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Prevention of Lidocaine Aerosol-induced Bronchoconstriction with Intravenous Lidocaine

Yonca Bulut, M.D.,* Carol A. Hirshman, M.D.,† Robert H. Brown, M.D., M.P.H.‡

Background: **Lidocaine applied topically provokes bronchoconstriction in persons with hyperreactive airway disease. The authors questioned whether intravenous lidocaine would prevent lidocaine-aerosol induced bronchoconstriction. They compared the effects of lidocaine administered intravenously and by the aerosol route on baseline airway tone, and on the prevention of histamine-induced bronchoconstriction in five Basenji-Greyhound dogs.**

Methods: **Dogs were pretreated with either intravenous or aerosol lidocaine followed by histamine aerosol challenge. On separate days, dogs were pretreated with intravenous lidocaine, followed by aerosol lidocaine administration at similar doses. Airway caliber was assessed using high-resolution computed tomography. Data were analyzed by two-way analysis of variance. Serum lidocaine concentrations were obtained.**

Results: **Histamine alone decreased the airway area by 32 ± 3%. Lidocaine administered intravenously or by the aerosol route significantly inhibited histamine-induced bronchoconstriction. There was no significant difference between the two routes in preventing histamine-induced bronchoconstriction. At the dose that inhibited histamine-induced bronchoconstriction, lidocaine administered by the aerosol route decreased baseline airway area by 27 ± 3% ($P < 0.01$), whereas intravenous lidocaine had no effect. Intravenous lidocaine prevented lidocaine aerosol-induced bronchoconstriction, and the combination of intravenous and aerosol lidocaine significantly dilated the airways by 20 ± 5% ($P < 0.01$ compared with control).**

Conclusion: **An intravenous bolus of lidocaine prevents the initial bronchoconstriction induced by lidocaine when administered as an aerosol. (Key words: Bronchoconstriction, lidocaine).**

*Fellow, Department of Anesthesiology and Critical Care Medicine.

†Professor of Anesthesiology and Critical Care Medicine, Environmental Health Sciences, and Medicine.

‡Assistant Professor of Anesthesiology and Critical Care Medicine, Environmental Health Sciences, and Radiology.

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Address reprint requests to Dr. Bulut: The Johns Hopkins School of Hygiene and Public Health, Division of Physiology/Room 7006, 615 North Wolfe Street, Baltimore, Maryland 21205.

LIDOCAINE, administered either systemically[1-4] or topically as an aerosol,[5,6] has been used to block various airway reflexes in humans and is useful in preventing irritant-induced bronchoconstriction during anesthesia.[7,8] Blockade of irritant reflexes by an intravenously administered lidocaine bolus is short-lived,[4] whereas reflex blockade after lidocaine by the aerosol route lasts longer. Thus topical application of the drug would be of greater use when timing of the irritant stimulus is not predictable. In healthy persons, lidocaine administered as an aerosol produces little effect on pulmonary mechanics.[9,10] In contrast, in patients with reactive airway disease[11-13] and in Basenji-Greyhound dogs, which have nonspecific airway hyperreactivity,[7] lidocaine administered by the aerosol route produces some initial degree of bronchoconstriction. We questioned whether lidocaine administered as an aerosol activated airway reflexes and initiated irritant-induced bronchoconstriction, and if so whether an intravenous bolus of lidocaine would prevent this effect.

Histamine produces bronchoconstriction by both direct and reflex mechanisms in many species, including the dog[14,15] and the human.[16] We showed previously that histamine produced bronchoconstriction in dogs that was completely blocked by atropine when measured by high-resolution computed tomography (HRCT),[17] which can visualize airways as small as 1 mm in diameter. Thus histamine constricts the airways that are measured by HRCT, largely by atropine-sensitive mechanisms, and can be used as a model of reflex-induced bronchoconstriction.

First we quantified the dose of lidocaine administered by the intravenous and aerosol routes that prevented histamine-induced bronchoconstriction in Basenji-Greyhound dogs. Then we compared the effect of that dose of lidocaine, administered either intravenously or as an aerosol, on baseline airway tone and determined whether intravenous lidocaine

pretreatment prevented the bronchoconstriction provoked by lidocaine aerosols.

Methods

This study protocol was approved by the Johns Hopkins Animal Care and Use Committee. Studies were performed on five Basenji-Greyhound dogs. The dogs were anesthetized with thiopental (15 mg/kg induction dose followed by 10 $mg \cdot kg^{-1} \cdot h^{-1}$ given as an intravenous maintenance dose), paralyzed with 0.5 mg/kg succinylcholine, and the trachea were intubated with an 8.5-mm inner diameter endotracheal tube. During the study, the dogs were supine and the lungs were ventilated with a volume-cycled ventilator (Harvard Apparatus, Millis, MA) delivering 100% oxygen at a tidal volume of 15 ml/kg and at a rate of 18 breaths/min.

Airway Imaging

High-resolution computed tomography scans were obtained using a Somatom Plus Scanner (Siemens, Iselin, NJ) with a 1-s scan time, 137 kVp, and 220 mA. The images were reconstructed as a 256 × 256 matrix using a maximum zoom of 4.0 (12-cm field of view). The optimal spatial resolution of scanner was 0.35 mm. Thirty-five to 45 contiguous sections were obtained starting at the carina and proceeding caudally, using a 1-mm table feed and 2-mm slice thickness. The dogs were apneic and at functional residual capacity during scanning (approximately 2 min). Images were reconstructed using a high spatial-frequency (resolution) algorithm that enhanced edge detection, and at a window level of −450 Hounsfield Units (HU) and window width of 1,350 HU. These window settings previously were shown to allow optimal lung resolution.[18] All airways that could be visualized approximately perpendicular to the scan plane (long-short axis less than 1.5:1) under all experimental conditions were measured. For repeated image analysis within each experiment and across experiments on different days, proximal anatomic landmarks, such as airway or vascular branching points, were identified on the control-state HRCT images. After the challenges, the same airways in a given animal were then evaluated using images matched by these landmarks.

Airway Measurements

The HRCT images were transferred as 16-bit data images to a UNIX-based work station and reduced to eight-bit images, which were then analyzed using the airway-analysis module of the volumetric image and display analysis software package (Department of Radiology, Division of Physiologic Imaging, University of Iowa, Iowa City, IA). To measure airway areas, an operator drew a rough estimate of the lumen isocontour within the lumen of the airway. The software program then automatically located an isocontour perimeter of the airway lumen by sending out rays like the spokes of a wheel to a predesignated pixel intensity level that defined the lumenal edge of the airway wall. The length of the rays were set at 6 pixels. The software program used an algorithm for edge detection based on the "full-width-half-maximum" principle. The program defined the edge of the wall by those points along the rays at which the pixel intensity changed to one half its maximum through the wall. All full and partial pixels (full pixel size = 0.24 mm^2 with our settings) within the adjusted isocontour were counted and represented the airway area. The results obtained with the software program have been shown to be accurate, reproducible, resistant to operator bias.[19]

Protocol

Each dog served as its own control. On separate days at least 1 week apart, the dogs were pretreated randomly with either lidocaine given intravenously, lidocaine given as an aerosol, or neither followed by histamine aerosol challenge. Lidocaine given by the aerosol route was administered by a Hudson nebulizer (model 3000; Temecula, CA) placed on the inspiratory limb of a circular anesthesia system adjacent to the Y-connector. Five milliliters of 4% lidocaine (Abbott Laboratories, Abbott Park, IL) were nebulized over a 10-min period (fig. 1a). Ten minutes after the lidocaine aerosols were completely administered, histamine was given as a 3-mg/ml aerosol dose by a Hudson nebulizer for five breaths standardized to a peak pressure of 15 cm H_2O held for 2 s. The dose of histamine selected was based on previous studies showing that the dose selected decreased the airway lumenal area by approximately 40% when measured by HRCT.[20] High-resolution computed tomography scans were acquired before lidocaine administration, after completion of the lidocaine aerosol administration, and immediately after histamine administration. Intravenous lidocaine (Abbott Laboratories) was administered as a 2-mg/kg infusion for 10 min followed by an infusion of 5

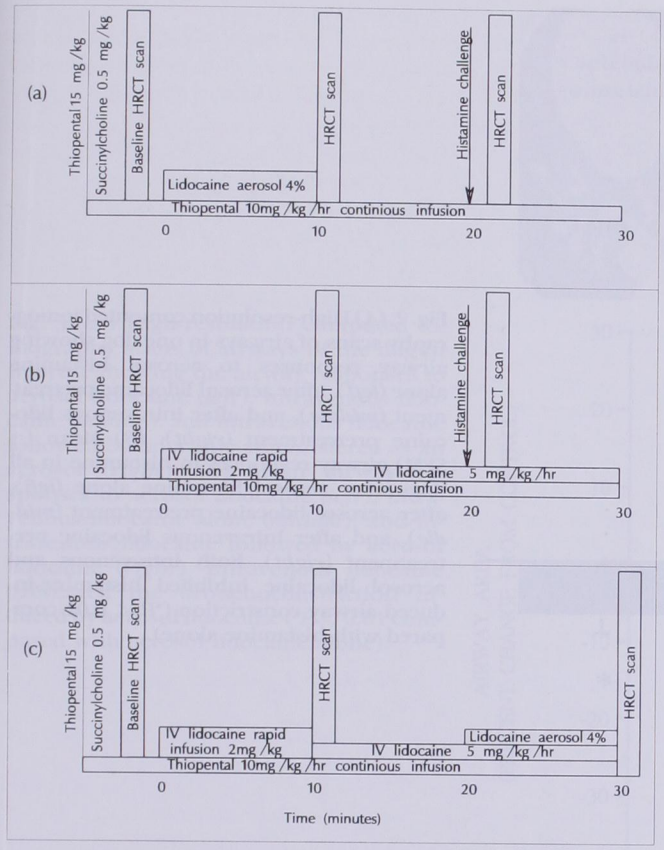


Fig. 1. Time course of (*a*) lidocaine aerosol followed by histamine challenge; (*b*) intravenous lidocaine followed by histamine challenge; (*c*) intravenous lidocaine followed by aerosol lidocaine.

$mg \cdot kg^{-1} \cdot h^{-1}$ (fig. 1b). Ten minutes after the start of the latter infusion, histamine was administered as an aerosol, as described previously. High-resolution computed tomography scans were obtained before lidocaine administration, after completion of the rapid infusion, and after histamine administration. On separate days, histamine aerosols (3 mg/ml) alone (n = 5 dogs) or saline aerosols alone (n = 2 dogs) were administered for five breaths to a peak pressure of 15 cm H_2O and held for 2 s.

To determine whether intravenous lidocaine pretreatment prevented lidocaine aerosol-induced bronchoconstriction, dogs were pretreated with 2 mg/kg lidocaine infused over 10 min followed by an infusion of 5 $mg \cdot kg^{-1} \cdot hr$ before lidocaine aerosol administration at the doses described above (fig. 1c). Ten minutes after the start of the 5-$mg \cdot kg^{-1} \cdot h^{-1}$ infusion, 4% lidocaine aerosol was administered for 10 min. High-resolution computed tomography scans were acquired before lidocaine infusion began, after the 2 $mg \cdot kg^{-1}$ infusion, and immediately after the administration of the lidocaine aerosol (fig. 1c).

Serum Lidocaine Levels

Five milliliters venous blood was drawn from each dog after the third set of HRCT scans were acquired. The venous blood samples were allowed to clot and were spun down, and lidocaine serum concentrations were measured by radioimmunoassay (TDx; Abbott Laboratories). The coefficient of variance was 6%.

Data Analysis

All data are presented as the mean ± SEM of the baseline for all measured airways. Fourteen airways were measured in each of the five dogs (for a total of 70 airways). The airways, which ranged in diameter from 1.9 to 13.5 mm, were matched under all conditions. The airway areas were calculated as a percentage change from baseline for all measured airways. The airway areas, as a percentage of baseline after intravenous and aerosol lidocaine administration and subsequent histamine administration, were analyzed by two-way analysis of variance, controlling for the individual dogs and for multiple airway measurements per dog. Results were considered significant at $P < 0.05$.

Results

Histamine decreased the airway area by 32 ± 3% ($P < 0.01$; figs. 2a and b). Lidocaine administered intravenously or as an aerosol inhibited histamine-induced bronchoconstriction ($P < 0.01$ compared with histamine alone). After pretreatment with lidocaine by the aerosol route, histamine decreased airway area by only 10 ± 5% of baseline, whereas during intravenous lidocaine administration, histamine decreased airway area by 7 ± 3% of baseline (figs. 2a and b). There was no significant difference between the two routes in preventing histamine-induced bronchoconstriction ($P = 0.25$). The effect of lidocaine did not differ according to either airway size or location ($P = 0.68$).

Intravenous lidocaine had no significant effect on baseline airway caliber ($P = 0.84$), whereas lidocaine administered as an aerosol significantly decreased airway area

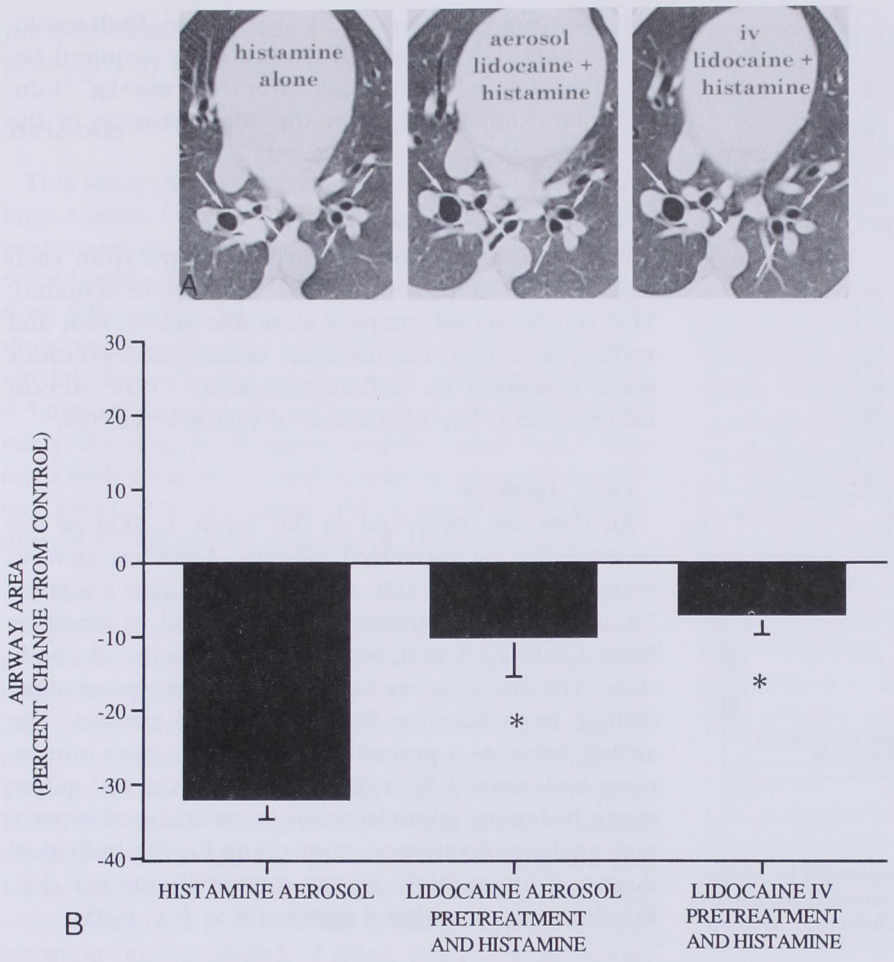


Fig. 2. (*A*) High-resolution computed tomography scans of airways in one dog showing airway responses to aerosol histamine alone (*left*), after aerosol lidocaine pretreatment (*middle*), and after intravenous lidocaine pretreatment (*right*). (*B*) Mean (± SEM) airway responses to histamine in all dogs after aerosol histamine alone (*left*), after aerosol lidocaine pretreatment (*middle*), and after intravenous lidocaine pretreatment (*right*). Both intravenous and aerosol lidocaine inhibited histamine-induced airway constriction (*$P < 0.01$ compared with histamine alone).

by 27 ± 3% ($P < 0.01$; figs. 3a and b). The decrease in airway area lasted less than 10 min, and airway caliber always returned to baseline before histamine was administered as an aerosol. Saline given by the aerosol route decreased airway area by 16 ± 2% (n = 2). The effect of saline aerosols on airway caliber was significantly different from that of lidocaine aerosol ($P = 0.01$).

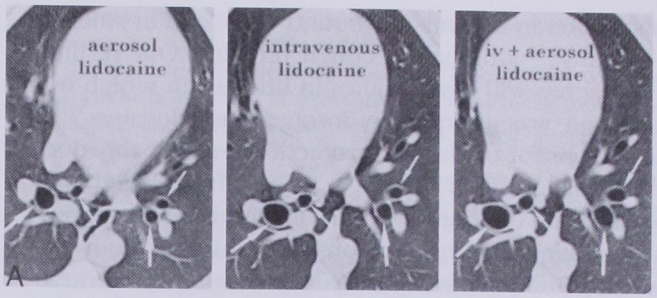
Intravenous lidocaine infused before aerosol lidocaine prevented lidocaine aerosol-induced bronchoconstriction. After lidocaine given both intravenously and as an aerosol, the airway area was significantly larger than control (airway area increased by 20 ± 5% [$P < 0.01$]; figs. 3a and b).

The mean serum lidocaine concentrations in the dogs treated with intravenous lidocaine was 3 ± 0.4 mg/l (range, 2 to 4.6 mg/l). The mean serum lidocaine concentrations in dogs treated with lidocaine by the aerosol route was 0.7 ± 0.4 mg/l (range, 0.3 to 1.1 mg/l). The mean serum lidocaine concentrations in dogs treated with intravenous lidocaine followed by aerosol lidocaine was 2.5 ± 0.4 mg/l (range, 1.7 to 3.2 mg/l).

Discussion

This study shows that lidocaine given as an aerosol at a dose that blocks histamine-induced bronchoconstriction provokes an initial bronchoconstriction. Furthermore, this bronchoconstriction can be prevented by pretreatment with intravenous lidocaine.

The initial bronchoconstriction observed in this study after the administration of lidocaine as an aerosol previously was reported to occur in patients with reactive airway disease[7,11–13] and in Basenji-Greyhound



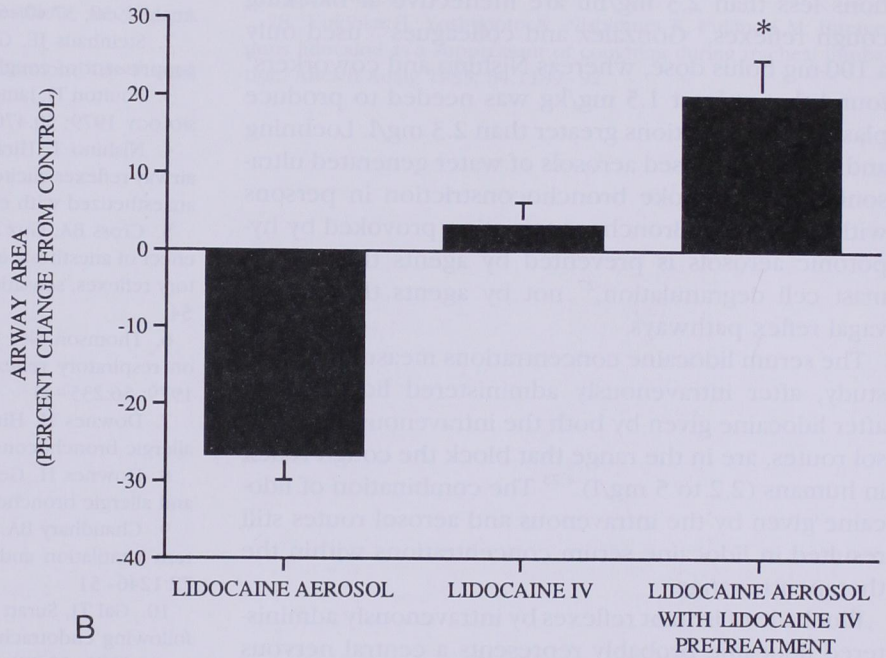


Fig. 3. (*A*) High-resolution computed tomography scans of airways of the dog in figure 2 showing the airway responses to aerosol lidocaine (*left*), intravenous lidocaine (*middle*), and intravenous lidocaine followed by lidocaine administered as an aerosol (*right*). (*B*) Mean airway responses to aerosol lidocaine (*left*), intravenous lidocaine alone (*middle*), and intravenous lidocaine followed by aerosol lidocaine (*right*). Intravenous lidocaine prevented the bronchoconstriction induced by aerosol lidocaine (*$P < 0.01$ compared with aerosol lidocaine alone).

dogs.[7] This initial bronchoconstriction may occur indirectly from the stimulation of irritant receptors in the airways or from release of inflammatory mediators and subsequent direct contraction of airway smooth muscle. The irritant effects of lidocaine may result from the pH, the tonicity of lidocaine aerosol solution, or from the preservatives in the lidocaine solution.[21,22] However, these are unlikely explanations for our findings, because the lidocaine solution used was isotonic (295 mOs), contained no preservatives, and was adjusted to a pH of 7.4. It is also unlikely that the initial bronchoconstriction resulted from the direct effect of inflammatory mediator release on airway smooth muscle, because intravenously administered lidocaine prevented this effect, and previous studies in this model have shown that intravenous lidocaine given at these serum concentrations had no protective effect on airways contracted with methacholine.[23]

The protective effect of intravenous lidocaine on lidocaine aerosol-induced bronchoconstriction suggests that the mechanism by which lidocaine aerosol causes bronchoconstriction is by activating reflexes mediated *via* afferent fibers of the vagus nerve, presumably by stimulating receptors located in the airway epithelium. Our results agree with those of Fish and Peterman,[13] who found that atropine aerosol pretreatment reduced or prevented lidocaine aerosol-induced bronchoconstriction in persons with asthma.

Our results with intravenous lidocaine are consistent with previous studies in which intravenous lidocaine, given in therapeutic serum concentrations, attenuated histamine-induced[23] and citric acid-induced[8] broncho-

constriction in Basenji-Greyhound dogs, and in studies in humans[2,24] attenuating cough reflexes. Our results do not agree with two studies in humans in which no protection was afforded by intravenous lidocaine.[25,26] The reasons for the lack of protection are probably due to the smaller doses of lidocaine used in the study by Gonzalez and colleagues[25] or to the nature of the stimulus provoking the bronchoconstriction in the study by Loehning and associates.[26] Serum lidocaine concentrations less than 2.3 mg/ml are ineffective at blocking cough reflexes.[4] Gonzalez and colleagues[25] used only a 100-mg bolus dose, whereas Nishino and coworkers[4] found that at least 1.5 mg/kg was needed to produce plasma concentrations greater than 2.3 mg/l. Loehning and associates[26] used aerosols of water generated ultrasonically to provoke bronchoconstriction in persons without asthma. Bronchoconstriction provoked by hypotonic aerosols is prevented by agents that inhibit mast cell degranulation,[27] not by agents that inhibit vagal reflex pathways.

The serum lidocaine concentrations measured in this study, after intravenously administered lidocaine or after lidocaine given by both the intravenous and aerosol routes, are in the range that block the cough reflex in humans (2.2 to 5 mg/l).[4,28] The combination of lidocaine given by the intravenous and aerosol routes still resulted in lidocaine serum concentrations within the therapeutic range.

Blockade of irritant reflexes by intravenously administered lidocaine probably represents a central nervous system effect, whereas reflex blockade after lidocaine aerosol administration results from both topical anesthesia and systemic effects of the absorbed drug. Aerosol administration of a drug maximizes the therapeutic effect while minimizing any toxic systemic effects. Thus higher concentrations of lidocaine can be delivered to the lung during aerosol administration, with lower resulting serum lidocaine concentrations.

Use of lidocaine administered as an aerosol has the advantages of ease of administration and longer duration of action, but it has the disadvantage of provoking bronchoconstriction in patients with reactive airway disease. On the other hand, intravenous lidocaine does not provoke bronchoconstriction, but its effects are short-lived and it has a greater potential for toxicity. An initial intravenous lidocaine bolus followed by aerosol lidocaine eliminates the initial bronchoconstriction and provides a longer duration of airway anesthesia.

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