Comparative Study on Anesthetic Potency of Dental Local Anesthetics Assessed by the Jaw-Opening Reflex in Rabbits

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The potency of 4 local anesthetics to dental pulp was compared. Drugs were 4% articaine with 12 μg/mL epinephrine (A12), 4% articaine with 6 μg/mL epinephrine (A6), 2% lidocaine with 12.5 μg/mL epinephrine (L), and 3% propitocaine with 0.03 IU/mL felypressin (P). Local anesthetics were injected into the dental root of the mandibular incisor. Electromyogram (EMG) of the digastiric muscle was measured during the jaw-opening reflex induced by electrical stimulation. The disappearance of the EMG wave was judged as positive evidence of anesthesia. The determination of ED50 of the anesthetic was made by probit analysis. The ED50 of the A12 was minimal in all the tested anesthetics throughout the entire course. The potency in the A6 was 2.8 times that of the L. The potency of the A12 at the 15-minute measurement was 3.8 times that of the A6. The ED50 of the P was higher compared with those of the other 3 groups. It was concluded that articaine showed quicker onset than lidocaine and propitocaine and that there was a need to increase the dosage to attain a quick onset or to extend the duration.

Key Words: Anasthetic potency; Dental local anesthetic; Jaw-opening reflex; Probit analysis; Electromyogram.

Only a few studies on the potency of the various local anesthetics have been reported because of the lack of an appropriate experimental model. We tested the potency of 4 types of local anesthetics extraorally and measured the response of the rabbit digastric muscle, which relates to jaw-opening reflex, by electromyogram (EMG) at various points in time after administration of the anesthetic. Probit analysis was employed to compute the ED50 (dosage of drug that is effective in 50% of the animals administered) and ED95 (dosage of drug that is effective in 95% of the animals administered) values at each point in time after administration of the anesthetic at which the EMG was measured. The ED50 and ED95 values were compared in order to study the 4 agents in terms of the amount of time after administration at which the drug took effect.

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METHODS

Subjects and Method of Observation of Anesthetic Effect

The subjects studied were 35 male Japan White rabbits weighing between 1.9 and 2.1 kg. This study was conducted in compliance with the Guidelines for the Treatment of Experimental Animals at the Tokyo Dental College and in accordance with the guidelines of the Japanese government. A 22-gauge in-dwelling catheter (Angiocath, Becton Dickinson, Sandy, Utah) was inserted into the auricular vein of each rabbit. The rabbits were anesthetized with the administration of 25–50 mg/kg thiopental sodium (Ravonal, Tanabe Seiyaku, Osaka, Japan). Tracheotomy was performed under spontaneous breathing, and the trachea was intubated with a 14–16 French size pediatric endotracheal tube (Blue Line Tracheal Tube, Portex, Kent, UK). Each rabbit was administered 0.5 mg/kg vecuronium bromide (Masclulax, Organon Technica bv, Boxtel, Netherlands) intravenously to prevent movement during preparation,

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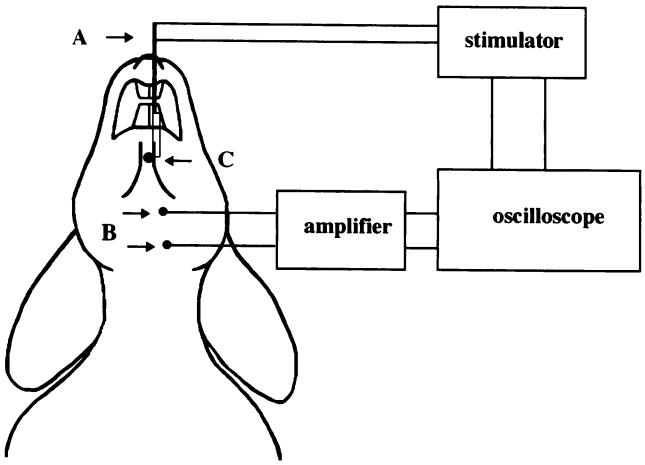

Figure 1. Illustration of experimental method. (A) Stimulating electrode; dental pulp of the mandibular incisor. (B) EMG electrode; digastric muscle. (C) Measurement of administration.

then put on a respirator (Harvard Apparatus Dual Phase Control Respirator Pump, Central Kagaku Boeki, Tokyo, Japan), and ventilated with room air.

Anesthetic potency was evaluated by EMG of the digastric muscle during electrical stimulation at the mandibular incisor.[1,2] The dental cavity of the incisor was performed by a dental drill. Under irrigation, a round bar #3 (Hager & Meisinger GmbH, Dusseldolf, Germany) was used to create an opening in the pulp chamber of approximately 1.5 mm in diameter from the labial side at the cervix. Two epoxy-coated silver acupuncture needles were placed approximately 3 mm apart on the pulp and were 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 to restrain free movement of the head. Two leads for the EMG were placed laterally on the same side as the tooth in which the stimulating electrode had been installed. After completing the surgical preparation, the rabbit was weaned from the respirator after recovery from thiopental sodium and vecronium bromide and spontaneous breathing was stabilized. An electrode stimulator (Stimulator DPS-05, Dia Medical System, Tokyo, Japan) was used to apply electrical pulp stimulation of an intensity of 10–15 V for a single stimulus 1 millisecond in duration at 30–60-second intervals. The EMG lead was connected to an amplifier (Bioelectric Amp 7923–1B, NEC-Sanei, Tokyo, Japan), and the results were visualized with an oscilloscope (Synchroscope SS-5703, Iwasaki Electric, Tokyo, Japan) and printed out on a recorder (Omniace RT-3104, NEC-Sanei) (Figure 1).

Local Dental Anesthetics

The four anesthetics studied were 4% articaine with 12 μg/mL epinephrine (A12 group) (Ubistesinforte®, ESPE, Seefeld, Germany), 4% articaine with 6 μg/mL epinephrine (A6 group) (Ubistesin®, ESPE), 2% lidocaine with 12.5 μg/mL epinephrine (L group) (Xylocaine®, Astra, Osaka, Japan), and 3% propitocaine with 0.03 IU/mL felypressin (P group) (Citanest®-Octapressin®, Astra).

Injection Site of Anesthetics and Observation Period

The stability of the EMG was confirmed by repeated electrical stimulation to the dental pulp, and the amplitude of the EMG of the digastric muscle during this period was adopted as a control. Local anesthetics were 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 was injected by the extraoral method in approximately 5–7 seconds using a 1-mL disposable syringe with a 26-gauge needle. The control EMG measurement was observed 20 minutes after completing the preparation of the experiment. Thereafter, EMG measurements were made at 2, 3, 5, 10, 12, 15, and 20 minutes after the administration of the local anesthetics. Bilateral mandibular incisors of a single rabbit were used for the experiment.

Dosage Setting of Local Anesthetics and Assessment of Anesthetic Potency

A preliminary experiment was performed in order to determine the adequate dosage of anesthetic in several rabbits. First, the maximal dosage that did not induce change on the EMG of the digastric muscle and the minimal dosage at which it showed flatness of the EMG were used to determine the standard dosages. By increasing or decreasing by 0.05-mL increments from the 2 standard dosages, the range of injection volumes was determined. As a result, the range of dosages was 0.025–0.18 mL for 4% articaine with 12 μg/mL epinephrine, 0.03–0.5 mL for 4% articaine with 6 μg/mL epinephrine, 0.1–0.5 mL for 2% lidocaine with 12.5 μg/mL epinephrine, and 0.15–0.5 mL for 3% propitocaine with 0.03 IU/mL felypressin. In cases where a dosage of 0.5 mL or more was needed, the injection of such a large amount resulted in direct invasion of the digastric muscle itself, which caused the disappearance of the EMG wave. Therefore, injections of more than 0.9 mL were excluded.

Statistical Analysis

Effectiveness (where effectiveness = number of EMG measurements that showed loss of the jaw-opening re-

flex at the particular time point measured/total number of EMG measurements made at that time point) was determined for each time point at which EMG measurements were made for each anesthetic. Probit analysis[3] was used to determine the ED50 and ED95 values. The ED50 or ED95 of local anesthetics 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 ED50 and ED95 (Figure 2). The difference between 2 anesthetics was considered to be significant when the confidence intervals did not overlap. The probit analysis was performed using statistical analysis of Soft SPSS.

RESULTS

The results are summarized in Tables 1 and 2 and Figure 3.

Comparison of the ED50 Values

When the potency of the test anesthetics was compared, we found that the A6 group compared with the L group showed a 2.8 times potency 5 and 10 minutes after administration. The ED50 of the A12 group was the lowest for all test anesthetics throughout the entire course, with a 3.6–4.2 times potency over the L group. The potency of the A12 group at its peak difference at the 15-minute measurement was 3.8 times that of the A6 group. The ED50 of the P group was higher compared with the other 3 groups, with the P group showing a 0.5–0.9 times potency over the L group.

Change in the ED50 Value Over Time

The difference in the ED50 value of the A6 group was greatest at the 2- and 3-minute measurements, and this difference was statistically significant compared with the other measurement stages. The A6 group showed values similar to those of the L group at the 20-minute postadministration measurement point. The ED50 of the L group was fairly stable up to the 12-minute measurement; however, it increased thereafter. The 2-, 3-, and 5-minute measurements of the P group were significantly higher compared with the other measurement stages. There was practically no change over time identified in the measurement stages of the A12 group. The pattern of changes in the ED95 value was similar to that seen in the ED50 value.

DISCUSSION

Study Method

There are several reports on observations of anesthetic potency of local anesthetics in the teeth. Previous animal models that have been used to study the effects of local dental anesthetics involved the use of the method of Buldring et al,[4] in which the skin contraction response was measured, and the Herr[5] and Jones[6] procedure, in which changes in rat tail elevation or vocalization, respectively, in response to electric stimulation were measured. However, these methods do not consider the effect of the anesthetic's penetration into tissues before reaching the pulp nor the effect of using a vasoconstrictor with the anesthetic. Therefore, these studies didn't simulate the clinical setting. Nearly all studies used the maxillary incisor tooth, where cortical bone is relatively thin and local anesthetics penetrate easily. In this study, we used the mandibular incisor as an injection site (where penetration of the injection anesthetics solution to the dental pulp is difficult because of thick cortical bone) and we used the research methods of Grieffie and Brunel,[1] which entails observation by EMG of the jaw-opening reflex of the digastric muscle, specifically observation of the efficacy of the local anesthetic through loss of the reflex over time. The results were then analyzed with the probit method to determine the ED50 and ED95 values. The jaw-opening reflex is induced by a pain stimulus, and this reflex involves at least 2 neural pathways: one causes relaxation of the jaw-closing muscle and the other causes contraction of the jaw-opening muscle.[7] This reflex may be a defensive mechanism that protects oral tissue from a pain stimulus in the oral cavity. With this model, (1) it is easier to monitor and record EMGs of the digastric muscle compared with the somatosensory-evoked potential, (2) reproducibility is sufficient, (3) quantitative evaluation is possible, and (4) effects due to differences among the digastric muscle of different animals are minimized by using probit analysis. Using this model, higher dosages (ED50 or ED95) were judged as having a weaker anesthetic potency. The reason for the extraoral administration of the local anesthetic at the mandibular incisor was because lingual administration of the local anesthetic was easier since rabbit incisor roots are located toward the lingual side of the mandible.

Comparison of Anesthetic Potency

It has been suggested that articaine has a quick onset and a strong anesthetic effect;[8–10] however, there has been no comparative quantitative study of the efficacy of articaine with other local anesthetics.

The A12 group showed local anesthetic potency at

Table 1. Effectivity of Each Local Anesthetic*

	2	3	5	10	12	15	20 (min)
Lidocaine							
0.1 ml	(0/5) 0%	(0/5) 0	(0/5) 0	(0/5) 0	(0/5) 0	—	—
0.15	(1/5) 20	(1/5) 20	(1/5) 20	(1/5) 20	(1/5) 20	(0/5) 0	—
0.2	—	—	(2/5) 40	(2/5) 40	(2/5) 40	(1/5) 20	(0/5) 0
0.25	(3/5) 60	(4/5) 80	(5/5) 100	(5/5) 100	(4/5) 80	(1/5) 20	(0/5) 0
0.3	(4/5) 80	(4/5) 80	(5/5) 100	(5/5) 100	(5/5) 100	(4/5) 80	(4/5) 80
0.4	(5/5) 100	(5/5) 100	—	—	—	(5/5) 100	(5/5) 100
0.5	—	—	—	—	—	—	(5/5) 100
Propotocaine							
0.15 ml	—	(0/5) 0	(0/5 0	(0/5) 0	(0/5) 0	—	—
0.2	—	(1/5) 20	(1/5) 20	(1/5) 20	(1/5) 20	(0/5) 0	—
0.25	(0/4) 0%	—	—	(3/5) 60	(1/5) 20	(0/5) 0	(0/4) 0
0.3	(0/4) 0	(2/5) 40	(3/5) 60	(5/5) 100	(4/5) 80	(2/5) 40	(0/4) 0
0.4	(2/4) 50	(3/5) 75	(4/5) 80	(5/5) 100	(5/5) 100	(5/5) 100	(4/4) 100
0.5	(3/4) 75	(3/5) 75	(5/5) 100	—	—	(5/5) 100	(4/4) 100
Articaine 6							
0.025 ml	—	(0/5) 0	—	—	—	—	—
0.03	—	—	(0/5) 0	(0/5) 0	—	—	—
0.04	(0/5) 0%	—	(0/5) 0	(0/5) 0	(0/5) 0	—	—
0.05	—	(1/5) 20	(2/5) 40	(2/5) 40	(1/5) 20	—	—
0.08	(2/5) 40	(3/5) 60	(3/5) 60	(3/5) 60	(3/5) 60	—	—
0.1	(2/5) 40	(4/5) 80	(5/5) 100	(5/5) 100	(5/5) 100	(0/5) 0	—
0.18	(4/5) 80	(5/5) 100	—	—	(5/5) 100	(2/5) 40	(0/5) 0
0.2	—	—	—	—	—	(3/5) 60	(1/5) 20
0.3	(5/5) 100	—	—	—	—	(4/5) 80	(2/5) 40
0.4	—	—	—	—	—	(5/5) 100	(4/5) 80
0.5	—	—	—	—	—	—	(5/5) 100
Articaine 12							
0.025 ml	—	—	(0/5) 0	(0/5) 0	—	—	—
0.03	(0/5) 0%	(0/5) 0	(0/5) 0	(0/5) 0	(0/5) 0	(0/5) 0	—
0.04	(0/5) 0	(0/5) 0	(2/5) 40	(3/5) 60	(0/5) 0	(1/5) 20	(0/5) 0
0.05	(4/5) 80	(4/5) 80	(5/5) 100	(5/5) 100	(2/5) 40	(1/5) 20	(1/5) 20
0.08	(5/5) 100	(5/5) 100	(5/5) 100	(5/5) 100	(2/5) 40	(3/5) 60	(3/5) 60
0.1	(5/5) 100	(5/5) 100	—	—	(5/5) 100	(5/5) 100	(4/5) 80
0.18	—	—	—	—	—	—	(5/5) 100

* Effectivity was determined according to loss of reflex EMG upon electrical pulp stimulation after local anesthetic administration; effectivity is number of rabbits with loss of jaw-opening reflex/total number of rabbits.

lower dosages at all observation points compared with the P and L groups, and the difference in dosage is statistically significant at all of the observation points. Since no increase in dosage was required over time, it can be assumed that the A12 group had fast onset and a long duration of anesthetic effect. This supports the characteristics of articaine that have already been reported.[8] In this study, we found a difference in efficacy and anesthetic duration between articaine with 6 μg/mL epinephrine and that with 12 μg/mL epinephrine, showing the tendency that added amounts of epinephrine contributed to a stronger effect than lidocaine. Comparing the ED50 values among the anesthetics, it was found that the A12 group showed 3.6–4.2 times the anesthetic efficacy of the L group, which suggests the possibility that a lower dosage of articaine can produce the same anesthetic effect as a given dosage of lidocaine. Sitzmann and Lindorf[11] reported that an articaine solution had higher bone permeability based on experimental results that showed that articaine had superior anesthetic efficacy on the mandibular tooth compared with lidocaine. Further, Takai et al[12] reported that 4% articaine with 10 μg/mL epinephrine showed double the anesthetic efficacy in infiltration anesthesia on volunteers compared with lidocaine with 12.5 μg/mL epinephrine. On the other hand, Vahatalo et al[13] reported that there was no significant difference in the effects of 4% articaine with 5 μg/mL epinephrine and 2% lidocaine with 12.5 μg/mL epinephrine upon infiltration anesthesia procedures on volunteers. Cowan[14] compared the anesthetic efficacy between 4% articaine with 5 μg/mL epinephrine and 2% lidocaine with 12.5 μg/mL epinephrine in infiltration anesthesia or in conduction anesthesia at foramen mentale and reported

Table 2. ED50 and ED95 Values of Local Anesthetics at Various Observation Stages*

Time (minutes)	*Lidocaine*	*Propitocaine*	*Articaine 6*	*Articaine 12*
ED50				
2	0.22 (0.19–0.25)	0.43 (0.34–4.39)	0.11 (0.09–0.15)	0.05 (0.03–0.09)
3	0.21 (0.18–0.24)	0.34 (0.26–0.56)	0.07 (0.07–0.08)	0.05 (0.03–0.09)
5	0.18 (0.15–0.22)	0.25 (0.23–0.27)	0.06 (0.05–0.11)	0.04 (0.03–0.08)
10	0.18 (0.15–0.22)	0.24 (0.19–0.28)	0.06 (0.05–0.11)	0.05 (0.04–0.06)
12	0.19 (0.17–0.22)	0.26 (0.23–0.3)	0.1 (0.09–0.11)	0.05 (0.04–0.07)
15	0.26 (0.23–0.3)	0.32 (0.26–0.42)	0.21 (0.18–0.24)	0.06 (0.04–0.11)
20	0.31 (0.21–0.46)	0.36 (0–†)	0.3 (0.23–0.41)	0.08 (0.06–0.11)
ED95				
2	0.35 (0.3–0.46)	0.58 (0.48–†)	0.23 (0.17–0.36)	0.08 (0.06–0.25)
3	0.34 (0.29–0.43)	0.62 (0.43–†)	0.14 (0.12–0.16)	0.08 (0.06–0.25)
5	0.25 (0.21–0.37)	0.35 (0.32–0.39)	0.1 (0.07–0.3)	0.06 (0.04–0.28)
10	0.25 (0.21–0.37)	0.32 (0.27–0.46)	0.1 (0.07–0.3)	0.07 (0.06–0.12)
12	0.28 (0.24–0.37)	0.36 (0.31–0.49)	0.16 (0.14–0.18)	0.08 (0.06–0.12)
15	0.36 (0.31–0.49)	0.42 (0.34–0.69)	0.34 (0.28–0.45)	0.1 (0.07–0.48)
20	0.4 (0.32–†)	0.42 (0–†)	0.45 (0.35–0.9)	0.14 (0.11–0.23)

* The figures in parentheses indicate the confidence limits (upper/lower). When the confidence limit is ∞ according to the computation, then the upper limit is represented with † and the lower limit with 0. (The values are rounded off to 2 decimal points).

that the success rate of articaine was only 94% while that for lidocaine was 100%. Haas et al[15] and Donaldson et al[16] reported that articaine administered through infiltration anesthetic procedures showed the same level of efficacy as propitocaine. Sommer et al[17] compared anesthetic efficacy on the ulnar nerve and reported that articaine without a vasoconstrictor showed an anesthetic effect of shorter duration than mepivacaine. When summarizing past studies, it is suggested that there was no significant difference in clinical local anesthetic efficacy between articaine and other local anesthetics when the epinephrine concentration was low, at around 5 μg/mL. The strong anesthetic efficacy of the A12 group in this study is suggested to be the result of the high concentrations of both articaine and epinephrine.

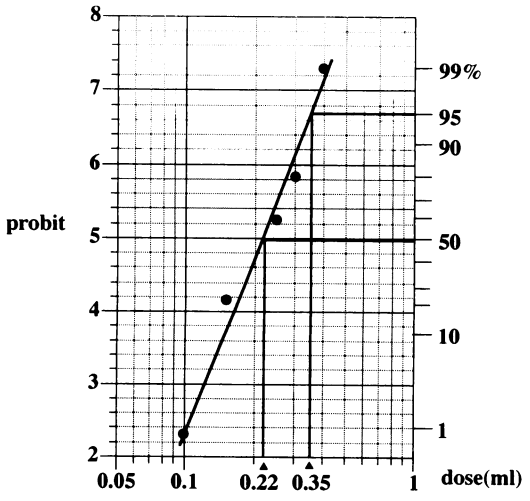

Figure 2. Example of probit analysis for 2% lidocaine with epinephrine (2 minutes).

The L group showed stronger efficacy than the P group up to 5 minutes after administration, and there was no change in dosage level over time at all observation points. As a result of the above, the anesthetic onset of the L group was swift, and the anesthetic effect was maintained for over 20 minutes. The ED50s of the L group were 1.2–2.0 times higher than those of the P group. This result closely resembles those of past reports, which have indicated that the L group showed 1.3–1.5 times the efficacy of the P group,[18] which supports the applicability of this experimental model in comparing the efficacy of local anesthetics.

To attain a particular anesthetic effect, a significantly higher dosage level for the P group was needed than for the other 3 groups at the 2- and 3-minute points and up to the 5-minute point, showing the weaker anesthetic efficacy for the P group. Further, to attain a particular anesthetic effect, the dosages of the P group at the 2-, 3-, and 5-minute points were significantly higher than the other measurement points of the P group, which suggests the need for massive doses of this agent for swift onset and duration of anesthetic efficacy. However, the P group did show the same level of local anesthetic efficacy as the L group after the 10-minute point. For the P group to attain the same anesthetic effect as the L group, there was a need to wait 10 minutes. Because the P group also required an increase in dosage level after 12 minutes, there was a significant difference between the P group and the other groups; however, it is suggested that this was due to the limits

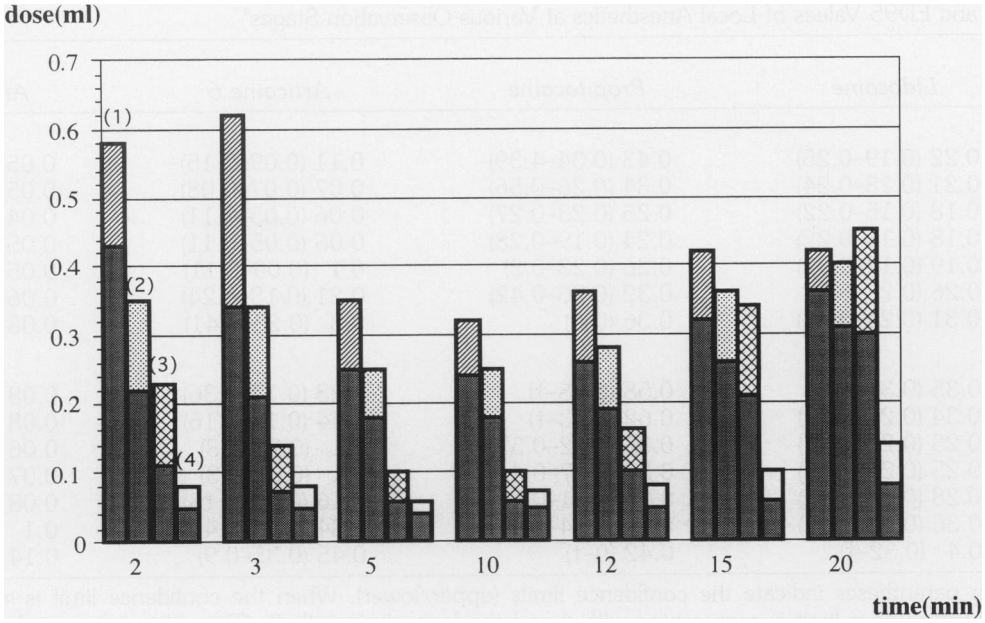

Figure 3. Comparison of the ED50 and ED95 values of local anesthetics at various observation stages (where ED95 is top and ED50 is bottom of the bar graph). (1) P group, (2) L group, (3) A6 group, (4) A12 group.

of the experimental model. In other words, after 20 minutes, the P group required massive dosages, over 0.5 mL, to attain the same anesthetic efficacy as the other agents, which resulted in an extremely large standard deviation in the dosage level. This may be the reason for being unable to identify a statistically significant difference.

A characteristic that was common to all 4 groups was that a specific amount of time was required before onset of the anesthetic effect. For all agents, it was necessary to wait 5–10 minutes after administration to attain sufficient anesthetic efficacy. In other words, to attain satisfactory local anesthetic efficacy for clinical use, there is a need to wait more than 5 minutes after administration of the local anesthetics before further treatment is begun. On the other hand, there is a need to increase the dosage level when (1) a swift anesthetic efficacy is needed, such as 2 or 3 minutes after administration, or (2) the duration of the anesthetic effect needs to be extended.

The A12 group showed efficacy at lower dosages, the shortest time before onset, and a longer duration of efficacy compared with the other 3 agents. This is an extremely desirable feature to a clinical dental practitioner, and thus it is suggested that 4% articaine with 12 μg/mL epinephrine is a highly potent local anesthetic for clinical use.

In conclusion, we provided electrical stimulation to the dental pulp of rabbits to determine anesthetic potency by observing the loss of the jaw-opening reflex of the digastric muscle through measurements made by EMG. Probit analysis was used to analyze the data. We found that there was a need to increase the dosage level of the local anesthetic drugs to attain a quick onset or to extend the duration. Comparing the dosage required to attain a particular anesthetic effect, we found that efficacy was in the order of 4% articaine with 12 μg/mL epinephrine, 4% articaine with 6 μg/mL epinephrine, 2% lidocaine with 12.5 μg/mL epinephrine, and 3% propitocaine with 0.03 IU/mL felypressin.

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