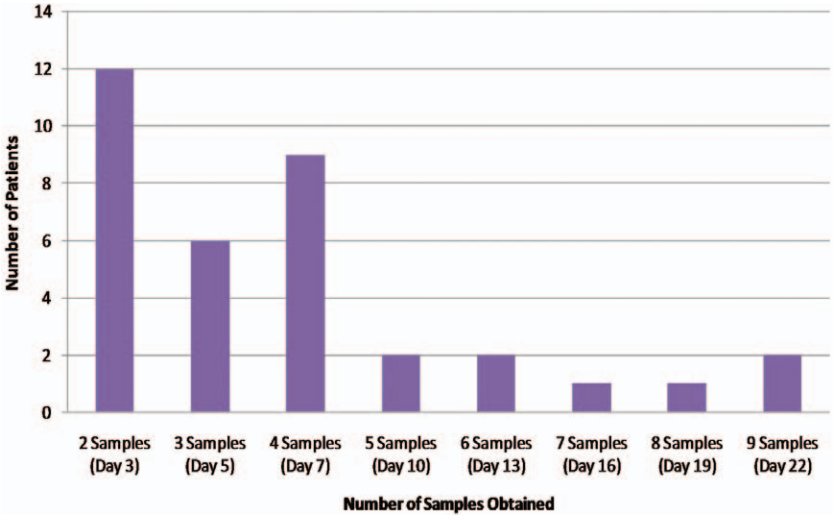

Figure 1. Number of samples obtained per patient. Of the 35 participating, 12 patients had a total of 2 samples obtained, 6 patients had a total of 3 samples obtained, 9 patients had a total of 4 samples obtained, etc…)

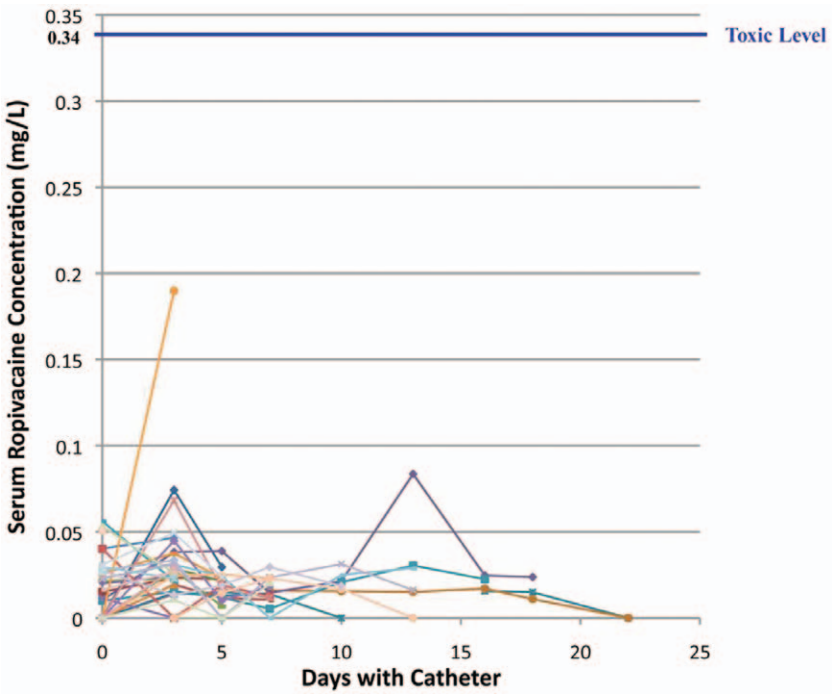

Figure 2. Free serum ropivacaine concentrations (mg/L) for each study participant for the total number of days that the catheter(s) remained in situ. The solid purple line denotes the lower limit of ropivacaine toxicity in healthy volunteers as demonstrated by Knudsen et al.[14]

in a patient who had received a femoral and sciatic peripheral nerve catheter for lower extremity surgery. Neither catheter was bolused with ropivacaine in the postsurgical period; both catheters initially infused 0.2% ropivacaine at 8 mL/h with the option of self-administering a 3 mL bolus every 20 minutes. The following day, the femoral catheter was increased to an infusion rate of 12 mL/h, and the sciatic catheter was decreased to a rate of 4 mL/h. Both catheters were removed 3 days after placement, and the patient was discharged from the study.

As evidenced in Table 3, our patients received a varied amount of local anesthetic, but the cumulative dose infused via the catheter can be large. Each catheter infused 0.2% ropivacaine at a rate of 2 to 12 mL/h with the opportunity for a patient-administered bolus of 3 mL every 20 minutes or 5 mL every 30 minutes. Patients returning to the operating room for surgery (typically every other day for trauma patients) had the catheter(s) bolused with 20 to 30 mL of 0.5% ropivacaine, and if a postoperative pain crisis occurred on the ward, the catheter(s) could be bolused with additional 0.2% ropivacaine (up to 10 mL, determined by time of last bolus). This routine performed over many days to weeks was the reason we sought to determine serum free ropivacaine concentrations within this patient population.

Caution must be exercised when extrapolating these results to the general population. Approximately, 94% of ropivacaine in plasma is bound to α_1-acid glycoprotein (AAG),[17] an acute phase protein. AAG has been shown to be increased in surgical[18] as well as in trauma patients.[19] Considering the severity of the trauma within this patient population, AAG concentrations may be higher than normally encountered in a routine surgical patient. Higher AAG levels would allow for more binding of ropivacaine, resulting in less circulation of the free form of drug.

Despite our reassuring results, our clinical practice has not increased basal infusion rates, as the risk of local anesthetic-induced myotoxicity[20–22] and neurotoxicity[23–25] has been clearly described in the anesthesia literature. A recent review by Nouette-Gaulain et al.[24] emphasized the in situ toxicity that local anesthetics produced by their effects on cell metabolism and tissue ultrastructure in the vicinity of neurons and muscles. Because these untoward events are both concentration- and time-dependent, our pain management doctrine has been to place equal emphasis on oral and IV components of pain medication in conjunction with the peripheral nerve catheters.

As with our previous study, we again had some difficulty with data collection with only 75% of consenting participants providing a minimum of 2 blood samples. In addition, as illustrated in Figure 2, not all participants had a baseline serum ropivacaine value of zero. Patients returning from overseas medical facilities may have received single injection peripheral nerve blocks before arrival at WRAMC/Walter Reed National Military Medical Center, and these data were sometimes unavailable to our team.

An additional limitation of this study is the timing of the blood sampling in relation to catheter boluses. Although we did not have any free serum ropivacaine concentrations that neared toxic values, we may not have "captured" the serum at the appropriate time interval.

In conclusion, we have found that in young, otherwise healthy patients hosting long-term peripheral nerve catheters, serum ropivacaine concentrations remain well below previously published toxic values despite a large amount of drug administration via the catheter(s). This does not preclude the need for ongoing monitoring for signs and symptoms of local anesthetic toxicity. Continual, close vigilance over these patients is maintained via an APS staffed by attending and resident physicians as well as acute pain nurses who repeatedly assess and reassess these patients for signs or symptoms of toxicity.

DISCLOSURES

Name: Lisa Bleckner, MD.
Contribution: This author helped design and conduct the study, analyze the data, and write the manuscript.
Attestation: Lisa Bleckner 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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Attestation: Bader Fileta performed the sample analysis.
Name: Robin Howard, MA.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Robin Howard has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Attestation: Chester C. Buckenmaier has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Terese T. Horlocker, MD.

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