The Local Pharmacokinetics of ^3H -Ropivacaine and ^{14}C -Lidocaine After Maxillary Infiltration Anesthesia in Rats

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The effects of infiltration anesthesia with ropivacaine on the dental pulp are considered to be weak. This may be partly associated with its permeation into the oral tissue. With the objective of investigating the local pharmacokinetics of ropivacaine and lidocaine following infiltration anesthesia, we injected ^3H -ropivacaine or ^{14}C -lidocaine to the palatal mucosa in rats, measured distributions of radioactivity in the maxilla, and compared the local pharmacokinetics of these agents. The animals were sacrificed at various times and the maxillas were removed. The palatal mucosa and maxillary nerve were resected, and the bone was divided into 6 portions. We measured radioactivity in each tissue and calculated the level of each local anesthetic ($n = 8$). Lidocaine diffused to the surrounding tissue immediately after the injection, whereas ropivacaine tended to remain in the palatal mucosa for a longer period. Lidocaine showed a higher affinity for the maxillary bone than ropivacaine. There was a correlation between the distribution level of local anesthetics in the maxillary bone and that in the maxillary nerve. The lower-level effects of infiltration anesthesia with ropivacaine on the dental pulp may be because ropivacaine has a high affinity for soft tissue, and its transfer to bone is slight.

Key Words: Ropivacaine; Lidocaine; Infiltration anesthesia; Local pharmacokinetics.

Since the clinical introduction of ropivacaine, its safety in the central nervous and cardiovascular systems compared with bupivacaine has attracted attention.¹ Ropivacaine is also widely used for infiltration anesthesia in Europe.^{2–4} Ropivacaine used for inferior alveolar nerve block has been reported to induce effective anesthesia with a long duration.^{5,6} On the other hand, there are individual differences in the effects of infiltration anesthesia with ropivacaine on the dental pulp, and its anesthetic efficacy has been reported to be lower than that of lidocaine.⁷ We hypothesized that a factor that contributed to less effective infiltration anesthesia with ropivacaine was its decreased permeability in oral tissue.

In this study, to examine the local distribution of ropivacaine and lidocaine after maxillary infiltration anesthesia, we injected radioisotope-labeled local anesthetics into the rat maxilla, and compared their distributions over time.

METHODS

Approval from the Animal Care Committee of the Nippon Dental University was obtained before the commencement of this study, and all experiments were conducted in accordance with the rules and guidelines concerning care and use for laboratory animal experiments.

Preparation of Local Anesthetics

^3H -ropivacaine (specific radioactivity, 0.317 GBq/mmol; radioactivity concentration, 0.093 GBq/mL) was prepared by adding ^3H -labeled ropivacaine hydrochloride

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Figure 1. Divisions of the maxilla. The arrow shows the site of the injection. The maxilla was divided into 6 parts, which were called as follows: 1, right incisive part (including the right incisor); 2, left incisive part (including the left incisor); 3, right maxillary part (including right molars; the zygomatic arch was removed); 4, left maxillary part (including left molars; The zygomatic arch was removed); 5, right palatal part; and 6, left palatal part. The palatal mucosa and nerves running in the maxilla (maxillary nerves) were detached from parts 3 and 4.

(Moravsek Biochemicals, Inc, Brea, Calif; specific radioactivity, 37 GBq/mmol; concentration, 1.85 GBq/mL) to 0.5% ropivacaine hydrochloride.

^{14}C -lidocaine (specific radioactivity, 2.81 MBq/mmol; concentration, 0.185 MBq/mL) was prepared by adding ^{14}C -labeled lidocaine hydrochloride (American Radiolabeled Chemicals, Inc, St. Louis, Mo; specific radioactivity, 2.035 MBq/mmol; concentration, 3.7 MBq/mL) to 2% lidocaine hydrochloride.

Preparation of Animals

Male Wistar rats aged 7 weeks (body weight, 250–280 g) were anesthetized by intraperitoneal administration of sodium pentobarbital (50 mg/kg). The rats were allocated to 2 groups: ^3H -ropivacaine group (group R) or ^{14}C -lidocaine group (group L). Twenty microliters of either radioisotope-labeled anesthetic was injected using a microsyringe with a 31G needle into the palatal mucosa proximal to the maxillary right molar over 30 seconds (Figure 1).

Measurement of Local Anesthetics

Animals were sacrificed 0.5, 2, 5, 10, 20, 30, and 60 minutes after anesthetic injection, and the maxilla of each animal was resected. The palatal mucosa and maxillary nerve were separated before the maxilla was divided into 6 parts (called right and left incisive,

maxillary, and palatal parts hereafter; Figure 1). The wet weight of each specimen was measured, and each tissue (150–200 mg) was placed in vials for the liquid scintillation counter, and 1 mL of a tissue solubilizer (Solvable, PerkinElmer, Inc, Waltham, Mass) was added. After incubation at 60°C for 3 hours with shaking, the specimen was neutralized by adding acetic acid to prevent chemiluminescence.

Measurement of Radioactivity

The specimens were mixed with 10 mL of a scintillation cocktail (AQUASOL-2®, PerkinElmer) and left in the dark at room temperature for 24 hours, and radioactivity (dpm) was measured using a liquid scintillation counter (LSC-6100, Aloka, Tokyo, Japan). The amount of each local anesthetic per wet tissue weight (ng/mg) was calculated from specific radioactivity.

Statistical Analysis

The local anesthetic concentrations in tissues are presented as mean $\pm$ SD. The differences in concentrations over period versus the peak value in each group were analyzed by 1-way ANOVA, Student-Newman-Keuls test. $P < .05$ was considered significant ($n = 8$).

Extraction and Separation of Ropivacaine or Lidocaine

To determine whether the radioactivity measured in each tissue was derived from ropivacaine, lidocaine, or their metabolites, ropivacaine and lidocaine were separated and quantified by thin-layer chromatography (TLC).

^3H -ropivacaine (200 μL) or ^{14}C -lidocaine (50 μL) was injected into the rat maxilla using a method similar to that above. The palatal mucosa and maxilla were resected 1 hour and 24 hours after the injection and cut into thin sections. Each cut tissue (200 mg) was mixed with 1 mL water, homogenized for 1 minute, and ultrasonicated with 1 mL ethanol. The suspension (1 mL) was centrifuged (4°C, 15,000g, 20 minutes), and the supernatant was used as samples for TLC.

As the TLC plate, Silicagel 60F₂₅₄® (Merck, Darmstadt, Germany) was used. The developing solvent was a mixture of 2-propanol, CH_3COOH , and 0.1 N HCl at a ratio of 56 : 15 : 9 (vol/vol/vol). After 20 μL of 40 mg/mL ropivacaine or 80 mg/mL lidocaine as a carrier was prespotted to the start line of the TLC plate, 50 μL of each sample extracted by the above method was applied. The plates were developed at room temperature (23°C) for 4 hours.

The area from the lower end of the plate to the solvent front was divided into 1–9 zones (1.8 cm long and 2 cm wide). Ropivacaine and lidocaine detected as dark spots by ultraviolet irradiation (wavelength : 253.7 nm) were confirmed.

Evaluation of Tissue Affinity of Ropivacaine and Lidocaine In Vitro

To evaluate the affinity of ropivacaine and lidocaine for oral tissue, equilibrium dialysis was performed.

Sixty milligrams of the palatal mucosa, maxillary nerve, brain, and liver and 0.4 mL of serum were collected. The maxillary bone (maxilla) was mixed with Dulbecco's phosphate-buffered saline (Invitrogen, Carlsbad, Calif), comminuted using a mortar, ultrasonicated, and centrifuged, and the supernatant was used as samples.

A microdialysis system (Bio-Teck International, Inc, Needville, Tex) was used for equilibrium dialysis. The palatal mucosa, maxillary nerve, brain, liver, or serum or the supernatant of the comminuted maxillary bone and 0.4 mL phosphate-buffered saline were placed in dialysis cups (molecular weight cutoff, 12,000 d), and equilibrium dialysis was performed using 200 mL of phosphate-buffered saline containing 0.05% ^3H -ropivacaine or 0.2% ^{14}C -lidocaine as an external solution at 4°C for 26 hours.

After dialysis, radioactivity in each sample was measured, and the amount of local anesthetic per wet weight of each tissue (nmol/mg) was calculated. For the maxillary bone and serum, the protein content (mg) in samples was measured using a BCA Protein Assay Kit (Pierce, Rockford, Ill), and the amount of local anesthetic per protein content (nmol/mg protein) was calculated.

RESULTS

Distribution of Local Anesthetics in the Oral Tissue

In the following, the highest anesthetic level in the tissue observed at the time points of observation was regarded as the maximum value.

Changes in the local anesthetic concentration in the following tissues were observed.

The ropivacaine concentration in the palatal mucosa (Figure 2A) reached the maximum (279.0 ± 23.3 ng/mg) 0.5 minutes after injection and significantly decreased to 60.5%, 78.9%, and 57.1% of the maximum value after 2, 5, and 10 minutes, respectively. No significant difference was observed between the

Figure 2. Concentrations of (A) ropivacaine and (B) lidocaine in the right palatal mucosa, maxillary part, and maxillary nerve. After 0.5% ^3H -ropivacaine or 2% ^{14}C -lidocaine was infiltrated into the right palatal mucosa proximal to the first molar of rats, each radioactivity in palatal mucosa (○), maxillary bone (□), or maxillary nerve (△) was measured with a liquid scintillation counter. The concentration (ng/mg wet weight) of ropivacaine or lidocaine was calculated from the specific radioactivity. Data are mean $\pm$ SD ($n = 8$). (A) The ropivacaine level in the palatal mucosa reached the maximum 0.5 minutes after the injection, and significantly decreased after 2, 5, and 10 minutes compared with the maximum level ($P < .01$). There was no significant difference in the anesthetic level between 2 and 5 minutes or between 5 and 10 minutes. The maximum level in the maxillary part was observed 0.5 minutes after the injection. The levels significantly decreased after 2 minutes ($P < .01$), and did not significantly change thereafter ($P < .01$). In the maxillary nerve, ropivacaine level reached the maximum after 0.5 minutes, and decreased to 10.4% of the maximum level after 2 minutes. (B) The lidocaine level in the palatal mucosa reached the maximum 0.5 minutes after the injection, and significantly decreased after 2 ($P = .028$), 5, and 10 minutes ($P < .01$). There was no significant difference in the lidocaine level between 2 and 5 minutes. The level after 10 minutes was significantly lower than that after 5 minutes ($P < .01$). The maximum level of lidocaine in maxillary part was observed 2 minutes after the injection. There was no significant difference in the lidocaine level between 2 and 5 minutes. In the maxillary nerve, the lidocaine level reached the maximum after 0.5 minutes, and, unlike ropivacaine, lidocaine level slowly decreased in length of time.

anesthetic concentration after 2 minutes and that after 5 minutes or between the level after 5 minutes and that after 10 minutes. The amounts of ropivacaine after 20, 30, and 60 minutes were 5.4, 7.0, and 2.1% of the maximum value.

The maximum level (846.1 ± 125.6 ng/mg) of lidocaine in the palatal mucosa (Figure 2B) was observed after 0.5 minutes and significantly decreased to 73.3, 66.3, and 44.0% after 2, 5, and 10 minutes, respectively. There was no significant difference between the lidocaine level after 2 minutes and that after 5 minutes. However, in contrast to ropivacaine, the level after 10 minutes was significantly lower than that after 5 minutes. The levels of lidocaine after 20, 30, and 60 minutes were 11.7, 1.0, and 1.7% of the maximum value.

The ropivacaine level in the maxillary part (Figure 2A) reached the maximum (85.2 ± 19.4 ng/mg) after 0.5 minutes and significantly decreased to 49.0 and

44.6% of the maximum after 2 and 5 minutes, respectively, but did not significantly change thereafter. The levels after 30 and 60 minutes were 4.5 and 1.3% of the maximum value.

The lidocaine level in the maxillary part (Figure 2B) after 2 minutes (188.7 ± 83.9 ng/mg) reached the maximum, being 2.2 times that after 0.5 minutes. The level after 2 minutes did not significantly differ from that after 5 minutes, but the level after 10 minutes was 38.9% of that after 2 minutes, showing a significant decrease. The levels after 30 and 60 minutes were 21.8 and 3.1% of the maximum value.

The ropivacaine level in the right maxillary nerve (Figure 2A) reached the maximum (115.2 ± 16.5 ng/mg) after 0.5 minutes and decreased to 10.4, 17.0, 6.5, and 5.3% of the maximum value after 2, 5, 10, and 60 minutes, respectively.

The lidocaine level in the maxillary nerve (Figure 2B) reached the maximum (207.7 ± 65.1 ng/mg) after 0.5 minutes and decreased to 79.7 and 52.2% of the maximum value after 2 and 5 minutes, respectively. In contrast to ropivacaine, the rate of decrease from 0.5 to 2 minutes after injection was slow. The level after 10 minutes was 10.3% of that after 0.5 minutes. Negligible lidocaine was detected after 20 minutes.

Thus, the ropivacaine levels in the palatal mucosa, maxillary part, and maxillary nerve reached the maximum 0.5 minutes after injection and significantly decreased 2 minutes after injection. However, in the palatal mucosa, in particular, no significant changes were observed in the ropivacaine level between 2 and 5 and between 5 and 10 minutes. The ropivacaine level in each tissue was only less than one tenth of the maximum value (palatal mucosa, 7.0%; maxillary part, 4.4%; maxillary nerve, 5.3%) after 30 minutes, and negligible after 60 minutes.

The time when the lidocaine level reached the peak differed among the tissues. In the palatal mucosa and maxillary nerve, the maximum value was observed immediately after injection and decreased thereafter. In the bone, the lidocaine level reached the maximum after 2 minutes and remained high until 5 minutes after injection.

The levels of both anesthetics in the right incisor and palatal parts (Figure 1, parts 1 and 5) and those on the other side (Figure 1, parts 2, 4, and 6) were negligible.

Extraction and Separation of Ropivacaine or Lidocaine in Tissue

Ropivacaine was detected in zone 5 and lidocaine in zone 4 (Figure 3A). After the development of each sample of 60 minutes or 24 hours after injection, the

radioactivity in each zone as a percentage of the total radioactivity of spots on the TLC plate was calculated.

In group R, after 60 minutes, the highest radioactivity was detected in zone 5, where the authentic ropivacaine was separated, for the palatal mucosa and maxilla. The radioactivity in each zone as a percentage of the total radioactivity of spots on the TLC plate was calculated. The radioactivity in the ropivacaine zone (zone 5) accounted for 91.0% (Figure 3B) for the palatal mucosa and 87.7% for the maxilla (Figure 3C). After 24 hours, more than 80% of the radioactivity was detected in zones other than zone 5 for both the palatal mucosa and maxilla (Figure 3B and C).

In group L, after 60 minutes, the highest activity was detected in zone 4, where the authentic lidocaine was separated, for both the palatal mucosa and maxilla. The radioactivity in zone 4 accounted for 89.5% for the palatal mucosa (Figure 3D) and 92.9% for the maxilla (Figure 3E). After 24 hours, radioactivity was negligible in both tissues (Figure 3D and E).

Tissue Affinity of Ropivacaine and Lidocaine In Vitro

The ropivacaine and lidocaine uptakes by the palatal mucosa, maxillary nerve, brain, and liver are shown in Figure 4A. The uptake of ropivacaine by the palatal mucosa was about twice that of lidocaine, and the uptake of ropivacaine by the maxillary nerve was about 12 times that of lidocaine. Figure 4B shows the amounts of ropivacaine and lidocaine in the supernatant of the comminuted maxilla. The latter was about 3.7 times the former.

Evaluation of the in vitro tissue affinity of ropivacaine and lidocaine by equilibrium dialysis showed a higher affinity of ropivacaine than lidocaine for the palatal mucosa, maxillary nerve, brain, liver, and serum, but not for the maxilla.

DISCUSSION

In infiltration anesthesia by suprapariosteal injection, local anesthetics pass the periosteum and bone foramina along the concentration gradient, reach the nerves in the maxilla, produce anesthetic effects, and also diffuse to areas surrounding the injection site. Therefore, in this study, we evaluated serial changes in the ropivacaine or lidocaine levels in the palatal mucosa at the needle insertion site, adjacent maxilla, and maxillary nerve.

Drugs that were present in the oral tissue until 60 minutes after injection were confirmed to be un-

Figure 3. Chromatogram of ropivacaine and lidocaine and radioactive metabolites derived from ^3H -ropivacaine and ^{14}C -lidocaine in the palatal mucosa and maxilla. ^3H -ropivacaine and ^{14}C -lidocaine were separated by thin-layer chromatography (TLC). The area from the lower end of the plate to the solvent front is divided into 1–9 zones. Spots were visualized with ultraviolet lamp (wavelength : 253.7 nm). Authentic ropivacaine and lidocaine were detected in zone 5 and zone 4, respectively. Radioactive substances that were extracted from the palatal mucosa (B and D) and maxilla (C and E) 1 hour (□) and 24 hours (■) after the injection of 0.5% ^3H -ropivacaine and 2% ^{14}C -lidocaine into the right palatal mucosa proximal to the first molar were separated by TLC. Radioactive substances in each silica gel zone were scratched from the plate and ^3H and ^{14}C radioactivity in the zone was measured with the liquid scintillation counter. The radioactivity in each zone as a percentage of the total radioactivity on the TLC plate was calculated. Data are mean $\pm$ SD ($n = 4$). In the palatal mucosa (B), 91.0% of total ^3H -radioactivity was detected in zone 5, and 87.7% in the maxilla (C) 1 hour after the injection. 89.5% of ^{14}C -radioactivity was detected in zone 4 in the palatal mucosa (D) and 92.9% in the maxilla (E).

changed ropivacaine or lidocaine by TLC analysis. Therefore, all radioactivity measured in the oral tissue was considered to be derived from ropivacaine or lidocaine that had not been metabolized, and radioactivity was converted to the amount of local anesthetic per tissue wet weight.

In the palatal mucosa at the injection site, we observed an inclination that the level of ropivacaine decreased at 2 minutes, then increased at 5 minutes, and then decreased at 10 minutes. However, the ropivacaine level remained high (65% of the maximum value) from 2 to 10 minutes after the injection, and no significant difference was observed among the values after 2, 5, and 10 minutes, which demonstrated

that ropivacaine was retained in the oral mucosa from immediately to 10 minutes after injection. Ropivacaine intradermally injected at a concentration of 0.25–0.75% decreases local blood flow at the injection site, producing peripheral vasoconstriction effects.^{8–10} Because of peripheral vasoconstriction in the palatal mucosa, the loss of anesthetics due to blood flow is slight, which may have been a reason for the absence of significant changes in the level in the palatal mucosa until 10 minutes after injection. In addition, the ropivacaine level after 20 minutes was about one tenth of that after 10 minutes, suggesting transfer to other tissues. The lidocaine level after 5 minutes or more was significantly lower than the maximum value, showing

Figure 4. Tissue affinity of ropivacaine and lidocaine in vitro. The affinity of ropivacaine and lidocaine for oral tissues was evaluated by equilibrium dialysis. (A) The amounts of ropivacaine and lidocaine in palatal mucosa, maxillary nerve, brain, and liver after equilibrium dialysis for 26 hours. The radioactivity was converted to the amount of local anesthetic per wet weight of each tissue (nmol/mg wet weight). The uptakes of ropivacaine by the palatal mucosa and maxillary nerve were twice and 12 times higher than those of lidocaine, respectively. (B) The amounts of ropivacaine and lidocaine in maxilla and serum after equilibrium dialysis. The level of local anesthetic per protein content of each tissue was calculated (nmol/mg protein). The amount of lidocaine in the maxilla was 3.7 times higher than that of ropivacaine.

rapid transfer from the palatal mucosa. This may be because of the rapid diffusion of lidocaine from the palatal mucosa to adjacent tissue by virtue of its high tissue permeability. In addition, 2% lidocaine has marked vasodilative effect, mainly because of the inhibition of action potentials via sodium channel blocking in vasoconstrictive sympathetic nerves,^{11,12} and, therefore, lidocaine distributed in not only the palatal mucosa but also in the maxilla and nerves at the injection site may have been rapidly transferred to the blood.

The diffusion of local anesthetics in tissue and their distribution amount over time are affected by the affinity for lipids and protein-binding ability.¹² We evaluated the in vitro affinity of ropivacaine or lidocaine for the palatal mucosa, and confirmed that the affinity of ropivacaine was about twice that of lidocaine. Rosenberg et al¹³ expressed the fat solubility of local anesthetics in terms of the n-heptane/buffer coefficient, and showed a higher fat solubility of ropivacaine (6.1) than lidocaine (2.1). In addition, the protein binding rate of ropivacaine (94%) has been reported to be about 1.5 times that of lidocaine (64%).¹⁴ Therefore, the strong affinity of ropivacaine for the palatal mucosa may be associated with both its high affinity for lipids and protein binding rate and a vasoconstriction-associated delay in its disappearance from the local area due to blood flow. A previous study on the application of ropivacaine for topical anesthesia of the oral mucosa reported its efficacy.¹⁵ The results of our study support this report.

In the maxilla on the injection side, ropivacaine rapidly decreased 2 minutes or more after injection, showing a rapid disappearance from the maxilla. The ropivacaine

level from immediately to 10 minutes after injection was compared between the maxillary bone and palatal mucosa directly above. The ropivacaine level after 5 minutes in the maxillary part was about one sixth of that in the palatal mucosa, suggesting only slight ropivacaine transfer from the palatal mucosa to maxilla. Lidocaine was considered to gradually disappear from the maxilla after 10 minutes or more. Equilibrium dialysis to evaluate tissue affinity showed a higher level of lidocaine than ropivacaine in the supernatant of the comminuted maxilla, suggesting a high affinity of lidocaine for substances in bone despite a difference in concentration between the 2 anesthetics used for dialysis. These results were considered to be associated with the retention of lidocaine in the maxilla. However, there have been no studies on the components of the maxilla for which lidocaine shows high affinity, and so further studies are necessary.

Thus, ropivacaine was not easily transferred from the palatal mucosa to the maxilla, whereas lidocaine tended to be transferred from the palatal mucosa to the maxilla and remained there.

The distribution level of ropivacaine in the maxillary nerve as well as the palatal mucosa and maxillary bone on the injection side reached a maximum immediately after injection, rapidly decreased, and became negligible. Thus, its distribution in the maxillary nerve as well as the maxilla was slight. The lidocaine level reached the maximum immediately after injection, gradually decreased until 5 minutes after injection, and rapidly disappeared after 10 minutes or more, showing that lidocaine tends to remain in the maxillary nerve. Changes in the lidocaine level in the maxillary nerve were correlated with those in the maxilla. The lidocaine retention time in the maxillary nerve appeared to be also correlated with the anesthetic's duration in the rat dental pulp nerves. Lidocaine may also exhibit a high affinity for nerves. However, evaluation of the in vitro affinity for nerve tissue showed a ropivacaine level per wet weight of the maxillary nerve about 12 times that of lidocaine, suggesting a much higher affinity of ropivacaine for nerve tissue. Thus, in the maxillary nerve, the in vitro differed from the in vivo results. We observed a peak in the concentration of ropivacaine in the palatal mucosa and maxillary nerve 5 minutes after the injection. It was considered that because of the strong affinity for the lipid and protein, ropivacaine slowly diffused from the injection site, accumulated in the mucosa and nerve, and showed a peak in the concentration 5 minutes later. Because lidocaine tends to remain in the maxilla, as described above, lidocaine that accumulated in the maxilla may have been transferred to the maxillary nerve.

In conclusion, 0.5% ropivacaine used in maxillary infiltration anesthesia showed a high affinity for the

palatal mucosa at the injection site, suggesting its usefulness for infiltration anesthesia of oral soft tissue. However, the bone permeability of ropivacaine was low, suggesting difficulty in utilizing its unique characteristics such as a long duration of action and vasoconstriction in infiltration anesthesia aiming at anesthetic effects on the dental pulp. However, studies have shown some patients responding to infiltration anesthesia with ropivacaine for dental treatment¹⁶ and favorable effects of this anesthesia after an increase in the ropivacaine concentration¹⁶ or the addition of a vasoconstrictor.⁷ Therefore, further studies are necessary to evaluate the influences of changes in the ropivacaine concentration or addition of a vasoconstrictor on ropivacaine distribution in the oral tissue.

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