Regional Anesthesia and Pain

The number of injections does not influence local anesthetic absorption after paravertebral blockade

[Le nombre d'injections n'influence pas l'absorption d'un anesthésique local après un bloc paravertébral]

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Purpose: The aims of this study are to determine if the injection of a single large dose of local anesthetics into the paravertebral space increases the risks of inducing toxicity compared with multiple small injections and to describe ropivacaine plasma concentrations resulting from paravertebral blockade.

Methods: Paravertebral blockade was performed using a solution of 10 mL ropivacaine 0.75%, 10 mL lidocaine CO_2 2% plus 0.1 mL epinephrine 1:1000 either by a single injection at T_3 or T_4 (Group S, $n = 6$) or by five injections of 4 mL each at T_2 to T_6 (Group M, $n = 8$). Blood samples were taken at zero, five, ten, 15, 20, 30, 45, 60 and 90 min and at two, three, four, five, six and eight hours. Ropivacaine and lidocaine plasma concentrations were measured by high performance liquid chromatography.

Results: Maximal plasma concentrations were comparable for lidocaine: 2.6 ± 1.3 (S) *vs* 2.6 ± 0.8 $\mu g \cdot mL^{-1}$ (M) and for ropivacaine: 1.3 ± 0.2 (S) *vs* 1.3 ± 0.1 $\mu g \cdot mL^{-1}$ (M). Area under the plasma concentration-time curve was higher in Group M for lidocaine: 577.6 ± 146.1 *vs* 401.7 ± 53.2 $mg \cdot min^{-1} \cdot mL^{-1}$ ($P = 0.04$) but similar for ropivacaine: 381.1 ± 95.4 (M) *vs* 363.1 ± 85.3 $mg \cdot min^{-1} \cdot mL^{-1}$ (S).

Conclusions: The injection of a single large bolus of local anesthetics into the paravertebral space does not increase its absorption. Maximal ropivacaine plasma concentrations resulting from paravertebral blockade are similar to those reported with equivalent doses of bupivacaine.

Objectif : *Les buts de cette étude étaient de déterminer si l'injection d'une dose unique d'un grand volume d'anesthésique local dans l'espace paravertébral en augmente l'absorption comparativement à l'injection de doses fractionnées et de décrire les concentrations plasmatiques obtenues après la réalisation d'un bloc paravertébral avec ropivacaïne.*

Méthode : *Un bloc paravertébral est réalisé avec une solution de 10 mL de ropivacaïne 0,75 % et 10 mL de lidocaïne CO_2 2 % adrénalinée (1:200,000) par une injection unique à T_3 ou T_4 (Groupe S, $n = 6$) ou cinq injections de T_2 à T_6 (Groupe M, $n = 8$). Les concentrations plasmatiques de lidocaïne et de ropivacaïne sont mesurées par chromatographie après prélèvement à zéro, cinq, dix, 15, 20, 30, 45, 60 et 90 min et à deux, trois, quatre, cinq, six et huit heures.*

Résultats : *Les concentrations plasmatiques maximales obtenues sont comparables dans les deux groupes pour la lidocaïne: 2,6 ± 1,3 (S) vs 2,6 ± 0,8 $\mu g \cdot mL^{-1}$ (M) et la ropivacaïne: 1,3 ± 0,2 (S) vs 1,3 ± 0,1 $\mu g \cdot mL^{-1}$ (M). L'aire sous la courbe concentration-temps du Groupe M est plus élevée pour la lidocaïne: 577,6 ± 146,1 vs 401,7 ± 53,2 $mg \cdot min^{-1} \cdot mL^{-1}$ ($P = 0.04$) mais comparable pour la ropivacaïne: 381,1 ± 95,4 (M) vs 363,1 ± 85,3 $mg \cdot min^{-1} \cdot mL^{-1}$ (S).*

Conclusion : *L'injection d'un grand volume d'anesthésique local dans l'espace paravertébral n'en n'augmente pas l'absorption. Les concentrations plasmatiques obtenues après la réalisation d'un bloc paravertébral avec ropivacaïne sont similaires à celles rapportées pour des doses équivalentes de bupivacaïne.*

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This study was supported by a grant from the Canadian Anesthesiologists' Society. Presented at the 12th World Congress of Anesthesiologists, Montreal, June 2000.

Accepted for publication August 21, 2000.

Revision accepted March 3, 2003.

PARAVERTEBRAL and intercostal blocks can lead to high plasma concentrations of local anesthetics.[1,2] Since local anesthetics injected in the paravertebral space diffuse in four directions, paravertebral blockade is sometimes performed by a single injection.[3–6] To date, there is no study comparing local anesthetic plasma concentrations obtained after injection of either a single large bolus or multiple small injections of local anesthetic into the paravertebral space.

Ropivacaine could be a good choice for paravertebral blockade due to its long-lasting action and its low cardiotoxicity.[7] Plasma concentrations of ropivacaine resulting from paravertebral blockade have not been reported.

The aims of this study were to determine if the single injection technique of paravertebral blockade could have a greater possibility of inducing toxic plasma concentrations of local anesthetics than the multiple injection technique and to describe ropivacaine plasma concentrations resulting from paravertebral blockade.

Methods

Our Institutional Ethics Committee approved this study and written informed consent was obtained for each patient. Fourteen patients participating in a clinical double-blind study design to evaluate the efficacy of the single injection technique of paravertebral blockade for minor breast cancer surgery who agreed to stay in the hospital for at least eight hours had local anesthetic plasma concentration measurements. Patients were excluded if they needed an axillary dissection, presented a history of allergic reaction to local anesthetics or had histories of neurologic or hemostatic disorders.

Patients in Group M received five paravertebral injections from levels T_2 to T_6 inclusively, whereas those from Group S received a single paravertebral injection at T_3 or T_4. After standard monitoring plus sedation with midazolam (1–3 mg *iv*) and fentanyl (50–150 µg *iv*), blocks were performed under sterile condition according to a standard technique of paravertebral blockade.[8] A mixture of 10 mL ropivacaine 0.75%, 10 mL lidocaine CO_2 2% and 0.1 mL of epinephrine 1:1000 was used. For patients in Group M, 4 mL of the solution were injected at each level. For patients in Group S, 3 mL of the solution were injected initially as a test dose, followed by 17 mL in four successive boluses. In both groups, the third and fourth cervical plexus rami were anesthetized by *sc* infiltration below the clavicle using an extra 100 mg lidocaine. For the surgery, the attending anesthesiologist could administer supplemental midazolam, fentanyl and/or propofol or resort to general anesthesia with the insertion of a laryngeal mask airway, higher doses of propofol and nitrous oxide if judged necessary.

A venous heparin-lock was installed for blood sampling on the opposite side of the *iv*. Blood samples of 6 mL were taken to measure the concentrations of ropivacaine and lidocaine at zero, five, ten, 15, 20, 30, 45, 60 and 90 min and at two, three, four, five, six and eight hours following the injection. This allowed for the detection of maximal concentrations (C_{max}) even if a second peak appeared at 244 min such as previously described by Kopacz *et al.* for ropivacaine.[2] Samples were placed on ice and centrifuged within one hour. Plasma samples were stored at -20°C until assayed.

Samples were prepared according to the technique reported by Björk *et al.* (precision of 10%).[9] To 1 mL sample of plasma, 5 µg bupivacaine were added as an internal standard, followed by 375 µL sodium carbonate 10% and extracted with 5 mL n-hexane:methylene chloride (4:1, v/v) by gentle agitation for 30 min. After centrifugation, organic layers were transferred to other tubes and evaporated to dryness. Residues were reconstituted with 250 µL mobile phase [70 mM sodium sulfate in 1.25 mM sulphuric acid: ACN 65:35 (v/v)], and analyzed using high performance liquid chromatography (HPLC) separation reported by Arvidsson and Eklund (precision of 10%), with some modifications.[10] Aliquots of 100 µL were injected into the analytical column (Hichrom S5 ODS 1) at 40°C of an HPLC system, with UV detection at 210 nm. Calibration curves ranged from 125 to 4000 $ng \cdot mL^{-1}$ plasma for ropivacaine and from 250 to 8000 $ng \cdot mL^{-1}$ plasma for lidocaine.

Statistical analysis was performed using a Chi square, Student's t tests with the Bonferroni correction, one-way or two-way ANOVA for repeated measures where appropriate. A $P < 0.05$ was considered significant.

Results

Both groups were comparable for age, weight, length, ASA physical status, length of surgery, sedation administered to perform the block or during the surgery, time to first request of an analgesic drug and analgesia requirements in the postoperative period (Table I). Mean maximal plasma concentrations were comparable between the two groups for lidocaine and ropivacaine (Figures 1 and 2; Tables II and III). Time to achieve maximal plasma concentrations was: 21.7 ± 18.4 min (Group S) *vs* 20.6 ± 12.1 min (Group M) for lidocaine and: 84.3 ± 35.7 min (Group S) *vs* 49.4 ± 21.3 min (Group M) for ropivacaine. The area under

TABLE I Demographic data

	Group S (n = 6)	*Group M (n = 8)*
Age (yr)	60.5 ± 11.8	62.9 ± 7.5
Weight (kg)	75.3 ± 10.1	65.2 ± 14.1
Length (cm)	163.8 ± 5.5	159.7 ± 6.4
ASA physical status (I/II/III)	(0/4/2)	(1/7/0)
Sedation administered to perform the technique		
Midazolam (mg)	0.8 ± 0.4	1.4 ± 0.6
Fentanyl (μg)	25.0 ± 7.4	75.0 ± 37.8
Length of surgery (min)	40.3 ± 18.0	38.6 ± 16.0
Number of anesthetized dermatoma	6.3 ± 0.8	5.5 ± 1.2
Intraoperative sedation		
Midazolam (mg)	0.8 ± 0.4	0.8 ± 0.7
Fentanyl (μg)	58.3 ± 58.5	65.6 ± 48.1
Propofol (mg)	78.0 ± 77.6	67.7 ± 97.8
Nitrous oxide (number of patients)	1	2
Postoperative analgesia		
Delay to first analgesic drug request (min)	416.7 ± 664.6	536.9 ± 397.4
Acetaminophen (mg)	664.6 ± 271.3	975.0 ± 662.8
Codeine equivalent (mg)*	223.0 ± 91.1	103.8 ± 190.3

Mean ± SD. * = three patients received *iv* meperidine which was converted to oral codeine equivalent (conversion factor: 4). *Rowlingston JC, Murphy TA.* Chronic pain. *In*: Miller RD (Ed.). Anesthesia, 5th ed., New York: Churchill Livingstone Inc., 2000: 2351–76.

TABLE II Pharmacokinetic data: lidocaine

Time (min)	*Group S (μg·mL⁻¹) (n = 6)*	*Group M (μg·mL⁻¹) (n = 8)*
5	2.2 ± 1.5	1.5 ± 1.2
10	2.3 ± 1.4	1.9 ± 0.9
15	2.0 ± 1.0	2.3 ± 1.0
20	1.8 ± 0.8	2.2 ± 0.6
30	1.6 ± 0.5	2.4 ± 0.7
45	1.7 ± 0.6	2.0 ± 0.6
60	1.5 ± 0.4	1.7 ± 0.6
90	1.5 ± 0.6	1.6 ± 0.5
120	1.8 ± 2.0	1.4 ± 0.4
180	1.2 ± 0.8	1.3 ± 0.3
240	1.0 ± 0.6	1.2 ± 0.6
300	0.9 ± 0.4	0.7 ± 0.2
360	0.6 ± 0.2	0.8 ± 0.4
480	0.5 ± 0.2	0.5 ± 0.2
C_{max} (μg·mL⁻¹)	2.6 ± 1.3	2.6 ± 0.8
Time to C_{max} (min)	21.7 ± 18.4	20.6 ± 12.1
AUC (mg·min⁻¹·mL⁻¹)	401.7 ± 53.2*	577.6 ± 146.1

Mean ± SD. *P = 0.04. C_{max} = maximal concentrations achieved; AUC = area under the curve.

TABLE III Pharmacokinetic data: ropivacaine

Time (min)	*Group S (μg·mL⁻¹) (n = 6)*	*Group M (μg·mL⁻¹) (n = 8)*
5	0.9 ± 0.6	0.9 ± 0.6
10	0.8 ± 0.3	1.0 ± 0.5
15	0.9 ± 0.3	1.0 ± 0.3
20	0.8 ± 0.2	1.0 ± 0.3
30	0.9 ± 0.2	1.1 ± 0.4
45	09 ± 0.3	0.9 ± 0.3
60	0.9 ± 0.3	0.8 ± 0.2
90	0.8 ± 0.2	0.8 ± 0.3
120	0.8 ± 0.3	0.7 ± 0.2
180	0.7 ± 0.2	0.7 ± 0.3
240	0.8 ± 0.1	0.6 ± 0.2
300	0.7 ± 0.3	0.6 ± 0.3
360	0.6 ± 0.4	0.6 ± 0.3
480	0.8 ± 0.5	0.7 ± 0.4
C_{max} (μg·mL⁻¹)	1.3 ± 0.2	1.3 ± 0.1
Time to C_{max} (min)	84.3 ± 35.7	49.4 ± 21.3
AUC (mg·min⁻¹·mL⁻¹)	363.1 ± 85.3	381.1 ± 95.4

Mean ± SD. C_{max} = maximal concentrations achieved; AUC = area under the curve.

the plasma concentration-time curve between zero and eight hours was higher in Group M for lidocaine: 577.6 ± 146.1 *vs* 401.7 ± 53.2 mg·min^{-1}·mL^{-1} (P = 0.04) but similar for ropivacaine: 381.1 ± 95.4 (Group M) *vs* 363.1 ± 85.3 mg·min^{-1}·mL^{-1} (Group S). Local anesthetic concentrations were < 6 μg·mL^{-1} for lidocaine and < 3 μg·mL^{-1} for ropivacaine for all patients at all times. No patients demonstrated signs or symptoms compatible with local anesthetic toxicity throughout the study.

Discussion

Local anesthetic plasma concentrations measured were comparable between the two techniques of paravertebral blockade. For lidocaine, C_{max} achieved were 2.6 ± 1.3 and 2.6 ± 0.8 μg·mL^{-1} for patients with single and multiple injections respectively, while values for ropivacaine peaked to 1.3 ± 0.2 and 1.3 ± 0.1 μg·mL^{-1} (Tables II and III). Though patients with the multiple injection technique tend to have slightly higher early concentrations, this was not statistically nor clinically significant. Indeed, area under the plasma concentration-time curve for lidocaine was even slightly higher in the multiple injection technique group. These results indicate that the injection of a single large bolus of local anesthetic does not increase its absorption and hence will not be prone to induce a higher risk of toxicity.

Absorption of local anesthetics is influenced by the site of injection, dosage and volume used, addition of a vasoconstrictive agent and pharmacologic profile of

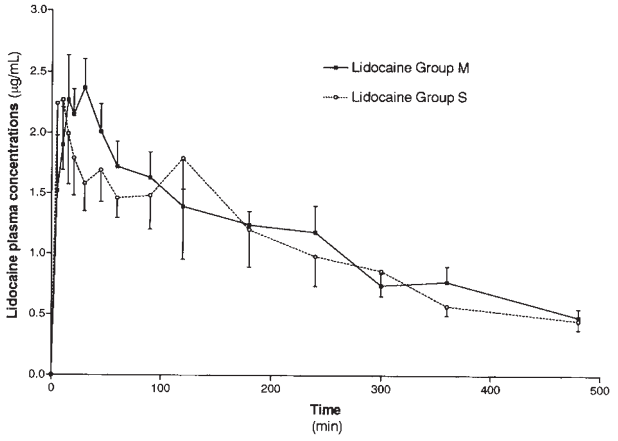

FIGURE 1 Lidocaine plasma concentrations. Mean ± SEM. Linear scale. Group S = single injection technique of paravertebral blockade; Group M = multiple (five) injection technique of paravertebral blockade.

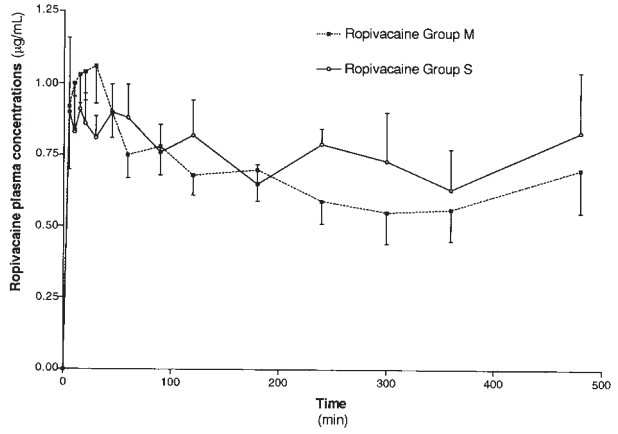

FIGURE 2 Ropivacaine plasma concentrations. Mean ± SEM. Linear scale. Group S = single injection technique of paravertebral blockade; Group M = multiple (five) injection technique of paravertebral blockade.

the local anesthetic itself.[11] Paravertebral and intercostal blocks are known to induce the highest local anesthetic concentrations while cutaneous infiltrations are less susceptible to lead to high blood concentrations and intoxications. When excessive blood concentrations of local anesthetics are achieved, the central nervous system (CNS) is usually affected first, while direct cardiac toxicity and cardiovascular collapse are associated with higher blood concentrations.[11] In the present study, none of the patients had blood levels compatible with CNS or cardiac toxicity since lidocaine concentrations were below 6 $\mu g \cdot mL^{-1}$ at all times and ropivacaine concentrations were below 3 $\mu g \cdot mL^{-1}$ in all the measurements done. None of the patients studied had clinical signs or symptoms indicative of CNS toxicity at any time. However, though the concentrations of local anesthetics measured were well below known toxic levels, it is important to take into account the fact that, for a mixture of local anesthetics, toxicities of the two agents are usually additive.[12] Anesthesiologists often use mixtures of local anesthetics in order to combine desirable properties, for example a rapid onset with lidocaine and long postoperative analgesia with ropivacaine or bupivacaine. There is also hope that maximal plasma concentrations of the two agents will not be achieved at the same time and that this will reduce the risk of inducing toxicity. Indeed, in the present study, maximal plasma concentrations of ropivacaine were achieved while lidocaine plasma concentrations were already decreasing, suggesting that the combination of these two agents for paravertebral blockade may indeed be interesting in terms of diminishing the risks of high blood local anesthetic concentrations.

Ropivacaine has gained wide popularity in the recent years among other anesthetic agents, mostly because of its claimed low cardiotoxicity compared to other long-acting local anesthetics such as bupivacaine.[7] Several adverse events have nevertheless been reported, leading most often to isolated CNS toxicity or to CNS toxicity with minor cardiovascular signs such as sinus tachycardia. Severe cardiac dysrythmias have, however, also been reported.[13–17] These adverse events were all attributed to the accidental intravascular injection of ropivacaine except for one patient who had repeated intoxication after doses of 6 and 4.5 $mg \cdot kg^{-1}$ of ropivacaine for brachial plexus blocks.[14] Using a two-compartment pharmacokinetic model, Muller *et al.* estimated that their patient who had grand mal seizure during an injection of ropivacaine for a sciatic block, reached a maximal concentration of 5.75 $mg \cdot L^{-1}$.[16] Though such a value was not observed in the present study, it is a concentration that can easily be achieved at or within 48 hr when ropivacaine is administered as a continuous infusion in an epidural or a plexus block.[18,19] However, since continuous infusion of local anesthetics are usually administered after major surgeries, the increase in α-glycoprotein that normally occurs in these situations may offer a certain degree of

protection by lowering free drug concentrations despite raising total blood concentrations of local anesthetics.[19]

Although comparisons from one study to another are always suboptimal, it seems reasonable to think that maximal concentrations achieved after the injection of ropivacaine into the paravertebral space are similar to those obtained with bupivacaine. Atanassoff *et al.* reported mean concentrations of bupivacaine of 1.44 ± 0.2 $\mu g \cdot mL^{-1}$ after the injection of 80 mg bupivacaine (16 mL bupivacaine 0.5%) while our patients had mean concentrations of 1.3 ± 0.4 $\mu g \cdot mL^{-1}$ with 75 mg ropivacaine (10 mL ropivacaine 0.75%).[20]

The most striking observation though in the present study is the fact that ropivacaine blood levels did not decrease, or very little, during the entire study period. The intrinsic vasoconstrictive properties of ropivacaine itself or the added epinephrine might be responsible for this phenomenon.[21] Ropivacaine may have been slowly and steadily liberated into the blood vessels during the entire study period (eight hours). Thus, blood concentrations of ropivacaine never achieved dangerous levels but apparent clearance was slow and blood concentrations were maintained at the same level for several hours.

In conclusion, the single injection technique of paravertebral blockade does not increase local anesthetic absorption. Maximal ropivacaine plasma concentrations resulting from paravertebral blockade are similar to those reported with equivalent doses of bupivacaine.

Acknowledgement

The authors wish to thank Mrs. Johanne Couture for her help in lidocaine and ropivacaine plasma concentration measurements.

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