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Intravenous Lidocaine and Bupivacaine Dose-dependently Attenuate Bronchial Hyperreactivity in Awake Volunteers

Harald Groeben, M.D., Andreas Schwalen, M.D.,† Stefan Irsfeld,* Sven Stieglitz,‡ Peter Lipfert, M.D.,§ Hans-Bernd Hopf, M.D.§*

Background: **In standard textbooks, intravenous lidocaine is recommended for intubation of patients with bronchial hyperreactivity. However, whether and to what extent intravenous local anesthetics attenuate bronchial hyperreactivity in humans is unknown. Accordingly, nine awake volunteers with known bronchial hyperreactivity were subjected to an inhalational challenge with acetylcholine before and during intravenous infusion of lidocaine, bupivacaine, or placebo in a randomized, double-blinded fashion.**

Methods: **Baseline acetylcholine threshold concentrations were determined 3–5 days before initiation of the investigation. The response to the acetylcholine challenge was defined as hyperreactive, if forced expiratory volume in 1 s decreased by at least 20%. In addition, the acetylcholine threshold for a 100% increase in airway resistance was obtained by body plethysmography. On seven different days, the acetylcholine challenge was repeated at the end of a 30-min intravenous infusion period of three doses of lidocaine (1, 3, and 6 $mg \cdot min^{-1}$) or bupivacaine (0.25, 0.75, and 1.5 $mg \cdot min^{-1}$), during saline placebo infusion, respectively. Acetylcholine-threshold concentrations were presented with the respective plasma concentrations of the local anesthetic.**

Results: **The infusion of lidocaine and bupivacaine resulted in plasma concentrations (means ± SD) of 0.29 ± 0.11, 1.14 ± 0.39, and 2.02 ± 0.5 $\mu g \cdot ml^{-1}$ for lidocaine and 0.11 ± 0.04, 0.31 ± 0.09, and 0.80 ± 0.18 $\mu g \cdot ml^{-1}$ for bupivacaine, respectively. Compared to baseline, the acetylcholine threshold for a 20% decrease of forced expiratory volume in 1 s as well as the threshold for a 100% increase in total airway resistance increased significantly with increasing plasma concentrations of both local anesthetics. Compared to placebo, acetylcholine threshold was almost quadrupled for lidocaine and tripled for bupivacaine with the highest plasma concentration of each local anesthetic.**

Conclusions: **In awake humans, intravenous lidocaine and bupivacaine both dose-dependently attenuated the hyperreactive response to a nonspecific inhalational challenge with acetylcholine. (Key words: Anesthetics, local: bupivacaine; lidocaine. Lungs: airway resistance.)**

FOR patients with bronchial hyperreactivity, intravenous application of local anesthetics is empirically recommended in standard textbooks[1,2] and review articles[3,4] to mitigate bronchoconstriction during tracheal intubation. In fact, in anesthetized dogs with bronchial hyperreactivity, intravenous lidocaine substantially suppressed bronchoconstriction evoked by a nonspecific (citric acid) as well as by a specific (Ascaris antigen) challenge.[5] Moreover, we showed recently, that intravenous bupivacaine attenuates bronchial hyperreactivity in predisposed patients.[6] However, it is unknown in humans whether this effect of intravenously administered local anesthetics on bronchial hyperreactivity is dose-dependent.

Therefore, the purpose of the current double-blinded study was to answer these questions: (1) Do bupivacaine and lidocaine dose-dependently attenuate bronchial hyperreactivity in predisposed humans when administered intravenously? and (2) Is there a difference between bupivacaine and lidocaine? Accordingly, awake volunteers with known bronchial hyperreactivity were subjected to an inhalational challenge with acetylcholine before and during intravenous infusion of different doses of lidocaine or bupivacaine in a randomized placebo-controlled manner. If intravenous local anesthetics affect bronchial hyperreactivity in predisposed humans in a dose-dependent manner, the bronchoconstriction in response to an inhalational challenge with acetylcholine should be attenuated or

* Staff Anesthesiologist, Institut für Klinische Anaesthesiologie.

† Resident, Klinik für Kardiologie, Pulmonologie und Angiologie.

‡ Medical Student.

§ Associate professor of Anesthesiology, Institut für Klinische Anaesthesiologie.

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Address reprint requests to Dr. Groeben: Department of Anesthesiology and Critical Care Medicine, University of Düsseldorf, Moorenstrasse 5, 40225 Düsseldorf, Germany.

even abolished with increasing plasma concentrations of the local anesthetics.

Materials and Methods

Volunteers

After approval of the local ethical committee and informed written consent was obtained, nine male volunteers (age 31 ± 2 years; mean ± SD) were enrolled in the randomized, double-blinded, placebo-controlled study. All volunteers had a history of either severe hay fever, asthma at childhood, or exercise-induced asthma. None of them received an antiobstructive medication within previous 10 days or corticosteroids within the 6 weeks preceding the investigation. None of them was a smoker.

Methods

The same air-conditioned room was used throughout the study to ensure that the humidity was constantly maintained and the room temperature (22°C) varied only by ±1°C. All measurements were performed during afternoons in the winter of 1993-94. The volunteers were sitting in a body plethysmograph during all measurements. A 16-G cannula was inserted on the right and left side into antecubital veins for infusion of the local anesthetics and withdrawal of blood samples for measurement of local anesthetic plasma concentrations, respectively.

Three to five days before the start of each volunteer's study sequence, bronchial hyperreactivity was confirmed by an inhalational provocation with acetylcholine.[7] Two volunteers did not respond with a 20% decrease in forced expiratory volume in 1 s (FEV_1; 15 and 17%, respectively) to the screening challenge and, consequently, were not enrolled in the study. The results of the screening acetylcholine challenges of all volunteers are given in table 1.

Acetylcholine inhalation was performed with an air-compressing nebulizer, triggered by inspiration (Jaeger, Würzburg, Germany). Each inhalation period lasted 2 min with a stepwise increase in the concentration of acetylcholine (0.5–1.0 and finally 3.0%) diluted in 0.9% saline solution, until a hyperreactive response was obtained. The response was defined as hyperreactive when FEV_1 had decreased by at least 20%.[7]

Forced expiratory volume in 1 s, vital capacity, and FEV_1 in percent of vital capacity (FEV_1 %) were obtained spirometrically. Total airway resistance (R_{aw}) was measured in a constant volume body plethysmograph (Jaeger, Würzburg, Germany)[8] with the panting technique carried out at a frequency of 1–0.5 Hz. Total airway resistance was determined as an average of five breaths, always before measurement of FEV_1.

Forced expiratory volume in 1 s, vital capacity, and R_{aw} were evaluated before and after the inhalation of acetylcholine. The acetylcholine threshold concentrations necessary for a 20% decrease in FEV_1[7] and a 100% increase in R_{aw}[9,10] were calculated for each subject. The acetylcholine threshold during placebo infusion was defined as baseline.

Three to five days after the screening challenge with acetylcholine, the responding volunteers received an intravenous infusion of either three doses of lidocaine or bupivacaine, respectively, or 0.9% saline placebo in a randomized, double-blinded fashion on seven different days. To reach steady-state plasma concentrations of the local anesthetics, each infusion was started 30 min before the inhalational challenge and was continued until the end of the challenge. Owing to personal reasons, one volunteer agreed only to four of seven inhalational challenges. In this volunteer, only the effects of saline placebo and lidocaine were investigated.

Lidocaine was administered as a continuous intravenous infusion of either 1, 3, or 6 $mg \cdot min^{-1}$ with a loading bolus of 15, 45, or 90 mg, respectively. Bupivacaine was infused in doses of 0.25, 0.75, and 1.5

Table 1. Screening FEV_1, R_{aw}, and Ach Thresholds of All Tested Volunteers

	Subject										
	1	2	3	4	5	6	7	8	9	10	11
FEV_1 (L)	3.69	4.44	3.98	5.54	5.86	5.99	4.31	3.78	4.23	4.68	4.17
R_{aw} ($mbar \cdot L^{-1} \cdot s$)	0.2	0.2	0.23	0.19	0.21	0.16	0.22	0.2	0.19	0.18	0.19
Ach threshold (% Ach)	0.69	2.54	1.03	0.47	2.1	2.71	2.01	1.79	0.59	Failed	Failed

FEV_1 = forced expiratory volume in 1 s; R_{aw} = airway resistance as measured by body plethysmography; Ach threshold = concentration of inhaled acetylcholine necessary for a 20% decrease in FEV_1.

$mg \cdot min^{-1}$ with a loading bolus of 3.75, 11.25, or 22.5 mg, respectively. The loading bolus was administered in 5 min. These doses are considered equieffective in view of their local anesthetic effect in isolated nerves[11] as well as in regional anesthesia[12] and the resulting local anesthetic plasma concentrations are in the range of those observed during major conduction blocks.[13–15]

Arterial blood pressure (Riva-Rocci) and heart rate (electrocardiogram) were evaluated before, after 5 min, and every 10 min after the start of each infusion, respectively.

To determine plasma concentrations of lidocaine and bupivacaine, venous blood samples were withdrawn immediately before and at the end of each inhalational challenge (table 2). The plasma local anesthetic concentration referring to the time of the inhalational challenge was taken as the arithmetic mean of these two concentrations. Lidocaine and bupivacaine plasma concentrations were determined by capillary gas chromatography (Sichromat 3, nitrogen detector, Siemens, Germany), as described previously,[13] using mepivacaine as an internal standard.

Data Analysis

Data were presented as means ± SD. The acetylcholine threshold for a 20% decrease in FEV_1 during saline placebo infusion was defined as baseline.

Two *a priori* null hypotheses were tested: (1) compared to baseline, intravenously administered lidocaine or bupivacaine does not change the acetylcholine threshold for a hyperreactive airway response; and (2) acetylcholine thresholds do not differ between the low, medium, and high lidocaine and bupivacaine dosing regimens, respectively. Comparisons within the lidocaine or bupivacaine group were made by repeated-measures analysis of variance followed by a *post hoc* paired *t* test. Local anesthetic plasma concentrations before and after the inhalational challenge were compared by a paired *t* test. Comparisons between the lidocaine or bupivacaine groups were performed by an unpaired *t* test with Bonferroni correction for multiple comparisons. Null hypotheses were rejected and significant differences assumed with $P < 0.05$.

Results

Compared to saline (placebo), neither lidocaine nor bupivacaine significantly altered baseline lung function (table 3). However, both local anesthetics increased acetylcholine threshold concentrations significantly with increasing plasma concentrations (fig. 1 and table 4). Thus, bronchial hyperreactivity appeared to be attenuated in a dose-dependent fashion.

Intravenous bolus injection followed by continuous infusion of the local anesthetics increased local anesthetic plasma concentrations to different degrees (tables 2 and 4). However, no statistically significant differences could be detected in the respective local anesthetic plasma concentrations before and after the inhalational challenge (table 2). Thus, steady-state conditions at the time of the inhalational challenge had been reached. Therefore, it appeared justified to use the arithmetic mean of both concentrations before and after the inhalational challenge to reflect the concentrations at the time of the inhalational challenge (table 4).

The effects of the increasing local anesthetic plasma concentrations on the acetylcholine thresholds for each volunteer are shown in figures 1A and 1B, the corresponding mean values for each local anesthetic plasma concentration as well as for saline placebo (baseline) are shown in table 4. Compared to baseline, acetylcholine threshold concentrations for a 20% decrease in FEV_1 increased dose-dependently during the infusion of the local anesthetics for each volunteer (fig. 1A),

Table 2. Plasma Concentrations of Lidocaine and Bupivacaine Immediately before and after Inhalational Challenge for the Low, Medium, and High Dose, Respectively*

	Low		Medium		High	
	Pre	Post	Pre	Post	Pre	Post
Lidocaine (n = 9) ($\mu g \cdot ml^{-1}$)	0.32 ± 0.15	0.26 ± 0.09	1.19 ± 0.30	1.09 ± 0.52	2.05 ± 0.38	1.99 ± 0.69
P before *vs.* after	0.136		0.389		0.707	
Bupivacaine (n = 8) ($\mu g \cdot ml^{-1}$)	0.11 ± 0.04	0.10 ± 0.05	0.31 ± 0.05	0.32 ± 0.05	0.85 ± 0.26	0.75 ± 0.18
P before *vs.* after	0.605		0.762		0.295	

* $P < 0.05$.

i.e., every increase in the local anesthetic plasma concentration led to a significant increase in the acetylcholine threshold (table 4). The different baseline acetylcholine thresholds in the lidocaine and bupivacaine groups are explained by the different number of volunteers in each group (see materials and methods).

The acetylcholine threshold for a 100% increase in airway resistance also increased significantly with increasing local anesthetic plasma concentrations, regardless of whether lidocaine or bupivacaine was infused (table 4).

Thus, intravenous lidocaine as well as bupivacaine dose-dependently attenuated bronchial hyperreactivity in awake volunteers.

Acetylcholine thresholds between the lidocaine and bupivacaine groups at each plasma concentration did not differ between both groups (table 4).

Heart rate and arterial blood pressure were not affected by the loading bolus or the continuous infusion of local anesthetics.

During the largest dose of lidocaine infused, eight of nine volunteers mentioned mild central nervous symptoms such as light-headedness and slight vertigo.

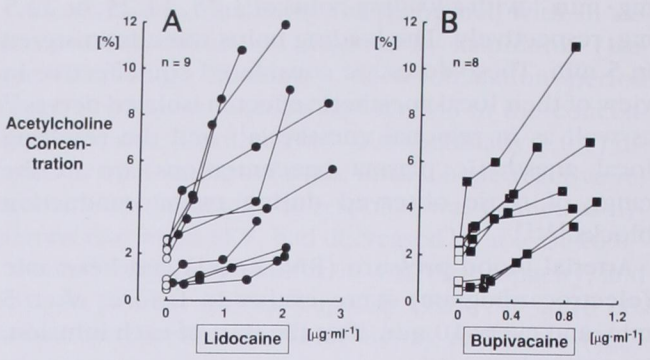

Fig. 1. Concentrations of inhaled acetylcholine necessary for a 20% decrease of forced expiratory volume in 1 s. Y-axis shows acetylcholine concentrations, X-axis lidocaine (*A, left*) or bupivacaine (*B, right*) concentrations, respectively. Each symbol represents the response of one volunteer subjected to an inhalational challenge during intravenous infusion of placebo (open symbols) or three different doses of either lidocaine or bupivacaine (full symbols). The individual plasma concentrations with the corresponding acetylcholine thresholds are shown for each challenge. The local anesthetics were administered as described in methods. The inhalational challenges were performed on 7 different days. Each increase in the plasma concentration of the local anesthetic resulted in a corresponding increase in the acetylcholine threshold. Thus, both local anesthetics dose-dependently increased the acetylcholine threshold in volunteers with bronchial hyperreactivity.

Discussion

Our results demonstrate that both lidocaine and bupivacaine significantly and dose-dependently attenuate bronchial hyperreactivity in awake humans.

The results were obtained under the premises that the infused doses of lidocaine and bupivacaine led to clinically relevant plasma concentrations, that it was appropriate to subject volunteers with known bronchial hyperreactivity to a nonspecific inhalational challenge, and that the study design was without systematic bias.

First, lidocaine and bupivacaine are two of the most commonly used local anesthetics and second, lidocaine is approved by the Food and Drug Administration for intravenous use as an antidysrhythmic drug. In our study, both local anesthetics were administered in doses leading to plasma concentrations in the range observed during regional anesthesia[13–15] or antidysrhythmic therapy with lidocaine.[16]

Second, bronchial hyperreactivity is not only one feature of asthma. In fact, bronchial hyperreactivity is found in hay fever, strong smoking, after viral infections of the upper airways, left heart failure, and pulmonary diseases like chronic obstructive pulmonary disease, sarcoidosis, and allergic fibrosis.[17,18] Patients suffering

Table 3. Effects of Placebo (saline), Lidocaine, or Bupivacaine Infusion on Lung Function

		Lidocaine (n = 9)			Bupivacaine (n = 8)		
	Placebo	1.0 mg · min^{-1}	3.0 mg · min^{-1}	6.0 mg · min^{-1}	0.25 mg · min^{-1}	0.75 mg · min^{-1}	1.5 mg · min^{-1}
FEV_1 (L)	4.55 ± 0.94	4.61 ± 1.03	4.63 ± 0.92	4.47 ± 0.93	4.69 ± 1.03	4.55 ± 1.16	4.61 ± 1.12
VC (L)	5.81 ± 0.89	5.85 ± 0.84	5.84 ± 0.58	5.70 ± 0.76	5.96 ± 0.91	5.97 ± 0.95	6.02 ± 1.01
FEV_1 (%)	79 ± 5.5	78 ± 8.0	79 ± 9.1	77 ± 7.2	78 ± 7.1	77 ± 8.0	76 ± 8.3
R_{aw} (mbar · L^{-1} · s)	0.20 ± 0.02	0.18 ± 0.03	0.19 ± 0.03	0.22 ± 0.03	0.20 ± 0.05	0.22 ± 0.05	0.21 ± 0.04

Data are mean ± SD. Measurements were made after a loading bolus followed by a 30-min infusion of each drug.
FEV_1 = forced expiratory volume in 1 s in liters and in % of the VC; VC = vital capacity; R_{aw} = airway resistance measured by body plethysmography.

Table 4. Ach Threshold for a 20% Decrease in FEV_1 and a 100% Increase in R_{aw} and the Corresponding Local Anesthetic Plasma Concentrations during Placebo, Lidocaine or Bupivacaine Infusion, Respectively

	Lidocaine (n = 9)				Bupivacaine (n = 8)			
	Placebo	1.0 mg · min^{-1}	3.0 mg · min^{-1}	6.0 mg · min^{-1}	Placebo	0.25 mg · min^{-1}	0.5 mg · min^{-1}	1.5 mg · min^{-1}
Plasma concentration (μg · ml^{-1})	—	0.29 ± 0.11*	1.14 ± 0.39†	2.02 ± 0.50‡	—	0.11 ± 0.04*	0.31 ± 0.09†	0.80 ± 0.18‡
Ach threshold FEV_1 (% acetylcholine)	1.51 ± 0.93	2.53 ± 1.79*	3.94 ± 3.06†	6.00 ± 4.14‡	1.62 ± 0.93	2.32 ± 1.57*	3.21 ± 1.93†	5.38 ± 2.79‡
Ach threshold R_{aw} (% acetylcholine)	1.57 ± 0.68	2.17 ± 1.6*	3.28 ± 2.18†	5.98 ± 3.6‡	1.73 ± 0.66	2.66 ± 2.3*	3.5 ± 1.92†	4.48 ± 1.95‡

Data are mean ± SD.

Ach threshold = concentration of inhaled acetylcholine necessary for a 20% decrease in FEV_1; FEV_1 = forced expiratory volume in 1 s; R_{aw} = airway resistance as measured by body plethysmography.

* $P < 0.05$ *versus* placebo.

† $P < 0.05$ *versus* lidocaine 1.0 mg · min^{-1} or bupivacaine 0.25 mg · min^{-1}.

‡ $P < 0.05$ *versus* lidocaine 3.0 mg · min^{-1} or bupivacaine 0.5 mg · min^{-1}.

from any of these diseases are at risk to develop bronchospasm after unspecific irritation of their airways.[3,4]

In general, the inhalation of acetylcholine causes bronchoconstriction *via* a complex mechanism involving cholinergic (vagal) efferents as well as smooth muscle cell stimulation.[19] In detail, airway constriction by acetylcholine inhalation may be mediated *via* neural pathways, *i.e.*, by stimulation of muscarinic receptors on parasympathetic nerve cells, by stimulating irritant receptors in the airway mucosa, and finally by binding to muscarinic receptors on smooth muscle cells.[20,21] Because the inhalational challenge with acetylcholine is testing bronchial hyperreactivity in general, like histamine and methacholine, but not a specific antigen in a sensitized patient, the challenge is called nonspecific.[22] Accordingly, to evaluate the effect of intravenous local anesthetics on bronchial hyperreactivity in general, volunteers with known bronchial hyperreactivity were subjected to a nonspecific inhalational challenge. The response to acetylcholine inhalation was evaluated by using a decrease in FEV_1 as well as an increase in R_{aw}, because these two parameters reflect different regions of the bronchial tree. A change in R_{aw} is reflective of the response of the larger airways whereas FEV_1 represents the whole bronchial tree, including the airway periphery.[22] Because we found no difference between these two thresholds, attenuation of bronchial hyperreactivity by intravenous local anesthetics seems not to be restricted to a specific region of the bronchial tree.

Finally, the sequence of different intravenous doses of local anesthetics and saline placebo was randomized and double blinded to avoid any bias by investigators or volunteers.

Thus, our study design appears to be appropriate to evaluate the effect of different doses of lidocaine and bupivacaine on bronchial hyperreactivity.

The recommendation of intravenous local anesthetics to attenuate bronchoconstriction after irritating stimulation in humans is based solely on clinical experience[1–4] and one study in anesthetized dogs.[5] Our study is the first in awake human volunteers to show a dose-dependent increase in the acetylcholine threshold, *i.e.*, the subjects were less susceptible to an inhalational challenge after intravenous application of lidocaine or bupivacaine.

Several mechanisms might explain this attenuating effect of intravenously administered local anesthetics on bronchial hyperreactivity.

First, intravenous local anesthetics might directly attenuate bronchial smooth muscle tone. *In vitro* topical application of lidocaine ($10^{-4} - 10^{-3}$ mol/l) to strips of pig trachealis muscle significantly attenuated the response to an acetylcholine as well as a hyperkalemic challenge.[23] However, the concentrations of local anesthetics used in these *in vitro* experiments exceeded local anesthetic plasma concentrations occurring during clinical use by far (10–100-fold). Thus, direct attenuation of bronchial smooth muscle tone seems not to be a likely explanation for the observed attenuation of bronchial hyperreactivity by intravenous lidocaine and bupivacaine in our awake volunteers.

Second, intravenous local anesthetics might attenuate nerve conduction and reflex arches involved in media-

tion of bronchial hyperreactivity. In fact, it has been demonstrated in animals that different reflexes (Betzold-Jarisch-Reflex, Cough-Reflex, intestinal stretch receptor reflex) are attenuated or even completely blocked after intravenous application of the local anesthetics procaine, tetracaine, and lidocaine.[24,25] Moreover, evaluation of the effects of topically applied lidocaine or bupivacaine on smooth muscle *in vitro* (isolated strips of rat tail artery) has shown that local anesthetics in clinically relevant concentrations (lidocaine $61 \cdot 10^{-6}$ mol $\cdot$ l^{-1}; bupivacaine $4 \cdot 10^{-6}$ mol $\cdot$ l^{-1}) inhibited preferentially smooth muscle contraction elicited by adrenergic nerve stimulation rather than those generated by direct stimulation of the smooth muscle cells by potassium or administration of norepinephrine.[26]

In addition, local nerve reflexes produced by stimulation of C-fiber nerve endings play a hypothetical role in the development of bronchial hyperreactivity, and therefore, the damage of bronchial epithelium as it occurs in asthma, hay fever, chronic obstructive pulmonary disease, and after viral infections of the airways might increase the reflex activity with concomitant increase in bronchial hyperreactivity.[27–29] Because intravenous or intramuscular application of local anesthetics attenuated or even suppressed directly recorded sympathetic nerve activity, at least in animals,[30,31] inhibition of neural conduction might explain the observed attenuation of bronchial hyperreactivity in our volunteers during intravenous application of local anesthetics. Thus, lidocaine and bupivacaine appear to inhibit smooth muscle contraction predominantly by attenuating nerve conduction rather than by direct suppression of smooth muscle cell contraction.

Finally, intravenous local anesthetics might have an influence on the central nervous system in attenuating bronchial hyperreactivity. This hypothesis is supported by experiments in anesthetized dogs. While intravenous administration of lidocaine (plasma concentrations 5.2 and 7.5 μg $\cdot$ ml^{-1}) significantly suppressed the directly recorded cardiac sympathetic activity, it did not decrease postganglionic nerve activity in response to preganglionic stimulation, *i.e.*, ganglionic transmission is not inhibited by the local anesthetic.[32] Therefore, these authors speculate, that lidocaine acts in the central nervous system or spinal cord to inhibit sympathetic activity centrally. In sharp contrast, intravenous lidocaine in doses that prevented centrally induced sympathetic arrhythmias (hypothalamic stimulation), failed to attenuate increased preganglionic sympathetic activity in anesthetized cats.[33] These results suggest that lidocaine acts *via* a peripheral rather than a central mechanism.[33] Thus, the contribution of a central nervous system effect of the local anesthetics to the attenuation of bronchial hyperreactivity in our volunteers appears rather uncertain and speculative, if present at all.

In summary, this study demonstrates for the first time in a prospective placebo-controlled manner that intravenous administration of lidocaine and bupivacaine dose-dependently decreases bronchial hyperreactivity. Although devoid of side effects, we cannot recommend bupivacaine for clinical use because it is not approved by the Food and Drug Administration for intravenous use.

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