Effects of Epinephrine on Lidocaine Pharmacokinetics and Blood Volume in the Dental Pulp

Shuichi Hashimoto, PhD, Mikiko Yamashiro, DDS, PhD,† Kyohei Fujita, DDS, PhD,† Asako Yasuda, DDS, PhD,† and Katsuhisa Sunada, DDS, PhD†*

Abstract

Introduction: Epinephrine potentiates and prolongs the efficacy of local anesthetics by reducing blood flow. We investigated the effect of epinephrine on the pharmacokinetics of lidocaine and the pulpal blood volume after maxillary infiltration anesthesia in rats. **Methods:** We measured the ^{14}C-radioactivity and ^{14}C-distribution in the maxilla and the dental pulp after the injection of 2% ^{14}C-lidocaine with or without 10 μg/mL epinephrine (n = 7) into the palatine mucosa proximal to the first molar. The blood volume in the pulp was measured using ^{99m}Tc-pertechnetate (n = 5). **Results:** When lidocaine was injected together with epinephrine, the lidocaine became widely distributed throughout the maxilla and was observed mainly in the first molar pulp. The lidocaine amount in the dental pulp at 10–60 minutes was more than 2 times higher than that after the injection of lidocaine alone. The relative pulpal blood volume after 20 minutes decreased to 63.1% of the value after the injection of lidocaine alone. **Conclusions:** We found that lidocaine had infiltrated into the molar pulp after infiltration anesthesia. Furthermore, our results suggested that epinephrine augmented the retention of lidocaine in the pulp. *(J Endod 2014;40:1370–1374)*

Key Words

Autoradiography, infiltration anesthesia, lidocaine amount in pulp, pulpal blood volume, rat, vasoconstrictive effect of epinephrine

From the *Research Center for Odontology, Tokyo, Japan; and †Department of Anesthesiology, The Nippon, Dental University, School of Life Dentistry at Tokyo, Tokyo, Japan.

Address requests for reprints to Dr Shuichi Hashimoto, Research Center for Odontology, The Nippon Dental University, School of Life Dentistry at Tokyo, 1-9-20 Fujimi, Chiyoda-ku, Tokyo 102-8159, Japan. E-mail address: shuichi@tky.ndu.ac.jp

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Although many reports have discussed the onset, duration, and efficacy of local anesthetics (1–3), only a few studies have investigated the distribution and diffusion process of local anesthetics in the oral tissue after intraoral anesthesia (4–6). We previously reported the pharmacokinetics of ^{14}C-lidocaine in the rat maxilla (7). However, the distribution of lidocaine to the dental pulp after infiltration anesthesia has not been reported.

Epinephrine is added to local anesthetic solutions to potentiate and prolong the anesthetic efficacy by reducing blood flow in the area of administration (8). The objective of this study was to investigate the effect of epinephrine on the pharmacokinetics of lidocaine in the maxilla and dental pulp and the pulpal blood volume after infiltration anesthesia. We injected ^{14}C-lidocaine with epinephrine into the rat maxilla and then used quantitative radioactivity and microautoradiography analyses to investigate the local pharmacokinetics of ^{14}C-lidocaine; we also measured the postanesthetic pulpal blood volume using red blood cells labeled with ^{99m}Tc-pertechnetate (9).

Materials and Methods

The animal experiment committee of Nippon Dental University, Tokyo, Japan, approved this study, which adhered to all the relevant regulations. Male Wistar rats (280–300 g) were used. Lidocaine (AstraZeneca, Osaka, Japan), ^{14}C-lidocaine (American Radiolabeled Chemicals, St Louis, MO), epinephrine (Daiichi-Sankyo, Tokyo, Japan), and ^{99m}Tc-pertechnetate (Nihon Medi-Physics, Tokyo, Japan) were obtained from the indicated sources.

Measurement of Lidocaine Concentrations in Maxilla

The rats (n = 7) were anesthetized with an intraperitoneal injection of sodium pentobarbital. Then, 20 μL 2% ^{14}C-lidocaine solution (2.83 MBq/mmol and 0.185 MBq/mL) with or without 10 μg/mL epinephrine was injected into the right palatine mucosa proximal to the first molar according to the method described by Kimi et al[7] (Fig. 1*A*). The rats were then decapitated at various time points after injection. The maxilla was divided into equal parts at the midline (Fig. 1*B*), and the right maxillary portion (including 3 molars) was divided into 3 sections (A, B, and C; 190–210 mg), each containing 1 molar, gingival, palatine mucosa, and maxillary bone.

Each section was minced with scissors in a vial and then dissolved in a solubilizer (Solvable; PerkinElmer, Waltham, MA). The ^{14}C-radioactivity in the solubilized sample was measured using a liquid scintillation system (LSC-6100; Aloka, Tokyo, Japan). The lidocaine concentration was calculated based on the specific radioactivity (MBq/mmol) and the measured radioactivity (Bq) and was represented as ng/mg of wet weight.

Measurement of Lidocaine Amounts in Molar Pulps

^{14}C-lidocaine with or without epinephrine was administered into the rat palate (n = 7) according to the method described previously. After removing the maxilla, the right maxillary 3 molars were extracted using pliers (Fig. 1*B*). All the apical foramens and accessory canals at the roots of each extracted molar were sealed using a composite resin (UNIFIL LOFLO; GC Corporation, Tokyo, Japan). The molar surface was washed 3 times in 50 mL 0.9% NaCl and was also washed 3 times in ethanol. Each molar was then crushed in a vial using nippers, and the exposed pulp was directly dissolved using the previously mentioned solubilizer. Finally, the ^{14}C-radioactivity in the pulp was measured. The lidocaine amount in the pulp was expressed as ng/pulp.

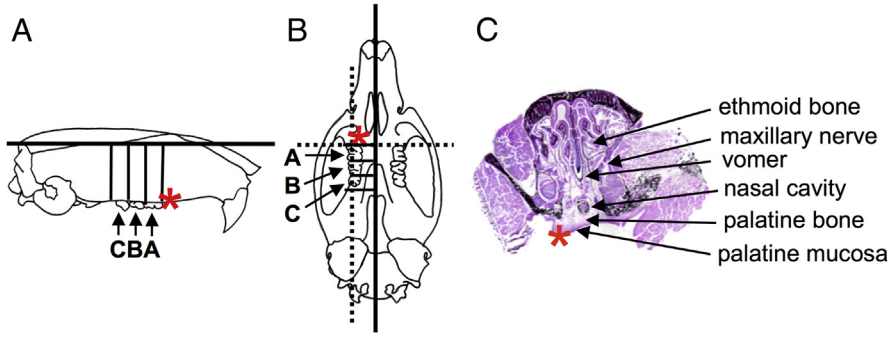

Figure 1. A schema showing the (*A* and *B*) sectioning of the rat maxilla and (*C*) a frontal specimen of the maxilla. Twenty microliters of a local anesthetic was injected into the palatine mucosa (*red asterisk*) proximal to the right first molar. The maxilla was cut along the solid line at (*A*) 10 mm above the margin of the gingiva of the molars and (*B*) was separated at the median line; (*A* and *B*) the right maxilla was removed and divided into 3 sections (A, B, C) along the solid line. Sections A, B, and C included the first, second, and third molars, respectively. (*B*) For the macroautoradiography, 20-μm-thick frontal and sagittal sections were sliced at the broken line. (*C*) The frontal specimen was stained with Mayer hematoxylin-eosin.

Autoradiogram Analysis of ^{14}C-lidocaine

The maxilla was excised from each rat at 2 or 20 minutes after the injection of 2% ^{14}C-lidocaine with or without 10 μg/mL epinephrine according to the method described previously. The extracted maxilla was embedded in 4% carboxymethylcellulose, frozen, and then sectioned frontally or sagittally at the injection point using a cryostat microtome (CM3050S; Leica Biosystems, Nussloch, Germany) (Fig. 1*B* and *C*). The ^{14}C-specimen (20 μm) was placed on an adhesive sheet and stuck to an x-ray film (BioMax XAR Film; Carestream Health, Rochester, NY). Only the frontal specimens on the sheet were stained with 0.25% eosin (Fig. 1*C*). The stained or nonstained specimens were then placed on top of an autoradiogram of the developed film, and the distribution of ^{14}C-lidocaine in the section was detected using a scanner.

Measurement of Pulpal Blood Volume

The pulpal blood volume was measured using *in vivo* methods for red blood cell (RBC) labeling with ^{99m}Tc-pertechnetate involving the use of stannous pyrophosphate (9, 10). After the injection of 0.1 mL stannous pyrophosphate (2 mg/mL) into the left femoral vein under general anesthesia, 0.1 mL ^{99m}Tc-pertechnetate (168 MBq/mL) was injected into the same vein 30 minutes later (n = 5). A 20-μL aliquot of each anesthetic was injected into the palate at 5 minutes after the administration of ^{99m}Tc-pertechnetate. The maxilla was extracted from the rat at 20 minutes after the injection, and the right 3 maxillary molars were removed. Using the same method described earlier, the apical foramens of the molars were sealed, and the molars were washed. The radioactivity of ^{99m}Tc-RBC in each molar was directly measured using an autowell γ-system (ARC-380CL, Aloka). To analyze the relative blood volumes, the radioactivity in the right first molar pulp was assigned a value of 100.

Statistical Analysis

Differences in the lidocaine amounts and ^{99m}Tc radioactivities between the 2 groups (with or without epinephrine) were analyzed using the unpaired t test. Changes within each group were analyzed using a nonrepeated measures analysis of variance. A P value <.05 was considered significant.

Results

Lidocaine Concentrations in Maxilla Sections

In section A (including the first molar), the lidocaine concentration reached a maximum at 2 minutes after the injection of lidocaine alone and then rapidly decreased (Fig. 2*A1*). When lidocaine and epinephrine were injected, the lidocaine concentrations also reached a maximum at 2 minutes. However, the lidocaine concentrations at 10, 20, and 30 minutes after the injection of lidocaine and epinephrine were 2.7, 2.4, and 2.9 times higher than those after the injection of lidocaine alone, respectively.

In section B (including the second molar), the lidocaine concentration peaked at 2 minutes after the injection of lidocaine alone and then rapidly decreased (Fig. 2*A2*). When lidocaine and epinephrine were injected, the lidocaine concentrations at 10–30 minutes were more than 1.9 times higher than those after the injection of lidocaine.

In section C (including the third molar), the lidocaine concentration reached a peak at 5 minutes after the injection of lidocaine (Fig. 2*A3*). When lidocaine and epinephrine were injected, the lidocaine concentrations at 10–30 minutes were at least 1.6 times higher than those after the injection of lidocaine.

Lidocaine Amounts in Molar Pulps

In the first molar pulp, the lidocaine amount reached a maximum at 2 minutes after the injection of lidocaine alone and then decreased (Fig. 2*B1*). This 2-minute value corresponded to 0.23% of the total amount of the administered lidocaine. When lidocaine and epinephrine were injected, the respective lidocaine amounts at 10, 20, 30, and 60 minutes after the injection of lidocaine and epinephrine were 2.0, 3.1, 3.7, and 16.4 times higher than those after the injection of lidocaine, respectively.

In the second molar pulp, the lidocaine amount peaked at 2 minutes after the injection of lidocaine alone and then gradually decreased (Fig. 2*B2*). This 2-minute value was about one sixteenth of that in the first molar pulp. When lidocaine and epinephrine were injected, the lidocaine amount increased slightly, reaching a maximum at 20 minutes. The lidocaine amounts in the pulp at 10–60 minutes were at least 2.6 times higher than those after the injection of lidocaine alone. In the third molar pulp, the concentration of lidocaine at 2 minutes after the injection of lidocaine was very low, regardless of the addition of epinephrine (Fig. 2*B3*).