ORIGINAL ARTICLE

Comparison of lidocaine and bronchodilator inhalation treatments for cough suppression in patients with chronic obstructive pulmonary disease

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Background: This study aimed to assess and compare the effectiveness of lidocaine and bronchodilator inhalation treatments for rapid cough suppression in patients with chronic obstructive pulmonary disease (COPD).

Methods: Prospective comparison study carried out in a tertiary emergency department. Consecutive COPD patients presenting with intractable cough were randomly assigned to receive lidocaine or terbutaline inhalation treatments for cough suppression. Patients with dyspnoea, unstable vital signs, and pneumonia or neoplasm on chest x ray were excluded. A subjective, 10 point questionnaire based cough severity score was used for assessing the outcome.

Results: The final study sample included 127 patients (mean (SD) age, 69.2 (12.1) years; 33.1% women) of whom 62 received nebulised lidocaine and 65 nebulised bronchodilator. The cough severity score was significantly reduced one hour after inhalation treatment with both lidocaine and bronchodilator, with no significant difference in efficacy. Common but mild side effects in the lidocaine group included oropharyngeal numbness and bitter taste, and, in the bronchodilator group, tremor and palpitation. Dyspnoea, dizziness, and nausea and vomiting were equally uncommon in both groups. None of these problems caused any of the patients to discontinue their treatments and no allergic reactions were reported.

Conclusions: Both lidocaine and bronchodilator inhalation treatments are equally effective for short term cough suppression in patients with COPD.

Cough is an explosive, defensive mechanism, which clears foreign material and excess mucus accumulating in the tracheobronchial tree. Patients who experience intractable coughing frequently visit their family doctors or chest physicians, despite the widespread availability of over the counter antitussive medications. The primary goals of treatment are facilitation of expectoration, elimination of airway irritation, and suppression of stimulation of cough receptors.^{1 2}

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction with symptoms related to breathing, such as cough, exertional dyspnoea, expectoration, and wheeze. Episodes of intractable cough may occur in conjunction with airway hyperresponsiveness and may be treated with inhaled sympathomimetic bronchodilators.^{3 4} Lidocaine, when administered via nebuliser, has been shown to be safe and effective in suppressing cough related to airway procedures such as bronchoscopy^{5–8} and in the treatment of refractory cough in several broad categories of patients (those with infective, obstructive, restrictive, or neoplastic disease).^{9–11}

Intractable cough can influence daily activity, and complications such as pneumothorax, syncopal episodes, and cardiac arrhythmias may be devastating. Rapid relief of severe cough is important because if left untreated, cough can become a vicious cycle of "cough", "airway irritation", and "stimulation of cough". This study aimed to examine and compare short term effectiveness of lidocaine and bronchodilator inhalation treatments for cough suppression in patients with COPD during their visits to the emergency department (ED).

METHODS

Study population

Over a six month period in 2003, we prospectively enrolled consecutive adult patients who presented to a teaching hospital ED with intractable cough. The criteria for inclusion were:

- subjective complaint of intractable cough
- clear and alert mental state
- documented past medical history of COPD
- verbal consent for cough suppression via inhalation treatment.

We excluded patients with:

- unstable initial vital signs
 - systolic blood pressure <90 mm Hg or
 - pulse rate <50 or >120 per minute or
 - respiratory rate <10 or >30 breaths per minute
- respiratory distress (laboured breathing)
- hypoxaemia (oxygen saturation <90%) documented on pulse oximetry
- evidence of pneumonia or neoplasm on chest x ray.

Study design and questionnaire survey

We randomly assigned blinded eligible patients to receive prescriptions for either lidocaine or bronchodilator inhalation for cough suppression. We used opaque sealed envelopes to

The Cough Severity Score

10 (Most severe cough)
9
8
7
6
5
4
3
2
1 (No cough at all)

Please answer the questions by yourself.

Do not talk with ANYONE.

Thank you.

The Questionnaire

- Please try to rate your subjective perception of cough severity (from 1 to 10 points) according to the "cough severity score" as illustrated on the left:
 - Before inhalation treatment:
Score = _____
 - One hour after inhalation treatment:
Score = _____
- Please describe any discomfort that appears after the inhalation treatment: (multiple choices allowed)
 - ☐ Tremor (shaking).
 - ☐ Palpitation.
 - ☐ Numbness in the mouth or throat.
 - ☐ Bitter taste.
 - ☐ Shortness of breath.
 - ☐ Nausea or vomiting.
 - ☐ Dizziness.
 - ☐ Other: _____

Figure 1 Questionnaire for self-determination of severity of cough.

randomly assign the participating patients to one of the two study groups. The main investigator was not involved in any of the interventions and was blind to group allocation. The physicians prescribing the inhalation treatments were also blind to the allocation of treatments. The only health personnel not blinded to group allocation were the research nurses who delivered the inhalation treatments and distributed the questionnaires.

A specially designed questionnaire (fig 1) was completed by each patient to self-determine the severity of their cough before and one hour after the inhalation treatment. The subjective cough severity score was graded on a 10 point scale where no cough = 1 point and most severe cough = 10 points (fig 1). All the patients remained under surveillance for at least two hours after the inhalation treatment was complete.

The institutional review board determined that the study protocol met the criteria for exemption because both preparations are routinely used for cough suppression, the side effects are minor, and even if not participating in the study, the patients would have been prescribed one of the preparations. In addition, the patients gave witnessed verbal informed consent prior to enrolment.

Figure 2 Flow diagram showing enrolment and allocation of patients to the lidocaine or bronchodilator group. COPD, chronic obstructive pulmonary disease.

Inhalation treatment

The patients inhaled aerosol with a nebuliser driven by compressed oxygen using a mouthpiece. For the lidocaine group, the aerosol solution was prepared by diluting 1 mg/kg cardiac lidocaine with saline solution to achieve a total volume of 4 ml. For the bronchodilator group, the same volume of aerosol solution was prepared by mixing 2 ml terbutaline (Bricanyl 5 mg; AstraZeneca, Sweden) with 2 ml saline solution. The overall nebulisation time was 15–25 minutes per treatment. All patients were asked not to eat or drink for one hour after the inhalation treatment. No other antitussive agents were prescribed in the ED prior to completion of the questionnaire.

Statistical analysis

Parametric interval data are presented as mean (SD) and were compared using the *t* test. Non-parametric interval data are presented as median (25th–75th interquartile range) and were compared using Wilcoxon's matched pairs test (between dependent groups) or the Mann-Whitney U test (between independent groups). Categorical data are presented as number (%) and were compared using the χ^2 test. We defined the outcome measures for the study as the differences within and between the treatment groups with regard to the changes in the cough severity scores between baseline and one hour post-inhalation. All analyses were carried out with STATISTICA version 6.0 (Statsoft, Inc.). Statistical significance was set at $p < 0.05$ (two tailed).

RESULTS

Figure 2 illustrates the enrolment and allocation of the patients to the two study groups. Of 554 patients with intractable dry cough, 182 patients with a history of COPD were recruited for the study. Of these, 55 were then excluded based on the exclusion criteria (see Methods and fig 2). The final study population included 127 patients (mean (SD) age, 69.2 (12.1) years; 33.1% women) of whom 62 were allocated at random to receive inhaled lidocaine and 65 to receive inhaled bronchodilator for cough suppression. Patient characteristics and clinical data of the two groups were statistically similar (table 1). Most patients from both groups had already taken over the counter oral "cough medicines" before their visit to the ED, and most of them actually had experience of treatment with nebulised bronchodilator in the

Table 1 Baseline demographic of the patients participating in the present study

	Lidocaine group (n = 62)	Bronchodilator group (n = 65)	p value
Age (years), mean (SD; range)	68.5 (12.4; 47–95)	69.9 (11.9; 46–92)	0.54
Women*	22 (35.5)	20 (30.8)	0.57
Prior over the counter antitussives*	53 (85.5)	58 (89.2)	0.53
Wheeze on auscultation*	58 (93.6)	55 (83.6)	0.11
Experience of nebulised bronchodilator use*	52 (83.9)	56 (86.2)	0.72
Vital signs			
Systolic blood pressure (mm Hg)†	129.1 (21.4)	128.8 (24.3)	0.95
Pulse rate (min)†	96.0 (15.8)	92.3 (14.3)	0.17
Respiratory rate (breaths/min)†	19.4 (3.9)	19.9 (3.8)	0.48
Body temperature (°C)†	36.8 (1.0)	36.7 (1.0)	0.47

*Categorical data are given as number (%); †continuous data are given as mean (SD).

past. Over 80% had some degree of wheezing on auscultation although respiratory distress was absent.

Baseline cough scores before treatment were similar in the lidocaine and bronchodilator groups and that the cough severity score of patients in both groups reduced significantly to a similar extent one hour post-inhalation from a median score of 8 to 3 points (table 2). The adverse effects observed after the inhalation treatments are listed in table 3. Frequency of oropharyngeal numbness and bitter taste was significantly higher in the lidocaine than in the bronchodilator group (61.3% *v* 4.6%, *p* < 0.01; and 54.8% *v* 6.2% *p* < 0.01, respectively). On the other hand, the bronchodilator group had a much higher proportion of tremor (92.3% *v* 4.8%, *p* < 0.01) and palpitation (90.8% *v* 8.1%, *p* < 0.01) and palpitation (90.8% *v* 8.1%, *p* < 0.01). Dyspnoea, dizziness, and nausea and vomiting were equally uncommon in both the groups. No patient discontinued the treatment because of any of the abovementioned problems and we did not observe any allergic reactions.

DISCUSSION

In Taiwan, it is not uncommon for patients to visit the ED because of intractable cough. A significant proportion of these patients (33% in our cohort) have a documented history of COPD.

Cough is a subjective symptom that is difficult to quantify. Measurements of cough severity are inconsistent and not well established.¹² Hence, we did not use any specific measurement criteria to define "intractable cough" in our study. We considered eligible patients as those who had unmanageable cough severe enough for them to seek help from the ED. The study of cough has inherent limitations for several reasons: cough is influenced by psychological factors¹³; isolated cough is poorly reproducible¹⁴; and spontaneous resolution occurs.¹⁵ Consequently, a previously unpublished, linear 10 point questionnaire score was used as a tool for patients to subjectively self-determine the severity of their cough. Although it has not been validated against objective criteria, this cough severity score assumes a linear scale that is easy to conceptualise.

Table 2 Intra and intergroup comparison of the cough severity scores*

	Lidocaine group (n = 62)	Bronchodilator group (n = 65)	p value
Score before treatment	8 (7–9)	8 (7–8)	0.21
Score after treatment	3 (2–3)	3 (2–5)	0.44
p value	<0.01	<0.01	

*The score of cough severity (fig 1) ranged from 1 (no cough) to 10 points (most severe cough) and are given as median (25th–75th interquartile range) and compared using Wilcoxon's matched pairs test (between dependent groups) or the Mann-Whitney U test (between independent groups).

To our knowledge this is the first study to compare the cough suppressing effects of inhaled bronchodilator with those of inhaled lidocaine in COPD patients. Earlier studies showed that inhalation of bronchodilator may alleviate symptoms such as difficulty breathing and cough in patients with evidence of airflow obstruction during exacerbations.^{3–4} Our study shows that inhaled terbutaline can effectively suppress intractable cough episodes in COPD patients in the absence of respiratory distress. This may be the result of inhibition of occult bronchoconstriction by the β_2 -agonist, though the exact mechanism of action is not known. Tremor and palpitation, which are frequently observed during terbutaline inhalation, are the results of β sympathetic stimulation.

Lidocaine has been extensively studied as an anaesthetic for bronchoscopy, bronchography, and bronchoalveolar lavage.^{5–8} It has been shown to alleviate irritant induced cough^{9–11} and bronchoconstriction without long term adverse effects. Our study substantially adds to the evidence that inhalational administration of lidocaine can effectively alleviate intractable cough in patients with COPD. The issue of lidocaine induced bronchoconstriction remains controversial. Although Liistro *et al*¹⁶ and Groeben *et al*¹⁷ found that extensive upper airway anaesthesia with 10% lidocaine could induce transitory airway obstruction, several reports reached opposite conclusions when aerosolised lidocaine was administered at lower concentrations (as in our study). Enright *et al*¹⁸ showed that inhalation of lidocaine inhibited exercise induced bronchospasm in asthmatic patients. In primates,¹⁹ pretreatment with aerosolised lidocaine not only extinguished the cough reflex, but also decreased bronchial susceptibility to methacholine. Hunt *et al*¹⁰ studied the effects of nebulised lidocaine on patients with severe asthma and did not find any reduction of peak flow or forced expiratory volume at 1 second. No worsening of cough, wheezing, or chest tightness was reported. Rosario *et al*²⁰ also demonstrated improvement in airway obstruction when asthmatic patients were treated with nebulised lidocaine. Thus, we did not use any bronchodilator pretreatment in our study prior to lidocaine inhalation. Although spirometric tests or blood gas

Table 3 Intergroup comparison of the adverse effects*

	Lidocaine group (n = 62)	Bronchodilator group (n = 65)	p value
Tremor	3 (4.8)	60 (92.3)	<0.01
Palpitation	5 (8.1)	59 (90.8)	<0.01
Oropharyngeal numbness	38 (61.3)	3 (4.6)	<0.01
Bitter taste	34 (54.8)	4 (6.2)	<0.01
Dyspnoea	5 (8.1)	4 (6.2)	0.67
Nausea/vomiting	4 (6.5)	3 (4.6)	0.65
Dizziness	2 (3.2)	4 (6.2)	0.44

*Values are number (%)

measurements were not done, all patients from the lidocaine group completed the inhalation treatment without bronchospastic events requiring additional bronchodilator treatment.

In previously reported systemic toxic reactions to lidocaine the effects were related to plasma concentrations. However, several studies of nebulised lidocaine have failed to find significant serum levels of lidocaine or toxicity with individual doses as high as 500 mg.^{21–23} We did not check the serum levels in our patients because of the small doses used (1 mg/kg). Only transient topical effects occurred with lidocaine inhalation, namely, oropharyngeal numbness and bitter taste. All of these side effects are mild and well tolerated.

Our study has a number of limitations that need to be addressed. Firstly, we included a narrow spectrum of patients—only those with a documented past medical history of COPD. Most of these patients had wheezing on auscultation and were accustomed to bronchodilator inhalation. Secondly, the research nurses who delivered the inhalation treatments and distributed the questionnaires were not blinded. Thirdly, only short term outcomes were assessed—that is, one hour after therapy. However, we did not consider long term outcome in the study design because stable COPD patients treated for cough at an ED will not stay long enough for further evaluation. Finally, this study was carried out at a single institution. These findings should be corroborated in patients attending multiple institutions.

We conclude that both lidocaine and bronchodilator inhalation treatments are equally effective for short term cough suppression in patients with COPD. Perhaps inhaled lidocaine could be another treatment option for patients with COPD and intractable cough that cannot be controlled by other means.

CONTRIBUTORS

C-F Chong developed the study protocol, organised and interpreted the data, and wrote the paper. C-C Chen, H-P Ma, Y-C Wu, and Y-C Chen collected the data and helped in data entry. T-L Wang supervised all aspects of the study.

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