# Comparative Study on Anesthetic Potency Depending on Concentrations of Lidocaine and Epinephrine: Assessment of Dental Local Anesthetics Using the Jaw-Opening Reflex

**Shinobu Ohkado, DDS, PhD, Tatsuya Ichinohe, DDS, PhD, and Yuzuru Kaneko, DDS, PhD**
Department of Dental Anesthesiology, Tokyo Dental College, Chiba, Japan

Anesthetic potency of a local anesthetic on the dental pulp was investigated by increasing or decreasing the concentration of lidocaine and that of epinephrine. An electromyogram of the digastric muscle in Japan White male rabbits was recorded during the jaw-opening reflex induced by electrical stimulation of the dental pulp. Probit analysis was used for the determination of the 50% effective volume ($ED_{50}$) values of the anesthetic. The anesthetics used were plain 2% lidocaine solution (2Lid-0 group), 2% lidocaine solution with 12.5 μg/mL of epinephrine (2Lid-1/8 group), 2% lidocaine solution with 6.25 μg/mL of epinephrine (2Lid-1/16 group), and 4% lidocaine solution with 5 μg/mL of epinephrine (4Lid-1/20 group). No anesthetic effect was shown in the 2Lid-0 group. The 2Lid-1/8 group indicated adequate anesthetic potency with the smallest dosage at all observation periods. The potency in the 2Lid-1/16 group was 0.3–0.5 times, and that in the 4Lid-1/20 group was 0.3–0.4 times as much as the 2Lid-1/8 group. The decrease in epinephrine concentration produced the decrease in the anesthetic potency on the dental pulp independent of lidocaine concentration. These results suggest that the increase in lidocaine concentration may not compensate the decrease in epinephrine concentration.

**Key Words:** Local anesthetic; Jaw-opening reflex; Dental pulp.

A local anesthetic is usually mixed with a vasoconstrictor in clinical dentistry. Epinephrine, felypressin, norepinephrine, and levonordefrin are used as vasoconstrictors.

Since vasoconstriction induced by epinephrine remarkably enhances the local anesthetic potency,[1–4] a combination of lidocaine and epinephrine is recommended for optimal anesthetic effects for tooth pulp treatment.[5]

Epinephrine has several stimulative effects on the cardiovascular system because of its sympathomimetic actions.[6–8] These effects present a risk factor of myocardial ischemia in geriatric patients and in patients with low reserve capacity in cardiorespiratory functions such as those with cardiovascular diseases. For these reasons, a lower concentration of epinephrine is preferable. The decreased concentration of epinephrine, however, may decrease the anesthetic potency on the teeth. It would be desirable if the anesthetic potency did not decrease in spite of a lowered epinephrine concentration when provided with the increased concentration of an anesthetic.

In the present study, therefore, the anesthetic potency of a lidocaine solution with various lower concentrations of epinephrine was tested to clarify whether the depression of anesthetic potency due to lowered epinephrine concentration can be compensated through an increase in lidocaine concentration. The potency of tooth anesthesia depends on the anatomical structure

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Address correspondence to Dr Yuzuru Kaneko, Department of Dental Anesthesiology, Tokyo Dental College, 1-2-2, Masago, Mihama-ku, Chiba, 261-0011 Japan.

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around the tooth. Penetration of the alveolar bone by a local anesthetic is more rapid in maxillary incisors than in mandibular molars. A comparison of the anesthetic potency should be performed in teeth in which it is difficult to obtain adequate anesthesia. In this study, the anesthetic potency was examined in mandibular incisors in rabbits. These teeth are covered with thick cortical bone like the mandibular molars, which have anatomical features attenuating the anesthetic potency. The anesthetic potency was assessed using an electromyogram (EMG) of the digastric muscle in the jaw-opening reflex following electrical stimulation of the dental pulp in mandibular incisors.[9–12]

## MATERIALS AND METHODS

This study was conducted in compliance with the Guideline for the Treatment of Experimental Animal at the Tokyo Dental College.

### Subjects and Method of Observation of Anesthetic Potency

The subjects studied were 56 Japan White male rabbits weighing 1.8–2.1 kg.

The auricular marginal vein was cannulated with a 22–24-gauge indwelling catheter (Angiocath, Becton Dickinson, Sandy, UT, USA). The rabbits were anesthetized with 25–50 mg/kg of thiopental sodium (Ravonal, Tanabe Seiyaku, Osaka). Tracheotomy was performed under spontaneous breathing, and the trachea was intubated with a 14–16 French pediatric endotracheal tube (Blue Line Tracheal Tube, Portex, Kent, UK). The rabbits were administered 0.5 mg/kg of vecuronium bromide (Musculax, Organon Technica bv, Boxtel, Tokyo) intravenously to prevent movement during preparation, then put on a respirator (Harvard Apparatus Dual Phase Control Respirator Pump, Central Kagaku Boeki, Tokyo) and ventilated with room air.

Anesthetic potency was evaluated by an EMG of the digastric muscle during electrical stimulation of the dental pulp at the mandibular incisor. The dental cavity of the incisor was perforated using a dental drill. Under irrigation, a round bar #3 (Hager & Meisinger GmbH, Dusseldolf, Germany) was used to create an opening in the pulp chamber. Two epoxy-coated silver acupuncture needles were inserted approximately 3 mm apart in the pulp and fixed there. After the electrodes for stimulation were installed, the rabbit was maintained in a supine position. The neck was slightly extended, and the head was fixed with a plaster cast to restrain free movement. Two leads for the EMG were placed laterally on the same side as the tooth in which the stimulating electrode had been installed at a position that allowed the best orientation for EMG recordings of the digastric muscle. After completing the surgical preparation, the rabbit was weaned from the respirator after recovery from thiopental sodium and vecuronium bromide and spontaneous breathing was stabilized. A small dose of diazepam (Horizon, Yamanouchi Seiyaku, Tokyo) was injected for sedation throughout the experiment.

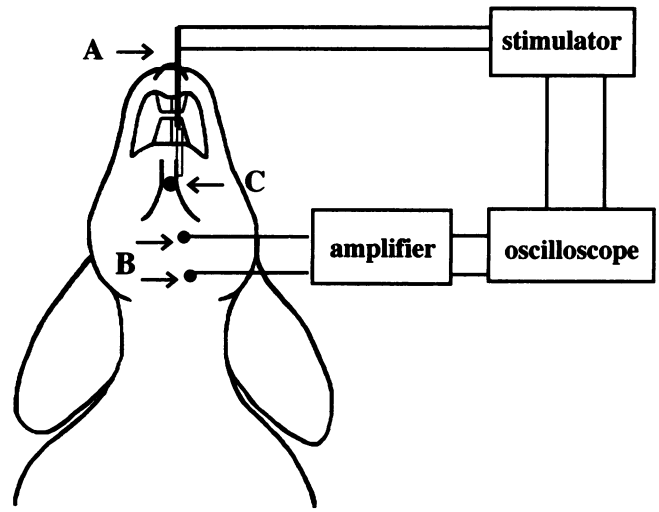


**Figure 1.** Schematic of the experimental method. Anesthetic potency was evaluated by an electromyogram (EMG) of the digastric muscle during electrical stimulation of the dental pulp at the mandibular incisor. A pair of electrode stimulators was used to apply single electrical pulp stimulation. The EMG leads were connected to an amplifier, and the responses were visualized with an oscilloscope and printed out on a thermal-dot recorder.

An electrode stimulator (Stimulator DPS-05, Dia Medical System, Tokyo) was used to apply single electrical pulp stimulation with an intensity of 10–15 V, 1 millisecond in duration at 30–60 second intervals. The EMG leads were connected to an amplifier (Bioelectric Am; 7923–1B, NEC-Sanei, Tokyo). The EMG responses were visualized with an oscilloscope (Synchroscope SS-7503, Iwatu Electric, Tokyo) and printed out on a thermal-dot recorder (Omniace RT-3104, NEC-Sanei, Tokyo) (Figure 1).

### Local Dental Anesthetics

The 4 anesthetics studied were 2% lidocaine solution without epinephrine (2Lid-0 group), 2% lidocaine solution with 12.5 μg/mL (2Lid-1/8 group), 2% lidocaine solution with 6.25 μg/mL epinephrine (2Lid-1/16

group), and 4% lidocaine solution with 5 μg/mL epinephrine (4Lid-1/20 group). Lidocaine (Xylocaine) obtained from AstraZeneca (Osaka) was used for the 2Lid-0 and 2Lid-1/8 groups. Anesthetic solution for the 2Lid-1/16 group was made by mixing of the same volume of the 2Lid-1/8 and 2Lid-0 group anesthetics. The solution for the 4Lid-1/20 group was made from the original powder of lidocaine and epinephrine supplied by AstraZeneca. All anesthetics ranged from 2.5 to 4.2 in pH.

### Injection Site of Anesthetics and Observation Period

The stability of the EMG was confirmed by repeated electrical stimulation to the dental pulp. The amplitude of the EMG of the digastric muscle during this period served as a control. Local anesthetic was injected into the lingual side of the dental root of the mandibular incisor. This area was confirmed through palpation of the bulging bone. The anesthetic solution was injected by the extraoral method in approximately 5–7 seconds using a 1-mL disposable syringe with a 26-gauge needle. EMG recordings were made at 1, 3, 5, 7, 10, 15, and 20 minutes after the administration of local anesthetics. Both mandibular incisors of each rabbit were used for the experiment with a sufficient interval for the disappearance of local anesthetic effect.

### Dosage Setting of Local Anesthetics and Assessment of Anesthetic Potency

A preliminary experiment was performed to determine the adequate dosage of anesthetics in several rabbits. First, the maximal dosage that did not induce changes in the EMG of the digastric muscle and the minimal dosage at which flatness of the EMG occurred were used to determine the standard dosages. By increasing or decreasing by 0.05-mL increments from the 2 standard dosages, 5 injection volumes were determined. As a result, the dosage was 0.9 mL or more for the 2Lid-0 group, 0.15–0.35 mL for the 2Lid-1/8 group, 0.5–0.75 mL for the 2Lid-16 group, and 0.55–0.75 mL for the 4Lid-20 group. Although a dosage of 0.9 mL or more was needed for the 2Lid-0 group, the injection of such a large amount might result in direct invasion to the digastric muscle itself, which causes disappearance of the EMG wave. Therefore, injections of more than 0.9 mL were excluded.

Judgment of anesthetic potency was made by complete depression of the electromyographic wave elicited by electrical stimulation of the dental pulp. This study was performed 6 times for each dosage in each anesthetic group. Potency rate was calculated by dividing the number of animals in which the EMG wave disappeared by the total number of animals for each injection volume. Anesthetics were compared by 50% effective volume ($ED_{50}$).

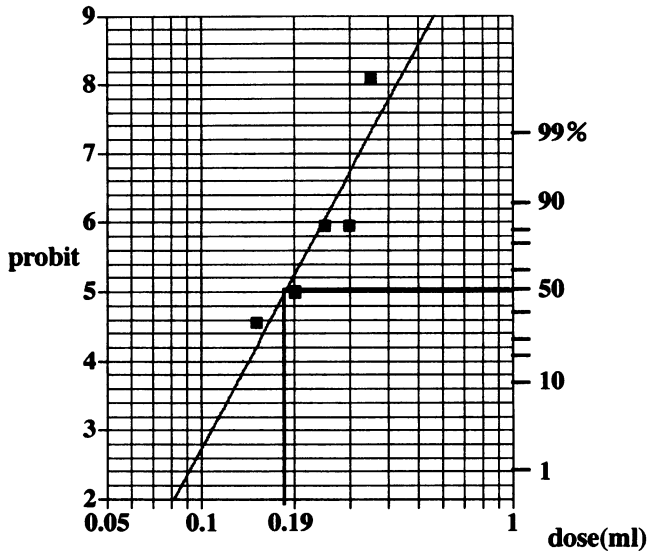


**Figure 2.** An example of probit analysis (2Lid-1/8 group 3 minutes after the administration). The $ED_{50}$ values of the local anesthetic were calculated from a linear regression line between anesthetic volumes and the probit values, where the volume was plotted on the abscissa and the probit value of the potency rate of anesthetics was plotted on the ordinate.

### Statistical Analysis

Probit analysis was used to determine $ED_{50}$ values.[13] The $ED_{50}$ value of a local anesthetic was calculated from a linear regression line of anesthetic volume and the probit value, where the volume was plotted on the abscissa and the probit value of the potency rate of anesthetics was plotted on the ordinate. A 95% confidence interval was determined for each $ED_{50}$ value. The difference between 2 anesthetics was considered to be significant when the confidence intervals did not overlap. The probit analysis was performed using SPSS (Figure 2).

## RESULTS

The results are summarized in Figure 3.

In a comparison of the anesthetic potency among various local anesthetics, the 2Lid-1/8 group required the smallest dosage to obtain the $ED_{50}$ value at any time after administration. The maximal potency in the 2Lid-1/16 group was 0.5 times as much as that in the 2Lid-1/8 group. Likewise, the maximal potency in the 4Lid-1/20 group was 0.4 times as much as that in the 2Lid-

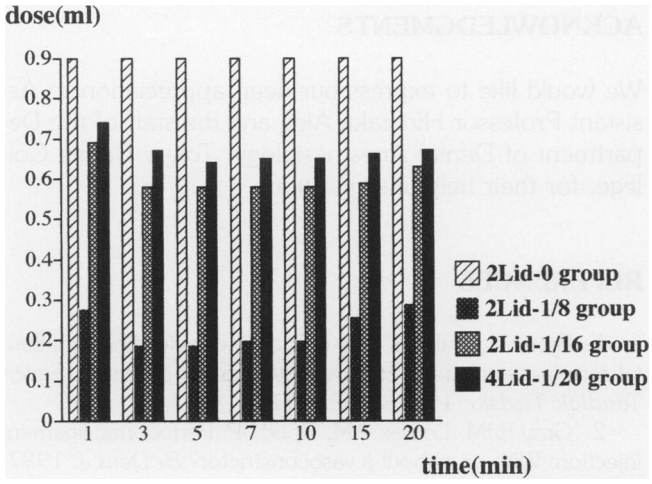


**Figure 3.** A comparison of the $ED_{50}$ values of local anesthetics at various observation stages. The 2Lid-1/8 group required a smaller dosage to obtain $ED_{50}$ values at any time after administration compared with the other groups. The maximal potency of the 2Lid-1/16 group was 0.5 times as much as that of the 2Lid-1/8 group and the 4Lid-1/20 group was 0.4 times as much as the 2Lid-1/8 group. The 4Lid-1/20 group did not show any significant differences in anesthetic potency in comparison with the 2Lid-1/16 group, indicating that the former was 0.9 times as much as the latter.

1/8 group. The 4Lid-1/20 group did not show any significant differences in anesthetic potency comparing with the 2Lid-1/16 group.

The volume of anesthetics required to obtain the $ED_{50}$ did not show any statistically significant differences at each period after the administration in each group. There were no significant differences in the onset time among the 3 groups.

Since the 2Lid-0 group required a very large injection volume to obtain sufficient anesthetic potency on the dental pulp, an electromyographic examination of the digastric muscle could not assess the potency in this group.

Two rabbits in the 4Lid-1/20 group were excluded from the present study because of convulsions and abrupt respiratory arrest immediately after injection of a local anesthetic.

## DISCUSSION

### Study Method

There are several reports[1,3,4] on the anesthetic potency of local anesthetics in the teeth. Nearly all are of studies using the maxillary incisor tooth, where cortical bone is relatively thin and local anesthetics penetrate easily. The anesthetic potency on the teeth depends on several anatomical factors. For example, penetration of the local anesthetic is inhibited in the mandibular molar with thick cortical bone. If teeth less sensitive to anesthetics are used for study, the discrimination of anesthetic potency may be rather easy. In this study, we used the mandibular incisor as an injection site, where penetration of injected anesthetic solution to the dental pulp is difficult because of thick cortical bone.

The mouth opens reflexively through the contraction of the digastric and other jaw-opening muscles when pain is produced in dental pulp, gingiva, or the periodontal ligament.[10,11] This phenomenon is called the jaw-opening reflex. The impulses of pain or mechanical stimulation through the second or third division of the trigeminal nerve induce a reflex discharge to the branch of the trigeminal nerve innervating the jaw-opening muscles via the reflex center in the brain stem. All types of stimulations of the pulp nerve are recognized as pain.[14] The jaw-opening reflex does not occur if local anesthetics interfere with conduction of the impulses evoked by painful stimulations.

### Influence of Epinephrine on Anesthetic Potency

Many reports[1–4] note that anesthetic potency is increased with the addition of epinephrine. The same result was observed in this study. The 2Lid-0 group required a markedly larger volume to obtain $ED_{50}$ than did the other groups, indicating an extremely weak anesthetic potency. The lidocaine mixed with 2 different concentrations of epinephrine had increased anesthetic potency over the plain lidocaine solution.

The anesthetic potency increased when the epinephrine concentration was elevated in the 2Lid-0, 2Lid-1/16, and 2Lid-1/8 groups under the same lidocaine concentration. These results indicated that anesthetic potency is dependent on epinephrine concentration. Although the addition of epinephrine up to a concentration of 10 μg/mL increased the anesthetic potency, the contribution of higher concentrations of epinephrine on the anesthetic potency was relatively small.[1] In contrast, there are controversial reports[15] in which results of comparisons between epinephrine concentrations of 4 and 20 μg/mL showed no differences, not only in anesthetic potency but also in the duration of action. These results may come from observation in the human maxillary anterior.

The addition of a vasoconstrictor to a local anesthetic prolongs the duration of anesthesia but does not enhance the potency of anesthesia.[16] Since the anesthesia in the skin and mucous membrane is adequate even with a weak anesthetic, we agree with the concept of the phenomenon[16] of the relation between epinephrine and anesthetic potency. However, epinephrine greatly influences the potency of anesthesia by enhancing penetration of a local anesthetic through the alveolar bone to

the teeth. This study confirmed that the differences of epinephrine concentration greatly influenced anesthetic potency, even with the use of a more potent anesthetic, lidocaine.

The influence of epinephrine on anesthetic potency may be explained as follows. A local anesthetic produces anesthesia through the arrival of the anesthetic agent to the apex of the tooth root by penetration through the alveolar bone. For a local anesthesia without a vasoconstrictor, the anesthetic drug injected into the submucosal space is mainly absorbed rapidly into the intravascular space, and thereby a volume of the drug is lost before arrival to the root of the tooth.

Although anesthetic potency in the tooth is enhanced with an increased concentration of an anesthetic,[1] our hypothesis that the decreased anesthetic potency induced by a lower concentration of epinephrine can be compensated by an increase in anesthetic concentration was not confirmed because the anesthetic potency of the 4Lid-1/20 group with higher lidocaine concentration was the same as that in the 2Lid-1/16 group with lower lidocaine concentration. This suggests that the intravascular absorption of lidocaine was greater in the solution with the higher concentration of lidocaine. In contrast, it is considered that the local anesthetic potency is enhanced with the addition of higher concentrations of epinephrine because vascular constriction provides retention of a greater volume of anesthetic agents at local injection sites. However, the use of a high concentration of epinephrine was not consistent with our aim of trying to decrease cardiovascular side effects. Among the anesthetics studied, 2% lidocaine solution with 12.5 μg/mL of epinephrine, which had been commercially available, was the strongest anesthetic solution, and when the concentration of epinephrine was lowered by half, the anesthetic potency of this solution decreased to less than 50%. To retain the same anesthetic potency, the volume of the anesthetic must be more than doubled. In that case, the volume of epinephrine is larger than in the former solution. Therefore, sufficient understanding of the relationships among the concentration of epinephrine, injection site, and anesthetic potency is important for a practical use of anesthetics in patients with cardiovascular diseases when the side effects of epinephrine as well as painless dental treatment must be considered.

In conclusion, anesthetic potency on the dental pulp decreased when the concentration of epinephrine was decreased in the presence of the same concentration of lidocaine solution. Potency also decreased when the concentration of epinephrine was decreased although that of lidocaine was increased. These results suggest that the increase in lidocaine concentration may not compensate the decrease in epinephrine concentration.

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