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Airway Anesthesia Alone Does Not Explain Attenuation of Histamine-induced Bronchospasm by Local Anesthetics

A Comparison of Lidocaine, Ropivacaine, and Dyclonine

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Background: **Lidocaine inhalation attenuates histamine-induced bronchospasm while evoking airway anesthesia. Because this occurs at plasma concentrations much lower than those required for intravenous lidocaine to attenuate bronchial reactivity, this effect is likely related to topical airway anesthesia and presumably independent of the specific local anesthetic used. Therefore, the authors tested the effect of dyclonine, lidocaine, and ropivacaine inhalation on histamine-induced bronchospasm in 15 volunteers with bronchial hyperreactivity.**

Methods: **Bronchial hyperreactivity was verified by an inhalational histamine challenge. Histamine challenge was repeated after inhalation of dyclonine, lidocaine, ropivacaine, or placebo on 4 different days in a randomized, double-blind fashion. Lung function, bronchial hyperreactivity to histamine, duration of local anesthesia, and lidocaine and ropivacaine plasma concentrations were measured. Statistical analyses were performed with the Friedman and Wilcoxon rank tests. Data are presented as mean ± SD.**

Results: **The inhaled histamine concentration necessary for a 20% decrease of forced expiratory volume in 1 s (PC_{20}) was 7.0 ± 5.0 mg/ml at the screening evaluation. Lidocaine and ropivacaine inhalation increased PC_{20} significantly to 16.1 ± 12.9 and 16.5 ± 13.6 mg/ml ($P = 0.007$), whereas inhalation of dyclonine and saline did not (9.1 ± 8.4 and 6.1 ± 5.0 mg/ml, $P = 0.7268$). Furthermore, in contrast to saline and lidocaine, inhalation of both ropivacaine and dyclonine significantly decreased forced expiratory volume in 1 s from baseline ($P = 0.0016$ and 0.0018, respectively). The longest lasting and most intense anesthesia developed after dyclonine inhalation (48 ± 13 *vs.* 28 ± 8 [lidocaine] and 25 ± 4 min [ropivacaine]).**

Conclusion: **Both lidocaine and the new amide local anesthetic ropivacaine significantly attenuate histamine-induced bronchospasm. In contrast, dyclonine, despite its longer lasting and more intense local anesthesia, does not alter histamine-evoked bronchoconstriction and irritates the airways. Thus, airway anesthesia alone does not necessarily attenuate bronchial hyperreactivity. Other properties of inhaled local anesthetics may be responsible for attenuation of bronchial hyperreactivity.**

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LIDOCAINE, both when inhaled or injected, attenuates bronchial hyperreactivity in response to a variety of stimuli.[1–4] However, when lidocaine is applied by inhalation as compared with intravenous administration, the same attenuation of histamine-induced bronchospasm is achieved with significantly lower lidocaine plasma concentrations.[4] Because the effect of intravenously administered lidocaine is strictly dose-dependent,[5] additional or different mechanisms must be involved to explain this differential effect. Lidocaine inhalation may lead to higher airway tissue concentrations involving structures different from those affected after intravenous administration. Alternatively, lidocaine inhalation might, by profound topical airway anesthesia itself, attenuate bronchoconstriction in response to histamine.

Thus, to assess the relation between attenuation of histamine-evoked bronchoconstriction and topical anesthesia, we compared the effects of different local anesthetics, *i.e.*, lidocaine, ropivacaine, and dyclonine. Ropivacaine is a new amide local anesthetic chemically related to lidocaine, whereas dyclonine belongs to a different group of local anesthetics classified as ketones. Dyclonine is exclusively used for topical anesthesia and is effective during bronchoscopy or awake endotracheal intubation.[7]

To test the hypothesis that topical anesthesia by itself attenuates histamine-evoked bronchospasm, independent of the local anesthetic used, we evaluated the effects of aerosolized lidocaine, ropivacaine, dyclonine, or saline in volunteers with bronchial hyperreactivity. To assess potentially irritating effects on airways, we also measured lung function before and after inhalation of the three local anesthetics or saline. Furthermore, the effect of all three local anesthetics and plasma concentrations of lidocaine and ropivacaine were measured.

Methods

Subjects

After obtaining study approval from the ethics committee at the Universität Essen, Essen, Germany, and written informed consent, 15 subjects (9 women, 6 men; age, 31.8 ± 8.1 yr [mean ± SD]) were enrolled in this

randomized, double-blind, placebo-controlled study. The subjects were of normal height (178 ± 7.8 cm) and weight (74 ± 15.9 kg). The subjects had active asthma (n = 10) or significant hay fever (n = 5), and all had symptoms consistent with airway hyperreactivity. None of the subjects was a smoker. Eight subjects used a ß-adrenergic inhaler, four on a regular and five on an as-needed basis, and two used inhaled corticosteroids. None of the subjects received a ß-adrenergic medication within the last 12 h before the measurements, and none had used theophylline preparations or systemic corticosteroids within the last 3 months. All 15 volunteers also participated in a second study with inhalational histamine challenges addressing effects of different concentrations of lidocaine as an aerosol, including the dose used in this study.

Measurements

Lung function measurements were performed in a body plethysmograph (Masterlab Jaeger, Würzburg, Germany) with an integrated spirometer (Jaeger) in each subject at the same time of day (± 1 h). On the initial screening visit, baseline vital capacity, forced expiratory volume in 1 s (FEV_1), maximal expiratory flow at 50% of the vital capacity, and maximal inspiratory flow at 50% of the vital capacity were assessed. This was followed by an inhalational challenge with histamine to confirm bronchial hyperreactivity. Bronchial hyperreactivity was defined by a decrease of FEV_1 of at least 20% from baseline after the inhalation of histamine in a concentration less than 18 mg/ml.

Blood was drawn from an antecubital vein to measure lidocaine and ropivacaine plasma concentrations. Lidocaine was measured by an immunofluorescence assay (Abbott TDx System; Abbott, Wiesbaden, Germany; lower level of detection 0.1 μg/ml, coefficient of variation < 3%),[8] whereas ropivacaine was measured by high-pressure liquid chromatography (Waters 2690, Eschborn, Germany; with photo diode array detector spectrophotometric election at 200 nm; lower level of detection 0.01 μg/ml, coefficient of variation < 0.5%).

Histamine Aerosol Challenge

Aerosol inhalation was performed with a nebulizer driven by compressed air at 30 psi (DeVilbiss No. 646; DeVilbiss, Somerset, PA) using a mouthpiece and a nose clip. The subjects were instructed to inspire from functional residual capacity to inspiratory capacity at an inspiratory flow rate of less than 0.6 l/s. At end inspiration the subjects were advised to hold their breath for 5 s. Nebulization was triggered by inspiration and maintained for 0.8 s (Spira elektro 2 flow meter; Respiratory Care Center, Hämeenlinna, Finland). This maneuver was repeated five times.

Subjects were initially 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 0.075 mg/ml, which was trebled on each subsequent challenge up to a maximal concentration of 18 mg/ml. The time interval between inhalations of increasing histamine concentrations was kept constant. Trebling doses of histamine diphosphate were chosen instead of the usual doubling dose with respect to the half-life of lidocaine and the number of challenges, and to minimize possible tachyphylaxis of the histamine effect. One to 2 min after inhalation of each aerosol dose, FEV_1 was measured a total of three times, and the largest FEV_1 was accepted.

Challenges were discontinued if subjects had symptoms of chest tightness or difficulty breathing or a decrease in FEV_1 of at least 20% from the prechallenge baseline, or if they had received the maximal concentration of histamine diphosphate. The histamine threshold concentration necessary for a 20% decrease in FEV (PC_{20}) was calculated for each subject.[9]

For each individual, two histamine concentrations lower than the PC_{20} was considered the starting concentration for all subsequent challenges. If a subject in one of the subsequent histamine challenges did not reach a 20% decrease in FEV_1, PC_{20} was calculated by extrapolation.[9]

For consistency, all lung function measurements were made by a single investigator (H. G.) who was blind as to the drugs administered.

Lidocaine, Ropivacaine, Dyclonine, and Saline Inhalation

Lidocaine and dyclonine were diluted in saline without additives, whereas ropivacaine was used in the commercially available solution (Astra Chemicals, Wedel, Germany). Aerosols were produced by a nebulizer driven by compressed air at 30 psi (DeVilbiss No. 646). The start of nebulization was triggered (Spira elektro 2 flow meter) after inhalation of 100 ml air. The volunteers took deep tidal breaths with a nebulization time of 2 s with each breath, and they were advised to perform a 5-s breath hold at the end of each inspiration. The inhalation was continued until the complete solution was aerosolized. Topical anesthesia was tested in 5-min intervals by touching the uvula and the posterior pharyngeal wall with a cotton swab.

Protocol

Baseline lung function was assessed on each study day. Further measurements were postponed if the actual FEV_1 differed by more than 7% from the initial baseline obtained on the day of the screening visit.

On a total of four tests on 4 different study days, in random order and in a double-blind fashion, the subjects inhaled lidocaine (4%), ropivacaine (1%), dyclonine (1%), or saline (0.05 ml/kg). The total dose was

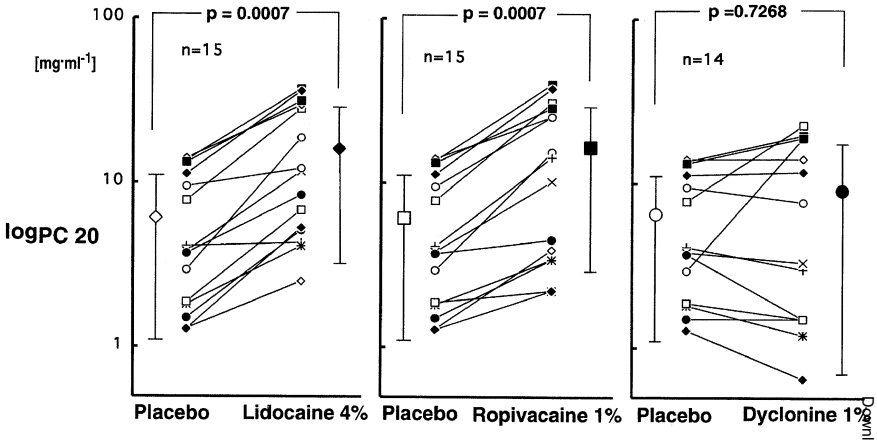

Fig. 1. Histamine concentrations (log scale) inducing a 20% decrease of forced expiratory volume in 1 s (PC_{20}) after placebo *versus* 4% lidocaine (*left*), 1% ropivacaine (*middle*), or 1% dyclonine (*right*), respectively. Data are from 59 inhalational challenges with histamine performed on 4 different days in 15 individuals with bronchial hyperreactivity. Each pair of symbols represents the response of individual subjects with the mean response (± SD) shown to the left and right of the individual responses. Lidocaine and ropivacaine inhalation significantly increased the histamine threshold compared with placebo, whereas dyclonine did not.

2.0 mg/kg for lidocaine and 0.5 mg/kg for ropivacaine and dyclonine, respectively. With this dose regimen, the volunteers always inhaled a volume of 0.05 ml/kg. Lung function was measured directly after the inhalation of the local anesthetics or placebo. Subsequently, the histamine challenge was repeated. Venous blood was drawn from an antecubital vein before the start of the inhalation and every 5 min for up to 75 min.

Data Analysis

Data are presented as mean ± SD. The following *a priori* null hypotheses were tested: (1) inhalation of local anesthetics does not change baseline lung function regardless of the used substance; (2) inhalation of local anesthetics does not change the response to a histamine challenge compared with placebo, regardless of the used substance; and (3) all three local anesthetics evoke topical anesthesia of the same duration. Comparisons were made by the Friedman test followed by Wilcoxon signed-rank test with Bonferroni correction of the α error for multiple comparisons. Null hypotheses were rejected and significant differences assumed with $P < 0.05/n$ as indicated.

Results

Histamine-induced bronchospasm was significantly attenuated only by lidocaine and ropivacaine inhalation. In contrast, dyclonine, despite its profound topical anesthesia, did not attenuate histamine-induced bronchospasm. Furthermore, only ropivacaine and dyclonine inhalation elicited a significant initial airway irritation.

Both lidocaine and ropivacaine inhalation increased PC_{20} to 16.1 ± 12.9 and 16.5 ± 13.6 mg/ml ($P = 0.0007$), respectively (fig. 1). In contrast, dyclonine inhalation did not change PC_{20} (9.1 ± 8.4 mg/ml) compared with placebo ($P = 0.7268$). Histamine threshold (PC_{20}) after saline inhalation (6.1 ± 5.0 mg/ml) did not differ from the threshold obtained at the screening visit (7.0 ± 5.0 mg/ml; $P = 0.8203$).

Inhalation of saline (placebo) and lidocaine did not alter FEV_1 (3.73 ± 0.56 *vs.* 3.65 ± 0.59 l and 3.69 ± 0.58 *vs.* 3.58 ± 0.54 l, respectively), whereas ropivacaine and dyclonine inhalation significantly decreased FEV_1 from 3.74 ± 0.59 to 3.50 ± 0.64 l ($P = 0.0016$) and from 3.69 ± 0.60 to 3.15 ± 0.76 l ($P = 0.0018$), respectively (fig. 2). In contrast, inhalation of either local anesthetics did not change the ratio of maximal expira-

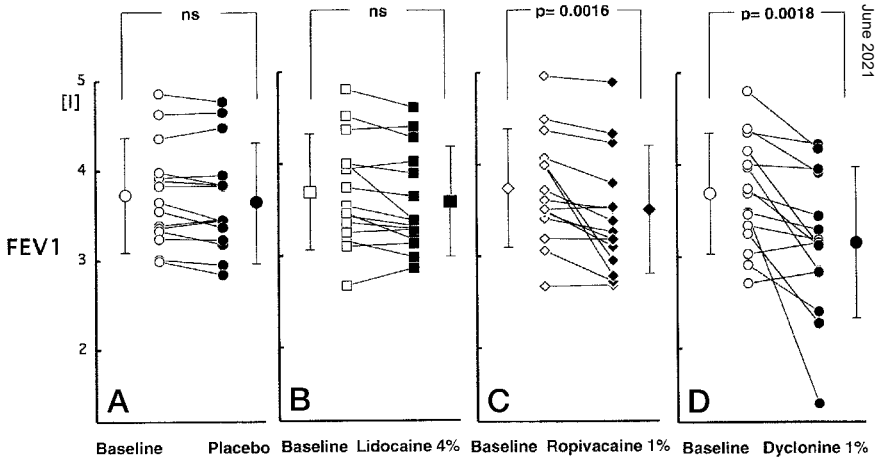

Fig. 2. Baseline forced expiratory volume in 1 s (FEV_1) on each day compared with inhalation of placebo (*A*), 4% lidocaine (*B*), 1% ropivacaine (*C*), and 1% dyclonine (*D*). Each pair of symbols represents the response of one volunteer. Mean values ± SD are presented to the left and right of the individual data. Both ropivacaine and dyclonine led to a significant decrease of FEV_1. *$P < 0.05$.

Table 1. Ratio of the Maximal Inspiratory and Expiratory Flow at 50% of the Vital Capacity (MIF_{50}/MEF_{50}) before and after Inhalation of 4% Lidocaine, 1% Ropivacaine, and 1% Dyclonine, Respectively

	MIF_{50}/MEF_{50}							
	Placebo		4% Lidocaine		1% Ropivacaine		1% Dyclonine	
	Before	After	Before	After	Before	After	Before	After
Mean	1.18	1.18	1.14	1.16	1.15	1.17	1.2	1.29
SD	0.63	0.66	0.58	0.53	0.59	0.61	0.55	0.60
P value	0.999		0.733		0.925		0.616	

tory over inspiratory flow rate at 50% of the vital capacity (table 1) used as a measure of changes in upper airway resistance.

Peak lidocaine plasma concentrations (0.77 ± 0.17 μg/ml) were far below the toxic threshold of 5.0 μg/ml, and ropivacaine peak plasma concentrations were 0.32 ± 0.09 μg/ml (fig. 3).

The duration of topical anesthesia was significantly longer after inhalation of dyclonine (48.3 ± 12.7 min) compared with lidocaine (27.5 ± 7.9 min; $P = 0.0009$) and ropivacaine (24.6 ± 4.2 min; $P = 0.0007$; fig. 4). Furthermore, 9 of 15 volunteers spontaneously mentioned a much more intense topical anesthesia after dyclonine inhalation compared with lidocaine and ropivacaine.

Discussion

Attenuation of histamine-induced bronchospasm seems to be completely independent of topical airway anesthesia itself, because only lidocaine and ropivacaine inhalation significantly attenuated the response to a histamine challenge, whereas dyclonine did not. In addition, only ropivacaine and dyclonine inhalation elicited a significant initial airway irritation.

These results were obtained from 15 volunteers with moderate bronchial hyperreactivity, all in stable clinical condition on current medication or during their symptom-free interval. All measurements were made by the same investigator at the same time of day. To maximize reproducibility of the histamine challenge during the 4 study days, a 5-s breath hold at end inspiration was requested, and a fixed time of nebulization during inspiration and a fixed number of breaths were defined. Furthermore, inspiratory flow was controlled to minimize uneven aerosol distribution and turbulent airflow.[10] Because of its low day-to-day variability, FEV_1 was chosen to analyze the response to the histamine challenges on the different study days.[11–13] In this way, a high reproducibility of the test results could be assumed and the risk of unpredictable adverse responses to the histamine challenge was minimized.[14]

One percent dyclonine has been shown to be as effective for topical airway anesthesia as 4% lidocaine.[7] Ropivacaine was used because the topical anesthetic effect of ropivacaine is unknown. Because ropivacaine and bupivacaine are considered to have a similar potency and lidocaine and bupivacaine have a 4 to 1 potency ratio, we used 1% ropivacaine. This concentration turned out to be as effective as a 4% lidocaine solution.

Lidocaine and ropivacaine inhalation led to peak mean plasma concentrations of 0.77 and 0.32 μg/ml, respectively. These concentrations are far below the toxic

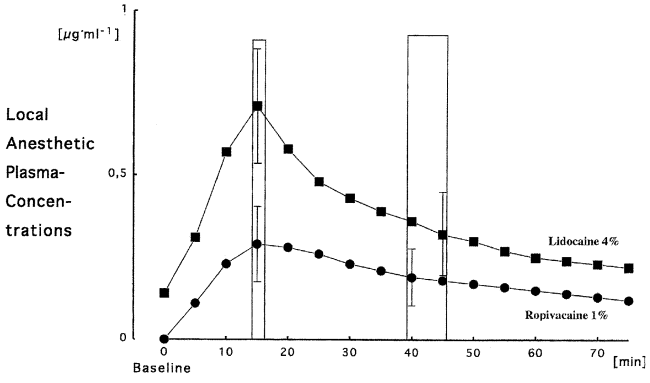

Fig. 3. Time course of plasma concentrations after inhalation of lidocaine (squares) and ropivacaine (circles). For clarity, error bars (± SD) were depicted only at the highest peak (first bar) and maximal histamine challenge (second bar) for each concentration. Peak plasma concentrations were always far below toxic ranges of lidocaine and ropivacaine.

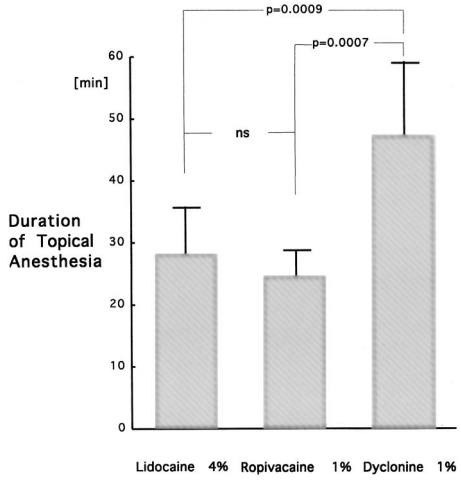

Fig. 4. Duration of local anesthesia after lidocaine, ropivacaine, or dyclonine inhalation. Local anesthesia lasted significantly longer after dyclonine inhalation compared with lidocaine or ropivacaine (mean ± SD, $P = 0.0166$).

threshold of 5 μg/ml for lidocaine and 0.9 μg/ml for ropivacaine. The lidocaine plasma concentrations (0.25–1.7 μg/ml) are well within the range reported in the literature after lidocaine inhalation.[15–20]

FEV_1 significantly decreased after inhalation of both ropivacaine and dyclonine. Airway irritation after local anesthetic inhalation, independent from the use of additives or the extent of bronchial hyperreactivity, was well in accordance with previous results.[1–4,16,21]

Two mechanisms might explain the initial decrease in FEV_1 after inhalation of ropivacaine and dyclonine. First, airway anesthesia may impair upper airway motility or perception of inspiration and expiration. In fact, altered inspiratory coordination of upper airway musculature after airway anesthesia was visualized during fiberoptic laryngoscopy and was suspected to cause upper airway obstruction.[21] Upper airway obstruction alters predominantly inspiratory rather than expiratory flow rates and therefore leads to an increase in the ratio of maximal expiratory flow over maximal inspiratory flow rates.[22,23] However, flow ratio remained unaltered in our subjects, making increased upper airway resistance unlikely. Second, initial bronchoconstriction after lidocaine inhalation, as visualized by high-resolution computed tomography, in intubated dogs is completely blocked by intravenous lidocaine pretreatment.[24] Because initial bronchoconstriction after ropivacaine and dyclonine inhalation was not associated with changes of the ratio of maximal inspiratory and expiratory flow rates, this effect is probably mostly caused by airway irritation.

Histamine inhalation evokes bronchoconstriction, both reflex-mediated and by direct stimulation of smooth muscle cells.[25,26] Therefore, topical anesthesia *via* local anesthetic tissue concentrations could possibly attenuate histamine-evoked bronchoconstriction by effects on the afferent or efferent reflex pathways or by direct depression of smooth muscle tone. Furthermore, effects evoked by local anesthetic tissue concentrations could be augmented or masked by systemic effects of absorbed local anesthetics.

Lidocaine and ropivacaine inhalation attenuated histamine-induced bronchospasm, whereas dyclonine, despite its profound topical anesthesia, did not. Thus, attenuation of bronchial hyperreactivity after lidocaine and ropivacaine inhalation can be regarded as an independent pharmacologic effect with the side effect of topical anesthesia. Nevertheless, this effect is still a result of topical administration because lidocaine plasma concentrations were by far too low to explain attenuation of bronchial hyperreactivity by a systemic effect caused by absorption of lidocaine or ropivacaine.[5] How lidocaine and ropivacaine attenuate histamine-induced bronchospasm is unclear. Lidocaine, in concentrations of approximately 10 μg/ml, attenuates nerve conduction in autonomic fibers and, in concentrations of 20–200 μg/ml, even directly depresses contraction of smooth muscle cells.[27,28] Lidocaine aerosol concentrations of 40 mg/ml might possibly evoke such airway tissue concentrations, but this has never been studied. Thus, effects on airway smooth muscle or neural structures may explain attenuation of histamine-induced bronchospasm after lidocaine and ropivacaine inhalation.[27,28]

Why topical anesthesia with dyclonine does not attenuate histamine-induced bronchospasm is open to speculation. Because attenuation of bronchial hyperreactivity must obviously be seen as an effect independent of topical airway anesthesia, different pharmacologic properties of the substances might be responsible. It's possible that penetration of dyclonine into the bronchial mucosa may not be deep enough to achieve high enough dyclonine tissue concentrations at the side where attenuation of hyperreactivity takes place. Further investigations focusing on effects in the bronchial mucosa and local anesthetic tissue concentrations may clarify these issues.

In conclusion, topical anesthesia alone does not explain attenuation of histamine-induced bronchospasm by local anesthetics. Obviously, topical airway anesthesia and attenuation of bronchial hyperreactivity are two independent effects. Therefore, for clinical use, dyclonine might serve as an effective alternative to lidocaine as far as topical anesthesia is concerned. However, where attenuation of bronchial hyperreactivity is required, dyclonine is not as effective as lidocaine and does not mitigate evoked bronchoconstriction. Moreover, because dyclonine causes significant airway irritation, it might even be considered contraindicated in patients with bronchial hyperreactivity.

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