Background: In 2 prior uncontrolled studies, nebulized lidocaine reduced oral glucocorticoid use in patients with severe glucocorticoid-dependent asthma.

Objective: We tested the safety and efficacy of nebulized lidocaine in a randomized, placebo-controlled study in patients with mild-to-moderate asthma.

Methods: We recruited 50 subjects (25 receiving lidocaine and 25 receiving placebo); all had a prebronchodilator FEV1 of 64% to 125% of predicted normal value and were treated with daily inhaled glucocorticoids (not systemic glucocorticoids) and bronchodilators for at least 2 months. Before treatment, subjects monitored their symptoms and peak flow values and maintained their medications for 2 weeks. At initiation, subjects inhaled either nebulized placebo (saline) or lidocaine (4%, 100 mg) 4 times daily. All subjects were instructed to reduce their inhaled glucocorticoid dosage by one half each week for 3 weeks and to discontinue glucocorticoid treatment at week 4. The subjects continued the nebulized lidocaine or placebo for a total of 8 weeks, monitored their symptoms, and used bronchodilators to control symptoms.

Results: Indicators of asthma severity showed benefit for the lidocaine-treated group: changes in FEV1 (P = .001), nighttime awakenings (P = .02), symptoms (P = .010), bronchodilator use (P = .010), and blood eosinophil counts (P = .020). Subjects in both groups reduced use of inhaled glucocorticoids comparably. Subjects receiving nebulized placebo showed increases in their symptom scores, bronchodilator use (P = .05 for both), and blood eosinophil counts (P = .01) and decreases in FEV1 (P = .001).

Conclusion: Nebulized lidocaine provided effective and safe therapy in subjects with mild-to-moderate asthma. (J Allergy Clin Immunol 2004;113:853-9.)

**Key words:** Asthma, glucocorticoids, lidocaine, eosinophils

Since their introduction in 1950,1 glucocorticoids have remained the most consistently effective therapy for asthma. Glucocorticoids potentiate antiinflammation2,3; for example, they shorten eosinophil survival in the presence of proinflammatory cytokines, such as IL-5, IL-3, and GM-CSF.4,5 Serendipitously, Ohnishi et al6 discovered that lidocaine potently shortens eosinophil survival, and its effects mimic those of glucocorticoids in being both concentration dependent and noncytotoxic.6,7 Lidocaine exerts these effects at 1.0 × 10−5 mol/L,7 a concentration easily achieved in the airway with nebulization devices.8,9 Nebulized lidocaine treatment of adults with severe glucocorticoid-dependent asthma reduced the oral glucocorticoid dosage in 17 of 20 subjects by 80% to 100%, whereas 3 of 20 subjects had no apparent response.10 Subsequently, nebulized lidocaine also was shown to benefit children with asthma.11,12 Because these prior studies were uncontrolled and in diverse patient populations with severe asthma, we conducted this randomized, placebo-controlled study.

**METHODS**

**Subject selection**

Fifty subjects were recruited from the Rochester, Minnesota, area (18 male and 32 female subjects) who satisfied the inclusion criteria: 18 to 65 years of age, American Thoracic Society criteria for asthma (allergic or nonallergic),13 prebronchodilator FEV1 of 64% to 125% of predicted normal value, and daily treatment with inhaled glucocorticoids (triamcinolone, flunisolide, beclomethasone, or fluticasone) and bronchodilators (β2-agonists, theophylline, or ipratropium) for a minimum of 2 months. Exclusion criteria included the following: lidocaine allergy; gastroesophageal reflux; pregnancy or lactation; respiratory infection within the preceding 4 weeks; other chronic lung disease; tobacco use within the preceding year; a life-threatening asthma attack or anaphylaxis with respiratory symptoms; cardiovascular, hepatic, or other chronic medical illness necessitating regular medication; systemic glucocorticoid use within the prior 2 months; regular use of nonsteroidal anti-inflammatory agents; use of leukotriene-modifying agents, sodium Cromoglycate, or nedocromil within the prior month; and treatment with methotrexate, gold, antimalarials, or intravenous immunoglobulin within the prior 6 months. The Mayo Clinic Rochester Institutional Review Board approved the protocol; all subjects provided written informed consent.

**Study design**

Subjects were recruited by LWH, EF, and JHB and enrolled by LWH and JB. KPO generated the allocation sequence and assigned participants to their groups. Subjects were stratified on the basis of sex and randomized in blocks of 4, such that within each block of 4 subjects, 2 were assigned to each treatment group. Thus equal numbers of each sex were randomized to each group. With a sample size of 25 subjects in each group, we had a statistical power of 0.90 for
detecting differences in group means, which were 0.65 of the pooled
within-group SD or larger as determined by using a 2-sided test with
an α level of 0.05.

Subjects underwent initial screening with a medical history,
physical examination, chest roentgenogram, spirometry, metha-
choline PD20 determination, complete blood count, total eosinophil
count, theophylline level when applicable, and measurements of
serum glucose, potassium, sodium, aspartate aminotransferase,
and creatinine. Female subjects of childbearing potential received
a pregnancy test before the study and were asked to maintain
contraception during the study. Subjects who at baseline were treated
with nebulized or metered-dose inhalers, such as salmeterol and
ipratropium, or with oral theophylline continued these medications as
needed.

Treatment methods and monitoring

After randomization, subjects were given symptom diaries and
peak flow meters and maintained their present medication program
for a 2-week baseline period before starting the nebulization treat-
ments. They recorded peak flows and symptoms in the morning on
arising and in the evening before retiring. Symptoms (exercise tol-
erance, cough severity, evidence of audible wheezing, and dyspnea)
were evaluated by using a 0- to 3-point scale where 0 is defined as
none, 1 is defined as mild (transient wheeze =30 minutes not more
than twice daily, occasional shortness of breath not restricting sleep or
activities, or cough present but not interfering with sleep or activities),
2 is defined as moderate (>2 wheezing episodes a day, any lasting >30
minutes, or both; frequent shortness of breath interfering with sleep or
activities; coughing spasms that interrupted sleep or activities), and 3 is
defined as severe (continuous wheezing, almost continuous shortness
of breath with severely restricted sleep or activities, ≥2
coughing spasms that interrupted sleep or activities). Nighttime
awakenings caused by cough or wheeze were recorded daily. After
this 2-week baseline period, the subjects returned their symptom
diaries, received new diaries, and began treatment with lidocaine or
placebo. All subjects inhaled their randomly assigned study
medication, either nebulized placebo (2.5 mL of normal saline) or
lidocaine (2.5 mL of 4% injectable solution without preservatives;
AstraZeneca Pharmaceuticals, Westborough, Mass), 4 times daily
(PARI LC Plus nebulizer and PARI Master compressor; PARI
Respiratory Equipment Inc, Richmond, Va). All subjects were
instructed to not eat or drink for 1 hour after the nebulization
treatment because of transient diminution of the gag and cough
reflexes in the lidocaine-treated group; however, almost all numbness
was gone by 20 minutes. Every 2 weeks, the subjects returned their
symptom diaries and obtained more of their assigned medication;
spirometry was repeated on weeks 2, 4, and 8. In all cases after
finishing the nebulization treatment, we waited 15 minutes before
performing the spirometry.

For the first 3 treatment weeks, all subjects were asked to reduce
their inhaled glucocorticoid medications by one half of the total
number of daily sprays each week and at week 4 to discontinue them.
The protocol specified continuation of nebulized drug for the entire
8-week treatment phase.

Safety monitoring

For safety, peak flows were measured twice daily by using a Personal Best peak flow device (Hollister-Stier Inc, Spokane,
Wash), with values classified into green, yellow, and red zones
according to the “Guidelines for the Diagnosis and Management of
Asthma.”14 Any subject whose peak flow fell into the yellow zone (a
reduction of at least 20% of their baseline personal best) was
instructed to use a bronchodilator immediately. Over the next 20
hours, if a peak flow reading in the yellow zone failed to return to the
green zone 3 consecutive times, the subject was instructed to resume
treatment with inhaled glucocorticoid (at their baseline dosage) and to
stop their study medication. Any subject who experienced 3
consecutive yellow-zone readings or 1 red-zone reading, which did
not reverse with bronchodilator, was instructed to stop use of their
study medication and classified as a treatment failure, and their study
participation was terminated. These subjects were instructed to report
to the study unit for an examination, for pulmonary function studies,
and to obtain a blood specimen for a complete blood and total
eosinophil count. A methacholine PD20 measurement was omitted in
subjects who had sustained peak flows of less than 80% of their
pretreatment baseline value and who did not respond to bronchodi-
lator treatment. Subjects whose participation was terminated were not
replaced. Subjects who terminated the study because of asthma
evacuation, as described above, were given the worst possible
symptom score (on the 0-3 scale, score of 3 for each of the 4
symptoms rated) for their last score on their final day.

Data analysis

The outcome variables were as follows: need to discontinue study
medication and resume topical glucocorticoid treatment, ability
to discontinue topical glucocorticoid treatment by week 4,
prebronchodilator FEV1, symptom scores, nighttime awakenings,
bronchodilator use, methacholine PD20, and blood eosinophil count;
all assessments were obtained at baseline and at weeks 4 and 8. If
a subject did not complete all 8 weeks of the treatment phase, for the
intent-to-treat analysis, we used the results from their final week with
a carry-forward approach to missing information. Final week is
defined as the last week of study participation for each subject.
Analyses on final-week results used intent-to-treat principles and
included all randomized subjects. Symptom scores and nighttime
awakenings were each averaged per week, and bronchodilator use
was averaged per day. We compared baseline symptom scores, scores
at the ends of study weeks 4 and 8 and the final week, and changes
from baseline in these scores between and within groups. Similar
comparisons were made for FEV1 in liters, FEV1 percent predicted,
total blood eosinophil count, and methacholine PD20. Comparisons
of bronchodilator use and nighttime awakenings were made for
baseline, the final week, and change from baseline between and
within study groups. Methacholine PD20 measurements in cumula-
tive units were compared by using the Mann-Whitney U test, with the
lowest ranks assigned to the subjects who left the study early in order
of days on study (ie, number of days to treatment failure), ranking
subjects without a PD20 value (because of low FEV1 values) next
according to their percent predicted FEV1, and ranking the remaining
subjects according to their PD20 values. Comparisons between study
medication groups used the Mann-Whitney U test. Comparisons
within each study group used the Wilcoxon paired signed-rank test.
Two-tailed P values of .050 or less were considered significant.
Because certain study variables displayed a marked skewness in their
distribution, we used nonparametric tests throughout (Statistica for
MacIntosh; StatSoft Inc, Tulsa, Okla).

RESULTS

Table I summarizes the subjects’ characteristics at the
beginning of the study (baseline). The treatment groups
had similar median values for age, FEV1 in liters, FEV1
percent predicted, methacholine PD20, daily inhaled
glucocorticoid use level in micrograms, nighttime awak-
enings, and number of blood eosinophils. Symptom
scores and bronchodilator use were significantly
greater in the lidocaine-treated group. The length of prior inhaled glucocorticoid use was comparable between the groups; the median for the lidocaine-treated subjects was 12 months (range, 2 months–6 years), and the median for the control subjects was 13 months (range, 2 months–6 years). Also, the types of inhaled glucocorticoids were comparable between the groups; in both groups only 4 subjects were using fluticasone, and the remaining 21 were using triamcinolone, beclomethasone, flunisolide (21 patients in each group), and fluticasone (4 in each group) also showed no statistical difference. Mean symptom scores can have values from 0 (none) to 3 (severe) and rate wheeze, cough, and shortness of breath at rest and during exercise. Usually, subjects scored themselves on these 4 parameters twice daily for 7 days for a total of 56 observations each week. We averaged over all available scores for the week.

Five subjects were noncompliant and did not complete the study (but they are included in the intent-to-treat analysis). One placebo-treated subject did not return for the first treatment visit, and 2 never returned after the week 4 visit; 1 lidocaine-treated subject enrolled in another study after randomization and used an exclusionary medication (week 3), and 1 never returned after week 4. Fifteen subjects (9 receiving lidocaine and 6 receiving placebo) did not complete the full 8-week trial for various reasons. These included worsening asthma symptoms (4 receiving lidocaine and 6 receiving placebo), treatment intolerance (4 receiving lidocaine), and nonasthma-related hospitalization for renal calculi (1 receiving lidocaine). Of the 4 lidocaine-treated subjects who dropped because of treatment intolerance, 1 had a cold feeling in the throat (no decrease in FEV1), 1 experienced a feeling of claustrophobia (no decrease in FEV1), 1 had a cough caused by the medication, and 1 had wheezing after lidocaine use (a 16% decrease in FEV1 within 15 minutes after treatment). The percentage of subjects that dropped out did not differ significantly between the groups (9 [36%] in the placebo group and 11 [44%] in the lidocaine group). There were no serious adverse effects, no hospitalizations for asthma, and no deaths.

**DISCUSSION**

Prior uncontrolled studies of adults10 and children11,12 with severe asthma requiring systemic glucocorticoids showed that nebulized lidocaine is a safe and effective steroid-sparing treatment. In this randomized, placebo-controlled study, nebulized lidocaine replaced inhaled glucocorticoids in subjects with mild-to-moderate asthma; its effects on pulmonary function, symptom scores, and blood eosinophils were comparable with those of glucocorticoids. This study was double blind, but when asked, all lidocaine-treated subjects believed they had...
received the study drug compared with 5 subjects in the placebo group. Others have also demonstrated the inability to blind a lidocaine nebulization. Finally, with the vagaries of randomization on the basis of sex, at baseline the groups differed, with the lidocaine group having more severe symptoms and increased bronchodilator use. During the study, the placebo group showed worsening lung function, an increase in symptom scores, and a corresponding increase in eosinophil counts as inhaled glucocorticoids were withdrawn. Although these changes in asthma severity might be interpreted as a regression to the mean, it appears more likely to reflect the effect of withdrawing inhaled glucocorticoids.

No signs of lidocaine toxicity were observed in the treated subjects by using a 4% concentration and a total dosage of 100 mg per use. Lidocaine toxicity occurs when serum levels exceed 5 to 6 μg/mL and includes muscle twitching, seizures, arrhythmias, paresthesias, and respiratory arrest. Serum levels of greater than 1 μg/mL are not reached until greater than 300 to 400 mg is administered to the human airway, either by means of direct instillation or by means of nebulization (unpublished data, L. W. Hunt and G. J. Gleich). Three subjects dropped out of the study because of lidocaine intolerance (oral and pharyngeal hypesthesia). Another subject had reduced airflow (16%) induced by the 4% lidocaine and was disenrolled. Reduced airflow has been observed in a minority of patients in our long-term clinical cohort and by others. The mechanism of this effect is obscure, and prior analysis has shown that it is not related to histamine responsiveness. Harrison and Tattersfield reported that in 20 subjects with asthma,}

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<tr>
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<td>FEV₁ (% predicted)</td>
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<td>Week 4</td>
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*Comparison of median changes from baseline between groups (Mann-Whitney U test). All “change from baseline” variables are defined as week - baseline.
†Comparison of median changes from baseline within groups (Wilcoxon signed-rank test): a2-tail .01 < P ≤ .050; b .001 < P ≤ .010; c P ≤ .001.
‡Mean symptom scores are reported as described in Table I.
§Final week is defined as week 8 or the week (<8) actually completed (see text for more details).
‖Values tabulated are percentages with zero nighttime awakenings per week; comparisons on the basis of change from baseline in the number of nighttime awakenings.
inhalation of either saline or lidocaine comparably reduced FEV₁; in the lidocaine group inhalation of albuterol prevented reductions in FEV₁. Subsequently, Groeben et al. showed comparable results with inhaled albuterol and lidocaine. This ability of albuterol to prevent lidocaine bronchoconstriction suggests a method to improve the responses to lidocaine nebulization. Overall, 7 subjects in the lidocaine group left the study because of noncompliance, side effects, or an unrelated medical problem, whereas 4 subjects were dropped because of worsening asthma. The remaining 14 subjects (14/18) appeared to benefit from the lidocaine administration. This result is similar to that found earlier by Hunt et al., in which 17 of 20 patients with severe asthma benefited from lidocaine therapy and reduced or stopped prednisone administration.

In patients with asthma, peripheral blood eosinophil counts correlate directly with symptom severity and inversely with FEV₁. In our placebo group blood eosinophils increased as FEV₁ decreased (Table II). In contrast, blood eosinophils did not change in the lidocaine group. This is the first demonstration of lidocaine’s ability to alter a surrogate marker of inflammation in patients with asthma. Our initial interest in lidocaine as a treatment for asthma arose from the in vitro observations that lidocaine inhibited cytokine-induced eosinophil activation similarly to glucocorticoids. Subsequently, we found that lidocaine and glucocorticoids synergistically inhibit cytokine-induced eosinophil survival in vitro. Furthermore, glucocorticoids, but not 10⁻³ mol/L lidocaine, inhibition of eosinophil survival is overcome by increased cytokine concentrations, suggesting different

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12% worse/52% same/36% better

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inhibitory mechanisms. If these in vitro lidocaine effects occur in vivo, the combination of lidocaine and glucocorticoids might have greater beneficial effects than either alone. Alternatively, nebulized lidocaine alone would avoid the long-term detrimental effects of glucocorticoids, either administered parenterally or inhaled, on bone density.

Topical anesthetics alter the functions of numerous cells, including alveolar macrophages, mast cells, neutrophils, basophils, T lymphocytes, NK lymphocytes, and respiratory epithelial cells, and they suppress inflammation in animal models of disease. Numerous animal studies suggest that lidocaine has potent cellular anti-inflammatory effects. Lidocaine pretreatment of guinea pig tracheal preparations inhibited extravasated macromolecules after challenge with capsaicin, but lidocaine had no effect on plasma exudation responses after allergen challenge in these models. Lidocaine inhibited the hemodynamic and inflammatory response to endotoxemia in rabbits. Also, treatment of patients with ulcerative colitis with lidocaine enemas resulted in symptomatic relief and reduction in the numbers of CD4 and CD8 lymphocytes in the mucosa. Thus topical anesthetics tend to mimic glucocorticoids in that they reversibly affect many cell types; this might be critical for the beneficial effect of lidocaine observed in this study.

This randomized, placebo-controlled study shows that nebulized lidocaine can replace inhaled glucocorticoids for a short period of time (up to 4 weeks) in subjects with mild-to-moderate asthma and that withdrawal of inhaled glucocorticoids does not reduce pulmonary function or increase blood eosinophil counts. Thus nebulized lidocaine appears to represent a useful anti-inflammatory asthma treatment and an alternative to glucocorticoids.
We thank C. E. Reed, MD, for assistance in the design of this study and C. Adolphson and L. Arneson for preparation of the manuscript.

REFERENCES


