Regional Anesthesia and Pain

Intravenous ropivacaine bolus is a reliable marker of intravascular injection in premedicated healthy volunteers

[L'administration intraveineuse d'un bolus de ropivacaïne est un marqueur fiable de l'injection intravasculaire chez des volontaires sains prétraités]

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Purpose: We designed the following volunteer study to determine if an intravascular bolus dose of ropivacaine could be found that would reliably produce mild symptoms of central nervous system (CNS) toxicity in sedated humans.

Methods: After Ethics Committee approval and informed consent 15 volunteers were recruited. Cardiovascular (CVS) monitoring including pulse oximetry, electrocardiogram and non-invasive blood pressure monitoring was applied.

In phase 1, volunteers received in sequence placebo, 30 mg, 45 mg and 60 mg of ropivacaine as a 10-mL *iv* bolus over 20 sec with a two-hour rest period between each injection to allow plasma clearance of drug. Volunteers were asked to report symptoms of local anesthetic toxicity on a verbal response scale. After any dose volunteers reporting greater than three symptoms with a severity of > 3/10 for greater than three minutes were excluded from further study doses. The dose that consistently produced mild CNS toxic effects was chosen for phase 2 of the study.

In phase 2, volunteers were given *iv* midazolam 0.03 $mg \cdot kg^{-1}$ prior to bolus ropivacaine or placebo in a randomized double-blind crossover fashion. Volunteers were asked to report toxic symptoms and venous blood samples were obtained for ropivacaine assay.

Results: In phase 1, ropivacaine 60 mg was found to produce consistent mild symptoms of CNS toxicity. No volunteer experienced major CNS or CVS adverse effect during the study. After midazolam premedication all volunteers reported symptoms with bolus ropivacaine 60 mg. Mean peak ropivacaine venous concentration was 4.48 $mg \cdot L^{-1}$.

Conclusion: An intravascular bolus of ropivacaine 60 mg reliably produces mild CNS toxic symptoms in premedicated volunteers.

Objectif : *Déterminer si un bolus intraveineux de ropivacaïne peut produire de façon fiable de légers symptômes de toxicité du système nerveux central (SNC) chez des humains sous sédation.*

Méthode : *Nous avons obtenu l'approbation du Comité d'éthique, et le consentement éclairé des 15 volontaires recrutés. Le monitorage du système cardiovasculaire (SCV) comprenait l'oxymétrie de pouls, l'électrocardiographie et le monitorage non effractif de la tension artérielle. Pendant la phase 1, les volontaires ont reçu en séquence un placebo, 30 mg, 45 mg et 60 mg de ropivacaïne en un bolus iv de 10 mL pendant 20 sec suivi d'un repos de deux heures entre chaque injection pour permettre la clairance plasmatique. Les volontaires devaient déclarer tout symptôme de toxicité lié à l'anesthésique local sur une échelle de réponse verbale. Après chaque dose, les volontaires qui rapportaient plus de trois symptômes d'une sévérité > 3/10 pendant plus de trois minutes ne recevaient pas d'autres doses expérimentales. La dose qui a régulièrement produit des effets toxiques bénins du SNC a été choisie pour la phase 2 de l'étude. En phase 2, les volontaires ont reçu 0,03* $mg \cdot kg^{-1}$ *de midazolam avant un bolus de ropivacaïne ou un placebo selon un devis randomisé, croisé et à double insu. Les volontaires devaient rapporter les symptômes toxiques et des échantillons de sang veineux ont été prélevés pour le dosage de la ropivacaïne.*

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Résultats : *En phase 1, la dose de 60 mg de ropivacaïne a produit des symptômes bénins réguliers de toxicité du SNC. Aucun volontaire n'a subi d'effet indésirable important du SNC ou du SCV pendant l'étude. Après la prémédication avec le midazolam, tous les volontaires ont éprouvé des symptômes avec le bolus de 60 mg de ropivacaïne. La concentration veineuse maximale de ropivacaïne a été de 4,48 mg·L^{-1}.*

Conclusion : *Un bolus intravasculaire de 60 mg de ropivacaïne produit régulièrement des symptômes toxiques du SNC chez des volontaires prétraités.*

TO safeguard against intravascular boluses of local anesthetic in regional anesthetic practice, incremental dosing is used whilst observing the patient for any untoward symptoms or signs of toxicity. Patients that have been sedated are less likely to detect intravascular injection of local anesthetic.[1]

Ropivacaine has been shown to possess a greater margin of cardiovascular (CVS) safety than bupivacaine at concentrations that produce central nervous system (CNS) effects and could possibly be given in a dose that would elicit CNS symptoms in the sedated patient without causing major CNS or CVS system adverse effects.[2–6]

We designed the following volunteer study to determine if an intravascular bolus dose of ropivacaine could be found that would reliably produce mild symptoms of CNS toxicity in sedated humans. This could represent a useful test of accidental intravascular injection in patients undergoing regional anesthesia in clinical practice.

Methods

The study was given Ethical approval by the University Health Network Research Ethics Board and each volunteer gave informed consent to take part in the study. The study was performed in two phases. The first phase of the study was to determine the dose of *iv* bolus ropivacaine that consistently produced mild toxic symptoms in unpremedicated volunteers. In the second phase of the study we aimed to further determine if the dose obtained from the first phase of the study continued to produce symptoms in premedicated volunteers. In addition, we measured plasma ropivacaine levels to correlate onset and offset of symptoms with venous plasma levels.

In the first phase of the study we recruited 15 volunteers classified as American Society of Anesthesiologists physical status I or II (12 males, three females; age 29–48 yr; weight 50–130 kg). Excluded were volunteers who were pregnant or who had a history of seizure or allergy to local anesthetic agents.

All volunteers fasted overnight and received no premedication. On the morning of the study a 20-gauge *iv* cannula was placed in the dorsum of the hand to permit delivery of the study drug. Volunteers were supine and monitored continuously with electrocardiograph (ECG), non-invasive blood pressure measurement (NIBP) and pulse oximetry (SpO_2). Hemodynamic and oxygen saturation data were recorded at baseline and every minute after *iv* bolus of study drug for 30 min. All volunteers were educated about common symptoms of mild local anesthetic CNS toxicity including perioral paresthesia, metallic taste, tinnitus and lightheadedness.

Volunteers received in sequence, a 10-mL *iv* bolus over 20 sec consisting of placebo, 30, 45 and 60 mg of ropivacaine (Astra Pharma Inc., Mississauga, ON, Canada). Each test period was separated by two hours to allow clearance of the study drug. This time was chosen to avoid plasma ropivacaine accumulation based on the distribution half-life when given by *iv* injection ($t_{½}\alpha$ = 14 ± 7 min).[7]

Volunteers were asked to report symptoms of local anesthetic toxicity at one-minute intervals for ten minutes and then five-minute intervals for 20 min after each injection. Volunteers scored symptom severity on an 11-point verbal response scale (VRS) graded between 0 (no symptoms) and 10 (worst imaginable symptoms). For safety reasons volunteers who reported, after any injection, more than three symptoms of CNS toxicity with a severity score greater than 3/10 lasting more than three minutes were withdrawn from further study.

The first phase was used to determine the optimal dose of *iv* bolus ropivacaine that produced consistent mild symptoms of CNS toxicity.

In phase 2 of the study we examined symptoms and associated plasma ropivacaine levels after bolus *iv* ropivacaine in the presence of *iv* premedication. From the first phase of the study we chose the bolus dose of ropivacaine that produced consistent mild CNS symptoms of local anesthetic toxicity. Volunteers from the previous phase of the study who had previously received the chosen dose of ropivacaine were recruited. No other selection criteria were applied to the 15 volunteers from the first phase of the study other than availability and having received ropivacaine 60 mg in the first phase of the study.

Volunteers fasted overnight. On the morning of the study in the supine position an *iv* cannula was placed and attached to saline 0.9% 1 L given as a slow infusion. An 18-G *iv* cannula was placed for delivery of an *iv* bolus of ropivacaine and a 14-G cannula was placed in the contralateral forearm for withdrawal of blood

samples. Non-invasive hemodynamic monitoring (NIBP, ECG and SpO_2) was placed.

Each volunteer was given 0.03 mg·kg^{-1} *iv* midazolam. After a ten-minute interval to simulate the placement of block needle or epidural catheter each volunteer received placebo or ropivacaine as a 10-mL *iv* bolus over 20 sec in a randomized double-blind crossover fashion. Volunteers were asked to report symptoms of local anesthetic toxicity with regard to type, severity (using VRS) and duration at zero, one, two, three, four, five, eight, ten, 15, 20, 30, 40, 60, 90 and 120 min from the time of injection. CVS parameters (NIBP, heart rate and SpO_2) were measured at the same time as recording of symptoms. Venous samples were withdrawn at zero, one, two, three, four, five, eight, ten, 15, 20, 30, 40, 60, 90 and 120 min from the time of injection. A two-hour rest period was allowed between either ropivacaine and saline injection or saline and ropivacaine injection (depending on randomization) and allowed collection of data and venous samples between injections. All data were collected by a blinded investigator. Blood samples were centrifuged immediately to separate the plasma fraction and frozen at -20°C until assay. Total plasma ropivacaine concentrations were determined by gas chromatography with a detection sensitivity of 0.003 mg·L^{-1}.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 10.0, Chicago, IL, USA). Hemodynamic data and differences in symptoms perceived between volunteers were analyzed using independent samples t test.

Results

Fifteen volunteers entered phase 1 of the study. Volunteer demographics are shown in Table I. Three out of 15 volunteers experienced symptoms that met exclusion criteria. Two were excluded after 30 mg and one after 45 mg of ropivacaine. The highest dose received by these volunteers was 0.33, 0.6 and 0.56 mg·kg^{-1} of ropivacaine respectively. The remaining twelve volunteers tolerated all three bolus doses of ropivacaine (30, 45 and 60 mg) and completed the first phase of the study. Major CVS or CNS toxic effects did not occur at any dose administered. One volunteer complained of muscle twitching (blinking) at the 60 mg dose. The only statistically significant CVS change between groups was an increase in mean arterial pressure from 94.9 mmHg [standard deviation (SD) 19] with the placebo injection to 101.2 mmHg (SD 23.5) with ropivacaine 45 mg ($P = 0.02$). There were no other CVS changes. The mean tolerated *iv* bolus of ropivacaine was 0.79 mg·kg^{-1} (SD 0.24 mg·kg^{-1}, range 0.33–1.2 mg·kg^{-1}).

Eight of 12 volunteers who had received the maximum *iv* bolus dose of ropivacaine (60 mg) according to the study protocol in the first phase were available and recruited for the second phase. The eight volunteers recruited for phase 2 did not differ statistically in number or severity of symptoms from the four volunteers who passed phase 1 and were not available. All eight volunteers perceived symptoms of mild local anesthetic toxicity by three minutes (mean 1.4 min, SD 0.8, range 1–3) from bolus injection. All symptoms had regressed completely by ten minutes (mean 6.3 min, SD 2.8, range 2–10). Symptoms were typical for mild local anesthetic toxicity and included perioral paresthesia, numbness in the mouth, metallic taste, ringing in the ears and lightheadedness. Symptoms experienced by volunteers following ropivacaine injection are presented in Table II. No volunteers suffered major CNS adverse effects. One volunteer complained of twitching of facial muscles after injection of ropivacaine (volunteer #12). No volunteer experienced symptoms with the placebo injection in the second phase of the study.

Volunteers who took part in the second phase of the study experienced similar symptoms to when they received the same dose of ropivacaine in the first phase of the study. There were no statistical differences with regard to number, severity, onset, offset or duration of symptoms produced by ropivacaine bolus between volunteers who had and had not received premedication (Table III available as additional material at www.cja-jca.org). The number of mild CNS toxic symptoms related to ropivacaine 60 mg *iv* bolus both with and without premedication is shown in Figure 1. The mean dose of ropivacaine was 0.87 mg·kg^{-1} (SD 0.25, range 0.46–1.2 mg·kg^{-1}). Two sets of venous samples were spoiled due to freezer malfunction and could not be analyzed. In the volunteers who had completed venous samples the mean ropivacaine dose was 0.8 mg·kg^{-1} and the mean venous maximum concentration (C_{max}) was 4.48 mg·L^{-1} (SD 2.3, range 2.27–8 mg·L^{-1}). The mean time to maximum venous concentration was 4.16 min (SD 3.86, range 1–10 min). Correlation of venous concentration compared to time for each volunteer is shown in Figure 2.

There were no significant differences between placebo and ropivacaine with regard to NIBP, heart rate or SpO_2 at any point in the second phase of the study.

Discussion

In this study the administration of bolus ropivacaine 60 mg produced consistent mild symptoms of local

TABLE I Demographic data of 15 subjects in phase 1 with maximum tolerated dose of ropivacaine

Subject	*Age (yr)*	*Weight (kg)*	*Sex*	*Max dose (mg)*	*Max dose/kg (mg·kg^{-1})*
1	31	85	M	60	0.7
2	29	53	F	30	0.6
3	35	64	M	60	0.94
4	48	80	M	45	0.56
5	35	75	M	60	0.8
6	41	62	M	60	0.97
7	37	69	M	60	0.87
8	53	90	M	30	0.33
9	40	130	M	60	0.46
10	39	65	M	60	0.92
11	38	90	M	60	0.67
12	35	51	F	60	1.1
13	35	50	F	60	1.2
14	36	90	M	60	0.67
15	38	59	M	60	1
Mean	38	74.2		55	0.79
Range	29–53	50–130		30–60	0.33–1.2

TABLE II Frequency of symptoms experienced by eight volunteers in phase 2 following ropivacaine 60 mg bolus injection

Symptoms	*Volunteers experiencing symptom Volunteer number (total)*
Visual disturbance	
- Blurred vision	12 (1)
Hearing disturbance	
- Ringing	9, 12, 14 (3)
- Buzzing	15 (1)
- Fullness	10, 12, 13, 14 (4)
Mouth discomfort	
- Metallic taste	10, 13 (2)
- Tingling around the mouth/tongue	12 (1)
- Numbess around the mouth and tongue	9 (1)
- Dryness	14, 15 (2)
Musculoskeletal discomfort	
- Muscular twitching	12 (1)
- Pins and needles	10, 11, 15 (3)
Others	
- Headache	14 (1)
- Dizziness	6, 10, 12 (3)
- Light-headedness	12 (3)

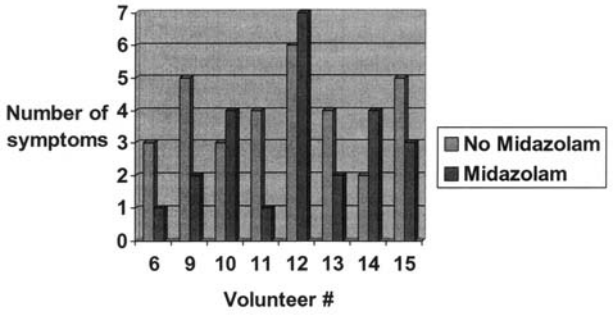

FIGURE 1 Number of mild central nervous systems toxic symptoms related to ropivacaine 60 mg injection both with and without premedication.

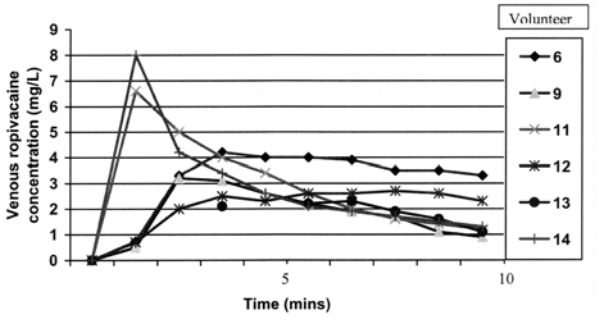

FIGURE 2 Correlation of ropivacaine plasma concentration against time for each volunteer in phase 2.

anesthetic toxicity in 12 volunteers and, when administered to eight premedicated volunteers, was found to be a reliable test of intravascular administration. An intravascular bolus of ropivacaine 60 mg was not associated with any major CVS or CNS adverse effects in this study. However with the small numbers of volunteers recruited no comment can be made about safety of the use of this test dose in clinical practice.

Several recent case reports describing partial or complete accidental intravascular administration of ropivacaine have documented CNS adverse effects without major CVS side effects at doses varying between 0.44 to 6 mg·kg^{-1}.[8–12] One case did note CVS toxic effects with a dose of 2.5.mg·kg^{-1} used for sciatic nerve block with estimated total plasma levels at time of injection of 7.5 mg·L^{-1}.[12] In our study we noted no CVS effects at doses up to 1.2 mg·kg^{-1}. This was despite the highest ropivacaine plasma concentration being in excess of 8 mg·L^{-1}. In addition mean C_{max} in our study was 4.48 mg·L^{-1}. As expected this concentration was significantly higher (4.48 mg·L^{-1} compared to 2.1 mg·L^{-1}) when ropivacaine was administered by bolus *iv* injection rather than by *iv* infusion as in previous studies.[13,14] One case did

report[11] seizures at a calculated venous plasma level of 5.75 $mg \cdot L^{-1}$ and this was lower than some of the peak concentrations measured in this study. The absence of seizures in the volunteers in this study may have been for two reasons. Firstly all volunteers received midazolam whereas the patient in the noted report[11] did not. Midazolam may have a protective anticonvulsant effect. Secondly, as noted in our own data, peak venous plasma levels may underestimate arterial concentrations. Therefore, the actual peak in the case report may have been greater than calculated had arterial plasma concentrations been measured.

The other concern with a test dose or incremental dosing is that the patient must be able to perceive symptoms despite previously administered sedative agents in order to prevent further accidental intravascular administration of local anesthetic agent. A previous study examining 2-chloroprocaine and bupivacaine found that sedated volunteers could not reliably detect the *iv* bolus of bupivacaine.[1] However in the present study ropivacaine 60 mg given as an *iv* bolus was detected by all volunteers and in clinical practice may provide warning of intravascular injection.

All volunteers experienced symptoms with the *iv* bolus of ropivacaine in the presence of premedication. There appeared to be no decrease in the number or severity of symptoms after the administration of 0.03 $mg \cdot kg^{-1}$ *iv* midazolam. This suggests that either the perception of symptoms of local anesthetic toxicity are not diminished by *iv* midazolam or that our dose of midazolam was not high enough. However this dose was selected because it is used in clinical practice for regional anesthesia in our own institution.

Three volunteers were excluded from the first phase of the study because of excessive number and severity of symptoms. It could thus be questioned as to whether ropivacaine 60 mg is a safe dose for other volunteers. However the dose at which these volunteers were withdrawn was small (from 0.33–0.56 $mg \cdot kg^{-1}$) compared to the maximum dose administered (1.2 $mg \cdot kg^{-1}$) to other volunteers. The criteria we used for assessing symptoms (VRS) were influenced by subjectivity and one of the excluded volunteers also experienced two symptoms with placebo. In addition, none of the excluded volunteers experienced CVS symptoms or developed signs of CVS toxicity at the highest dose administered. Increased magnitude of number and severity of symptoms could be associated with likelihood of developing adverse CNS or CVS adverse effects. In a study such as this one, the safety of volunteers is of primary concern. We wanted to withdraw any volunteer before they experienced excessive symptoms and well in advance of experiencing any CNS or CVS adverse effects.

This study has a number of limitations and any conclusions should be drawn in the knowledge that the data were obtained in a small number of volunteers. A larger clinical study is required to further determine the reliability and safety of ropivacaine 60 mg as a marker of intravascular injection. All subjective responses are open to variation. We tried to reduce this in the second phase by performing each injection in a randomized, double-blind manner.

The measurement of NIBP, heart rate and pulse oximetry in this young adult population is likely to be an insensitive measure of CVS adverse effects compared to previously used measures such as ECG and echocardiographic data. Subtle CVS changes such as decrease in stroke volume and contractility that were detected in previous studies[13,14] might have been detected had we used these techniques. However our data give reassurance that no gross CVS changes were occurring within the dose range used.

Venous plasma levels of local anesthetic are notably unreliable with regard to the temporal relationship with time of injection. This is demonstrated with our own data. However peak venous plasma levels give a reflection of the arterial concentration achieved and thus still give important safety data. We decided not to perform arterial puncture in this study because of the potential morbidity from an unnecessary arterial puncture in a volunteer population.

In summary this study found that ropivacaine 60 mg when given as an *iv* bolus provides consistent mild CNS symptoms of local anesthetic toxicity in premedicated volunteers without any CVS adverse effects and was found to be a reliable test of intravascular injection in this population. No major CNS or CVS symptoms or signs were elicited despite total venous plasma ropivacaine levels being twice that found in previous infusion studies.[13,14]

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