Comparison of Local Anesthetics as Bronchodilator Aerosols

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Lidocaine aerosols have been ineffective at preventing airway constriction provoked by non-reflex stimuli. To determine if there were any advantages to using more potent amide-type local anesthetics or local anesthetics from other chemical classes, the authors compared the protection afforded by pretreatment with aerosols of lidocaine, bupivacaine, hexylcaine, and procaine against a subsequent prolonged challenge (5 min) with 10% citric acid aerosols in barbiturate-anesthetized Basenji-Greyhound dogs. The local anesthetics were administered as aerosols (4% solutions) for 10 min immediately preceding the citric acid challenge. In control experiments, that employed pretreatment with aerosols of isotonic saline rather than local anesthetics, the citric acid challenge aerosol increased pulmonary resistance by an average of 3.3 ± 0.8 (±SE) cm H₂O·l⁻¹·s during the first 15-min postchallenge, and reduced dynamic compliance by one-third during this time. None of the local anesthetics prevented citric-acid-induced changes in pulmonary mechanics. The average increase in pulmonary resistance (0–15 min postchallenge) elicited by citric acid aerosols in dogs pretreated with lidocaine, hexylcaine, bupivacaine, and procaine were 2.1 ± 0.6, 2.1 ± 0.6, 3.2 ± 1.3, and 3.3 ± 1.0 cm H₂O·l⁻¹·s, respectively. The authors concluded that local anesthetic aerosols have little or no effect against other than reflex bronchoconstriction, and none of those tested were more effective than lidocaine. (Key words: Aerosols: local anesthetics. Anesthetics, local: bupivacaine; hexylcaine; lidocaine; procaine. Lung: bronchus; compliance; respiratory resistance.)

BRONCHOCONSTRICTION may be caused by one or more of three mechanisms: reflex stimulation; release of locally active mediators; and direct actions on airway smooth muscle. Local anesthetic aerosols block a variety of airway reflexes, including reflex-mediated bronchoconstriction. In addition, when administered as aerosols, local anesthetics might achieve high enough concentration in lung tissue to directly affect mediator release or smooth muscle tone. Although in vitro studies have demonstrated that high concentrations of lidocaine inhibit release of allergic mediators and directly relax airway smooth muscle, in vivo administration of lidocaine as an aerosol has been of little or no use in the treatment of other than reflex-mediated bronchoconstriction. Thus, lidocaine aerosols acutely provoke rather than alleviate bronchoconstriction in asthmatic patients, and are ineffective at preventing antigen-induced bronchoconstriction in the Basenji-Greyhound (BG) dog model of asthma. These failures imply that the lidocaine concentrations that are achieved in vivo after aerosol administration are inadequate to produce the inhibitory effects observed in experiments with isolated tissues.

Preceding in vitro studies with guinea pig tracheal chain indicated that drugs which were more potent as local anesthetics were also more potent in relaxing the intrinsic tone of airway smooth muscle. However, when the tracheal chains were contracted further with carbachol, the ester-type local anesthetics (irrespective of local anesthetic potency) were markedly more potent than amide-type local anesthetics in relaxing the pharmacologically enhanced tone. These studies suggested that ester-type local anesthetics, such as procaine or hexylcaine, might be more effective than lidocaine for use as bronchodilator aerosols, since they might achieve high enough levels to produce effects other than topical anesthesia.

To test this hypothesis, we pretreated BG dogs for 10 min with aerosols of lidocaine, bupivacaine, procaine, or hexylcaine, and then delivered a prolonged (5-min) challenge with citric acid aerosols. Since this challenge produces intense bronchoconstriction which is independent of airway reflexes, a reduction in the response in drug-treated animals implies a bronchodilator action unrelated to topical anesthesia.

**Methods**

The studies were performed on five BG dogs, weighing 16 to 22 kg. Aerosol challenges were delivered during thiopental anesthesia at about one-week intervals, and each dog served as its own control. The dogs were not premedicated and were anesthetized standing, supported by a sling. After induction of anesthesia with

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Received from the Departments of Pharmacology and Anesthesiology, School of Medicine, The Oregon Health Sciences University, Portland, Oregon. Accepted for publication August 12, 1982. Supported by NIH Grants GM-24524 and HL-25831 and the Department of Anesthesiology Research and Education Society.

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intravenous thiamylal (12–15 mg/kg), the dogs were paralyzed with succinylcholine (1 mg/kg), intubated with an 8.5 to 9.0 mm cuffed endotracheal tube, and mechanically ventilated (Harvard Apparatus Co., Millis, Massachusetts) with 100% oxygen at a tidal volume of 400 ml and a frequency of 15 min⁻¹. Additional increments of thiamylal (2 mg/kg) and succinylcholine (0.2 mg/kg) were administered as needed at approximately 20-min intervals. An esophageal balloon (Dysemblances, Blue Bell, Pennsylvania) was placed in the esophagus and positioned at the point where recorded end-expiratory pressure was lowest. The balloon contained 0.8 ml air. A separate catheter connected to suction was placed in the esophagus to keep it empty of air and liquid. Transpulmonary pressure (P_L) was measured with a differential transducer (Hewlett Packard 270, Waltham, Massachusetts) connected to the esophageal balloon and to a needle inserted into the endotracheal tube. Airflow (V) was measured with a pneumotachograph head (Hewlett Packard 2100) and a differential flow transducer (Hewlett Packard 47304A). Pressure and flow signals were recorded with a Hewlett Packard 47601 polygraph. Dynamic compliance (C_dyn) was calculated by dividing tidal volume by the difference in pressure between points of zero flow. Pulmonary resistance (R_L) was calculated using the method of Von Neergaard and Wirz by dividing P_L minus elastic pressure by V at mid-tidal volume. Apparatus resistance, determined by ventilating a mechanical lung analog with known parameters, was subtracted from the resulting value to give R_L. R_L and C_dyn were calculated from a mean of seven consecutive breaths. The electrocardiogram was monitored with a Grass 79 (Quincy, Massachusetts) polygraph. End-tidal CO₂ was monitored with a Beckman LB 1 infra-red analyzer (Palo Alto, California) and was maintained at close to 4.5% with the tidal volume and frequency employed in these experiments (see above).

Aerosols were delivered by a Hudson 3000 nebulizer (Hudson Co., Temecula, California) driven by compressed oxygen and inserted between the inspiratory limb of a circle anesthesia system and the endotracheal tube. The nebulizer delivered aerosol particles with a mass median diameter of 5.7 μm. Ten percent citric acid was made up in distilled water and administered as an aerosol for a 5-min period. R_L and C_dyn were measured prior to challenge, immediately after challenge, and at 5-min intervals following challenge for 15 min.

In separate weeks, each dog was challenged without preceding treatment, after pretreatment with a 0.9% saline aerosol (control), and after pretreatment with aerosols of 4% lidocaine, hexylcaine, bupivacaine, or procaine. Pretreatment aerosols were administered for a 10-min period ending 2 min before start of the challenge aerosol. Lidocaine aerosols employed the marketed 4% solution (Astra Pharmaceutical Products, Inc. Worcester, Massachusetts) with a pH of 6.1; hexylcaine aerosols employed the marketed 5% solution (Merck Sharp & Dohme, West Point, Pennsylvania) diluted with distilled water to 4%, with a pH of 3.0; bupivacaine HCl (Winthrop Laboratories, New York, New York) and procaine HCl (Sigma Chemical Company, St. Louis, Missouri) crystals were dissolved in distilled water, and 0.75 ml NaOH added to raise the pH to between 4 and 5. These values of pH were chosen to avoid precipitation of the local anesthetic and to prevent alkaline hydrolysis of the ester-type drugs.

Citic acid-induced changes in pulmonary mechanics were expressed as the increase in R_L (ΔR_L) above the prechallenge value, and as the ratio (f C_dyn) of C_dyn after and before challenge. For ease of comparison, ΔR_L and f C_dyn were averaged at 0, 5, 10, and 15 min post-challenge to give mean scores for each pretreatment aerosol; mean scores between treatment categories (saline aerosol, no pretreatment aerosol, lidocaine aerosol, bupivacaine aerosol, procaine aerosol, and hexylcaine aerosol) were compared by analysis of variance. Blood levels of lidocaine, hexylcaine, and bupivacaine were determined by gas chromatographic assay as described previously. Proacine levels were not determined. Blood drug levels were determined immediately after completion of the pretreatment aerosol, and at 0, 5, 10, and 15 min following completion of the challenge aerosol.

Results

In control experiments employing saline pretreatment aerosols, subsequent challenge with citric acid aerosols elicited marked increases in ΔR_L and decreases in C_dyn (fig. 1), which were maximal at 5 min after completion of the challenge aerosol, and were relatively well-maintained during the 15-min observation period. R_L increased from a prechallenge control of 1.3 ± 0.1 cmH₂O·l⁻¹·s (mean ± SE) to a maximum of 5.4 ± 1.1 cmH₂O·l⁻¹·s at 5 min post challenge, and C_dyn decreased from 125 ± 24 ml/cmH₂O to a minimum of 75 ± 20 ml/cmH₂O at 5 min postchallenge. The mean ΔR_L for the 15-min postchallenge period was 3.9 ± 0.8 cmH₂O·l⁻¹·s, and during this period C_dyn was reduced by one-third (f C_dyn = 0.67 ± 0.08). Citric-acid-induced changes in R_L were slightly, but consistently less after pretreatment with lidocaine or hexylcaine aerosols, than in the same animals pretreated with a saline aerosol or challenged without a pretreatment aerosol. However, the differences were small and the scatter sufficiently great so that statistical significance was not attained be-
between the various treatment categories (fig. 2). Citric-acid-induced decreases in $C_{\text{dyn}}$ were virtually identical in all treatment categories (fig. 3).

Blood levels of lidocaine, hexylcaine, and bupivacaine were maximal at the end of the 10-min pretreatment aerosol and averaged 0.92 ± 0.17, 0.22 ± 0.06, and 0.61 ± 0.06 µg/ml, respectively; 17 min later, at the end of the observation period, blood drug levels averaged 0.49 ± 0.08, 0.07 ± 0.02, and 0.51 ± 0.1 µg/ml, respectively.

**Discussion**

BG dogs have airways hyperreactive to a variety of stimuli, and reactivity to 10% citric acid is an especially striking example. Aerosols of 10% citric acid do not elicit bronchoconstriction in mongrel dogs, but produce marked increases in $R_L$ and decreases in $C_{\text{dyn}}$ in BG dogs. The response to a short (2-min) challenge with 10% citric acid is mediated primarily by reflex pathways since it is prevented or markedly attenuated by pretreatment with atropine. However, the 5-min challenge employed in this study is associated with release of bronchoactive mediators. The response to the 5-min challenge is not altered by pretreatment with atropine, but is prevented or attenuated by isoproterenol or cromolyn sodium (a mast cell stabilizer). Furthermore, postchallenge plasma after the 5-min challenge (but not after the 2-min challenge) contains a substance that contracts guinea pig ileum with the slow time course characteristic of leukotrienes.

Ascaris antigen aerosols also can elicit bronchoconstriction in sensitized animals by both reflex- and mediator-related pathways. In some mongrel dogs, stimulation of vagal reflex pathways may play a predominant role in ascaris antigen-induced bronchoconstriction; however, in the BG dog, the vagal component is small and, as with the 5-min citric acid aerosol, ascaris antigen aerosols provoke large increases in $R_L$ and decreases in $C_{\text{dyn}}$, despite pretreatment with large doses of atropine. In BG dogs that have been sensitized to ascaris antigen, the intensity of bronchoconstriction provoked by the 5-min citric acid aerosol challenge is very closely

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**Figure 1:** Response to the 5-min citric acid challenge in dogs pretreated with saline aerosols (mean ± SE; n = 5). Shaded bar indicates the challenge aerosol; abscissa represents elapsed time after challenge.

**Figure 2:** Comparative effects of different local anesthetics on citric-acid-induced $\Delta R_L$ (cmH$_2$O·L$^{-1}$·s$^{-1}$). Values for $\Delta R_L$ represent the average increase in $R_L$ during the first 15-min postchallenge. Brackets show SE (n = 9). There were no significant differences between treatment groups.
correlated with the response to ascaris antigen aerosols, indicating that common bronchoconstrictor mechanisms are involved in both challenges. We chose to employ the 5-min citric acid challenge for the present study for two reasons: 1) the reflex component was even less than with ascaris antigen, and 2) the citric acid challenge did not require prior immunologic sensitization.

In vitro studies have shown that high concentrations of lidocaine, in the millimolar range, can directly relax airway smooth muscle, and inhibit release of allergic mediators. Similar concentrations cannot be achieved by systemic administration without incurring profound toxicity, but might be achieved locally in the lung after aerosol administration. In a preceding study with BG dogs that were sensitive to ascaris antigen, pretreatment with 4% lidocaine aerosols afforded no protection against the bronchoconstrictor response to antigen aerosols, although large doses of lidocaine were administered and blood lidocaine concentrations approached antiarrhythmic levels. In the present study, we tested three other local anesthetics, which in in vitro studies were considerably more potent than lidocaine in relaxing either intrinsic (bupivacaine) or carbachol-induced (procaine, hexylcaine) tone in guinea pig trachealis muscle. However, none of the local anesthetics tested provided significant protection against the increase in $R_t$ and decrease in $C_{dyn}$ elicited by the 5-min citric acid challenge.

During the 10-min pretreatment period, about 10 ml of local anesthetic solution was aerosolized. A large part of this was lost into room air through the exhaust valve of the circle anesthesia system, or retained within the system. Nevertheless, both lidocaine and bupivacaine produced blood levels similar to those achieved during epidural anesthesia. Hexylcaine blood levels were consistently lower, suggesting either a slower absorption or more rapid metabolism. Hexylcaine is not metabolized by serum cholinesterase, but is metabolized by tissue esterases in both liver and lung.

In summary, our results indicate that local anesthetic aerosols provide little or no protection against mediator-induced bronchoconstriction, and that none of the local anesthetics tested were more effective than lidocaine. We believe that this failure probably reflects tissue drug levels that are too low to produce direct effects on smooth muscle tone or mediator release. However, substantially larger doses would be both difficult to administer as aerosols and potentially toxic from the standpoint of systemic absorption.

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