

Evidence for Therapeutic Uses of Nebulized Lidocaine in the Treatment of Intractable Cough and Asthma

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Request

What evidence is available to support the use of nebulized lidocaine in intractable cough and asthma?

Response

BACKGROUND

Lidocaine is an amide local anesthetic and class 1b antiarrhythmic that is Food and Drug Administration–approved for use in local anesthesia and the treatment of ventricular arrhythmias. As an extension of its use topically to prevent cough during bronchoscopic procedures, lidocaine, administered via nebulization, has been used for the treatment of intractable cough and asthma. Delivered systemically, lidocaine can reach toxic plasma concentrations ($>6 \mu\text{g/mL}$).^{1,2} However, in general, nebulized dosage forms provide direct drug delivery to the lung, with minimal systemic drug absorption and fewer adverse effects compared with other formulations.³⁻⁵

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OBJECTIVE: To summarize the efficacy and safety data for use of nebulized lidocaine in intractable cough and asthma.

DATA SOURCES: A literature search was conducted using PubMed (through November 2012), International Pharmaceutical Abstracts (1970-December 2012), and Cochrane Library (up to 2012) with the search terms nebulization, nebulized or nebulised; administration, inhalation; cough; asthma; and lidocaine. Results were limited to human studies published in the English language. Referenced citations from relevant publications were also reviewed.

STUDY SELECTION AND DATA EXTRACTION: All articles identified from the data sources were reviewed for inclusion. Clinical trials and descriptive studies that discussed use of nebulized lidocaine for treatment of intractable cough and asthma were included in the review.

DATA SYNTHESIS: Seventeen studies were identified for review. Seven studies (6 descriptive studies and 1 clinical trial) evaluating the use of nebulized lidocaine in intractable cough reported efficacy in doses ranging from 10 mg to 400 mg. Five clinical trials in asthma showed conflicting results regarding improvement in pulmonary function and glucocorticoid-sparing effects. General improvements in pulmonary function as well as the initial bronchoconstriction induced by nebulized lidocaine in subjects with baseline bronchial hyperreactivity were investigated in 5 studies. Overall, the available evidence does not appear to preclude the use of lidocaine as a treatment option for intractable cough after failure of traditional cough suppressants. Data on its use for short-term glucocorticoid-sparing effects in asthma are conflicting. Study limitations, including design, small sample size, and inconsistencies in method and adjunctive therapies, should be considered. Nebulized lidocaine is well tolerated; however, reports of initial bronchoconstriction have occurred.

CONCLUSIONS: Although nebulized lidocaine is not first-line therapy in intractable cough and asthma, it may provide an alternative treatment option in patients who cannot tolerate or are unresponsive to other treatments. Appropriate monitoring precautions should be used to ensure patient safety.

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While it is known that lidocaine inhibits conduction of nerve impulses by decreasing membrane permeability to sodium resulting in an increased threshold for excitation and diminished progression of membrane depolarization,¹² its mechanism in the suppression of cough and management of asthma symptoms is less defined. When delivered via nebulization, lidocaine suppresses the cough reflex induced by mechanical and chemical stimulation by acting locally to inhibit conduction of afferent nerve impulses and topically anesthetizing the oropharynx and large airways.^{6,7} General numbing of the airways has been reported to provide improved tolerance to respiratory irritants (eg, cigarette smoke, noxious fumes).⁷ In addition, in patients with asthma, inhibition of neural output from receptors in the airways has been shown to prevent eosinophil activation by cytokines and subsequent inflammation of the airways caused by damage to epithelial and smooth muscle cells.⁸ Eosinophil blood counts are directly related to symptom severity and inversely related to changes in forced expiratory volume in 1 second (FEV₁). Similar to glucocorticoids, nebulized lidocaine has been shown to suppress production of eosinophils without affecting FEV₁.⁸

Deposition of a nebulized dosage form into the respiratory tract is dependent on the drug, delivery device, and patient-specific factors. For a drug to be amenable to nebulization, with minimal irritation to the respiratory tract, it must be sterile, isotonic (300 mOsm/L), and preservative-free, with pH balanced to the airway epithelium (~6).⁴ Lidocaine for nebulization is not commercially available¹; however, preservative-free lidocaine hydrochloride solution for injection satisfies these requirements.²

Particles should have a mass median aerodynamic diameter (MMAD) of 1–5 µm; smaller particles will be readily exhaled, while larger particles will become trapped in the device or may deposit only in the oropharynx and large bronchi.^{4,9} Particle size will vary depending on the nebulization system.¹⁰ Jet nebulizers, the most common type, use pressurized gas to vaporize a solution for inhalation. Ultrasonic nebulizers produce an aerosol through the use of high-frequency ultrasonic waves and allow for more rapid nebulization with smaller required volumes than do jet nebulizers.^{3,10} The respiratory fraction, or amount of drug delivered by the nebulizer, is affected by the type of nebulizer and patient variables (eg, proper nebulizer use, breathing patterns, airway obstruction). As a result, the percentage of nebulized drug that reaches the lung is highly unpredictable but has been reported to range between 8% and 12% for most nebulizers.⁵

The use of nebulized lidocaine is not mentioned in treatment guidelines for cough, asthma, or chronic obstructive pulmonary disease (COPD).^{11–14} In this article, we evaluate the evidence supporting off-label uses of nebulized lidocaine for treatment of intractable cough and asthma and

safety data associated with these uses. Clinical trial details are reported in Table 1.

LITERATURE REVIEW

Intractable Cough

The efficacy of nebulized lidocaine (10–400 mg) for suppression of intractable cough has been reported in 6 descriptive studies and 1 small controlled clinical trial. Intractable cough was defined as patient-reported cough despite use of common cough suppressants; prior failed treatments were specified in some studies.^{15–21} In 1 case series, nebulized lidocaine 1–4% (10–20 mg) every 4 to 6 hours as needed, preceded by albuterol 5 mg, produced nearly instantaneous relief of intractable cough in 21 patients who had obstructive, restrictive, or infective airway disease.¹⁵

In another case series, 3 patients with intractable cough secondary to upper respiratory tract infection were treated with a single nebulization session of lidocaine 10 mg and bupivacaine 5 mg. The cough stopped and did not recur.¹⁶ A single-blind clinical trial (N = 127) in subjects with persistent cough secondary to COPD compared nebulized lidocaine 1 mg/kg and terbutaline 5 mg for the immediate suppression of intractable cough.¹⁷ Assessment of cough severity was determined using a 10-point questionnaire completed by participants at baseline and 1 hour following treatment, with 1 being complete cough suppression and 10 being severe cough. Treatment with either lidocaine or terbutaline resulted in significant improvements in cough severity compared with baseline assessments (median score at baseline, 8 in each group; median score after treatment, 3 in each group), but no significant difference between treatments was evident (p = 0.44).¹⁷

The use of higher doses of nebulized lidocaine (400 mg, preceded by albuterol 2–5 mg) to suppress intractable cough was noted in 3 patients with cough secondary to lung cancer, with immediate effects that persisted for 1 week or more.¹⁸ A chart review was conducted in 4 patients receiving palliative care for various diagnoses (ie, end-stage heart failure, esophageal squamous cell carcinoma, small-cell lung cancer, anaplastic thyroid carcinoma). Prior failed treatments included nebulized fentanyl in 1 patient and hydromorphone and midazolam in another. Each patient received nebulized lidocaine 100 mg with oxygen 4–6 L/min; cough severity was measured by the Edmonton Symptom Assessment System cough index (none, mild, moderate, severe). Prior to lidocaine administration, 3 patients were ranked as having severe cough and 1 as having moderate cough. Improvement was noted in 2 of the patients with severe cough.¹⁹

Another case series included 1 patient with probable erosive esophagitis-induced cough that persisted despite multiple treatments (ie, β-agonists, ipratropium, theophylline, antihistamines, diazepam, metoclopramide, phenothiazines), 1

Table 1. Efficacy and Safety Trials of Nebulized Lidocaine

Reference	Design	Regimen	Participants	Primary End Point	Results
Chong (2005) ¹⁷	R, SB, AC	Lidocaine 1 mg/kg Terbutaline 5 mg 1 treatment; study open for 6 months of recruiting	N = 127 COPD, intractable cough	Effect on short-term cough suppression, measured by subjective cough severity score (range 1-10)	Median cough score at baseline: 8 in each group Change in cough score after treatment: -5 Median score after treatment: 3 (95% CI: lidocaine 2-3, terbutaline 2-5; $p < 0.01$ vs baseline; between-group comparison $p = 0.44$) AEs: lidocaine: oropharyngeal numbness, bitter taste; terbutaline: tremor, palpitation ($p < 0.01$ for each comparison)
Prakash (1990) ²²	R, SB, PC, CO	Nebulized lidocaine 4% (80 mg) Nebulized saline as placebo 1 treatment-each of 2 days (lidocaine treatment day and normal saline treatment day)	N = 18 Asthma; nonsmokers, age 15-40 years, not receiving glucocorticoids	Change in pulmonary function 15 and 30 minutes after nebulized lidocaine; pulmonary function measurements included FVC, FEV ₁ , FEV ₁ /FVC, Raw, V ₂₅ , V ₅₀	Lidocaine results in short-term bronchodilation of large airways/bronchoconstriction of small airways After 15 minutes, V ₅₀ decreased (1.6 ± 0.94 vs 1.44 ± 0.89 L/sec; $p < 0.05$) Raw decreased ($p < 0.05$); airway conductance increased ($p < 0.05$) After 30 minutes, returned to baseline No AE reported other than bronchoconstriction
Abuan (2010) ⁷	R, DB, PC, PG 12 weeks	Nebulized lidocaine 40 mg twice daily Placebo twice daily Pretreatment: albuterol Pts. continued baseline short-acting bronchodilators	N = 99 Mild to moderate (FEV ₁ $\geq 60\%$) asthma; glucocorticoid-naïve	Efficacy of nebulized lidocaine for mild to moderate asthma in pts. who never used glucocorticoids vs placebo	FEV ₁ change from baseline: lidocaine +0.01 L vs placebo +0.02 L ($p = 0.90$) FEV ₁ % predicted change from baseline: lidocaine +0.4% vs placebo +0.7% ($p = 0.88$) AE: hypoesthesia, oropharyngeal numbing
Hunt (1996) ⁸	OL 1-26 months (mean, 12)	Nebulized lidocaine initial dose: 2%, 40 mg 4 times/day; after 2-4 weeks: 4%, 100 mg 4 times/day Pts. continued bronchodilators and inhaled glucocorticoids; oral glucocorticoid dose slowly reduced after 1 week in stable pts.	N = 20 Severe glucocorticoid-dependent asthma; mean 19.1 years (range 4-50 years) receiving stable prednisone therapy (mean 24 mg/day; range, 3-65 mg/day) mean, 6.5 years (range 0.3-32 years) and inhaled glucocorticoids (triamcinolone, ≥ 16 sprays/day or flunisolide, ≥ 10 sprays/day)	Reduction in oral glucocorticoid use	17/20 pts. reduced oral prednisone use 80-100%; no improvement in 3; 4 pts. who reduced oral prednisone dose maintained symptom control Within 15 minutes, plasma lidocaine concentrations undetectable (<0.5 $\mu\text{g/mL}$) AE: steroid withdrawal symptoms, bitter taste, vomiting without nausea ($n = 2$), chest tightness ($n = 1$), asthma exacerbations
Abuan (2010) ⁷	R, DB, PC, PG 20 weeks	Nebulized lidocaine 40 mg twice daily Placebo twice daily Pretreatment with albuterol Subjects continued baseline short-acting bronchodilators and inhaled glucocorticoids	N = 114 Severe (FEV ₁ 35-85%) asthma, receiving baseline oral glucocorticoids (prednisone 5-70 mg; mean dose: lidocaine, 11.9 mg; placebo, 11.4 mg; mean duration: lidocaine, 7.4 years; placebo, 6.7 years) and inhaled glucocorticoids (mean duration: lidocaine, 8.4 years; placebo, 7.9 years)	Number of pts. with severe asthma able to reach $\geq 50\%$ reduction in oral glucocorticoid dose, accompanied by clinical stability for ≥ 4 weeks	Number of responders at 20 weeks significantly greater in placebo group vs lidocaine group (32.8% vs 14.3%, respectively; $p = 0.02$) AE: asthma exacerbations

AC = active-controlled; AE = adverse effect; CO = crossover; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; OL = open-label; PC = placebo-controlled; PG = parallel-group; R = randomized; Raw = airway resistance; SB = single-blind; V₅₀ = flow rate at 50% of VC; VC = vital capacity.

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Table 1. Efficacy and Safety Trials of Nebulized Lidocaine (continued)

Reference	Design	Regimen	Participants	Primary End Point	Results
Hunt (2004) ²³	R, DB, PC, PG 8 weeks	Nebulized lidocaine 4% (100 mg) 4 times/day Placebo (saline) 4 times/day Pts. continued baseline bronchodilators and inhaled glucocorticoids Glucocorticoid dose reduced by half each week; discontinued at week 4	N = 50 Mild to moderate asthma (FEV ₁ 60-125%), receiving inhaled glucocorticoids (median dose, triamcinolone, beclomethasone, flunisolide, or fluticasone 800 µg/day; range: lidocaine, 150-2250 µg/day; placebo, 100-2060 µg/day)	Changes in markers of asthma severity	FEV ₁ decreased after 8 weeks (lidocaine -0.02 L vs placebo -0.38 L; <i>p</i> < 0.001) Change in FEV ₁ % predicted: lidocaine 0 vs placebo -9% (<i>p</i> < 0.001) Change in bronchodilator use from baseline: lidocaine -0.6 vs placebo +0.3 puffs/day (<i>p</i> = 0.002) Nighttime awakenings improved in 36% of lidocaine group and 12% of placebo group (<i>p</i> = 0.017) Change in symptom scores: lidocaine -0.10 vs placebo +0.23 (<i>p</i> = 0.29) Increase of blood eosinophils from baseline: lidocaine 0.02 × 10 ⁹ /L vs placebo 0.09 × 10 ⁹ /L (<i>p</i> = 0.03) AE: 4 pts. discontinued treatment early due to intolerance: cough (1), wheezing (1), "cold feeling in throat" (1), worsening asthma symptoms (1) No serious AEs reported
Groeben (1999) ²⁴	R, DB, PC, CO	Nebulized lidocaine 10% (5 mg/kg) Intravenous lidocaine (1.5 mg/kg loading dose; 3 mg/kg/h infusion) Placebo: saline, intravenous or nebulized 1 treatment on each of 3 days (intravenous lidocaine, inhaled lidocaine, or placebo)	N = 15 Moderate bronchial hyperreactivity (ie, asthma, COPD, hay fever)	Change in histamine threshold, FEV ₁ , and peak lidocaine plasma concentration with intravenous vs nebulized lidocaine after histamine challenge	Histamine threshold doubled in response to nebulized or intravenous lidocaine (between-group comparison, <i>p</i> > 0.05; <i>p</i> = 0.0007 vs placebo) Peak lidocaine plasma concentration significantly lower with nebulized lidocaine (1.5 vs 2.4 µg/mL; <i>p</i> = 0.023) FEV ₁ decreased only with nebulized lidocaine (mean change, -7.3%; <i>p</i> = 0.005)
McAlpine (1989) ²⁵	OL, PC, CO	Nebulized lidocaine 4% (240 mg) Placebo: nebulized saline 1 treatment on each of 2 days (histamine challenge day and lidocaine treatment day)	N = 20 Asthma	Change in pulmonary function and histamine threshold in response to nebulized lidocaine following histamine challenge	Change in FEV ₁ (mean ± SEM): lidocaine -7.53% ± 3.56% vs placebo +0.92 ± 2.44% FEV ₁ decreased >15% from baseline in 5 pts. (range -16.1% to -42.1%) No correlation between extent of FEV ₁ decline in lidocaine group and baseline histamine threshold (indicator of asthma severity)
Groeben (2000) ²⁶	R, DB, PC, CO	Nebulized lidocaine: 1% (0.5 mg/kg) 4% (2 mg/kg) 10% (5 mg/kg) Placebo: nebulized saline 1 treatment on each of 4 days (lidocaine 1%, 4%, 10%, placebo)	N = 15 Mild asthma or significant hay fever	Change in bronchial reactivity following histamine challenge	Change in FEV ₁ from baseline: decreased with all 3 doses (1%, -3.2%; 4%, -2.9%; 10%, -5.0%); only 10% lidocaine significant vs baseline (<i>p</i> = 0.0012) Effects on histamine threshold: lidocaine 1%, 4%, 10% increased threshold by 5.7 mg/mL (<i>p</i> = 0.0045 vs placebo), 10.0 mg/mL (<i>p</i> = 0.0007 vs placebo), and 12.2 mg/mL (<i>p</i> = 0.0007 vs placebo; <i>p</i> = 0.9999 vs 4%)
Groeben (2000) ²⁷	R, DB, PC, CO	Nebulized lidocaine 10% (5 mg/kg) Nebulized albuterol 1.5 mg Nebulized lidocaine 10% (5 mg/kg) plus albuterol 1.5 mg Placebo: nebulized saline 1 treatment on each of 4 days (lidocaine, salbutamol, lidocaine + salbutamol, placebo)	N = 15 Mild bronchial hyperreactivity (ie, asthma, COPD, hay fever)	Change in pulmonary function and histamine threshold after administration of nebulized lidocaine, albuterol, lidocaine plus albuterol, and placebo following histamine challenge	Change in FEV ₁ from baseline: lidocaine -0.28 L (-7.1%; <i>p</i> = 0.005); albuterol +0.18 L (<i>p</i> = 0.008); lidocaine plus albuterol +0.19 L (<i>p</i> = 0.007) Change in VC from baseline: lidocaine 0.14 L (- <i>p</i> = 0.311); albuterol +0.09 L (<i>p</i> = 0.009); lidocaine plus albuterol +0.16 L (<i>p</i> = 0.008) Effects on histamine threshold: lidocaine or albuterol doubled threshold (<i>p</i> = 0.0007 vs placebo); lidocaine plus albuterol quadrupled threshold (<i>p</i> = 0.002 vs lidocaine)

AC = active-controlled; AE = adverse effect; CO = crossover; COPD = chronic obstructive pulmonary disease; DB = double-blind; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; OL = open-label; PC = placebo-controlled; PG = parallel-group; R = randomized; Raw = airway resistance; SB = single-blind; V₅₀ = flow rate at 50% of VC; VC = vital capacity.

patient with lisinopril-induced cough that persisted after lisinopril discontinuation, and 1 patient with paroxysms of coughing secondary to parietic vocal cords. Each patient received treatment with nebulized lidocaine 30 mg twice daily for 6 weeks to 1 year and experienced sustained control of their cough symptoms.²⁰

A case report in a pediatric patient with psychogenic cough refractory to cough suppressants, antihistamines, antibiotics, β -agonists, and glucocorticoids noted cough resolution following a single nebulizer treatment with lidocaine 30 mg. Nebulized lidocaine was also successful in pediatric patients with similar symptoms; none required more than 48 hours of therapy.²¹

Asthma

Five trials have evaluated nebulized lidocaine 40-160 mg for improvement in pulmonary function and glucocorticoid-sparing effects in individuals with mild to severe asthma.^{7,8,22,23} The effects of nebulized lidocaine on pulmonary function in patients with chronic stable asthma were evaluated in a randomized, single-blind, crossover study (N = 18).²² Bronchodilator treatments were discontinued 24 hours prior to baseline measurements. Subjects received nebulized lidocaine 4% (80 mg) or normal saline over 8 minutes. Pulmonary function, blood pressure, and heart rate were measured 15 and 30 minutes after completion of treatments. The only measure of pulmonary function that was significantly affected by lidocaine nebulization was flow rate at 50% of vital capacity (V_{50}) 15 minutes after nebulization, which was significantly reduced (1.6 ± 0.94 to 1.44 ± 0.89 L/sec; $p < 0.05$), suggesting bronchoconstriction of the small airways; however, bronchodilation of the large airways was evident due to decreased airway resistance ($p < 0.05$) and increased airway conductance ($p < 0.05$) in nearly half the subjects. No change in pulmonary function was noted 30 minutes after lidocaine inhalation.²²

Another study (N = 99) evaluating nebulized lidocaine (40 mg twice daily) in glucocorticoid-naïve patients with mild to moderate asthma measured the change from baseline in FEV₁ after 12 weeks of treatment.⁷ Lidocaine was nebulized 15-30 minutes after pretreatment with albuterol. Overall, subjects receiving nebulized lidocaine failed to show improvement in pulmonary function (FEV₁, FEV₁% predicted, morning and evening peak expiratory flow [PEF]).⁷

Oral glucocorticoid-sparing effects of nebulized lidocaine were investigated in 2 studies over 12 months and 20 weeks, respectively, with conflicting results.^{7,8} Nebulized lidocaine (40-160 mg 4 times daily) was evaluated in an open-label study of subjects (N = 20) with severe asthma and glucocorticoid-induced hypercortisolism.⁸ Treatment was initiated at 40 mg 4 times per day and dosage increas-

es were allowed after 2-4 weeks of treatment. Participants were allowed to continue their drug regimens (including bronchodilators and inhaled glucocorticoids) while being treated and were asked to monitor peak flow rates daily. If improvements in respiratory function (stabilized peak flow rates and symptom resolution) were noted after 1 week of treatment, systemic glucocorticoid doses were reduced.

Overall, treatment with nebulized lidocaine resulted in extensive reductions in glucocorticoid doses (80-100%) in most (17 of 20) of subjects; 13 subjects were able to discontinue therapy. Prednisone doses at the end of the treatment period ranged from 0.5 mg to 10 mg daily, a significant reduction from baseline (mean, 24 mg; range, 3-65 mg). Lower glucocorticoid doses limited adverse effects in many subjects; 13 individuals experienced resolution of their cushingoid appearance. All plasma lidocaine concentrations were undetectable ($<0.5 \mu\text{g/mL}$).⁸

The second study evaluated nebulized lidocaine (40 mg twice daily, preceded by albuterol) in subjects (N = 114) with severe glucocorticoid-dependent asthma (mean baseline prednisone dose, 11.4 mg and 11.9 mg in placebo and lidocaine groups, respectively) over 20 weeks of treatment.⁷ The primary end point was the number of participants able to achieve a 50% or greater reduction in glucocorticoid dose with clinical stability for 4 or more weeks. At week 4, glucocorticoid doses were reduced every 2 weeks until a 10-mg dose was attained. Overall, more subjects in the placebo group reached the primary end point than did those in the lidocaine group (32.8% vs 14.3%; $p = 0.02$). No significant improvements in pulmonary function (FEV₁, FEV₁% predicted, PEF) were noted.⁷

In a randomized, placebo-controlled study of subjects (N = 50) with mild to moderate asthma (FEV₁ 60-125%) receiving daily inhaled glucocorticoids and bronchodilators, nebulized lidocaine was studied as an alternative to medium- to high-dose inhaled glucocorticoid therapy.²³ After a 2-week evaluation period in which participants monitored peak flow rates and recorded symptoms, they received either nebulized lidocaine 4% (100 mg) 4 times daily or normal saline in addition to their baseline inhaled glucocorticoids (median, 800 $\mu\text{g/day}$ of triamcinolone, beclomethasone, flunisolide, or fluticasone) and their bronchodilators for 8 weeks. Subjects reduced the dose of their inhaled glucocorticoid by half each week and discontinued inhaled glucocorticoid therapy at week 4. After 8 weeks of treatment and 4 weeks following glucocorticoid discontinuation, indicators of asthma function were significantly improved in subjects receiving nebulized lidocaine versus those receiving placebo. Improvement in FEV₁ from baseline (both liters and % predicted) was noted in participants receiving nebulized lidocaine (+0.02 L vs -0.38 L with placebo; 0% vs -9% with placebo, respectively; both $p < 0.001$).

Reductions in symptom scores (-0.10 on a scale of $0-3$; $p = 0.029$) and bronchodilator use (-0.6 puffs/day; $p = 0.002$) from baseline in the lidocaine group were statistically significant but not clinically significant.²³ Because of the brevity (8 weeks) of this study, the duration of benefit associated with nebulized lidocaine for replacement of inhaled glucocorticoids is unclear. Use of nebulized lidocaine in patients with stable asthma may provide an alternative step-wise approach to maintaining control while reducing use of medium- to high-dose glucocorticoids and adverse effects.¹³

SAFETY

Preservative-free lidocaine solution for injection administered via nebulization has been reported to cause initial bronchoconstriction in individuals with baseline bronchial hyperreactivity (eg, asthma, COPD, hay fever).²⁴⁻²⁷ In 4 studies, reflex bronchoconstriction was simulated by using histamine as an airway irritant.²⁴⁻²⁷ A clinical trial comparing intravenous and nebulized lidocaine 10% (5 mg/kg) in subjects ($N = 15$) with moderate bronchial hyperreactivity found that both routes of administration doubled the histamine threshold; however, nebulized lidocaine also produced an initial decline in FEV_1 (mean, -7% from baseline; $p = 0.005$).²⁴ Another trial in subjects ($N = 20$) with asthma found that lidocaine-induced bronchoconstriction occurred regardless of the severity of asthma.²⁵ A study investigating 3 doses of nebulized lidocaine (1% at 0.5 mg/kg, 4% at 2 mg/kg, and 10% at 5 mg/kg) in participants ($N = 15$) with mild asthma showed a dose-related increase in bronchoconstriction, with decreases in FEV_1 ranging from -3% to -5% .²⁶

The initial bronchoconstriction associated with inhalation of lidocaine can be prevented by pretreatment with a bronchodilator.²⁷ In subjects ($N = 15$) with mild bronchial hyperreactivity, a greater increase in the histamine threshold was produced by albuterol 1.5 mg plus nebulized lidocaine 5 mg/kg versus either drug alone, and pretreatment with albuterol prevented the initial lidocaine-induced decrease in FEV_1 .²⁷ In most of the descriptive studies and clinical trials included in this review, bronchoconstriction was not reported as an adverse effect resulting from lidocaine nebulization in doses ranging from 10 mg to 400 mg, despite lack of prophylaxis with a short-acting β -agonist.^{8,16,17,19-21,23} Although asthma exacerbation occurred in some of the studies, bronchoconstriction was reported in only 1 study but resolved within 30 minutes following nebulization.²²

Plasma concentrations associated with nebulized lidocaine are well below toxic levels. The highest dose of nebulized lidocaine in the reviewed clinical trials (10% lidocaine dosed at 5 mg/kg) yielded a peak lidocaine plasma concentration of $1.5 \mu\text{g/mL}$, which was significantly lower

than concentrations seen with intravenous administration.^{24,27} Doses in the 40- to 160-mg range yielded lidocaine plasma concentrations that were undetectable ($<0.5 \mu\text{g/mL}$).⁸ While lidocaine toxicity has been reported with other topical dosage forms at a dose of 300 mg,²⁸ no reports with nebulized lidocaine were identified.

Other than initial bronchoconstriction, the only adverse effects frequently associated with nebulized lidocaine were bitter taste and transient oropharyngeal numbness.^{7,8,17,24,27} Steroid withdrawal symptoms and asthma exacerbations were noted in patients whose high-dose glucocorticoids were tapered to discontinuation.^{7,8}

DISCUSSION

Evidence supporting the use of nebulized lidocaine for the treatment of intractable cough is limited to case series and 1 small clinical trial.¹⁵⁻²¹ In general, the strength of the studies was compromised by descriptive designs and subjective end points. Variations in nebulized lidocaine dosages, respiratory fractions associated with different nebulizers, comorbidities responsible for cough, and failed treatments prior to initiation of lidocaine across the studies make it difficult to determine an ideal dosing regimen and identify appropriate patients who would most likely benefit from nebulized lidocaine. The clinical trial investigating nebulized lidocaine for the treatment of cough secondary to COPD demonstrated equal efficacy and better tolerability compared with terbutaline.¹⁷ Although this finding suggests that nebulized lidocaine may be a safe alternative to conventional respiratory treatments for suppression of intractable cough in COPD, the lack of inclusion of patients with cough resulting from other underlying disease states makes extrapolation of these data difficult. Negative publication bias is another possible limitation to the data.

Five trials have evaluated nebulized lidocaine for improvement in pulmonary function and glucocorticoid-sparing effects in subjects with mild to severe asthma.^{7,8,22,23} These studies provide insight for the use of nebulized lidocaine in patients with severe asthma for whom relatively few treatment options exist outside of high-dose glucocorticoids. Three studies^{8,22,23} noted improvement in pulmonary function measures and 2 reported significant reductions in oral or inhaled glucocorticoid doses following treatment.^{8,23} Conversely, 2 trials reported no improvements in pulmonary function and no glucocorticoid-sparing effects.⁷ The studies noting positive outcomes shared similarities in inclusion and exclusion criteria, baseline pulmonary function, and treatment protocols (ie, lidocaine dose and frequency, restriction of adjunctive medications, nebulizers). Limitations to these studies include inconsistency in design, difficulty in blinding subjects to lidocaine administration, small sample sizes, and lack of confidence intervals, which hinders interpretation of clinical signifi-

cance^{7,8}; however, the studies were strengthened by the evaluation of objective clinical end points, low attrition rates, and good external validity. The 2 studies that did not see improvements with use of nebulized lidocaine used smaller dosages and included patients with suspected COPD due to smoking (≥ 10 pack-years) and profoundly reduced baseline pulmonary function (FEV_1 , mean 1.7 L; $FEV_1\%$ predicted, 59.1%) compared with subjects in other studies (FEV_1 , mean 2.7–3.1 L; $FEV_1\%$ predicted, 79–90%).^{7,8,23} In addition, participants were administered a short-acting β -agonist 15–30 minutes prior to lidocaine nebulization. This treatment may have confounded the improvements in FEV_1 and $FEV_1\%$ predicted noted in prior studies and improved previously reported intolerances (ie, bronchoconstriction) to treatment.

Lidocaine-induced reflex bronchoconstriction due to airway irritation was seen in clinical trials focusing on bronchial reactivity; however, the lidocaine-induced initial decrease in FEV_1 reported in the studies (–3% to –7.5%) did not meet the threshold that is considered to be clinically significant in obstructive airway disease (decrease of $>15\%$).^{24–27} Bronchoconstriction was reported in only 1 clinical trial investigating the efficacy of nebulized lidocaine.²² Bronchoconstriction may be prevented by administering a prophylactic dose of a bronchodilator prior to lidocaine nebulization; if bronchoconstriction does occur, it is likely to be clinically irrelevant.

Summary

Based on existing data, nebulized lidocaine (10–400 mg) may be an efficacious and safe treatment option for cough that has failed to respond to traditional antitussive agents. However, the evidence reviewed here was limited to descriptive studies and 1 small clinical trial; larger controlled clinical trials are needed to validate the clinical usefulness of nebulized lidocaine in this condition. Studies on the use of nebulized lidocaine in asthma are conflicting. While improvements in respiratory function and a glucocorticoid-sparing effect have been noted in some studies, others have not replicated these findings. Differences in study populations may account for these inconsistencies. Nebulized lidocaine was well tolerated and safe; however, initial bronchoconstriction is possible and asthma exacerbation may occur if glucocorticoid doses are reduced too rapidly. Although nebulized lidocaine is not a first-line treatment, it may represent an unconventional alternative for the treatment of intractable cough and may provide temporary reductions in steroid doses for patients with severe asthma who are experiencing glucocorticoid-induced adverse effects.

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EXTRACTO

Evidencia Sobre el uso Terapéutico de Lidocaína Nebulizada en el Tratamiento de la Tos y el Asma

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Ann Pharmacother 2013;47:578-85.

OBJETIVO: Realizar un compendio de los datos de eficacia y seguridad disponibles sobre el uso de lidocaína nebulizada en tos persistente y asma.

FUENTES DE DATOS: Se realizó una búsqueda en PubMed (hasta noviembre 2012), International Pharmaceutical Abstracts (1970–diciembre 2012) y Cochrane Library (hasta 2012) utilizando los términos de búsqueda nebulization, nebulized, o nebulized; administration; inhalation; cough; asthma; y lidocaine. Se limitaron los resultados a los estudios en humanos publicados en inglés. También se revisaron las citas bibliográficas de las publicaciones relevantes localizadas.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se revisaron para su inclusión todos los artículos identificados en las fuentes utilizadas. Se incluyeron en la revisión todos los ensayos clínicos y los estudios descriptivos que versaban sobre el uso de lidocaína nebulizada para el tratamiento de la tos persistente y el asma.

SÍNTESIS DE DATOS: Se identificaron 17 estudios para su revisión. Siete estudios (6 descriptivos y un ensayo clínico) evaluaban el uso de lidocaína nebulizada en el tratamiento de la tos persistente en dosis desde 10 a 400 mg. Cinco ensayos clínicos en asma mostraron resultados conflictivos sobre la mejora de la función pulmonar y el descenso en el uso de corticoides. En 5 estudios se investigaron la mejoría general de la función pulmonar y de la broncoconstricción inicial inducidas por lidocaína nebulizada en sujetos con hiperreactividad bronquial de base. En general, la evidencia disponible

no parece excluir el uso de lidocaína como tratamiento opcional de la tos persistente tras el fracaso de los antitusivos tradicionales. Su empleo para disminuir el uso a corto plazo de glucocorticoides en asma es conflictivo. Deben considerarse las limitaciones de los estudios evaluados, tales como el diseño, el pequeño tamaño de las muestras, las inconsistencias en la metodología y el uso de terapias coadyuvantes. La lidocaína nebulizada se tolera bien; sin embargo se han comunicado casos de broncoconstricción inicial.

CONCLUSIONES: Aunque la lidocaína nebulizada no es un tratamiento de primera línea para la tos persistente y el asma, puede constituir una opción terapéutica alternativa en pacientes que no toleran o no responden a otros tratamientos. Deben tomarse precauciones de monitorización adecuadas para asegurar la seguridad de los pacientes.

Traducido por Juan del Arco

RÉSUMÉ

Données Cliniques Portant sur l'Utilisation de la Lidocaïne en Nébulisation dans le Traitement de la Toux et de l'Asthme Réfractaire

RM Slaton, RH Thomas, JW Mbathi

Ann Pharmacother 2013;47:578-85.

OBJECTIF: Résumer les données d'efficacité et d'innocuité portant sur l'utilisation de la lidocaïne en nébulisation dans la toux et l'asthme réfractaires.

SOURCES DES DONNÉES: Une recherche documentaire a été effectuée dans PubMed (novembre 2012), International Pharmaceutical Abstracts (1970-décembre 2012), et dans la Cochrane Library (jusqu'en 2012) en utilisant les termes de recherche suivants: nebulization, nebulized or nebulized, administration, inhalation, cough, asthma, et lidocaine. Les résultats ont été limités aux humains et en langue anglaise. Les citations des publications pertinentes ont également été examinées.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles identifiés à partir des sources de données ont été examinés pour inclusion dans l'analyse. Les essais cliniques et les études descriptives ayant discuté de l'utilisation de la lidocaïne en nébulisation pour le traitement de la toux réfractaire et de l'asthme ont été inclus dans l'étude.

SYNTHÈSE DES DONNÉES: Dix-sept études ont été identifiées. Sept études (6 études descriptives et un essai clinique) évaluant l'utilisation de la lidocaïne en nébulisation dans la toux rebelle ont rapporté une efficacité avec des doses allant de 10 à 400 mg. Cinq essais cliniques en asthme ont démontré des résultats contradictoires concernant l'amélioration de la fonction pulmonaire et de la réduction de l'administration des glucocorticoides. Les améliorations générales de la fonction pulmonaire ainsi que de la bronchoconstriction induite par la lidocaïne par nébulisation chez les sujets présentant une hyperréactivité bronchique ont été étudiées dans 5 études. Dans l'ensemble, les données disponibles ne semblent pas poser un obstacle à considérer l'utilisation de la lidocaïne comme option de traitement pour la toux rebelle après l'échec des antitussifs traditionnels. Son utilisation à court terme dans l'asthme est contradictoire. Les limites des études, y compris la conception, la petite taille des échantillons et des incohérences dans la méthode et des traitements d'appoint doivent être prises en considération. La lidocaïne en nébulisation est bien tolérée, mais des cas de bronchoconstriction initiale ont été rapportés.

CONCLUSIONS: Bien que la lidocaïne en nébulisation n'est pas un traitement de première intention dans l'asthme et la toux rebelle, elle peut constituer une option alternative de traitement chez les patients qui ne tolèrent pas ou ne répondent pas aux autres traitements. Des précautions de surveillance appropriées doivent être utilisées pour assurer la sécurité des patients.

Traduit par Nicolas Paquette-Lamontagne