Central nervous system side effects are less important after *iv* regional anesthesia with ropivacaine 0.2% compared to lidocaine 0.5% in volunteers

[Les effets secondaires neurologiques sont moins importants après une anesthésie régionale iv réalisée avec de la ropivacaine à 0,2 % comparée à la lidocaïne à 0,5 %]

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Purpose: Following release of a double tourniquet for intravenous regional anesthesia (IVRA), ropivacaine was shown to have a longer duration of action and less central nervous system (CNS) side effects than lidocaine. This study examines the correlation of CNS side effects to plasma levels of lidocaine 0.5% and ropivacaine 0.2% when injected intravenously for IVRA.

Methods: In a double-blind, cross-over study, ten volunteers received IVRA with 40 mL ropivacaine 0.2% or lidocaine 0.5% at least four days apart. Both cuffs of a double-cuff tourniquet remained inflated until they could no longer be tolerated. The incidence, duration and intensity of CNS side effects were recorded at three, ten, and 30 min after tourniquet release and correlated with simultaneous venous blood samples.

Results: There was a lower incidence of CNS side effects with ropivacaine (6/10 volunteers) when compared to lidocaine (10/10 volunteers). There was also less duration of these side effects (mean $\pm$ SD, 5.1 ± 5.2 min vs 11.7 ± 6.7 min). Measured total plasma levels were highest at ten minutes with ropivacaine 0.2% ($1.2 \pm 0.3 \mu\text{g}\cdot\text{mL}^{-1}$) and at three minutes with lidocaine 0.5% ($1.7 \pm 0.6 \mu\text{g}\cdot\text{mL}^{-1}$). Peak CNS symptoms correlated with measured venous plasma levels for lidocaine, but occurred earlier with ropivacaine.

Conclusions: We observed a lower incidence of CNS side effects with ropivacaine as compared to lidocaine. Although ropivacaine's greater lipid solubility should, theoretically, lead to more CNS side effects, this was, likely, offset by slower release from tissues and lesser percentage of unbound (free) drug.

Objectif : Utilisée après le relâchement d'un double garrot pour l'anesthésie régionale intraveineuse (ARIV), la ropivacaine semble démontrer une action prolongée et moins d'effets secondaires centraux que la lidocaïne. La présente étude voulait vérifier la corrélation entre les effets secondaires sur le SNC et les niveaux plasmatiques de lidocaïne à 0,5 % et de ropivacaine à 0,2 % administrées par voie iv pour l'ARIV.

Méthode : Dix sujets volontaires ont participé à l'étude à double insu avec permutation et ont reçu une ARIV avec 40 mL de ropivacaine à 0,2 % ou de lidocaïne à 0,5 % à quatre jours d'intervalle au moins. Les deux manchons d'un garrot à double ballonnets sont demeurés gonflés jusqu'à ce qu'ils ne soient plus tolérés. L'incidence, la durée et l'intensité des effets secondaires sur le SNC ont été enregistrées à trois, dix et 30 min après le relâchement du garrot et mises en corrélation avec des échantillons de sang veineux prélevés simultanément.

Résultats : L'incidence des effets négatifs sur le SNC a été plus faible avec la ropivacaine (6/10 sujets) qu'avec la lidocaïne (10/10 sujets) et de plus courte durée (moyenne $\pm$ écart type, $5,1 \pm 5,2$ min vs $11,7 \pm 6,7$ min). Les niveaux plasmatiques totaux ont été plus élevés à dix minutes avec la ropivacaine à 0,2 % ($1,2 \pm 0,3 \mu\text{g}\cdot\text{mL}^{-1}$) et à trois minutes avec la lidocaïne à 0,5 % ($1,7 \pm 0,6 \mu\text{g}\cdot\text{mL}^{-1}$). Les symptômes neurologiques maximaux étaient en corrélation avec les niveaux plasmatiques veineux pour la lidocaïne, mais sont survenus plus tôt avec la ropivacaine.

Conclusion : La ropivacaine, comparée à la lidocaïne, a provoqué moins d'effets secondaires centraux. La plus grande liposolubilité de la ropivacaine devrait, en théorie, provoquer plus d'effets neurologiques, mais cela a été contrebalancé, semble-t-il, par la libération plus lente par les tissus et un pourcentage plus faible de la fraction libre.

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Presented in part at the Annual Meeting of the American Society of Anesthesiologists (ASA) October 14-18, 1999, San Francisco, California, USA.

Accepted for publication September 12, 2001.

Revision accepted November 16, 2001.

LOCAL anesthetics account for 5 to 10% of all reported adverse reactions to anesthetic drugs.¹ Both the central nervous and the cardiovascular systems are the primary target organs of local anesthetic toxicity. Feared complications are seizures, cardiac arrhythmias, and cardiac arrest. Mild central nervous system (CNS) side effects normally precede more serious ones as well as cardiac sequelae. Signs and symptoms of CNS toxicity include lightheadedness, dizziness, tinnitus, and metallic taste. Higher local anesthetic plasma levels induce convulsions, followed by coma and respiratory depression. Cardiovascular toxicity is characterized by reduced myocardial contractility and interference with conduction.

Reports of major complications such as seizures, cardiac arrest or death following intravenous regional anesthesia (IVRA) are scarce in the literature, but exist.^{2,3} In a prospective investigation⁴ of complication rates, three of 11,229 patients after IVRA developed a seizure after deflation of the tourniquet. A survey⁵ among North American anesthesiologists who frequently use IVRA confirmed that severe CNS and cardiovascular side effects do occur.

Lidocaine 0.5% is used frequently for IVRA. By the mid-eighties the longer-lasting local anesthetic ropivacaine was introduced into clinical practice. In contrast to currently used local anesthetics, ropivacaine is not prepared as a racemic mixture but as a pure left enantiomer. It is structurally related to mepivacaine and bupivacaine, with a clinical profile similar to the latter. The *s*-enantiomers have been shown to substantially reduce systemic toxicity when compared to their racemic counterparts. Four volunteer studies compared ropivacaine to lidocaine or bupivacaine and found potential advantages of ropivacaine over the other two local anesthetics.⁶⁻⁹ All noted less CNS and absent serious cardiac side effects with ropivacaine. These studies did not investigate, however, the quantification of CNS effects and their correlation to local anesthetic plasma levels. The present investigation examines duration, intensity, and the correlation of CNS side effects to venous plasma levels following IVRA with lidocaine and ropivacaine as local anesthetics.

Methods

Approval for the study was obtained from the Yale Human Investigational Committee. Ten healthy, unsedated volunteers participated in this randomized, double-blind, cross-over investigation comparing lidocaine 0.5% and ropivacaine 0.2% for IVRA. Study drugs were injected into the dorsum of the non-dominant hand at least four days apart. A second *in* line was placed into an antecubital vein of the dominant

arm for emergency drug administration. Volunteers were monitored continuously with echocardiography (ECG) leads II and V₅, pulse oximetry, and noninvasive blood pressure measurements.

Following exsanguination by gravity, the proximal cuff of a double-cuff tourniquet placed on the subject's upper arm was inflated to a pressure of 250 mmHg. Limb occlusion pressure was verified by loss of pulse oximetry tracing; local anesthetic (40 mL) was then injected over one minute. When the proximal tourniquet pressure became unbearable (verbal numerical pain score, VNPS=10), the distal cuff was inflated followed by release of the proximal tourniquet. During inflation and following deflation of the distal tourniquet, the volunteers were questioned about CNS side effects and asked to rate them on a verbal numerical intensity scale between 0–10. The incidence, duration, and intensity of CNS side effects were recorded at three, ten, and 30 min post tourniquet release and correlated with venous local anesthetic plasma levels which were sampled at the same time points. Local anesthetic plasma levels were determined by means of gas chromatography. After completion of the experiment, on study-day two, volunteers were asked to compare the intensity of CNS side effects between the two days.

Data are expressed as mean $\pm$ SD and were analyzed using Wilcoxon rank and paired *t* tests for non-parametric and parametric data, respectively; *P* < 0.05 was considered statistically significant.

Results

Volunteers were comparable with respect to age, weight and height. Total tourniquet inflation time was 72 ± 22 and 72 ± 19 min for lidocaine and ropivacaine respectively (*P*=*ns*).

During tourniquet inflation, no CNS side effects were reported by the volunteers, no cardiac arrhythmias were observed. Following deflation of the distal tourniquet there was a lower incidence of CNS side effects with ropivacaine as compared to lidocaine. While all volunteers receiving lidocaine reported lightheadedness, dizziness, metallic taste, or tinnitus, only six of ten subjects with ropivacaine experienced these mild CNS side effects. Duration of the side effects was shorter with ropivacaine as compared to lidocaine (5.1 ± 5.2 min *vs* 11.7 ± 6.7 min, *P*=0.028). Also, when asked for intensity, perceived CNS symptoms were markedly less intense after ropivacaine. A statistically significant difference was noted for verbal numerical intensity scores for dizziness, lightheadedness, tinnitus, and metallic taste at three minutes, and for lightheadedness and tinnitus after ten minutes following tourniquet release (Figure 1).

FIGURE 1 Verbal numerical intensity scores of mild central nervous system side effects.

FIGURE 2 Venous local anesthetic plasma levels at baseline (time 0) and during 30 min after tourniquet release.

Measured venous local anesthetic plasma levels were highest at three minutes with lidocaine ($1.7 \pm 0.6 \mu\text{g}\cdot\text{mL}^{-1}$) and at ten minutes with ropivacaine ($1.2 \pm 0.3 \mu\text{g}\cdot\text{mL}^{-1}$) after tourniquet deflation (Figure 2). Peak CNS symptoms correlated with measured venous plasma levels for lidocaine, but occurred earlier with ropivacaine (Figures 1 and 2). In both groups no cardiac arrhythmias were observed in the two ECG leads.

Discussion

The present cross-over study examined the correlation of CNS side effects with venous local anesthetic plasma levels after *iv* injection of lidocaine 0.5% and ropivacaine 0.2% respectively. None of the unsedated volunteers experienced severe CNS symptoms such as

seizures or cardiovascular events with either of the two agents. Overall, fewer subjects experienced mild CNS side effects after ropivacaine. Also, the duration and intensity of lightheadedness, dizziness, tinnitus, and metallic taste were less with this agent as compared to lidocaine. Although ropivacaine's greater lipid solubility should, theoretically, lead to more frequent, longer, and more intense CNS side effects, this most likely was offset by the agent's slower release from tissue secondary to its higher protein binding capacity (95% *vs* 65%) and, consequently, lesser percentage of unbound (free) drug (5% *vs* 35%). The peak of the described CNS symptoms correlated well with measured lidocaine plasma levels but occurred at a time when ropivacaine plasma concentration was still low. At the time of ten minutes when venous plasma was sampled, ropivacaine plasma levels, however, might have exceeded their peak already. Another reason for maximum effects appearing before maximum venous plasma concentrations could be the arteriovenous difference in concentrations.

Lidocaine IVRA is safe and effective, being associated with rapid onset of anesthesia after injection and termination of analgesia after release of the tourniquet. Deflation of the tourniquet five minutes after administration of $2.5 \text{ mg}\cdot\text{kg}^{-1}$ of lidocaine 0.5% resulted in no signs of cardiac or serious CNS effects,¹⁰ yet symptoms of tinnitus between 20 and 70 sec after deflation were noted. In the present study, peak symptoms occurred three minutes after deflation. However, the tourniquet had been inflated on an average for approximately one to one and a half hours. Presumably more lidocaine is bound to tissue proteins (Na^+ receptors) during this longer tourniquet time, and is then released slowly after deflation. This aspect is underlined by an investigation showing that approximately 70% of lidocaine remains within the tissues of the previously isolated limb after tourniquet release, the remainder entering the systemic circulation in the subsequent 45 min.¹¹ Release of tissue-bound lidocaine is increased when the limb is exercised, emphasizing the necessity of keeping the previously anesthetized extremity quiescent after tourniquet deflation.

Pharmacokinetic washout data are available for lidocaine following IVRA,^{11,12} but do not exist for ropivacaine. Ropivacaine is structurally related to bupivacaine; its ability to bind to proteins as well as its pK_a are also very similar if not equivalent to bupivacaine. Bupivacaine, however, binds tightly to activated sodium channels at low plasma concentrations ($<0.2 \mu\text{g}\cdot\text{mL}^{-1}$) displaying fast on - slow off kinetics. Consequently, the release of a bolus of bupivacaine as it occurs on deflation of the tourniquet has been associated with the

occurrence of toxic ventricular dysrhythmias including ventricular fibrillation resistant to conventional therapy.^{13,14} Due to the lower lipophilicity and thereby lower overall toxicity of ropivacaine, it may be more suitable for IVRA than bupivacaine. Its margin of safety was found to be approximately 25% higher than bupivacaine following continuous *iv* infusion.⁸ Two articles reported of patients accidentally receiving high dosages of ropivacaine intravascularly and the patients failed to develop life-threatening cardiovascular side effects.^{15,16} More recently, after sciatic nerve block with presumable intravascular injection of 30 mL of ropivacaine 0.75%, bradycardia with QRS enlargement and inversion of T-waves were reported.¹⁷ Still, no ventricular tachycardia or fibrillation developed after ropivacaine which was the case in patients accidentally receiving bupivacaine intravascularly. These latter patients could not be successfully resuscitated.

Ropivacaine's higher ability to bind to tissue proteins, leading eventually to delayed release from its binding sites after tourniquet release, may be the principal reason why there was a lower incidence, duration, and intensity of CNS side effects in patients, when compared to lidocaine. Further studies are required to clarify if ropivacaine is an alternative to lidocaine for IVRA.

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