Oral Mucosal Injection of a Local Anesthetic Solution Containing Epinephrine Enhances Muscle Relaxant Effects of Rocuronium

Asako Ninomiya, DDS, Yui Terakawa, DDS, PhD, Nobuyuki Matsuura, DDS, PhD, Tatsuya Ichinohe, DDS, PhD, and Yuzuru Kaneko, DDS, PhD

Department of Dental Anesthesiology, Tokyo Dental College, 1-2-2 Masage, Mihama-ku, Chiba 261-8502, Japan

The purpose of this study was to examine how submucosal injection of a clinically relevant dose of a lidocaine hydrochloride solution containing epinephrine affects the muscle relaxant effects of rocuronium bromide. Sixteen patients scheduled for orthognathic surgery participated in this study. All patients were induced with fentanyl citrate, a target-controlled infusion of propofol and rocuronium bromide. Anesthesia was maintained by total intravenous anesthesia. After nasotracheal intubation, an infusion of rocuronium bromide was started at 7 $\mu\text{g}/\text{kg}/\text{min}$, and the infusion rate was then adjusted to maintain a train of four (TOF) ratio at 10 to 15%. The TOF ratio just prior to oral mucosal injection of a 1% lidocaine hydrochloride solution containing 10 $\mu\text{g}/\text{mL}$ epinephrine (LE) was taken as the baseline. TOF ratio was observed for 20 minutes, with 1-minute intervals following the start of injection. Mean epinephrine dose was $85.6 \pm 18.6 \mu\text{g}$ and mean infusion rate of rocuronium bromide was $6.3 \pm 1.6 \mu\text{g}/\text{kg}/\text{min}$. TOF ratio began to decrease 2 minutes after the injection of LE, reached the minimum value at $3.1 \pm 3.6\%$ 12 minutes after the injection, and then began to recover. We conclude that oral mucosal injection of LE enhances the muscle relaxant effects of rocuronium bromide.

Key Words: Rocuronium; Lidocaine with epinephrine; Muscle relaxant effects.

The action of muscle relaxants is affected by a variety of drugs. Ephedrine shortens onset time, while β -receptor blocker prolongs it.¹ Aminoglycoside antibiotics,² calcium channel blockers, and magnesium sulphate prolong duration,^{3,4} whereas anticonvulsant drugs including carbamazepine shorten it.⁵ Propitocaine, lidocaine, and other local anesthetics prolong duration,⁶ while epinephrine produces dual effects of antagonizing neuromuscular relaxation through α -adrenergic effects and enhancing neuromuscular relaxation through β -adrenergic effects.⁷⁻⁹

Most of these reports are focusing on drug interactions between muscle relaxants and intravenously administered drugs. In oral and maxillofacial surgery, local anesthetic solutions containing epinephrine are administered submucosally in the surgical field. However, there are as yet no reports concerning interaction between muscle relaxants and such regionally administered local anesthetic solutions containing epinephrine. Regionally administered local anesthetics and epinephrine are rapidly absorbed into the blood during general anesthesia and demonstrate higher plasma concentrations than during conscious condition.^{10,11} It is therefore suggested that these drugs may affect the muscle relaxant effects.

In this study, we investigated the effect of regional administration of clinically relevant doses of lidocaine hydrochloride solution containing epinephrine on the muscle relaxant effects of rocuronium bromide.

Received December 21, 2010; accepted for publication October 5, 2011.

Address correspondence to Dr Asako Ninomiya, Department of Dental Anesthesiology, Tokyo Dental College, 1-2-2 Masage, Mihama-ku, Chiba 261-8502, Japan; asakoninomiya@tdc.ac.jp.

Anesth Prog 59:18-21 2012

© 2012 by the American Dental Society of Anesthesiology

ISSN 0003-3006/12

SSDI 0003-3006(12)

Subject Characteristics (Mean $\pm$ SD)

Gender (female/male)	13/3
Age (y)	24.0 $\pm$ 6.3
Height (cm)	161.7 $\pm$ 7.8
Body weight (kg)	54.9 $\pm$ 9.2
Body mass index	21.0 $\pm$ 4.0

METHODS

Subjects comprised 16 patients scheduled for orthognathic surgery, aged 17–36 years and classified in the American Society of Anesthesiologists (ASA) physical status I or II. After institutional approval, informed consent to participate in this study was obtained from each subject. All subjects were free from abnormal functions of kidney or liver and neuromuscular disease, and no drugs affecting neuromuscular transmission were used.

Prior to induction of general anesthesia, standard monitoring providing electrocardiography, noninvasive blood pressure, pulse rate, and SpO₂ measurement was performed. An acceleration-sensing muscle relaxation monitor (S/5 Patient Monitor, Datex-Ohmeda, Helsinki, Finland) was set up. Stimulating electrodes of the muscle relaxation monitor were secured to the skin along the ulnar nerve in the right forearm, and mechanosensors were attached to the right thumb and index finger. Additional monitoring during general anesthesia included body temperature, end-tidal CO₂, and invasive blood pressure measurement.

Anesthesia was induced with 100 μ g fentanyl citrate (fentanyl, Fentanest, Daiichi Sankyo, Tokyo, Japan), intravenously, followed by a target-controlled infusion of propofol (Diprivan, AstraZeneca, Osaka, Japan) administered to achieve a predicted effect-site concentration of 4.0 μ g/mL. After the subjects lost consciousness, 0.6 mg/kg rocuronium bromide was administered, and nasotracheal intubation was performed. Anesthesia was maintained by total intravenous anesthesia using room air, oxygen, and propofol. Supplemental analgesia during surgery was provided by repeated administration of fentanyl citrate or continuous infusion of remifentanyl hydrochloride (Ultiva, Janssen Pharmaceutical, Tokyo, Japan) to maintain stable hemodynamic condition.

After nasotracheal intubation, an infusion of rocuronium bromide was started at 7 μ g/kg/min, and the infusion rate was then adjusted to maintain a train of four (TOF) ratio at 10 to 15%. The TOF ratio just prior to oral mucosal injection of a 1% lidocaine hydrochloride solution containing 10 μ g/mL epinephrine (1% Xylocaine, AstraZeneca) (LE) was taken as the baseline, and TOF ratio was observed for 20 minutes, with 1-minute intervals following the start of administration. The rate of rocuronium bromide continuous

Time course of train of four (TOF) ratio after the administration of a local anesthetic solution. TOF value began to decrease 2 minutes after the administration of the 1% lidocaine hydrochloride solution containing 10 μ g/mL epinephrine, reached minimum value at $3.1 \pm 3.6\%$ after 12 minutes, and began to recover thereafter.

Mean $\pm$ SD, $n = 16$.

* $P < .05$ vs control (time 0).

infusion was kept constant during the 20 minutes when TOF ratio was monitored. TOF changes were observed only in subjects for whom a local anesthetic solution was given 50 minutes or more after the start of continuous infusion of rocuronium bromide. Subjects were excluded from the study if drugs with circulatory action were used prior to or during observation of TOF.

Data are expressed as mean $\pm$ standard deviation. Repeated measures analysis of variance followed by Dunnett test was used for statistical analysis. P value less than .05 was considered statistically significant.

RESULTS

The Table shows characteristics of the subjects. Mean volume of LE was 8.6 ± 1.9 mL, and mean epinephrine dose was 85.6 ± 18.6 μ g. The mean duration from the start of continuous infusion of rocuronium bromide to oral mucosal injection of LE was 111.3 ± 49.8 minutes. Mean infusion rate of rocuronium bromide during this period was 6.3 ± 1.6 μ g/kg/min. The control value of TOF ratio was $15.1 \pm 8.2\%$. TOF ratio 1 minute after the injection of LE increased in 6 cases, decreased in 5 cases, and did not change in 3 cases. TOF ratio began to decrease 2 minutes after the injection of LE, reached the minimum value at $3.1 \pm 3.6\%$ 12 minutes after the injection, and then began to recover (Figure).

DISCUSSION

Results of this study indicate that during continuous infusion of rocuronium bromide, regional administration

of LE enhanced its muscle relaxant effects for 10–15 minutes. We monitored TOF ratio to evaluate the muscle relaxant effects of rocuronium bromide in this study. TOF ratio as well as single twitch height would be reduced after the administration of nondepolarizing muscle relaxants.¹² Therefore, it is suggested that both TOF ratio and single twitch height would be further reduced if epinephrine could enhance muscle relaxant effects during rocuronium bromide infusion. It is reported that TOF ratio monitoring is superior to single twitch height monitoring to appropriately evaluate the effects of nondepolarizing muscle relaxants because TOF ratio is more sensitive for the muscle relaxant effects than single twitch height.¹²

Increased blood flow in muscle tissue after ephedrine administration is reported to shorten the onset time of vecuronium.¹ The mechanism of this effect is thought to be increased supply of vecuronium to muscle tissue due to increased blood flow. Based on this report, the authors performed animal experiments using male Japanese white rabbits to inject 2% lidocaine hydrochloride solution containing 6.25 µg/mL epinephrine (Xylestesin-A, 3M, Tokyo, Japan) to the oral mucosa. It was confirmed that blood flow in the masseter tissue was increased by 30% (unpublished data). Therefore, increased blood flow in muscle tissue might be also possible in this study. However, simulation of the predicted blood and effect-site concentrations of rocuronium at the injection of LE using IV_Sim3 software¹³ provided mean values of 1.43 ± 0.31 µg/mL and 1.44 ± 0.32 µg/mL, respectively. Therefore, it is difficult to attribute the changes in TOF ratio observed in this study to increased blood flow in muscle tissue.

Epinephrine has dual effects on neuromuscular junctions. In the initial period after administration, increased acetylcholine release via α -adrenergic effects at nerve endings produces inhibitory effects on muscle relaxation.^{6–8} Thereafter, β -adrenergic effects at end plates cause hyperpolarization, which raises the reaction threshold to acetylcholine and causes muscle relaxation-enhancing effects.^{6–8} At plasma epinephrine concentrations below 400 pg/mL, β -adrenegic effects are dominant; at 400 pg/mL and above, both α - and β -adrenergic effects are observed.^{14,15} The peak plasma epinephrine concentration after oral mucosal injection of LE in our study is predicted as approximately 1000 pg/mL.¹⁶ It is therefore indicated that both α - and β -receptors were activated after LE injection in this study. TOF ratio increased or decreased in nearly equal numbers 1 minute after administration of LE. It is suggested that in cases demonstrating a rapid rise in plasma epinephrine concentration, α -adrenergic effects appeared initially, and β -adrenergic effects occurring thereafter produced the enhanced muscle relaxant effects. In contrast, in cas-

es demonstrating a gradual rise in plasma epinephrine concentration, β -adrenergic effects occurring at low plasma epinephrine concentration masked α -adrenergic effects that occurred thereafter, and only enhancement of the muscle relaxant effects might be observed.

Further investigation will be needed to measure plasma epinephrine concentration under similar conditions and observe TOF ratio with a concomitant use of α - or β -receptor blocking agents. In this study, lidocaine was administered along with epinephrine. Lidocaine enhances muscle relaxant effects at the blood concentration of 2.5 ± 0.8 µg/mL,¹⁷ while predicted peak lidocaine blood concentration in this study would be 1.0–1.2 µg/mL.¹¹ Therefore, we believe that enhancement of muscle relaxant effects attributable to lidocaine was minimal, and that the results from this study are attributable primarily to the muscle relaxant effects of epinephrine on neuromuscular junctions.

In conclusion, oral mucosal injection of LE enhanced the muscle relaxant effects of rocuronium bromide.

REFERENCES

1. Szmuk P, Ezri T, Chelly JE, Katz J. The onset time of rocuronium is slowed by esmolol and accelerated by ephedrine. *Anesth Analg*. 2000;90:1217–1219.
2. Dupuis JY, Martin R, Tatrault JP. Atracurium and vecuronium interaction with gentamicin and tobramycin. *Can J Anaesth*. 1990;37:945.
3. Takasaki Y, Narumi Y, Shimizu C, Ochi G, Nagaro T, Arai T. Diltiazem potentiates the neuromuscular blockade by vecuronium in humans [in Japanese]. *Masui*. 1995;44:503–507.
4. Fuchs-Buder T, Wilder-Smith OGH, Borgeat A, Tassonyi E. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. *Br J Anaesth*. 1995;74:405–409.
5. Loan PB, Connolly FM, Mirakhur RK, Kumar N, Faring P. Neuromuscular effects of rocuronium in patients receiving beta-adrenoreceptor blocking, calcium entry blocking and anticonvulsant drugs. *Br J Anaesth*. 1997;78:90–91.
6. Usubiaga JE, Wikinski JA, Morales RL, Usubiaga LEJ. Interaction of intravenously administered procaine, lidocaine and succinylcholine in anesthetized subjects. *Anesth Analg*. 1967;46:39–46.
7. Omote T, Namiki A, Iwasaki H. Effects of catecholamines on the neuromuscular blocking action of a nondepolarizing muscle relaxant-Part II. Experimental studies on anti-neuromuscular blocking actions of catecholamines and the mechanisms of these actions in the dog [in Japanese]. *Masui*. 1985;11:1478–1497.
8. Bowman WC, Raper C. Effects of sympathomimetic amines on neuromuscular transmission. *Br J Pharmacol Chemother*. 1966;27:313.
9. Bowman WC, Raper C. Adrenotropic receptors in skeletal muscle. *Ann N Y Acad Sci*. 1967;139:741.

10. Homma Y, Ichinohe T, Kaneko Y. Oral mucosal blood flow, plasma epinephrine and haemodynamic responses after injection of lidocaine with epinephrine during midazolam sedation and isoflurane anaesthesia. *Br J Anaesth*. 1999;82: 570–574.
11. Ito S. A study on changes of serum and plasma lidocaine concentrations in dentistry [in Japanese]. *J Jpn Dent Soc Anesthesiol*. 1979;7:212–234.
12. Aaron FK, Monika MK, George GN. The relationship between acceleromyographic train-of-four fade and single twitch depression. *Anesthesiology*. 2002;96:583–587.
13. Uchida O, Nakao M. *TCI Software Guidebook* [in Japanese]. 1st ed. Tokyo, Japan: Kokuseido; 2003:124–133.
14. Clutter WE, Bier DM, Shah SD, Cryer PE. Epinephrine plasma metabolic clearance rate and physiologic threshold for metabolic and hemodynamic action in man. *J Clin Invest*. 1980;66:94–101.
15. Galster AD, Clutter WE, Cryer PE, Collins JA. Epinephrine plasma thresholds for lipolytic effects in man measurement of free fatty acid transport with [$^{1-13}$ C]palmitic acid. *J Clin Invest*. 1981;67:1729–1738.
16. Ichinohe T. The effect of intraoral administration of epinephrine on plasma catecholamine concentration, circulation, metabolism and respiration during general anesthesia with mechanical ventilation [in Japanese]. *J Jpn Dent Soc Anesthesiol*. 1985;13:388–409.
17. Munakata K, Suzuki T, Watanabe N, et al. Influence of epidural lidocaine injection on vecuronium-induced neuromuscular blockade [in Japanese]. *Masui*. 2004;53: 1377–1380.