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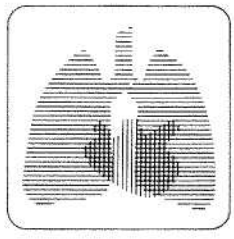

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The Response to Lidocaine in Bronchial Asthma*

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The effect of aerosol administration of lidocaine (40 mg and 100 mg doses) was examined in 22 patients with stable asthma. The initial response in all was a fall of approximately 20 percent in expiratory air flow rates within five minutes after administration of the drug. Thereafter, a bimodal response occurred. Group 1 (12 patients) continued to exhibit this reduction, with the following maximal decreases after ten minutes of delivery of the drug: −24.6 percent decrease in the forced vital capacity (FVC); −38.0 percent decrease in the forced expiratory volume in one second ($FEV_{1.0}$); and −42.6 percent decrease in the maximal midexpiratory flow rate (MMEFR). Group 2 (ten patients) manifested a significant improvement in airway resistance, with the following maximal increases at approximately 45 minutes after administration: 11.8 percent increase in FVC; 25.2 percent increase in $FEV_{1.0}$; and 41.0 percent increase in MMEFR. These changes were greatest with the 100 mg dose of lidocaine. Intravenously administered lidocaine (1 mg/kg of body weight) aborted the initial bronchoconstriction in all patients but was only mildly effective as a bronchodilator. Lidocaine was also capable of protecting against challenge with methacholine chloride. The possible mechanisms of this divergent response are discussed.

Since the synthesis of lidocaine in 1943, its clinical use has been primarily limited to its function as a local anesthetic agent and for cardiac antiarrhythmic activity. We recently showed that administration of lidocaine was able to prevent and reverse contractions induced by a variety of substances in the tracheal muscle of guinea pigs. This relaxant effect of lidocaine on smooth muscle was unaffected by β-adrenergic or cholinergic blockade. The nonspecificity of lidocaine's effect suggested a membrane-stabilizing action via a pathway common to many agonists.[1] The current clinical use of lidocaine indicates the safety of this agent, and its demonstrated relaxant effect on bronchial muscle *in vitro* suggested that the drug was worthy of clinical evaluation as a bronchodilator in patients with asthma.

Materials and Methods

Twenty-two patients with chronic stable bronchial asthma who exhibited an improvement of 20 percent or more in the forced expiratory volume at one second ($FEV_{1.0}$) and the maximum midexpiratory flow rate (MMEFR) within ten minutes of administration of a 150 μg metered dose of isoproterenol sulfate delivered by a Freon-propelled unit (Medihaler-Iso) were selected. There were 12 female and ten male patients, with a mean age of 36 ± 13 years; there was no significant age difference between the sexes. Informed consent was obtained from all patients, and all drugs, including bronchodilator agents, were withheld for 12 hours prior to testing. All patients were studied on three different days with a minimum of a 24-hour interval between any two days of study, and each study generally was conducted at the same time of day (9:00 AM or 1:30 PM). Baseline data consisted of the best of two maneuvers for forced expiratory vital capacity (FVC) recorded on a spirometer (Cardio-Pulmonary Instruments Corp., model 220) and the mean of two measurements (agreeing within 5 percent) of airway resistance (Raw) and thoracic gas volume (Vtg) determined in a whole-body plethysmograph, with calculated specific airway conductance ($Gaw/V_L = Gaw/Vtg$, where Gaw is airway conductance).[2] A stable state was defined as values for FVC and $FEV_{1.0}$ within 15 percent of the initial baseline values.

Each patient then received, by random allocation, either 2.5 ml of a 0.9 percent saline solution, 40 mg of lidocaine (1.0 ml of a 4 percent solution of Xylocaine), or 100 mg of lidocaine (2.5 ml of a 4 percent solution of Xylocaine), administered as aerosols via mouthpiece from a nebulizer (DeVilbiss No. 40 at 10 L/min) powered from a tank of 100 percent oxygen. The design of the study was double-blind; however, most patients could discern the taste of lidocaine. The aerosols were activated on inspiration only with basal tidal ventilation. The average duration of nebulization was ten minutes. Pulse rate and blood pressure were recorded before, during, and every 15 minutes after administration of the aerosols. Duplicate determinations of FVC and Gaw/V_L were made at 5, 15, 30, 45, and 60 minutes after the completion of delivery of the aerosol. In 13 patients, plasma levels of lidocaine were drawn from an indwelling venous

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heparin lock every 15 minutes for one hour and were analyzed by the method described by Keenaghan.[3] Symptoms and side effects were continuously monitored. The effects of aerosol administration of physiologic saline solution and 40 mg of lidocaine were also studied similarly in seven normal subjects.

We also evaluated the effect of inhalation of methacholine (Mecholyl) chloride on five patients pretreated with aerosol administration of 100 mg of lidocaine. The patients were studied on two separate days. On the first day, after determining baseline spirometric data and Gaw/VL, patients were given two inhalations of a solution containing 2.5 mg of methacholine chloride per milliliter, and the observations were repeated at 5, 15, and 30 minutes. On the second day, after measurements of baseline spirometric data and Gaw/VL, patients were pretreated with aerosol administration of 100 mg of lidocaine. After 15 minutes, two inhalations of methacholine chloride (solution of 2.5 mg/ml) were given, and the FVC and Gaw/VL were recorded at 5, 15, and 30 minutes. In two patients the possible interaction of atropine and lidocaine was also studied. After determining control values for FVC and Gaw/VL, both patients were given 1.0 mg of atropine intravenously, and the FVC and Gaw/VL were measured after 5 and 15 minutes. At the end of this period, the patients were given 40 mg of lidocaine by aerosol administration; and spirometric data, Gaw/VL, and plasma levels of lidocaine were determined at 5, 15, 30, 45, and 60 minutes.

All patients had a history of previous exposure to lidocaine (usually dental). Cutaneous reactions to the lidocaine aerosol, with sterile physiologic saline solution as a control, were negative in all instances.

Student's *t*-test was employed to evaluate differences between groups, with a P value less than or equal to 0.05 considered significant. All calculations were computed by a calculator (Hewlett-Packard model 9801A) and statistical programs (Hewlett-Packard). In all of the studies, the changes following aerosol administration of saline solution are compared to baseline values, whereas administration of lidocaine is compared to administration of saline solution.

Results

Overall Response of Patients

Following inhalation of 40 mg or 100 mg of lidocaine, all patients exhibited a significant reduction in $FEV_{1.0}$, MMEFR, and Gaw/VL at the five-minute and 15-minute periods, compared to inhalation of physiologic saline solution at comparable intervals; for example, the mean fall in percentage in $FEV_{1.0}$ after five minutes of aerosol inhalation was -8.1 ± 5.8 percent for saline solution, -20.2 ± 24.7 percent ($P < 0.02$) for 40 mg of lidocaine, and -20.8 ± 24.7 percent ($P < 0.05$) for 100 mg of lidocaine. The MMEFR and Gaw/VL were also significantly reduced at the five-minute and 15-minute periods. No significant changes in FVC were noted at any time.

When the data from all patients were tabulated together at 30, 45, and 60 minutes, no statistically significant differences in spirometric values or Gaw/VL were observed between the treatments with saline solution and lidocaine; however, following the initial reduction in expiratory air flow indices after administration of lidocaine, the patients appeared to exhibit different patterns of response. In some patients the reduced air flow persisted for 30 to 60 minutes following inhalation of lidocaine. In others a significant improvement in pulmonary function above baseline values was observed. Accordingly, the patients were divided into two groups by responses which were defined as an improvement of 15 percent or more in $FEV_{1.0}$ or MMEFR (or both), regardless of the interval of time studied. Group 1 (mean age, 41 ± 12 years) comprises those patients who failed to show an improvement of 15 percent. Group 2 (mean age, 32 ± 13 years; not different from group 1, $P < 0.9$) exhibited a rise of 15 percent or more in expiratory flow indices when aerosol administration of lidocaine was compared to saline solution at the same interval of time.

No statistically significant changes were observed in blood pressure or pulse rate in all studies with 40 or 100 mg of lidocaine. Additionally, no hypotension, toxicity to the central nervous system, or abnormalities of pulse rate were noted; and nausea, vomiting, dizziness, headache, rash, and pruritus were not encountered.

Responses of Groups

Group 1. Twelve of the 22 patients exhibited a fall in expiratory flow which persisted for periods up to 45 to 60 minutes following inhalation of the lidocaine aerosol (Table 1). The maximal mean reduction in $FEV_{1.0}$ was -32.2 ± 25.5 percent at five minutes after administration of 100 mg of lidocaine ($P = 0.02$), compared to a decrease of -9.9 ± 6.7 percent in $FEV_{1.0}$ after treatment with saline solution. The mean decrease in $FEV_{1.0}$ averaged -16.7 percent to -32.2 percent over 5 to 60 minutes after inhalation of 100 mg of lidocaine but was significantly different from the saline solution only up to 30 minutes. This was also true for MMEFR. Similar trends were observed in FVC and Gaw/VL during the 60 minutes of measurements, with statistical significance cited in Table 1. The responses to administration of 40 mg of lidocaine were qualitatively similar to those observed after administration of 100 mg of lidocaine, but the mean percentage of decrease in cited measurements tended to be smaller. In fact, after 15 minutes, administration of 40 mg of lidocaine produced no significant difference in pulmonary function from treatment with saline solution (Fig 1).

The maximal change, analyzed independent of time, following administration of either 40 mg or 100 mg of lidocaine, in comparison to administration of saline solution at that specific time, is depicted in Figure 2. The most severe decreases in all measurements studied were seen after administra-

Table 1—*Percentage of Change in Pulmonary Variables in Group 1 at Various Times after Administration of Aerosols

Time and Aerosol	FVC Mean ± SD	P	$FEV_{1.0}$ Mean ± SD	P	MMEFR Mean ± SD	P	Gaw/VL Mean ± SD	P
5 min								
Physiologic saline	−7.3 ± 6.1	...	−9.9 ± 6.7	...	−10.6 ± 11.5	...	7.2 ± 14.9	...
Lidocaine (40 mg)	−11.3 ± 11.4	NS	−23.0 ± 22.0	NS	−30.8 ± 27.5	=0.05	−35.6 ± 19.9	<0.01
Lidocaine (100 mg)	−22.6 ± 19.5	<0.05	−32.2 ± 25.5	=0.02	−40.9 ± 25.3	<0.01	−44.8 ± 29.9	<0.01
15 min								
Physiologic saline	−5.3 ± 6.3	...	−10.0 ± 7.3	...	−14.3 ± 15.0	...	1.1 ± 20.5	...
Lidocaine (40 mg)	−12.1 ± 11.6	NS	−23.3 ± 16.6	<0.05	−32.3 ± 19.2	=0.05	−27.8 ± 15.2	<0.05
Lidocaine (100 mg)	−17.8 ± 19.9	=0.05	−31.0 ± 25.7	<0.05	−37.4 ± 22.9	<0.02	−40.9 ± 27.6	<0.02
30 min								
Physiologic saline	−4.2 ± 6.2	...	−7.8 ± 7.3	...	−13.6 ± 14.5	...	−7.7 ± 30.4	...
Lidocaine (40 mg)	−4.7 ± 11.7	NS	−16.6 ± 19.4	NS	−25.8 ± 21.1	NS	−11.6 ± 17.1	NS
Lidocaine (100 mg)	−16.9 ± 17.7	=0.05	−24.6 ± 20.5	<0.05	−33.5 ± 18.0	<0.02	−36.8 ± 27.1	NS
45 min								
Physiologic saline	−3.1 ± 8.0	...	−8.9 ± 8.0	...	−15.1 ± 17.2	...	−0.5 ± 12.5	...
Lidocaine (40 mg)	−3.6 ± 13.8	NS	−9.6 ± 18.8	NS	−16.5 ± 23.9	NS	−6.6 ± 18.9	NS
Lidocaine (100 mg)	−11.9 ± 17.6	NS	−19.7 ± 20.7	NS	−26.3 ± 21.3	NS	−30.2 ± 28.0	NS
60 min								
Physiologic saline	−3.5 ± 9.8	...	−6.8 ± 10.6	...	−10.6 ± 23.6	...	12.7 ± 3.7	...
Lidocaine (40 mg)	−4.4 ± 13.2	NS	−8.6 ± 20.7	NS	−12.8 ± 27.1	NS	−10.5 ± 26.0	NS
Lidocaine (100 mg)	−11.3 ± 13.9	NS	−16.7 ± 16.8	NS	−21.0 ± 19.5	NS	−20.5 ± 35.7	NS

*NS, Not significant.

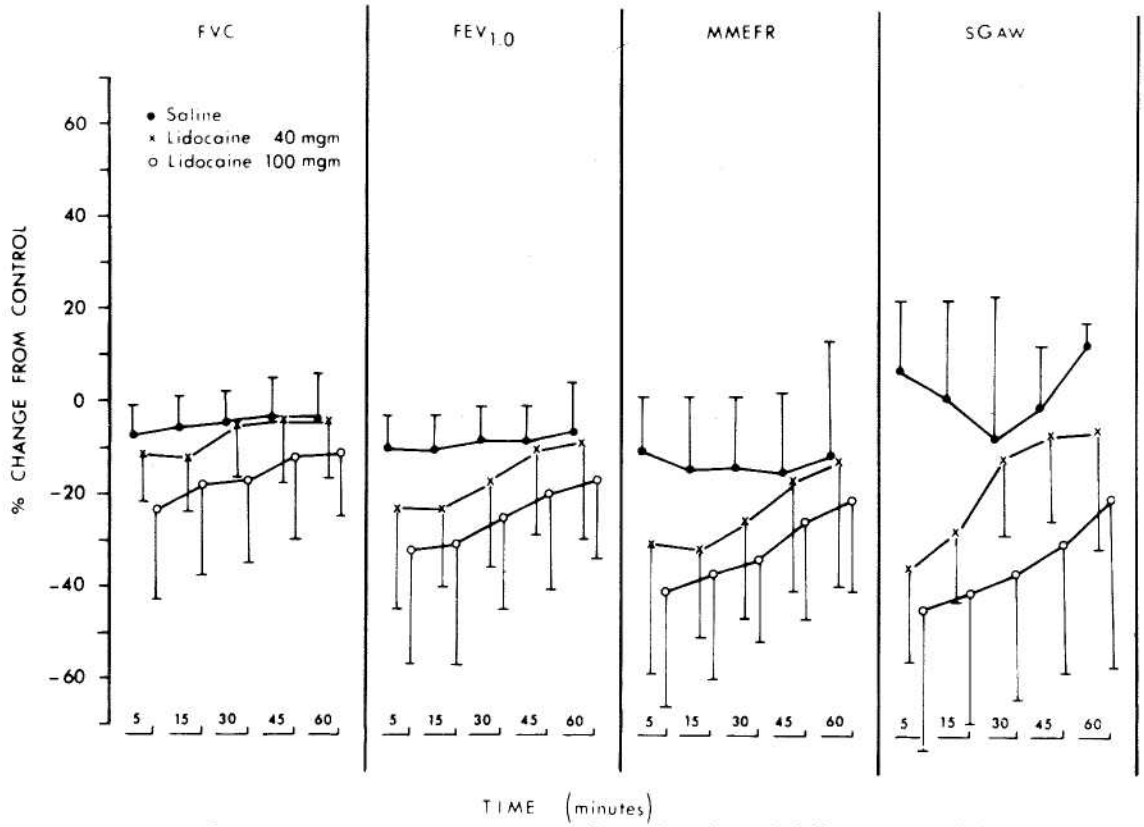

FIGURE 1. Changes in FVC, $FEV_{1.0}$, MMEFR, and Gaw/VL (SGaw) following aerosol delivery of physiologic saline solution or lidocaine (40 mg or 100 mg) at 5, 15, 30, 45, and 60 minutes in group 1 (12 patients). Each point represents mean percentage change ± 1 SD compared to baseline values. Statistical analyses for lidocaine are compared to saline solution, and saline solution is compared to baseline for that day of study.

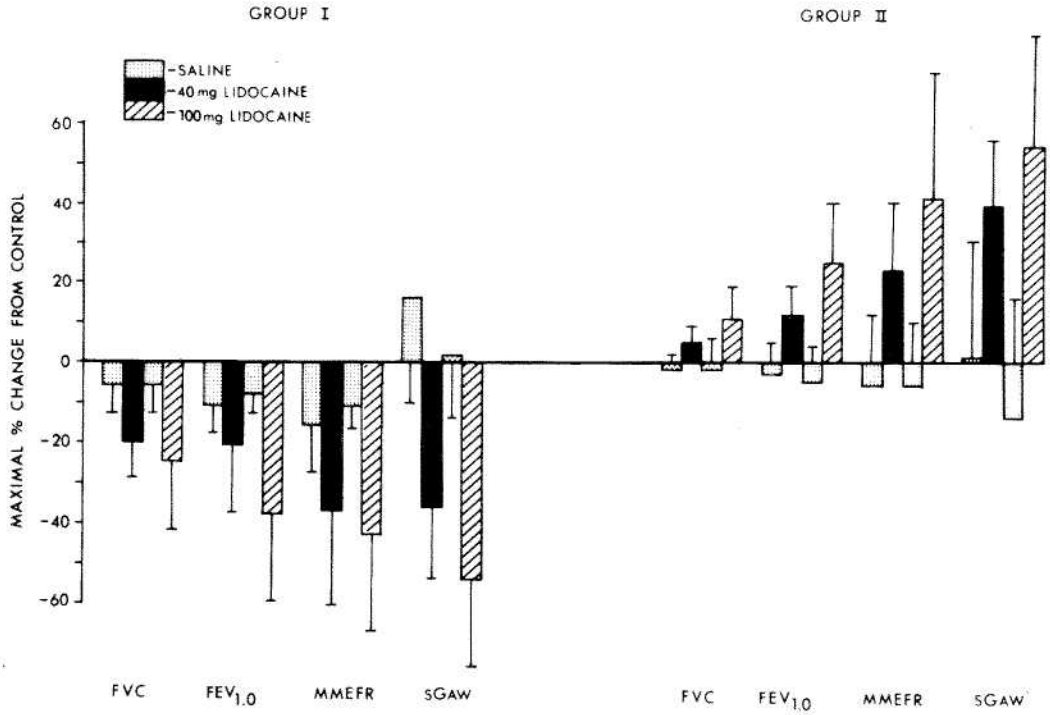

FIGURE 2. Maximal percentage change, independent of time, in FVC, $FEV_{1.0}$, MMEFR, and Gaw/VL (SGaw) following aerosol inhalation of physiologic saline solution or lidocaine (40 mg or 100 mg) in group 1 and group 2 (means ± 1 SD). Comparison of lidocaine (40 mg and 100 mg) is to saline solution. Saline solution is compared to baseline values for each day of study.

tion of 100 mg of lidocaine, *ie:* FVC, −24.6 ± 17.2 percent ($P < 0.001$) at 10.5 ± 10.1 minutes; $FEV_{1.0}$, −38.0 ± 22.1 percent ($P < 0.001$) at 10.5 ± 8.3 minutes; MMEFR, −42.6 ± 23.5 percent ($P < 0.001$) at 12.3 ± 9.8 minutes; and Gaw/VL, −54.1 ± 22.1 percent at 6.4 ± 3.8 minutes ($P < 0.001$). The changes following administration of 40 mg of lidocaine, while showing similar trends, were of lesser magnitude and were only significant for FVC and Gaw/VL at mean times of 10 and 8.3 minutes, respectively.

Group 2. Ten patients revealed a pattern of improved indices of expiratory air flow following an initial increase in flow resistance (Table 2 and Fig 3). In this group a significant decrease in $FEV_{1.0}$ and MMEFR occurred at five minutes following aerosol administration of 40 mg of lidocaine, compared to inhalation of saline solution. No significant differences in any of the measurements of pulmonary function existed between administration of saline solution and of 100 mg of lidocaine during this same period of time (Fig 3); however, at 45 minutes following administration of 100 mg of lidocaine, significant increases occurred in FVC (7.2 ± 8.5 percent; $P < 0.01$), $FEV_{1.0}$ (13.2 ± 16.5 percent; $P < 0.02$), and MMEFR (23.5 ± 27.4 percent; $P < 0.05$). At one hour, similarly significant increases were observed in FVC (8.5 ± 9.6 percent; $P < 0.01$), $FEV_{1.0}$ (16.0 ± 18.5 percent; $P < 0.02$), and MMEFR (25.7 ± 34.7 percent; $P < 0.05$). The 40 mg dose of lidocaine, while generally nonsignificant, also tended to produce increases in air flow at 45 to 60 minutes. Values for Gaw/VL were improved but also were not statistically significant in comparing administration of saline solution to 40 mg or 100 mg of lidocaine.

Again, the analysis for the maximal changes, analyzed independent of time, following administration of either 40 mg or 100 mg of lidocaine, in comparison to saline solution, is depicted in Figure 2. The improvements in indices of expiratory flow and Gaw/VL are both highly significant and of large magnitude; for example, following administration of 100 mg of lidocaine, compared to saline solution, the rise in FVC was 11.8 ± 8.1 percent ($P < 0.001$) at 45.0 ± 15.0 minutes, and the rise in $FEV_{1.0}$ was 25.2 ± 15.4 percent ($P < 0.001$), maximal at 49.3 ± 18.8 minutes. For MMEFR a maximal increase of 41.0 ± 31.2 percent ($P < 0.01$) was observed at 46.9 ± 16.9 minutes; and for Gaw/VL a maximal increase of 54.0 ± 26.5 percent ($P < 0.001$) at 40.0 ± 18.1 minutes was observed. With 40 mg of lidocaine, a similar pattern was noted, with changes of smaller magnitude; but all values were significantly greater than after administration of saline solution.

Maximal Reduction in Both Groups

The maximal bronchoconstrictor response to administration of lidocaine was compared in the two groups (Table 3). With 40 mg of lidocaine, there

Table 2—*Percentage of Change in Pulmonary Variables in Group 2 at Various Times after Administration of Aerosols

Time and Aerosol	FVC Mean ± SD	FVC P	$FEV_{1.0}$ Mean ± SD	$FEV_{1.0}$ P	MMEFR Mean ± SD	MMEFR P	Gaw/VL Mean ± SD	Gaw/VL P
5 min								
Physiologic saline	−5.9 ± 2.8	. . .	−5.8 ± 3.4	. . .	−6.0 ± 10.3	. . .	3.2 ± 21.6	. . .
Lidocaine (40 mg)	−12.4 ± 13.4	NS	−17.9 ± 15.8	=0.05	−26.5 ± 19.4	<0.05	−21.9 ± 20.3	NS
Lidocaine (100 mg)	−2.9 ± 10.5	NS	−8.3 ± 17.5	NS	−10.6 ± 26.3	NS	−6.2 ± 30.9	NS
15 min								
Physiologic saline	−3.5 ± 2.4	. . .	−3.3 ± 3.8	. . .	−1.0 ± 9.4	. . .	5.1 ± 20.8	. . .
Lidocaine (40 mg)	−6.5 ± 9.7	NS	−12.5 ± 17.9	NS	−20.4 ± 23.0	<0.05	−13.5 ± 17.3	NS
Lidocaine (100 mg)	3.0 ± 13.9	NS	3.0 ± 21.5	NS	4.2 ± 30.9	NS	3.2 ± 30.5	NS
30 min								
Physiologic saline	−1.1 ± 1.7	. . .	−3.1 ± 4.0	. . .	−5.8 ± 6.4	. . .	−0.1 ± 26.0	. . .
Lidocaine (40 mg)	0.8 ± 4.3	NS	−3.4 ± 9.8	NS	−8.3 ± 18.8	NS	13.9 ± 25.3	NS
Lidocaine (100 mg)	4.1 ± 8.1	NS	7.7 ± 16.7	NS	12.5 ± 27.2	NS	26.0 ± 36.5	NS
45 min								
Physiologic saline	−3.8 ± 3.9	. . .	−2.9 ± 5.2	. . .	−2.4 ± 10.9	. . .	−1.4 ± 17.1	. . .
Lidocaine (40 mg)	3.4 ± 2.6	<0.01	2.4 ± 7.3	NS	2.4 ± 20.6	NS	25.2 ± 28.9	NS
Lidocaine (100 mg)	7.2 ± 8.5	<0.01	13.2 ± 16.5	<0.02	23.5 ± 27.4	<0.05	29.5 ± 39.4	NS
60 min								
Physiologic saline	−2.3 ± 3.6	. . .	−3.1 ± 5.0	. . .	−1.9 ± 11.9	. . .	6.9 ± 36.3	. . .
Lidocaine (40 mg)	2.4 ± 2.9	<0.02	5.5 ± 8.2	<0.05	8.0 ± 22.8	NS	20.9 ± 29.7	NS
Lidocaine (100 mg)	8.5 ± 9.6	<0.01	16.0 ± 18.5	<0.02	25.7 ± 34.7	<0.05	33.9 ± 44.1	NS

*NS, Not significant.

was a similar fall in FVC, $FEV_{1.0}$, MMEFR, and Gaw/VL in both group 1 and group 2 ($P < 0.2$). With 100 mg of lidocaine, the following differences were noted: (1) the maximal fall in FVC in group 1 was −24.6 ± 17.2 percent but was only −8.6 ± 11.4 percent in group 2 ($P = 0.05$); (2) the maxi-

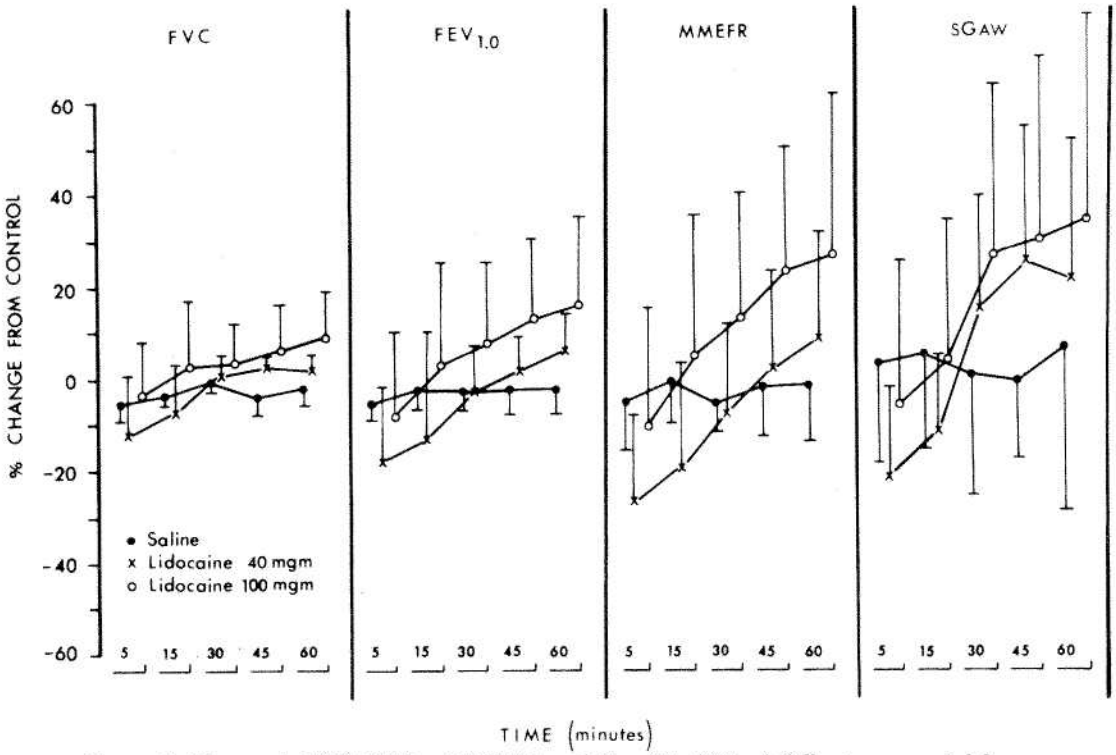

FIGURE 3. Changes in FVC, $FEV_{1.0}$, MMEFR, and Gaw/VL (SGaw) following aerosol delivery of physiologic saline solution or lidocaine (40 mg or 100 mg) at 5, 15, 30, 45, and 60 minutes in group 2 (ten patients). Each point represents mean percentage change ± 1 SD compared to baseline values. Statistical analysis for lidocaine is compared to saline solution.

Table 3—*Mean Maximal Percentage Decrease in Pulmonary Variables after Lidocaine Aerosol

Variable and Group	Dose of Lidocaine 40 mg	Dose of Lidocaine 100 mg
FVC		
Group 1	−20.0 ± 8.6	−24.6 ± 17.2**
Group 2	−12.7 ± 13.0	−8.6 ± 11.4**
$FEV_{1.0}$		
Group 1	−21.4 ± 17.2	−38.0 ± 22.1†
Group 2	−18.6 ± 16.7	−14.4 ± 15.3†
MMEFR		
Group 1	−36.6 ± 23.6	−42.6 ± 23.5
Group 2	−27.1 ± 20.1	−23.6 ± 20.7
Gaw/VL		
Group 1	−36.0 ± 17.6	−54.1 ± 22.1‡
Group 2	−26.9 ± 16.9	−21.2 ± 21.1‡

*Table values are mean maximum percent decreases ± SD.
**P = 0.05.
†P = 0.02.
‡P < 0.02.
All values not significant unless so cited.

mal fall in $FEV_{1.0}$ was −38.0 ± 22.1 percent in group 1 and was −14.4 ± 15.3 percent in group 2 (P = 0.02); (3) for MMEFR the maximal decreases were not significantly different for either group; and (4) for Gaw/VL, there was a decrease in group 1 of −54.1 ± 22.1 percent vs −21.2 ± 21.1 percent in group 2 (P < 0.02). Control values for FVC, $FEV_{1.0}$, Raw, and Gaw/VL for groups 1 and 2 (Table 4) revealed essentially no significant differences prior to administration of lidocaine (except for FVC).

Plasma Levels of Lidocaine

Plasma levels of lidocaine were determined in 13 patients at specified intervals of time following aerosol administration of 40 mg or 100 mg of lidocaine (Table 5). The maximal mean level of lidocaine in the plasma was 0.25μg/ml at 45 minutes after administration of 100 mg of lidocaine. While the concentrations in the plasma were lower after administration of 40 mg of lidocaine, no significant difference was observed between the treatments with 40 mg or 100 mg of lidocaine, or between groups 1 and 2.

Table 4—*Control Values Prior to Administration of Lidocaine*

	Group 1	Group 2
FVC, percent of predicted	83 ± 17*	96 ± 10*
FVC, L	3.45 ± 1.27	3.54 ± 0.71
$FEV_{1.0\%}$, observed	59 ± 10	65 ± 13
MMEFR, percent of predicted	40 ± 18	53 ± 21
Raw, cm H_2O/L/sec	5.26 ± 1.95	4.66 ± 1.68
Gaw/VL, L/sec/cm H_2O/L	0.064 ± 0.025	0.082 ± 0.042

*P = 0.05.
All values not significant unless so cited.

Table 5—*Plasma Levels of Lidocaine (μg/ml) after Aerosol Administration

Time after Administration	Dose of Lidocaine 40 mg	Dose of Lidocaine 100 mg
0 min	0	0
5 min	0.06 ± 0.04	0.14 ± 0.06
15 min	0.08 ± 0.05	0.17 ± 0.04
30 min	0.10 ± 0.05	0.18 ± 0.09
45 min	0.09 ± 0.06	0.25 ± 0.34
60 min	0.05 ± 0.02	0.14 ± 0.05

*Table values are mean plasma levels ± SD.

Intravenously Administered Lidocaine

A total of 75 to 100 mg of lidocaine (1.0 mg/kg), diluted in 100 ml of a 5 percent solution of dextrose in water, was infused intravenously over five to ten minutes, and the results were compared with an infusion of saline solution in five patients of both groups. The maximal changes in FVC and $FEV_{1.0}$ were significantly greater (P < 0.02) in the lidocaine-infused group between 5 and 15 minutes after the infusion. The mean maximal change after infusion of saline solution was −0.2 percent for FVC and +1.6 percent for $FEV_{1.0}$. Lidocaine increased FVC by 7.1 percent and $FEV_{1.0}$ by 3.0 percent. The MMEFR was not different. No patient of either group 1 or 2 who exhibited the initial or late falls in FVC or flow rates following aerosol administration of lidocaine did so with the intravenous administration. Mean plasma levels of lidocaine were 3.06μg/ml at five minutes, 0.64μg/ml at 15 minutes, and 0.43μg/ml at 45 minutes. Blood pressure and pulse rate showed no significant changes.

Challenge with Methacholine Aerosol

Following two inhalations of methacholine administered via nebulizer (DeVilbiss No. 40), five patients of group 2 had mean decreases of approximately 21 to 27 percent in FVC, 35 to 40 percent in $FEV_{1.0}$, and 50 to 55 percent in MMEFR (Fig 4A). On a subsequent day, these patients received aerosol pretreatment with 100 mg of lidocaine. Following an interval of 15 to 30 minutes (until each patient returned to baseline values), challenge with methacholine was instituted. Administration of lidocaine significantly reduced the bronchoconstrictor effect of methacholine; FVC fell to 5.3 ± 8.1 percent (P = 0.05), $FEV_{1.0}$ fell to 8.9 ± 12.2 percent (P < 0.05), and MMEFR fell to 18.7 ± 2.8 percent (P = 0.05) at the 30-minute interval.

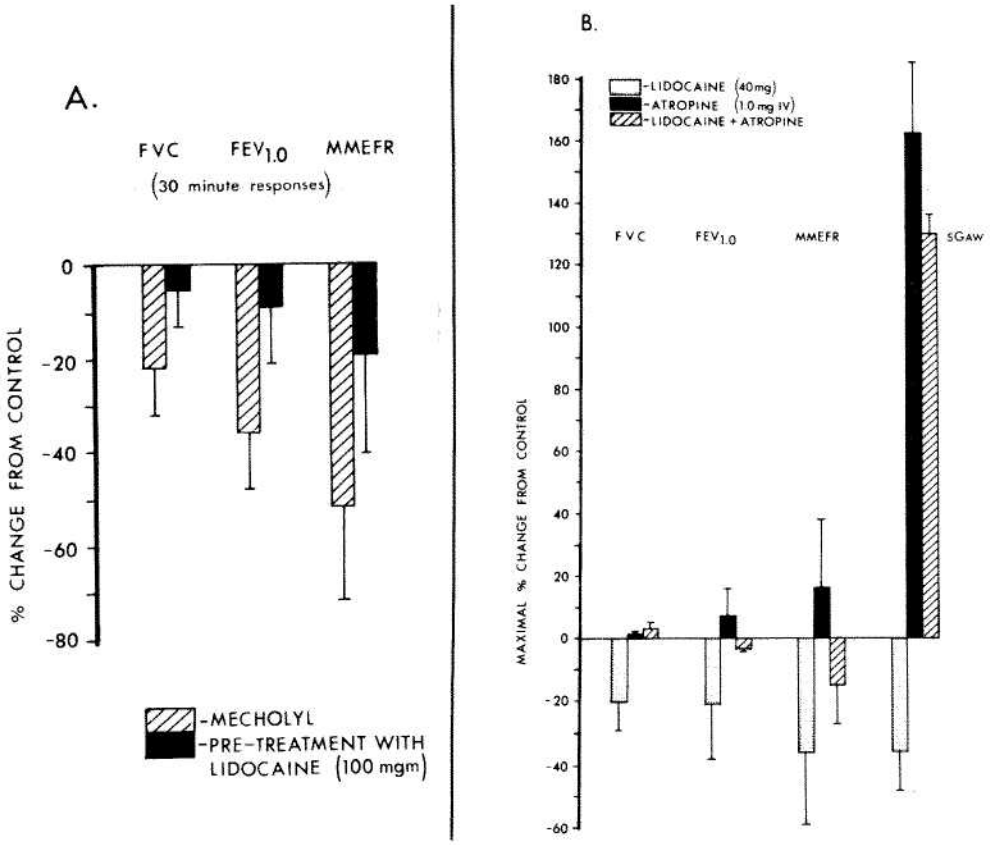

FIGURE 4. A, Changes in FVC, $FEV_{1.0}$, and MMEFR after two inhalations of methacholine (Mecholyl) chloride (2.5 mg/ml), before and after pretreatment with 100 mg of lidocaine in five patients from group 2 (means ± 1 SD). B, Changes in FVC, $FEV_{1.0}$, and Gaw/VL (SGaw) following aerosol inhalation of lidocaine (40 mg) or following intravenously administered atropine (1 mg) or following combination of aerosol administration of 40 mg of lidocaine plus intravenous administration of 1 mg of atropine (means ± 1 SD).

Atropine

Two patients of group 1 were given 1.0 mg of atropine intravenously. Spirometric analysis was performed at 5 and 15 minutes. Then 40 mg of lidocaine was given by aerosol administration. Measurements were followed for 30 minutes (maximal duration of atropine-induced tachycardia), and no fall in FVC, $FEV_{1.0}$, or Gaw/VL was seen in patients who previously exhibited a large reduction in these indices with administration of lidocaine alone; however, a measurable fall in MMEFR from 48 L/min to 36 L/min (25 percent) was observed in one patient, and a fall from 147 L/min to 138 L/min (6 percent) was seen in the other (Fig 4B).

Effects in Normal Volunteers

Seven adults (mean age, 30 ± 8 years) received saline solution and 40 mg of lidocaine. There were no significant differences in FVC, $FEV_{1.0}$, or MMEFR between lidocaine and saline solution at any interval of time, and no side effects or complication were noted.

DISCUSSION

The results of this study reveal a bimodal response to aerosol administration of lidocaine following an initial reduction of approximately 20 percent in indices of expiratory air flow in all patients. One group (group 1) of 12 asthmatic patients continued to exhibit a reduction in measurements of pulmonary function for approximately 60 minutes, whereas the other ten patients (group 2) showed a significant improvement in air flow.

Miller and Awe[4] also observed a rise in Raw and a fall in MMEFR after patients with reversible obstructive disease breather 1.0 percent lidocaine mist (generated by an ultrasonic nebulizer) for 20 minutes via an open face mask. These investigators[4] suggested that lidocaine acted as a primary irritant. The time course of their patients was not presented, so the late bronchodilator phenomenon we report may not have been observed. In one other series with asthmatic patients, of 296 anesthetic inductions, the incidence (4.8 to 7.6 percent) of "asthmatic wheezing" was not different with and without topical administration of lidocaine, and any adverse effect was believed to be due to the endo-

tracheal intubation.[5] In a recent clinical study with normal subjects, the bronchodilator action of lidocaine against ultrasonic mist-induced bronchospasm was described, but administration of lidocaine alone had no adverse effect upon these normal subjects.[6] The cause of this variation in bronchial reaction to lidocaine is difficult to explain.

In vitro data on the effect of lidocaine in the tracheal muscle of guinea pigs reveal some features which may clarify the bimodal response to lidocaine observed in our study. Under isometric conditions the resting tracheal smooth muscle responds to administration of lidocaine in a dose-dependent bimodal manner; an initial significant increase in tension is followed by a reduction in tension below the baseline level as the concentration of lidocaine is increased. These changes in basal tension are temporally limited, with tensions returning to control levels despite the continued presence of the drug. The tonic phenomenon is dependent upon the following two major mechanisms: (1) release of prostaglandins, since the bimodal response is entirely blunted with administration of indomethacin and is associated with an increase in effluent prostaglandin $F_{2\alpha}$ and a rise in the ratio of prostaglandin $F_{2\alpha}$ to prostaglandin E_{1+2}; and (2) Ca^{++} ion, whose presence is required for the development of tension and which can be blocked by specific inhibitors of Ca^{++} ion transport, such as La^{3+} or D600 ([isopropyl-(*N*-methyl-*N*-homoveratryl)-γ-aminopropyl]-3,4,5-trimethophenylacetonitril) (Earle B. Weiss, M.D., unpublished data).[7] Similar biphasic observations occur in vascular smooth muscle. *In vitro* studies of various local anesthetic agents, including lidocaine, demonstrate a stimulation of spontaneous contractions or increase in the basal tone of strips of vascular smooth muscle at low concentrations of the drugs.[8,9] The initial stimulative action has also been seen *in vivo* with an increase in peripheral vascular resistance following intra-arterial administration of mepivacaine in human volunteers.[10] As in tracheal muscle, the phenomenon is dependent upon dosage, with inhibition of myogenic activity and vasodilatation *in vitro* and *in vivo* following administration of higher concentrations of local anesthetic drugs, including lidocaine. These effects are believed to represent a local interaction of lidocaine with calcium.[9] Low doses of lidocaine are believed to displace Ca^{++} ion from membranes to the interior of the muscle cell, leading to activation of contractile proteins. Higher doses of lidocaine binding cytoplasmic Ca^{++}, in excess of the activator Ca^{++}, lead to myorelaxation.

The application of *in vitro* results with local anesthetic drugs to relationships *in vivo* presents certain difficulties. In particular, considerations of dosage are important in relating basic pharmacologic findings to clinical therapy, since the results of investigations in animals indicate variation in dose-to-organ response. It has been estimated that in animals, intravenous administration of 2 mg of procaine per kilogram of body weight is capable of endoanesthesia of sensory receptors, paralysis of parasympathetic ganglia, and interference with cardiac conduction. At an intravenous dosage of approximately 5 mg/kg, procaine-induced analgesia and relaxation of smooth muscle are observed, while at higher intravenous dosages (5 to 10 mg/kg), relaxation of striated muscle is seen, and at 20 mg/kg, paralysis of sympathetic ganglia or antihistaminic action is observed.[11] Thus, as an approximation, specific effects, even within the same structure ("the airways"), could vary according to the administered, as well as the effective, dosage and could yield, as we have observed, varying results.

The divergent responses of the airways to administration of lidocaine observed in this asthmatic population may, in addition to the processes described previously, be due to differences in basic pharmacokinetic phenomena (including initial absorption, distribution volumes, effective tissue distribution, and rate of elimination); or the responses may, in part, represent biologically distinct actions on neural or muscular components (or both) of the reacting airway. During delivery by inhalation, a considerable amount of lidocaine may be lost to the atmosphere or by swallowing, particularly by spontaneously breathing, conscious patients. Evidence for this is obtained if one compares the blood levels of lidocaine following uptake from the trachea in man, which are lower than those following intravenous administration;[12] however, we observed that on two independent testings with aerosol administration of 40 mg or 100 mg of lidocaine, patients always reacted in the same pattern (*ie*, the airways of individuals in group 1 remained obstructed, and group 2 reacted with bronchodilatation). Also, the blood levels of lidocaine in groups 1 and 2 were statistically similar. Hence, it is unlikely that the method of delivery separates the bronchodilator from the bronchoconstrictor response. Assuming, then, approximately equal delivery of lidocaine, the results observed in our patients may be related to differences in effective tissue levels of lidocaine. That this is not due to initial differences in pulmonary function in groups 1 and 2 is shown by statistical analysis (Table 4). As a hypothesis based upon the preceding discussion, the contractile stimulus would then represent a lower tissue level of lidocaine in bronchial smooth muscle, with broncho-

constriction due to membrane Ca^{++} flux or release of prostaglandins, or both. The difference in the second airway response (group 2) would reflect greater tissue levels of lidocaine.

The lack of bronchoconstriction following intravenous infusion of lidocaine, despite adequate blood levels, indicates that this route of administration aborts initial bronchoconstriction; however, the bronchodilator effect of intravenously administered lidocaine at the 100 mg dosage, while present, was not as potent as with aerosol delivery. In this regard, it should be noted that even larger intravenous doses of lidocaine (150 to 200 mg) are required for adequate cough suppression for bronchographic studies.[13] The differences between levels of lidocaine in the arterial and venous blood following absorption during fiberoptic bronchoscopic study also relate to this problem, since arterial levels can be up to seven times greater than those of simultaneously obtained, paired venous samples.[14] Thus, even though our venous blood levels were low, initial absorption into the pulmonary circulation could have been greater than measured. Variations in the concentration of lidocaine in the blood and, hence, in bronchial responses relate not only to the route of administration but also to the site where a sample of blood for assay is taken. Finally, the divergent responses to administration of lidocaine may be due to intrinsic differences in asthmatic patients. The absence of any significant effect of lidocaine in normal subjects and yet the dual response in asthmatic patients may indicate variations in reactivity to the mechanism of lidocaine's basic action(s).

The protective effect of lidocaine against methacholine-induced bronchospasm is similar to results observed by other investigators. In the intact dog, Dain et al[15] found that administration of the local anesthetic drug, bupivacaine, inhibited the bronchomotor response to histamine. These authors[15] suggested that this action of bupivacaine was, in part, due to interference with afferent vagal conduction and afferent irritant receptors in the larger airways. Recently, Loehning et al[6] reported that the intratracheal administration of lidocaine by ultrasonic nebulization could prevent or reverse the increase in pulmonary resistance caused by the inhalation of water from an ultrasonic nebulizer. This effect could not be reversed or prevented by intravenous administration of lidocaine (bolus of 1 mg/kg, followed by infusion of 1 to 2 mg/min). Because of the sizes of the particles generated by ultrasonic nebulization, a direct effect on the small peripheral bronchi, rather than an inhibition of a vagal reflex mechanism, appeared to be a more plausible argument for the bronchodilator action of lidocaine.

The studies of Dain et al[15] and of Loehning et al[6] may indicate a beneficial effect of lidocaine by two distinct mechanisms. One is interruption of the neural afferent receptors in the upper airways, and the other is a direct action upon the smooth muscle cell in the peripheral airways. In either case, we should emphasize that the bronchoconstrictor action of lidocaine cannot be explained by an effect in the upper airways on the basis of the available information, since there is no evidence for lidocaine inducing a vagal reflex bronchoconstriction in some patients while inhibiting the reflex in others. Hence, this effect might be directly upon smooth muscle, as we described in the tracheal muscle of guinea pigs.[1] At present, it would appear that the net result of local anesthetic administration could be explained partially by inhibition of vagal reflexes and by a direct action on the smooth muscle itself, or by a combination of these factors.

The possible role of local anesthetic agents as clinical bronchodilator drugs requires further investigation. The broad antagonistic activity, both *in vitro* and *in vivo*, suggests a mechanism distinct from currently available agents, such as the sympathomimetic amines and derivatives of xanthine; however, the biphasic nature of the bronchial response to administration of lidocaine indicates that local anesthetic agents must be employed with care in asthmatic subjects, particularly when administered by the route of inhalation. The absence of a direct effect of lidocaine in normal subjects, compared with asthmatic patients, indicates that the drug may also be capable of distinguishing individuals with bronchial hyperreactivity. The results of this and other studies suggest that it may be possible to develop a new type of bronchodilator agent similar chemically to the currently available local anesthetic agents, which do not act by way of the β_2-adrenergic receptors in the lung.

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