Epinephrine Affects Pharmacokinetics of Ropivacaine Infiltrated Into Palate

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Pulpal anesthesia success rates for ropivacaine following maxillary infiltration anesthesia seem to be low. We investigated the hypothesis that the addition of epinephrine would affect the pharmacokinetics of ropivacaine by retaining ropivacaine in the mucosa of the injected area through the time-dependent distribution of ropivacaine in the rat maxilla and serum following maxillary infiltration anesthesia using ^3H -labeled ropivacaine. We then examined the vasoactivity of ropivacaine with or without epinephrine on local peripheral blood flow. The addition of epinephrine to ropivacaine increased ropivacaine concentrations in the palatal mucosa and adjacent maxilla by more than 3 times that of plain ropivacaine at 20 minutes. By observing the autoradiogram of ^3H -ropivacaine, plain ropivacaine in the maxilla was remarkably reduced 20 minutes after injection. However, it was definitely retained in the palatal mucosa, hard palate, adjacent maxilla, and maxillary nerve after the administration with epinephrine. Ropivacaine with epinephrine significantly decreased labial blood flow. This study suggests that 10 $\mu\text{g}/\text{mL}$ epinephrine added to 0.5% ropivacaine could improve anesthetic efficacy and duration for maxillary infiltration anesthesia over plain ropivacaine.

Key Words: Ropivacaine; Infiltration anesthesia; Epinephrine.

Ropivacaine, a levorotatory isomer (S-), has been widely used in clinical anesthesiology because of its decreased potential for systemic toxicity compared with the dextrorotatory isomer (R+)¹ as well as its high local anesthetic potency and long duration of action. The efficacy of dental conduction anesthesia with ropivacaine has been demonstrated.^{2–4} Kimi et al⁵ observed that ropivacaine has a strong affinity for the palatal mucosa and maxillary nerve but not for the maxilla in vitro, and the concentration remained high in the palatal mucosa, including the injection site. It is reported that the addition of 5 $\mu\text{g}/\text{mL}$ epinephrine to ropivacaine improves the

anesthetic efficacy and duration of maxillary infiltration anesthesia.⁶ However, there is no report demonstrating how epinephrine influences the efficacy of oral infiltration anesthesia with ropivacaine. We hypothesized that epinephrine affects the pharmacokinetics of ropivacaine by retaining ropivacaine in the mucosa of the injected area. The authors investigated the hypothesis using the time-dependent distribution of ropivacaine in the rat maxilla and serum following maxillary infiltration anesthesia using ^3H -labeled ropivacaine and then examined the vasoactivity of ropivacaine with or without epinephrine on the peripheral blood flow.

METHODS

This study was approved by the animal experiment committee of our university, and all procedures were

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Figure 1. Divisions of the maxilla. The palatal mucosa was removed from the areas of A and B. The maxilla part from the front end of the zygomatic arch to the end of the third molar was divided into 2 parts (C, D) along the solid line (—). The asterisk indicates the site of injection. The broken line (---) shows the position of a frontal section for the ^3H -autoradiogram. (A) Right palatal mucosa. (B) Left palatal mucosa. (C) Right maxilla part (including right molars; the zygomatic arch was removed). (D) Left maxilla part (including left molars; the zygomatic arch was removed).

performed according to the prescribed regulations. SPF Wistar male rats (weighing 250–300 g) aged 7–8 weeks were used in this study.

Measurement of Ropivacaine Concentration in the Maxillary Tissue and Serum

The injection of ropivacaine was performed according to our previous report.⁵ Under general anesthesia with an intraperitoneal injection of 50 mg/kg sodium pentobarbital, 20 μL of 0.5% ^3H -ropivacaine (Moravek Biochemicals, Brea, Calif; specific activity 0.321 GBq/mmol, 0.093 GBq/mL) or 0.5% ^3H -ropivacaine with 10 $\mu\text{g}/\text{mL}$ epinephrine was injected into the right palatal mucosa proximal to the first molar of the rat. The maxillary tissue was removed from rats 2, 5, 10, 20, 30, 40, 50, and 60 minutes after the injection ($n = 7$). The right and left palatal mucosa were removed from the maxilla. Then, the maxilla from the front end of the zygomatic arch to the end of the third molar was divided into right and left maxilla parts (Figure 1). After measurement of wet weight of each extracted tissue sample, the sample (150–200 mg) was put into a glass vial and solubilized with 1 mL of solubilizing agent (Solvable, PerkinElmer, Waltham, Mass) at 60°C for 2 hours. The chemical luminescence of the solubilized sample disappeared upon the addition of 50 μL of acetic acid. An aliquot 0.5 mL of blood was collected from the right femoral vein 2–90 minutes and 2–12 hours after the injection of each anesthetic ($n = 7$). The blood sample was centrifuged at 15,000g for 20 minutes at 4°C, and then 0.1 mL of serum was treated with the solubilizer and acetic acid.

The radioactivity (dpm) in the tissue or serum sample was measured using a liquid scintillation counter (LSC-

6100, Aloka Co., Ltd., Tokyo, Japan) after adding 10 mL of liquid scintillation cocktail (AQUASOL-2R, PerkinElmer). The amount of ropivacaine per wet weight of the tissue (ng/mg) was calculated from the measured value and the specific radioactivity. The concentration of radioactivity derived from ^3H -ropivacaine in the serum was expressed as dpm/mL.

Autoradiogram Analysis of ^3H -Ropivacaine Distribution in the Maxillary Tissue Using an X-Ray Film and an Imaging Plate

The autoradiogram analysis was carried out in accordance with our previous report.⁷ The maxilla part was extracted from the rat 2, 20, 40, and 60 minutes after injecting 20 μL of 0.5% ^3H -ropivacaine or 0.5% ^3H -ropivacaine with 10 $\mu\text{g}/\text{mL}$ epinephrine (Figure 1). The extracted maxilla was filled with 4% carboxymethyl cellulose sodium salt, frozen in hexane–dry ice, and frontally sectioned at the injection point with a cryostat microtome (CM3050S, Leica Microsystems GmbH, Wetzlar, Germany). The ^3H -sample section (20 μm) on an adhesive sheet (Transfer film, Leica Microsystems) was joined to an X-ray film (BioMax MS film, Kodak, Rochester, NY) combined with an intensifying screen (BioMax TranScreen LE, Kodak) and was kept at -80°C for 40 days. The X-ray film exposed to radiation was developed with an automatic developing machine. Then, the section on the sheet was stained with 0.25% eosin. The stained section was placed on an autoradiogram of the developed X-ray film, and then the distribution of ^3H -ropivacaine in the section was detected with a scanner (GT9500, Epson, Tokyo, Japan).

To determine the amount of ^3H -ropivacaine in the infiltrated area, the same ^3H -sample section used in the

Figure 2. Measurement of blood flow rate. The schema shows the locations of a probe of the flowmeter and injection of the agents. The blood flow rate was measured by the laser Doppler flowmetry with a contact-type probe. The probe was placed on the left upper lip under general anesthesia. Twenty microliters of each agent (0.9% NaCl [control], 10 $\mu\text{g}/\text{mL}$ epinephrine, 0.5% ropivacaine, or 0.5% ropivacaine with 10 $\mu\text{g}/\text{mL}$ epinephrine) was injected into the left upper lip adjacent to the angle of mouth with a 31-gauge needle. The blood flow rate was measured for 60 minutes after the injection of each solution ($n = 4$).

above experiment was also stuck to the imaging plate for ^3H (BAS-TR 2025, Fuji Photo Film, Tokyo, Japan) and was kept at room temperature for 40 days ($n = 5$). Analysis of the autoradiogram on the imaging plate was performed by an image analyzer (Typhoon 9410, GE-Healthcare Japan, Tokyo, Japan).

Measurement of Blood Flow Rate

To investigate the vasoactivity of 5% ropivacaine with or without 10 $\mu\text{g}/\text{mL}$ epinephrine, the blood flow rate in the left upper lip of rats was measured using a laser Doppler flow meter (ALF21, ADVANCE, Tokyo, Japan) under general anesthesia. A contact-type probe of the flow meter was fixed to the left upper lip, and 20 μL of the following solutions was injected into the left upper lip adjacent to the angle of mouth (Figure 2) under general anesthesia: 0.9% NaCl as a control, 10 $\mu\text{g}/\text{mL}$ epinephrine (Daiichi-Sankyo, Tokyo, Japan), 0.5% ropivacaine (AstraZeneca, Osaka, Japan), and 0.5% ropivacaine with 10 $\mu\text{g}/\text{mL}$ epinephrine. The labial blood flow rate was measured for 60 minutes after the injection ($n = 4$).

Statistical Analysis

Results are shown as mean $\pm$ SD. With regard to the change in ropivacaine concentration in the tissue and

serum, an alteration in each group was analyzed with non-repeated-measures analysis of variance, and the difference between the epinephrine additional group and epinephrine-free group was analyzed using Student's t test. Differences were considered significant at $P < .05$.

RESULTS

Ropivacaine Concentration in the Right Palatal Mucosa

The concentration of ropivacaine in the right palatal mucosa (Figure 3A) was measured over time after injecting ^3H -ropivacaine alone. The concentration reached the maximum value (219.5 ± 37.8 ng/mg wet weight) at 2 minutes after the injection and then decreased rapidly until 10 minutes. From 20 to 50 minutes after the administration, the ropivacaine concentration decreased to about 10% of the maximum value and then remained at low state. When ropivacaine was injected with epinephrine, the ropivacaine concentration in the right palatal mucosa reached the maximum value (252.1 ± 38.9 ng/mg wet weight) 2 minutes after the injection and remained at a high value (208.6 ± 37.5 ng/mg wet weight) until 10 minutes. The ropivacaine concentration in the right palatal mucosa between 10 and 60 minutes after the administration of ropivacaine with epinephrine was 3 to 5 times that after the administration of ropivacaine alone (Figure 3A).

Ropivacaine Concentration in the Left Palatal Mucosa

The ropivacaine concentration in the left palatal mucosa (Figure 3B), which is the opposite side from the injection site, reached the maximum value (13.4 ± 2.8 ng/mg wet weight) 2 minutes after injection with ropivacaine and decreased gradually until 20 minutes (Figure 3B). After that, the concentration changed with similar values (5–6 ng/mg wet weight) until after 40 minutes. The concentration of ropivacaine in the left palatal mucosa at 2 minutes after the injection was 6% of that in the right palatal mucosa. When ropivacaine with epinephrine was administered, the concentration of ropivacaine in the left palatal mucosa reached the maximum value (34.4 ± 1.6 ng/mg wet weight) at 5 minutes. The value was about 3 times higher than that after the administration of ropivacaine. The increasing tendency of ropivacaine concentration in the palatal mucosa by the addition of epinephrine was maintained until 60 minutes. In particular, a considerable quantity of ropivacaine (7.5

Figure 3. Distribution and concentration of ropivacaine in rat maxilla. After 0.5% ^3H -ropivacaine was infiltrated into the right palatal mucosa proximal to the first molar without ($\circ$) or with ($\bullet$) 10 $\mu\text{g}/\text{mL}$ epinephrine, the radioactivity in (A) right palatal mucosa, (B) left palatal mucosa, (C) right maxilla part, or (D) left maxilla part was measured with the liquid scintillation counter. The concentration (ng/mg wet weight) of ropivacaine was calculated by the specific radioactivity. Data are mean $\pm$ SD ($n = 7$). * $P < .05$ versus the ropivacaine group.

± 0.4 ng/mg wet weight) was detected at 60 minutes after the injection of ropivacaine with epinephrine, unlike that with the administration of ropivacaine alone. The ropivacaine concentration in the left palatal mucosa 2 minutes after the administration with epinephrine was 6% of that in the right palatal mucosa.

Ropivacaine Concentration in the Right Maxilla Part

The concentration of ropivacaine in the right maxilla part (Figure 3C) reached the maximum value (31.0 ± 6.9 ng/mg wet weight) within 2 minutes after the injection of the ropivacaine and decreased gradually until 30 minutes. The concentration at 50 minutes after infiltration anesthesia was reduced to 5.9% of the

maximum value. The maximum concentration of ropivacaine in this part was 14% of that in the overlaying right palatal mucosa. With the addition of epinephrine, the ropivacaine concentration in the right maxilla part was 52.2 ± 5.2 ng/mg wet weight 2 minutes after administration and was maintained at a similar value until 10 minutes. Then, the concentration decreased slightly until 60 minutes. The ropivacaine concentrations in the right maxilla part 2, 20, 30, and 50 minutes after the administration of ropivacaine with epinephrine were 1.7, 2.9, 6.0, and 7.6 times higher than those after the administration of ropivacaine alone, respectively. When ropivacaine was injected together with epinephrine, the ropivacaine concentration in the right maxilla 2 minutes after the injection was 21% of that in the right palatal mucosa.

Figure 4. Autoradiogram of ^3H -ropivacaine in a frontal section of the maxilla. ^3H -ropivacaine of 0.5% was infiltrated into the right palatal mucosa proximal to the first molar without (the left line) or with (the right line) 10 $\mu\text{g}/\text{mL}$ epinephrine. The maxilla removed 2, 20, 40, and 60 minutes after infiltration was frozen and sectioned at the injection point with the cryostat microtome. The section of 20 μm was exposed for 40 days at room temperature to MS-film with sensitization paper. Then, the sections were stained with 0.25% eosin. The stained section was put on top of the autoradiogram of MS-film and was scanned by a scanner with transmitted light.

Ropivacaine Concentration in the Left Maxilla Part

After the administration of both ropivacaine and ropivacaine with epinephrine, the ropivacaine concentration detected at 5 minutes after the infiltration anesthesia was the maximum value (ropivacaine: 3.1 ± 0.1 ng/mg wet weight, ropivacaine with epinephrine: 9.0 ± 2.1 ng/mg wet weight; Figure 3D). After 20 minutes, the ropivacaine disappeared from the left maxilla part.

Analysis of Ropivacaine Distribution in the Maxilla Using an Autoradiogram With X-Ray Film

To investigate the distribution of ^3H -ropivacaine in the maxilla after the injection, an autoradiogram of the maxillary frontal section was made and observed (Figure 4).

When plain ropivacaine was injected (Figure 4, left column), the infiltrated area of ropivacaine was limited to the right maxilla, which included the injection site. At 2 minutes after the administration of plain ropivacaine, ropivacaine infiltrated into the palatal mucosa, hard

palate, maxilla, maxillary nerve, and lower part of the right ethmoidal sinuses. After 20 minutes, ropivacaine was detected in the right palatal mucosa, hard palate, maxilla, and maxillary nerve. However, after 40 minutes, ropivacaine existed only around the administration site. After 60 minutes, a large proportion of ropivacaine had disappeared, with the exception of that at the injection point. On the other hand, when the ropivacaine was injected with epinephrine (Figure 4, right column), it extensively permeated into the palatal mucosa, hard palate, maxilla, and maxillary nerve, as well as into the central part of the ethmoidal sinuses in the injection side at 2 minutes after the administration. After 20 minutes, most of the ropivacaine disappeared from the ethmoidal sinuses, but the ropivacaine that was distributed in the palatal mucosa, hard palate, maxilla, and maxillary nerve was clearly retained. Furthermore, after 40 minutes, the ropivacaine distributed in the maxilla was barely reduced and was approximately the same as that at 20 minutes. The ropivacaine in the maxilla 40 minutes after the administration of ropivacaine with epinephrine remained over a very wide area compared with that after the injection of ropivacaine alone. A large amount of

Figure 5. Quantitative analysis of ^3H -autoradiogram. The section used for autoradiography in Figure 3 was exposed to the imaging plate also for 40 days at room temperature. Quantitative analysis of the ^3H -autoradiogram in the plate was performed by an image analyzer. ^3H -ropivacaine was infiltrated into the palatal mucosa without ($\circ$) or with ($\bullet$) epinephrine. The amount of autoradiographic signal in the section at 2 minutes after the injection of ropivacaine was indicated as 100 (2953 ± 18 dpm/section). The maximal amount of the signal existed in the maxilla at 2 minutes after the injection of ropivacaine with epinephrine. The radioactivity in this section was 4264 ± 29 dpm/section. Data are mean $\pm$ SD ($n = 4$). $*P < .05$ versus the ropivacaine group.

ropivacaine remained in the right palatal mucosa and hard palate even after 60 minutes.

Analysis of Ropivacaine Amount in the Maxilla Using an Autoradiogram With an Imaging Plate

To analyze the quantity of ^3H -ropivacaine distributed in the maxilla, the same frontal section that was used for the film autoradiography (Figure 4) was exposed to an imaging plate (Figure 5). The amount of autoradiographic signal in the section at 2 minutes after injection of ropivacaine was set as 100. The total ^3H -radioactivity in this section was 2953 ± 18 dpm/section ($n = 4$). The quantity of ropivacaine in the maxilla 20 minutes after the injection of ropivacaine decreased to about 17% of the 2-minute value and almost disappeared at 60 minutes. When ropivacaine was injected with epinephrine, the ropivacaine quantity in the maxilla at 2 minutes was hardly different from that after the injection of ropivacaine. However, by the addition of epinephrine, each quantity of ropivacaine at 20, 40, and 60 minutes

Figure 6. Concentration of radioactivity derived from ^3H -ropivacaine in the serum. After 0.5% ^3H -ropivacaine was infiltrated into the right palatal mucosa proximal to the first molar, without ($\circ$) or with ($\bullet$) 10 $\mu\text{g/mL}$ epinephrine, the radioactive concentration (dpm/mL) in the serum was measured with the liquid scintillation counter. Data are mean $\pm$ SD ($n = 7$). $*P < .05$ between the two groups.

was about 4 times that after the administration of ropivacaine alone.

The time variation of the ropivacaine distribution obtained by analysis of the autoradiogram accorded with the pharmacokinetics (Figure 3A and C) observed by quantification of ^3H -ropivacaine in the palatal mucosa and the maxilla part.

Ropivacaine Concentration in the Serum

After ^3H -ropivacaine alone was injected, the concentration of ^3H -radioactivity in the serum decreased rapidly and fell to 49% of the 2-minute value (the maximum value) at 50 minutes after the administration (Figure 6). Then, the concentration decreased gradually until 110 minutes. However, about 30% of the maximum concentration remained in the serum from 120 to 360 minutes. The serum concentrations of ^3H -radioactivity after the injection of ropivacaine with epinephrine were significantly lower from 2 to 50 minutes but higher from 70 to 150 minutes compared with ropivacaine alone.

Blood Flow Rate

The injection of 0.9% NaCl as a control did not significantly change the blood flow from 10 to 60 minutes after the injection. Compared with the control, 10 $\mu\text{g/mL}$ epinephrine remarkably reduced the blood

Figure 7. Effect of ropivacaine on the blood flow rate of rat upper lip. After 20 μ L of 0.9% NaCl (○), 0.5% ropivacaine (●), 10 μ g/mL epinephrine (△), or ropivacaine with epinephrine (▲) was injected to the rat upper left lip, the labial blood flow rate was measured by a laser Doppler flow meter (ALF21, ADVANCE) with a contact-type probe. Data are mean $\pm$ SD ($n = 4$). * $P < .05$ epinephrine versus ropivacaine with epinephrine.

flow rate until 40 minutes. The blood flow rate decreased to about 50% of the control value at 35 minutes after the injection. The reduced blood flow was restored to near the control value after 50 minutes. After the injection of 0.5% ropivacaine, the blood flow rate was varied similar to saline control until 2.5 minutes but gradually reduced thereafter compared with the control. The flow rate after 45 minutes decreased to 77% of the control value. Ropivacaine with epinephrine reduced the blood flow rate until 40 minutes after the injection. The low level of flow rate was maintained and was not restored to the control value until 60 minutes. The relative blood flow rates by epinephrine were 4.4 ± 0.5 and 5.4 ± 0.5 at 50 and 60 minutes later, respectively; those by ropivacaine with epinephrine were 3.0 ± 0.2 and 3.9 ± 0.7 , respectively. There were significant differences between the 2 groups in the blood flow rate at 50 and 60 minutes ($n = 4$, $P < .05$; Figure 7).

DISCUSSION

The results of this study demonstrated that 10 μ g/mL epinephrine retained ropivacaine in the palatal mucosa and bone of the injection area and prevented the rapid elevation of blood concentration after oral infiltration anesthesia.

Ropivacaine is used clinically for peripheral nerve block, postoperative analgesia, and epidural anesthesia.^{6–9} It is well known that the addition of epinephrine prevents the elevation of ropivacaine plasma concentra-

tions with peripheral nerve block, epidural, and intrathecal administration.^{10,11} The anesthetic efficacy of ropivacaine for dental anesthesia has been evaluated.^{2–4} However, it has been reported that individual differences are observed in the effects of infiltration anesthesia with ropivacaine for the dental pulp and that the anesthetic success rate increases and the duration of pulpal anesthesia is prolonged by adding 5 μ g/mL epinephrine.¹² Therefore, in this study, to investigate the effect of epinephrine on the pharmacokinetics of infiltrated ropivacaine, the time-dependent distribution in the maxilla and serum concentration of ropivacaine were analyzed after maxillary infiltration anesthesia with 5% ³H-ropivacaine with or without 10 μ g/mL epinephrine. In the palatal mucosa including the injection site (the right palatal mucosa), the ropivacaine concentrations from 20 to 60 minutes after the injection of ropivacaine with epinephrine were 3–5 times those after the injection of ropivacaine alone. Interestingly, 0.5% plain ropivacaine significantly decreased the labial blood flow rate from 40 to 60 minutes after the injection compared with the control. Therefore, the mild intrinsic vasoconstrictive effect of ropivacaine itself^{13,14} may prolong the vasoconstrictive effect of epinephrine, which lasted for 40 minutes. In the left palatal mucosa, contralateral to the injection site, the maximum ropivacaine concentration after the injection of ropivacaine with epinephrine was 3.1 times and the concentration at 60 minutes was 5.5 times those after the injection of ropivacaine alone. The result revealed that the added epinephrine exerted an effect on the contralateral side of the injection site as well. In the right maxilla part, the maximum ropivacaine concentration after the injection of ropivacaine with epinephrine (at 2 minutes) was 21% of that in the overlying palatal mucosa. The concentrations in the bone from 2 to 50 minutes after the injection with epinephrine were significantly higher those after the injection of ropivacaine alone. The results of the present study suggest that epinephrine facilitated the accumulation of ropivacaine in the palatal mucosa and then resulted in higher ropivacaine concentrations also in the bone.

The analysis of autoradiograms of frontal sections of the maxilla 2 minutes after the injection of ³H-ropivacaine with epinephrine showed extensive permeation of ropivacaine in the central part of the right ethmoidal sinuses. Even after 60 minutes, 13% of the maximum amount of ropivacaine remained in the palatal mucosa and hard palate. The results were consistent with the findings of the concentration of ropivacaine in the tissue, revealing that addition of epinephrine to ropivacaine markedly prolonged its local retention. Therefore, we concluded that the efficacy and duration of anesthesia

with 0.5% ropivacaine could be improved by the addition of 10 µg/mL epinephrine.

Thin-layer chromatography confirmed that more than 70% of ³H-labeled compounds detected in the serum within 60 minutes after the infiltration anesthesia with ³H-ropivacaine are nonmetabolized ropivacaine.⁵ In the present study, the ³H-radioactivity in the serum after the injection of ³H-ropivacaine with epinephrine into the maxilla was significantly lower than that after the injection of ³H-ropivacaine alone from 2 to 50 minutes after the injection. This result indicated that a rapid increase of the ropivacaine blood concentration was prevented by epinephrine. ³H-radioactivity at 360 minutes remained at a similar level as that at 200 minutes. ³H-labeled compounds in the serum after 6 hours and thereafter might be almost the recirculating metabolites of ropivacaine,^{15,16} which did not easily excrete from the rat body. In humans, ropivacaine is metabolized to 2,6-pipecoloxylidide and 3-hydroxyropivacaine by hepatic cytochrome P-450 enzymes. Both metabolites have significantly less local anesthetic potency than ropivacaine. However, in advanced renal disease patients, 2,6-pipecoloxylidide may accumulate and produce a toxic effect.¹⁷

For infiltration anesthesia in the dental field, anesthetics should diffuse well in the soft tissue and bone and then permeate into the nerve fibers, exerting their effects.¹⁸ The vasoactive effect of local anesthetics is closely involved in their regional and systemic absorption. Most local anesthetic agents possess some degree of vasodilating activity, which increases their own uptake into the blood vessels. Thus, lidocaine preparations for infiltration anesthesia in dentistry, otolaryngology, and plastic and other surgical fields, for example, contain epinephrine to decrease the rate of systemic absorption, which reduces peak plasma levels and the risk of local anesthetic toxicity and increases the duration of action and the depth of anesthesia.¹⁹ The effect of 10 µg/mL epinephrine on the localization and retention of ³H-ropivacaine at the injection area remained longer than that of ¹⁴C-lidocaine after the maxillary injection previously reported.²⁰ Ropivacaine at a concentration of 0.25%–0.75% has been reported to decrease the blood flow in its injection area.^{13,21–23} In this study, 0.5% ropivacaine also slightly reduced the labial blood flow of the rat. A significant decrease in the blood flow rate compared with that of the control was observed for a longer period after the injection of 0.5% ropivacaine with 10 µg/mL epinephrine than after the injection of 10 µg/mL epinephrine. Therefore, 0.5% ropivacaine significantly augmented the reduction of the labial blood flow rate by 10 µg/mL epinephrine.

Ropivacaine is a S(-)-enantiomer of n-alkyl-substituted pipecolyl xyliidines (a pipecoloxylidide: a homologue of

mepivacaine and bupivacaine). Mepivacaine and bupivacaine for clinical use are racemic mixtures of the enantiomers (50:50 mixtures).²⁴ The S(-)-enantiomers of bupivacaine and mepivacaine appear to be less toxic than the commercially available racemic mixtures of these local anesthetics.²⁴ It has been demonstrated that more S(-)- than R(+)-enantiomer of mepivacaine or bupivacaine is taken up by the lungs, thus reducing the concentration of the drug reaching the brain, where significantly more R(+)-enantiomer than S(-)-enantiomer is found.²⁵ Therefore, ropivacaine may be a safer long-acting amino-amide local anesthetic than levo-bupivacaine.

In conclusion, the results obtained in this study suggest that the addition of 10 µg/mL epinephrine retains a larger amount of ropivacaine for a longer duration in the mucosa and bone of injected area and implies that 0.5% ropivacaine with 10 µg/mL epinephrine is a more potent preparation for infiltration anesthesia in dentistry with less risk of systemic toxicity.

Conflict of Interest Statement

The authors report no conflict of interest.

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