

Combined Intravenous Lidocaine and Inhaled Salbutamol Protect against Bronchial Hyperreactivity More Effectively than Lidocaine or Salbutamol Alone

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Background: Airway instrumentation in persons with asthma is linked to the risk of life-threatening bronchospasm. To attenuate the response to airway irritation, intravenous lidocaine is recommended (based on animal experiments) and mitigates the response to histamine inhalation in asthmatic volunteers. However, the effects of lidocaine have not been compared with standard prophylaxis with β -sympathomimetic aerosols. Therefore, the effect of lidocaine, salbutamol, combined treatment, and placebo control were tested in awake volunteers with bronchial hyperreactivity.

Methods: After approval from the local ethics committee, 15 persons, who were selected because they showed a decrease in forced expiratory volume in 1 s (FEV₁) more than 20% of baseline in response to inhaled histamine in a concentration less than 18 mg/ml (PC₂₀), were enrolled in a placebo-controlled, double-blind, and randomized study. The challenge was repeated on four different days and the volunteers were pretreated with either intravenous lidocaine, inhalation of salbutamol, inhalation of salbutamol plus intravenous lidocaine, or placebo. Lidocaine plasma concentrations were also measured.

Statistical analyses included the Friedman test and Wilcoxon's rank sum.

Results: The baseline PC₂₀ was 6.4 ± 4.3 mg/ml. Intravenous lidocaine and salbutamol aerosol both significantly increased the histamine threshold to 14.2 ± 9.5 mg/ml and 16.8 ± 10.9 mg/ml, respectively (mean \pm SD). However, the combination of lidocaine and salbutamol significantly increased the PC₂₀ even further to 30.7 ± 15.7 mg/ml than did salbutamol or lidocaine alone.

Conclusions: In volunteers with bronchial hyperreactivity, both lidocaine and salbutamol attenuate the response to an inhalational histamine challenge, and their combined administration has much greater effects than does either drug alone. Accordingly, pretreatment of patients with bronchial hyperreactivity with both β -mimetic aerosol and intravenous lidocaine is recommended before airway irritation. (Key words: Airway resistance; asthma; bronchospasm; local anesthetics; lung.)

INSTRUMENTATION of the airway, such as tracheal intubation or bronchoscopy, can cause life-threatening bronchospasm. The closed-claim study of the American Society of Anesthesiologists revealed that 2% of the claims were related to bronchospasm and resulted in death or brain damage in more than 90% of these patients. In 69% of these patients, severe reflex bronchoconstriction occurred during induction of general anesthesia.¹

β -Adrenergic aerosols, such as salbutamol, and the intravenous administration of lidocaine have been recommended to prevent bronchospasm in patients with bronchial hyperreactivity who undergo airway instrumentation.^{2,3} Although β -adrenergic aerosols are recommended as a first-line treatment for acute bronchoconstriction, the cardiac side effects (*i.e.*, tachycardia and arrhythmia) still are a matter of concern.^{4,5} Therefore, an adjunct or alternative treatment with fewer cardiac side effects would be beneficial in patients at risk for myocardial ischemia, particularly when the drugs are used to prevent a potential risk and not to treat acute life-threatening bronchospasm.

The sodium channel blockers lidocaine and mexiletine significantly attenuate reflex bronchoconstriction after intravenous and oral administration, as tested by an in-

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Table 1. Demographic Data and Baseline Pulmonary Function of 15 Subjects with Bronchial Hyperreactivity at the Time of the Screening Visit

| Subject Number | Gender | Age (yr) | Weight (kg) | Height (cm) | VC (L) | FEV ₁ (L) | R _{tot} | PC ₂₀ (mgml ⁻¹) | Medication Used by Subjects |
|----------------|--------|----------|-------------|-------------|--------|----------------------|------------------|--|---|
| 1 | M | 28 | 80 | 183 | 6.33 | 4.15 | 0.25 | 6.3 | Salbutamol MDI as needed |
| 2 | M | 35 | 80 | 186 | 6.15 | 5.21 | 0.22 | 10.3 | None |
| 3 | M | 40 | 69 | 186 | 5.7 | 3.73 | 0.31 | 7.1 | Salbutamol MDI as needed |
| 4 | M | 37 | 103 | 184 | 5.05 | 3.71 | 0.53 | 0.97 | Fenoterol MDI + inhaled corticosteroids |
| 5 | F | 24 | 46 | 156 | 3.52 | 3.28 | 0.27 | 1.2 | Salbutamol MDI |
| 6 | M | 33 | 92 | 194 | 6.83 | 5.58 | 0.19 | 12.6 | Terbutaline MDI as needed + antihistaminic |
| 7 | F | 40 | 53 | 169 | 4.04 | 3.39 | 0.17 | 15.4 | None |
| 8 | F | 29 | 63 | 180 | 3.63 | 2.90 | 0.23 | 0.92 | Salbutamol MDI as needed |
| 9 | M | 42 | 65 | 170 | 4.22 | 3.12 | 0.20 | 6.2 | Fenoterol MDI as needed |
| 10 | F | 49 | 90 | 170 | 3.73 | 3.11 | 0.25 | 6.1 | None |
| 11 | F | 35 | 67 | 174 | 5.01 | 4.03 | 0.31 | 5.6 | None |
| 12 | M | 37 | 72 | 178 | 5.93 | 5.08 | 0.26 | 11.0 | None |
| 13 | F | 31 | 110 | 174 | 4.21 | 3.36 | 0.30 | 8.1 | Fenoterol MDI as needed |
| 14 | F | 29 | 63 | 180 | 3.51 | 2.94 | 0.29 | 0.51 | Salbutamol MDI + inhaled corticosteroids |
| 15 | F | 35 | 73 | 172 | 3.89 | 2.94 | 0.26 | 15.5 | Terbutaline MDI as needed + antihistaminic p.o. |
| Mean | | 34.9 | 75 | 177 | 4.78 | 3.77 | 0.27 | 7.2 | |
| SD | | 6.4 | 18 | 9 | 1.15 | 0.88 | 0.08 | 5.0 | |

MDI = metered dose inhaler; VC = vital capacity; FEV₁ = forced expiratory volume in 1 second; R_{tot} = total airway resistance; PC₂₀ = histamine concentration required for a 20% decrease in FEV₁.

halational histamine challenge.⁶ However, although lidocaine has been used to attenuate cardiac and cough reflexes for more than 20 yr,^{7,8} its effects have never been compared with standard treatment and prophylaxis with β -adrenergic aerosols. Furthermore, it has not been determined whether combined treatment with these drugs, which probably exert effects *via* different mechanisms, may be advantageous.

Accordingly, we assessed and compared in volunteers with bronchial hyperreactivity the effects of intravenously administered lidocaine, of inhalation of salbutamol, and of combined treatment on an inhalational challenge with histamine. We will show that lidocaine and salbutamol significantly attenuate bronchial hyperreactivity and that combined treatment even further decreases airway reactivity.

Methods

Participants

After we received approval from the local ethics committee and informed written consent, we enrolled 15 persons (age, 34.9 ± 6.4 yr; mean \pm SD) in this randomized, double-blind, placebo-controlled study. Eight of the volunteers were women and seven were men. All had either active asthma ($n = 9$), childhood asthma ($n = 1$), severe hay fever ($n = 3$), or chronic obstructive pulmo-

nary disease ($n = 2$) and showed symptoms consistent with airway hyperreactivity. Two of the volunteers smoked tobacco. Eight used an inhaler with β -adrenergic drugs—three regularly, five as needed—and two used inhaled corticosteroids. None of the volunteers used a β -adrenergic medication within at least the last 12 h before the measurement were obtained.

Measurements

The same air-conditioned room was used throughout the study; therefore, the humidity was kept constant, and the room temperature (22°C) varied only by $\pm 1^\circ\text{C}$. All measurements were performed for each participant at the same time of day (± 1 h). Lung function was measured using a body plethysmograph with an integrated spirometer (Jaeger, Würzburg, Germany). At the initial screening visit, baseline vital capacity (VC), forced expiratory volume in 1 s (FEV₁), and airway resistance were assessed (table 1), and bronchial hyperreactivity was confirmed in each volunteer using an inhalational provocation with histamine.⁶ Lidocaine plasma concentrations were determined by immunofluorescence assay (Abbott TDx System, Wiesbaden, Germany). The lower level of detection is 0.1 $\mu\text{g/ml}$, and the coefficient of variation is less than 3%.⁹ The blood samples were processed from 13 of 15 volunteers. During interventions, heart rate (electrocardiographic lead II) and arterial pressure (oscillometry) were also measured.

Aerosol Challenge. Aerosol inhalation was performed using a nebulizer (model 646, DeVilbiss, Somerset, PA) driven by compressed air at 30 psi using a mouth piece and a nose clip. The start of nebulization was triggered by integration of flow (Spira elektro 2 flow meter; Respiratory Care Center, Hämeenlinna, Finland) after inspiration of 500–750 ml and maintained for 0.6 s. The beginning of nebulization was set to 500 ml for volunteers with a VC less than 4 l, to 600 ml for those with a VC of 4 to 5.5 l, and to 750 ml for those with a VC of more than 5.5 l. The volunteers were instructed to inspire from functional residual capacity to inspiratory capacity at an inspiratory flow rate less than 0.6 l/s. At end-inspiration the volunteers were advised to hold their breath for 5 s. This maneuver was repeated five times. One or two minutes after inhalation of each aerosol dose, FEV₁ and VC were measured at least three times and the largest FEV₁ and VC were accepted.

Initially the volunteers were challenged with aerosolized saline, followed by increasing doses of histamine diphosphate (Sigma-Aldrich GmbH, Deisenhofen, Germany) diluted in saline. The starting concentration of histamine diphosphate was 0.074 mg/ml, which was trebled to 0.223, 0.67, 2, and 6 on each subsequent challenge up to a maximal concentration of 18 mg/ml. The time interval between increasing histamine concentrations was kept constant between 5 and 7 min.

Challenges were discontinued if the volunteers showed symptoms of chest tightness or difficulty in breathing, a decrease in FEV₁ of at least 20% from pre-challenge baseline, or had received the maximal concentration of histamine diphosphate (18 mg/ml). The histamine threshold concentration necessary for a 20% decrease in FEV₁ was calculated for each volunteer by linear regression over the challenge steps performed.¹⁰ Fifteen volunteer who had a decrease of 20% in FEV₁ within the range of histamine diphosphate concentrations tested were enrolled in the study. Five additional volunteers responded with a decrease in FEV₁ of less than 20% (range, 13–17%) to the histamine screening challenge, so consequently they were not enrolled.

In a given volunteer the starting concentration for all subsequent challenges was chosen two concentration steps lower than the concentration of histamine diphosphate that had caused a 20% decrease in FEV₁ (PC₂₀) in the screening visit. If a volunteer, because of one of the interventions, did not reach a 20% decrease in FEV₁ during the study days, the threshold was calculated by extrapolation.¹⁰

For consistency, all lung function measurements were

made by a single investigator (H.G.) who was blinded to the drugs administered.

Study Protocol. Two 18-gauge cannulas were inserted into right and left antecubital veins to infuse lidocaine or placebo and withdraw blood to measure lidocaine plasma concentrations, respectively. On each study day, baseline lung function was assessed, and further measurements were postponed if the actual FEV₁ differed by more than 7% from the baseline value measured during the screening visit. This was necessary on 2 of the 60 study days.

At four visits, in random order, and in a double-blinded manner, the volunteers received (1) salbutamol aerosol, (2) lidocaine intravenously, (3) salbutamol and lidocaine in sequence, or (4) placebo. This was accomplished as follows.

1. Salbutamol aerosol: The participants inhaled 1.5 mg salbutamol diluted in 1.5 ml saline followed by intravenous administration of saline (0.15 ml/kg over 20 min, followed by 0.3 ml · kg⁻¹ · h⁻¹ until the end of the histamine challenge).
2. Lidocaine intravenously: The participants inhaled 1.5 ml normal saline followed by intravenous administration of lidocaine (1.5 mg/kg lidocaine over 20 min followed by infusion of 3 mg · kg⁻¹ · h⁻¹ lidocaine of a lidocaine solution, 1%, to maintain lidocaine plasma concentrations until the end of the histamine challenge).
3. Combined lidocaine and salbutamol treatment: The participants received inhaled salbutamol and intravenous lidocaine in sequence with the same dosages and timing as described previously.
4. Placebo control: The participants inhaled saline and received saline intravenously according to the same infusion regimen and timing as described previously.

To determine lidocaine plasma concentrations, venous blood was drawn before the start of the lidocaine or saline infusions and, subsequently, at 5-min intervals for 90 min.

Data Analysis

Data were presented as mean ± SD. The following *a priori* null hypotheses were tested: (1) Intravenously administered lidocaine, salbutamol, or lidocaine and salbutamol combined do not change the histamine threshold compared with placebo. (2) The effects of combined treatment with salbutamol and lidocaine are not different than the effects of treatment with either salbutamol or lidocaine alone. Comparisons were made using the

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Table 2. FEV₁ and VC on Each Study Day and Posttreatment with Lidocaine, Salbutamol, Combined Lidocaine and Salbutamol, or Placebo (n = 15)

| | Lidocaine | | Salbutamol | | Lidocaine + Salbutamol | | Placebo | |
|----------------------|-------------|-------------|-------------|-------------|------------------------|-------------|-------------|-------------|
| | Baseline | Post | Baseline | Post | Baseline | Post | Baseline | Post |
| FEV ₁ (L) | 3.79 ± 0.87 | 3.79 ± 0.91 | 3.79 ± 0.86 | 3.97 ± 0.84 | 3.72 ± 0.86 | 3.93 ± 0.96 | 3.77 ± 0.89 | 3.73 ± 0.92 |
| P | | 0.865 | | 0.008 | | 0.033 | | 0.670 |
| VC (L) | 4.81 ± 1.17 | 4.88 ± 1.29 | 4.78 ± 1.12 | 4.87 ± 1.13 | 4.76 ± 1.19 | 4.89 ± 1.29 | 4.77 ± 1.20 | 4.88 ± 1.32 |
| P | | 0.427 | | 0.281 | | 0.096 | | 0.112 |

Values are mean ± SD.

FEV₁ = forced expiratory volume in 1 second; VC = vital capacity.

Friedman test followed by Wilcoxon's signed rank test with Bonferroni correction for multiple comparisons. The null hypotheses were rejected, and significant differences were assumed with an α error of less than 0.05.

Results

Table 1 shows the anthropometric data, the baseline lung function, and the PC₂₀ at the initial visit.

Baseline FEV₁ and VC on each study day also were compared with the FEV₁ and VC after treatment with lidocaine, salbutamol, lidocaine and salbutamol, and placebo. The FEV₁ significantly increased after the administration of salbutamol and salbutamol combined with lidocaine, whereas placebo and lidocaine alone did not significantly change baseline FEV₁ or VC (table 2).

Figure 1 shows lidocaine plasma concentrations after intravenous administration. Peak plasma concentrations at the end of the administration of the initial lidocaine infusion averaged 2.4 ± 0.6 μ g/ml when lidocaine was administered alone and was 2.2 ± 0.6 μ g/ml after salbutamol inhalation. These concentrations did not differ significantly from the concentrations at the end of the inhalational challenge (2.2 ± 0.5 μ g/ml and 2.1 ± 0.6 μ g/ml, respectively). As shown in figure 1, lidocaine plasma concentrations were maintained at a nearly constant concentration during the inhalation challenge.

The histamine threshold (PC₂₀) after intravenous and inhalational administration of placebo (6.4 ± 4.3 mg/ml histamine) did not differ significantly from the threshold obtained at the screening visit (7.2 ± 5 mg/ml).

Intravenous administration of lidocaine and inhalation of salbutamol each significantly increased the histamine threshold by more than 100% to 14.2 ± 9.5 mg/ml and to 16.8 ± 10.9 mg/ml, respectively. The combination of intravenous lidocaine and salbutamol aerosol increased the histamine threshold even further to 30.7 ± 15.7 mg/ml when compared with placebo. This threshold

was significantly higher than the thresholds observed after treatment with lidocaine or salbutamol alone. Figure 2 shows the thresholds for each volunteer on each study day.

Heart rate and arterial blood pressure were not affected significantly by lidocaine infusion (data not shown). However, one volunteer responded with a reproducible increase in heart rate (by 11–15 beats/min) after each salbutamol inhalation compared with the salbutamol-free study days.

Three of 15 volunteers noted mild symptoms such as light-headedness and slight vertigo during the intravenous administration of lidocaine, and one volunteer mentioned these symptoms during placebo administration.

Discussion

Prevention of bronchospasm in persons with bronchial hyperreactivity is desirable when airway instrumentation for general anesthesia or bronchoscopy is necessary. We found that lidocaine significantly attenuated bronchial hyperreactivity in awake volunteers with bronchial hyperreactivity as much as did an inhaled dose of 1.5 mg salbutamol. Furthermore, the combination of lidocaine and salbutamol attenuates bronchial hyperreactivity to a much greater extent than does pretreatment with either drug alone.

These results emerged from studies in 15 volunteers with moderate bronchial hyperreactivity. All were in a stable clinical condition during current medication period or during a symptom-free interval and were not exposed to their seasonal allergens. Volunteers with moderate bronchial hyperreactivity were selected because persons with more severe hyperreactivity would have been at greater risk during the challenges and might have shown a greater daily variability of lung function in response to a histamine challenge.¹¹

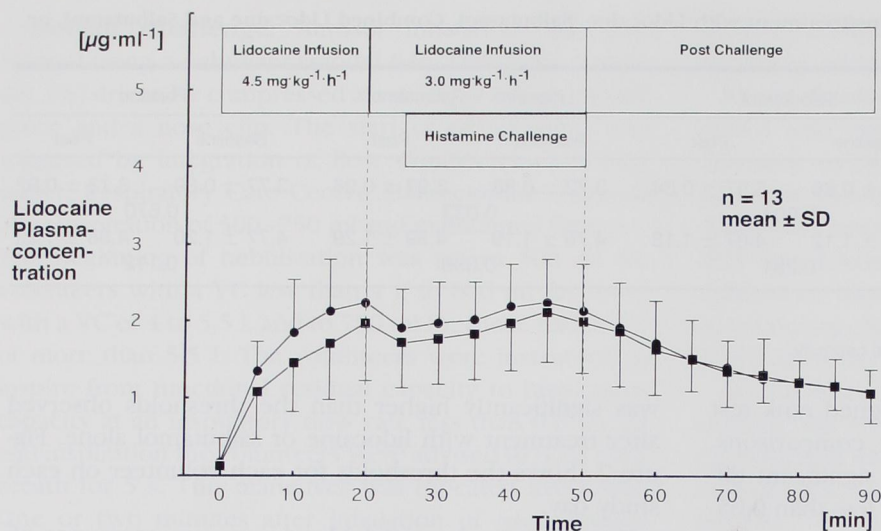


Fig. 1. The time course of lidocaine serum concentration with (squares) and without (circles) salbutamol pretreatment (mean \pm SD). The peak lidocaine concentrations are less than the toxic range of 5 $\mu\text{g}/\text{ml}$. With the continuous infusion of lidocaine after the loading dose, a nearly stable lidocaine concentration was maintained during the inhalational challenge; there is no significant difference in lidocaine concentrations at the end of the loading dose and at the end of the inhalational challenge.

A histamine challenge was chosen because it is well standardized, and the results obtained are comparable to our previous study.⁶ Histamine inhalation not only directly stimulates smooth muscle cells, as does methacholine, but also involves neural pathways.^{12,13} It has been shown by direct, single nerve fiber recordings from lung-irritant receptors that histamine causes irritation of

the airways that is similar to that caused by pharmacologically inert carbon dust or cigarette smoke.¹²

Therefore, a challenge with histamine is, to some extent, comparable to the stimulation evoked by tracheal intubation.

To minimize uneven distribution by turbulent air flow, the challenge was performed with control of inspiratory

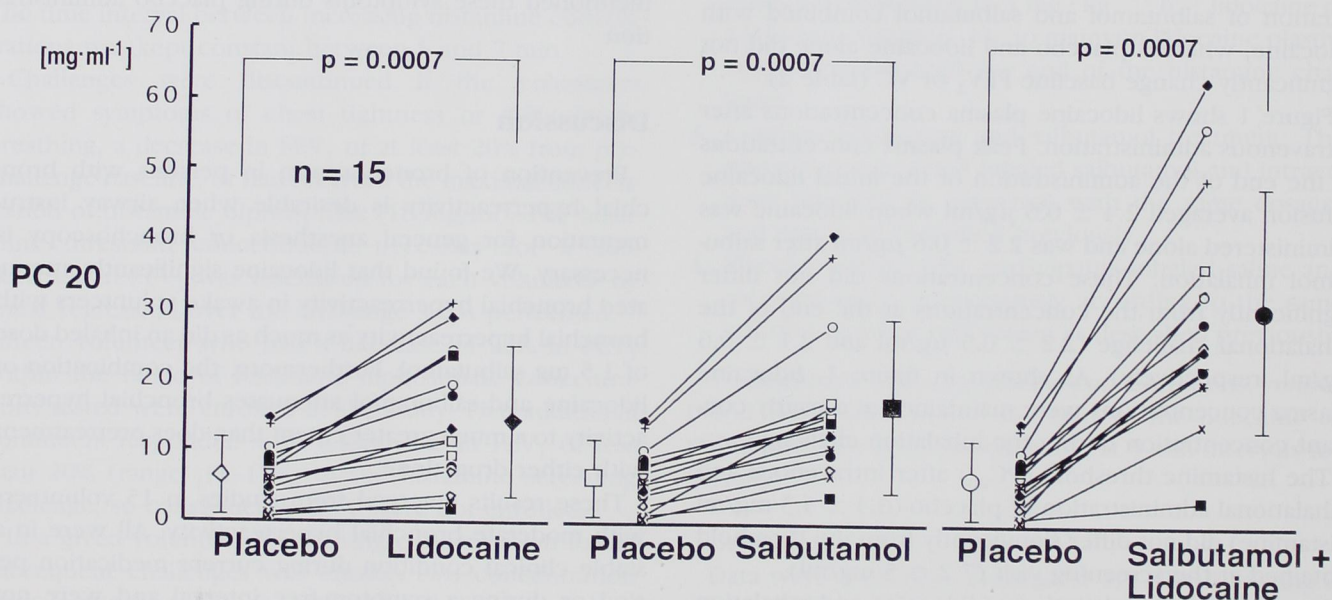


Fig. 2. Inhaled histamine concentrations inducing a 20% decrease in the forced expiratory volume in 1 s (FEV_1) before and after lidocaine (left), salbutamol (middle), and combined salbutamol and lidocaine (right) administration, respectively. Each pair of symbols represents the response of individual volunteers, whereas the mean response (\pm SD) is shown to the left and to the right of the individual responses. Data are from 60 inhalational challenges with histamine performed on four different days in 15 persons with bronchial hyperreactivity. Lidocaine and salbutamol both significantly increased the histamine threshold compared with placebo, with no statistical difference occurring between lidocaine and salbutamol. The combination of lidocaine and salbutamol also significantly increased the histamine threshold, but markedly more than lidocaine ($P = 0.0007$) or salbutamol ($P = 0.0008$) alone.

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flow, a 5-s breath hold at the end of inspiration, a defined time of nebulization during inspiration,¹⁴ and a fixed number of breaths to ensure high reproducibility of the challenges during each of the four study days. Maximal reproducibility of the challenge also was the reason to use the FEV₁ (that is associated with a low daily variability) as the variable to analyze the responses to histamine.¹⁵⁻¹⁷

The dose of lidocaine we chose was somewhat less than the dose used in a previous study in which we observed more severe side effects.⁶ In this way, we decreased lidocaine peak plasma concentrations and observed fewer volunteers with mild side effects than with the previous study. Frequent determinations of lidocaine plasma concentration indicated that lidocaine administration resulted in an initial increase but, of greater methodological importance, an almost constant lidocaine concentration throughout the challenge series (fig. 2).

Salbutamol led to a statistically significant increase in baseline FEV₁ by 5%. Although the change in baseline was significant in healthy persons, a shift of 5-10% is necessary to be clinically significant. In persons with asthma or chronic obstructive pulmonary disease, the change must be even greater to be clinically relevant.¹⁵⁻¹⁷ Therefore, it is unlikely that the baseline shift that was observed has a significant effect on the subsequent challenge.

In elderly patients, cardiac side effects are the main concern and limit the use of β -mimetic bronchodilators, as outlined recently in an editorial and an original article.^{4,5} Therefore, a moderate dose of salbutamol with a low risk for the occurrence of tachycardia or dysrhythmia was chosen. With this dose, no significant increase in heart rate with salbutamol inhalation was observed, although one volunteer showed a reproducible mild increase in heart rate after salbutamol inhalation. With a further increase in the dose of salbutamol, a higher incidence of cardiac side effects would have been possible. Thus, the dose of salbutamol chosen for pretreatment was protective against the histamine challenge but carried a low risk for cardiac complications. Similarly, the dose of lidocaine was chosen below the threshold for central nervous side effects. The mechanisms by which lidocaine attenuates bronchoconstriction may include direct effects on smooth muscle cells and neural blockade of vagal reflex pathways.¹⁸⁻²⁰

A direct relaxing effect of lidocaine on airway smooth muscle has been shown *in vitro* in which topical lido-

caine (10^{-4} to 10^{-3} M) significantly attenuated the contractile response of pig tracheal muscle strips to direct stimulation by acetylcholine and by hyperkalemia.¹⁹ However, lidocaine concentrations used in these experiments far exceed (10- to 100-fold) the lidocaine plasma concentrations observed during clinical use. Therefore, although it cannot be completely ruled out that direct effects on smooth muscle contribute to attenuation of bronchial hyperreactivity, this mechanism does not seem to be a likely explanation for attenuation of bronchial hyperreactivity by intravenous lidocaine observed in our volunteers.

It is more likely that nerve conduction blockade offers the main explanation for the effects of lidocaine. Lidocaine, in concentrations of $61 \cdot 10^{-6}$ M, abolishes constriction of rat tail arteries evoked by sympathetic nerve stimulation but not constriction induced by direct stimulation of smooth muscle cells by potassium or norepinephrine.²⁰ Furthermore, different reflexes (the Betzold-Jarisch reflex, the cough reflex, the intestinal stretch reflexes) are attenuated or even completely abolished after intravenous administration of lidocaine and other local anesthetics in clinically relevant concentrations in animals.^{21,22} Finally, in humans undergoing general anesthesia for surgery, intravenous lidocaine effectively suppressed the reflex-induced cough.^{7,23} Therefore, reflex suppression is the most likely mechanism to explain the protective effect of lidocaine as assessed by a histamine challenge in persons with bronchial hyperreactivity. That lidocaine attenuated airway reflexes but did not alter baseline bronchial tone is also consistent with unaltered lung function at baseline observed in this and in our previous study, in contrast to β -adrenergic aerosols with direct relaxing effects on smooth muscle cells.²⁴ The idea that both drugs attenuate the response to histamine by different mechanisms and the finding that both drugs were not administered to maximal effect (to minimize the side effects) can explain the marked effect of combined pretreatment, with lidocaine and salbutamol increasing PC₂₀ significantly more than either pretreatment alone.

In conclusion, intravenous lidocaine significantly attenuates bronchial hyperreactivity to an extent that is comparable to a moderate dose of salbutamol. Furthermore, the combination of intravenous lidocaine and inhaled salbutamol markedly increases the protective effect of either drug alone without increasing cardiac or central nervous side effects. Therefore, combined pretreatment with intravenous lidocaine and salbutamol

aerosol can be recommended to protect patients with bronchial hyperreactivity from noxious stimulation of their airways (such as during tracheal intubation or bronchoscopy), particularly those with a coexisting risk for myocardial ischemia.

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