

The effect of altering airway tone on the sensitivity of the cough reflex in normal volunteers

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ABSTRACT: Cough is frequently the presenting symptom of bronchial asthma, although cough can result from a wide variety of other respiratory diseases. Treatment of chronic cough has proved extremely difficult. It has been suggested that treatment with bronchodilators may reduce the symptom of cough. In this study the effect of altering airway tone on the sensitivity of the cough reflex was determined.

Twelve normal, healthy volunteers took part. The number of coughs following inhalations of single breaths of doubling concentrations of capsaicin (1.95–500 μ M) was recorded before and after doses of salbutamol, methacholine and saline which altered forced expiratory volume in one second (FEV₁) by $6.2 \pm 2.6\%$, $-8.8 \pm 3.2\%$ and $-0.18 \pm 1.38\%$, respectively. In a further study the cough response was recorded before and after doses of salbutamol and ipratropium bromide, both of which reduced baseline respiratory resistance and resistance measured after capsaicin.

Ipratropium bromide, salbutamol and methacholine, despite having significant effects on airway tone, did not change the sensitivity of capsaicin-induced cough. Thus, if bronchodilator drugs are antitussive in non-asthmatic patients, then this is unlikely to be due to an effect on the sensitivity of the cough reflex.

Eur Respir J, 1991, 4, 1076–1079.

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Keywords: Bronchodilators; capsaicin; cough; ipratropium; methacholine; salbutamol.

Received: February 14, 1991; accepted after revision June 10, 1991.

Cough is frequently the presenting symptom of patients with bronchial asthma [1], although cough may be caused by a wide variety of other respiratory diseases [2, 3]. The effective treatment of unproductive cough has proved extremely difficult. There is an ever expanding market of antitussive agents now available in the UK [4], the majority of which are generally considered to have little effect upon cough. Currently, the most effective antitussive agents are the centrally acting opiates. However, these drugs are associated with undesirable side-effects which limit their use [5].

Recently, there has been debate in the literature regarding the antitussive action of β_2 -adrenergic agonists and anticholinergic drugs. In favour of such antitussive actions, they reduce the response in asthmatics to inhaled citric acid [6]. Others have reported a reduction in self-reported daily coughing in patients suffering from acute cough associated with respiratory infections [7], as well as in chronic coughers presenting at allergy clinic [8]. In normals, Vesco *et al.* [9] have reported a reduction in cough frequency in patients given β_2 -agonists prior to fiberoptic bronchoscopy and both reduce the cough responsiveness in non-asthmatic volunteers to ultrasonically nebulized solutions [10]. POUNSFORD *et al.* [6] however, reported no effects on the cough response with such drugs in normals in response to inhaled citric acid.

The object of this study was to determine whether alteration of airway tone caused by the bronchodilating agents, salbutamol and ipratropium bromide and the bronchoconstricting agent, methacholine, would alter the sensitivity of the cough reflex in normal, healthy volunteers measured by capsaicin challenge.

Methods

Subjects

Twelve normal subjects (8 males, 4 female) of mean age 21 yrs (range 20–22 yrs) were recruited into these, double-blind, randomized studies. None of the subjects had any signs or symptoms of past or present respiratory disease. The study was approved by the Research Ethics Committee of the Royal Postgraduate Medical School, and Hammersmith and Queen Charlotte's Special Health Authority.

Materials

The drugs used in these studies included, salbutamol nebulizer solution 2.5 mg (Ventolin: Glaxo, Greenford, Essex, UK), ipratropium bromide nebulizer solution 0.25

mg (Atrovent: Boehringer Ingelheim Ltd, Bracknell, Berkshire, UK), methacholine 2–64 mg·ml⁻¹ (BDP, Poole, Dorset, UK) in saline 0.9% (Sterac: Ivex Pharmaceuticals Ltd, Larne, N. Ireland) and capsaicin 1.95 to 500 µM (Sigma, Fancy Rd, Poole, Dorset, UK) in saline 0.9% and 10% ethanol (BDP, Poole, Dorset, UK).

Lung function

The forced expiratory volume in one second (FEV₁) was measured using a dry wedge spirometer (Vitalograph) and the best of three values was recorded.

Total respiratory resistance (Rrs) was measured using a forced oscillation technique [11]. Each subject was seated with the palms supporting the cheeks and base of the mouth, and breathing quietly on a mouthpiece attached to the apparatus. Pseudorandom noise was applied at the mouth by a loudspeaker at 2 Hz intervals over the range 4–26 Hz for a 16 s period. Mouth pressure and flow were reported by a pair of Valedyne transducers. In these experiments the Rrs value was always recorded at a frequency of 6 Hz.

Methacholine challenge. This consisted of three preliminary measurements of airway resistance using the forced oscillation technique. Each subject was then given five breaths of saline by nebulization controlled by a dosimeter (PK Morgan Ltd, Gillingham, Kent, UK). Thirty seconds later, Rrs was recorded and the subject was then given the lowest dose of methacholine (1 mg·ml⁻¹). The procedure was repeated at 1 min intervals with doubling concentrations of methacholine until Rrs increased by 40%. The provocative concentration of methacholine that caused a 40% increase in Rrs (PC₄₀) was determined by interpolation.

Capsaicin challenge. The sensitivity of the cough reflex was assessed by capsaicin inhalation. Each subject inhaled single breaths from the nebulizer of random saline or capsaicin in doubling doses from 1.95 to 500 µM and the challenge was terminated when the subject coughed five times or when the top dose was inhaled. The number of coughs produced at each dose was recorded by the observer. The concentration of capsaicin which caused two or more coughs was recorded from the response.

Statistics

The data were analysed by a two way analysis of variance and the least significant difference test. The results were only considered statistically significant if $p < 0.05$.

Protocol 1

Six subjects (5 male, 1 female) made four visits to the laboratory, each visit being one week apart. On the first

visit methacholine challenge was performed to determine the PC₄₀.

The subsequent three visits consisted of an initial FEV₁ measurement followed by a capsaicin cough challenge. After 15 min, each subject was given one of three treatments of five breaths of saline, salbutamol (2.5 mg·ml⁻¹) or methacholine (PC₄₀) in a randomized, double-blind manner. At 1 min and 10 min after completion of the drug administration, FEV₁ and cough sensitivity to capsaicin were measured.

Protocol 2

Six subjects (three male, three female) attended the laboratory on three occasions, each one week apart. Each visit consisted of three baseline readings of Rrs. This was followed by determination of the sensitivity of the cough reflex to capsaicin. Five minutes later, Rrs was again measured before and after the inhalation of the highest concentration of capsaicin which had caused less than two coughs from the initial cough dose response. Fifteen minutes later, the subject was given 1 ml of either saline, salbutamol 2.5 mg·ml⁻¹ or ipratropium bromide 0.25 mg·ml⁻¹ in a randomized, double-blind manner. All drugs were given by nebulization via a nebulizer driven by compressed oxygen at a flow of 8 l·min⁻¹. Following administration of the drug, Rrs was measured before and after the same concentration of capsaicin used previously. A capsaicin cough response was then performed.

Results

Protocol 1

Methacholine significantly ($p < 0.05$) reduced FEV₁, the mean±SE maximum reduction observed being 8.8±3.2% at 1 min. In addition, salbutamol caused a significant ($p < 0.05$) increase in FEV₁ to a mean maximum of 6.2±2.6% at 10 min. No changes in FEV₁ were observed following saline (fig. 1). There were no statistically significant changes following either treatment in the log of the lowest concentrations of capsaicin causing two or more coughs (C₂) (fig. 2).

Protocol 2

The baseline and post-capsaicin Rrs measurements were reduced ($p < 0.05$) by ipratropium and salbutamol compared to saline. Ipratropium reduced the baseline and post capsaicin Rrs by 12±5 and 10±9%, respectively, and salbutamol by 12±9 and 22±8%, respectively (fig. 3). Neither treatment with salbutamol nor ipratropium bromide caused a significant change in the lowest concentration of capsaicin causing two or more coughs (C₂) (fig. 4) compared to saline.

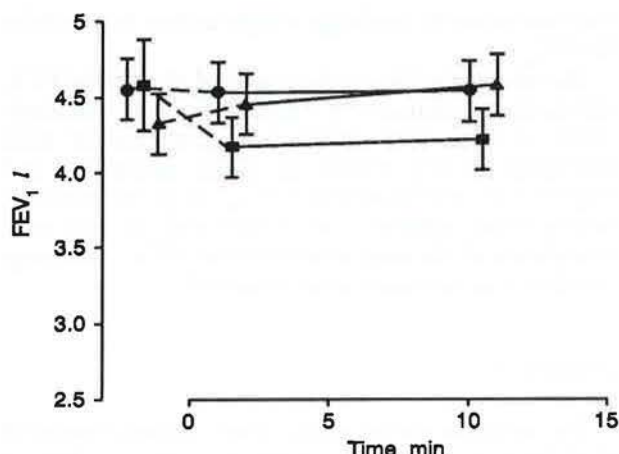


Fig. 1. — Mean \pm SE in FEV_1 before and at various times after inhalation of, saline (●), methacholine (■) and salbutamol (▲), in six normal subjects. FEV_1 : forced expiratory volume in one second.

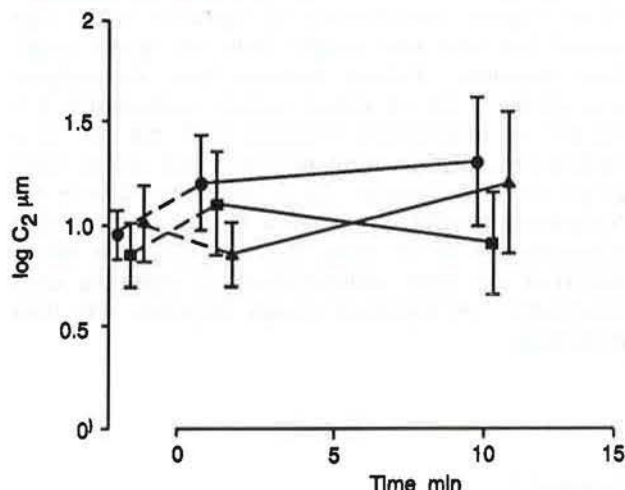


Fig. 2. — The mean \pm SE log concentrations of capsaicin causing two or more coughs (C_2) before and at various times after inhalation of saline (●), methacholine (■) and salbutamol (▲) in six normal subjects.

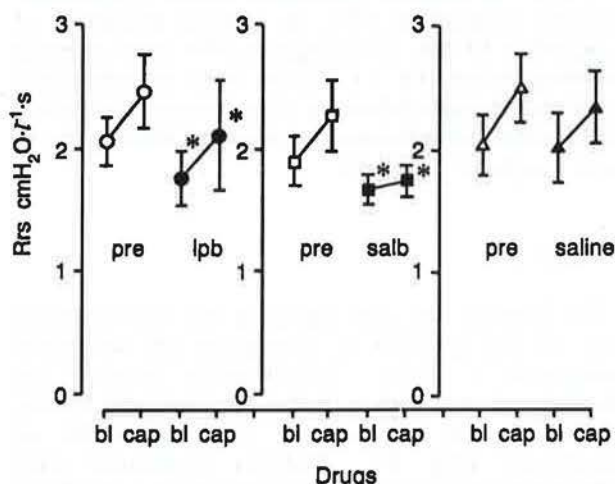


Fig. 3. — The mean \pm SE airways resistance (Rrs) at baseline (bl) and after capsaicin inhalation (cap) both before (○, □, ▲) and after ipratropium (●), salbutamol (■) and saline (▲), in six normal subjects. *: $p < 0.05$.

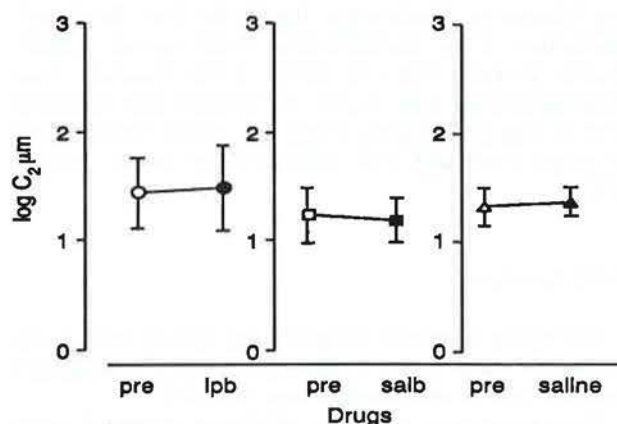


Fig. 4. — The mean \pm SE log concentration of capsaicin causing two or more coughs (C_2) both before (○, □, ▲) and after ipratropium (●), salbutamol (■) and saline (▲), in six subjects.

Discussion

The results indicate that changes in airway tone brought about by salbutamol or ipratropium (bronchodilation) or methacholine (bronchoconstriction) had no effect upon the sensitivity of the cough reflex as measured by capsaicin challenge in non-asthmatics, despite causing significant changes in airway tone. These drugs, however, have been shown to have antitussive actions in asthmatics [6], patients suffering with "allergic" cough [8] and in patients undergoing bronchoscopy [9]. These data suggest that although bronchodilators may be antitussive through alterations in airway tone in asthmatics, any antitussive effect in non-asthmatics is unlikely to be through such effects.

The cough often associated with asthma is thought to be due either to the bronchoconstriction, which produces changes in the airway wall that could trigger airway receptors, or to an increase in airway mediators, which may increase mucus secretion or directly trigger airway sensory nerve receptors leading to cough. The exact mechanisms by which bronchodilators alter the sensitivity of the cough reflex in asthmatics are not known, however it has been postulated that they may act to reduce the input from stretch receptors by causing bronchodilation [2]. In addition, they may alter mucociliary clearance [2]. It is also possible that β_2 -agonists could have direct effects on the sensory nerves via postulated inhibitory β_2 receptors; our results suggest that this may not occur in non-asthmatics. It has also been postulated that β_2 -agonists might exert direct effects upon the airway epithelium to alter the penetration of the tussive agent to the nerves.

Our data are consistent with those of POUNDSFORD *et al.* [6] but contrast with those of LOWRY *et al.* [10] who found that ipratropium resulted in fewer coughs than the placebo in 16 normal subjects. In addition, they found that their cough inhibition correlated with a small but statistically significant degree of bronchodilation as measured by specific airways conductance and FEV_1 in six normal subjects. The likely explanation for these differences is

that LOWRY *et al.* [6] induced cough by inhalation of ultrasonically nebulized solution, which may cause cough by triggering different mechanisms in the airway from capsaicin.

In the normal volunteers we were only able to detect small changes in FEV₁ following salbutamol, which we matched with equally small changes after mechacholine. We therefore used Rrs in the second study and confirmed our previous data that the anticholinergic agent can reduce both the baseline resistance and its increase following inhalation with sub-tussive concentrations of capsaicin [12]. This is consistent with the response being via the cholinergic reflex. The inhibitory effect of salbutamol is consistent with the capsaicin-induced increase in resistance being caused by an increase in airway smooth muscle tone.

Whether bronchodilator therapy is effective as an antitussive treatment in non-asthmatics will require large clinical studies in such patients with cough. If they are truly antitussive then the mechanism is unlikely to be secondary to change in airway tone leading to a reduction in the sensitivity of the cough reflex.

Acknowledgements: The authors would like to thank all the Clinical Pharmacology Bsc students at the Hammersmith Hospital for their kind assistance in this study.

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Effet des modifications du tonus des voies aériennes sur la sensibilité du réflexe de toux chez des volontaires normaux. C.A. Smith, D.L. Adamson, N.B. Choudry, R.W. Fuller.

RÉSUMÉ: La toux est fréquemment le symptôme de présentation de l'asthme bronchique, quoiqu'elle puisse résulter d'une large variété d'autres maladies respiratoires. Le traitement de la toux chronique s'est avéré extrêmement difficile. L'on a suggéré que le traitement par bronchodilatateurs pourrait réduire le symptôme toux. Dans cette étude, l'effet des modifications du tonus des voies aériennes sur la sensibilité du réflexe de toux a été déterminé. Y ont pris part 12 volontaires normaux bien portants. Le nombre de secousses de toux faisant suite à l'inhalation de respirations uniques de concentrations successivement doublées de capsaïcine (de 1.95 à 500 μ M) a été enregistré avant et après administration de doses de salbutamol, de méthacholine et de solution saline, qui modifiaient le VEMS respectivement de 6.2 (\pm 2.6%), de -8.8 (\pm 3.2%) et de -0.18 (\pm 1.38%). Dans une étude ultérieure, la réponse de toux a été enregistrée avant et après des doses de salbutamol et de bromure d'ipratropium qui, tous deux, réduisaient la résistance respiratoire de base et la résistance mesurée après capsaïcine.

Le bromure d'ipratropium, le salbutamol et la méthacholine, quoiqu'ayant des effets significatifs sur le tonus des voies aériennes, n'ont pas modifié la sensibilité de la toux induite par la capsaïcine. Dès lors, si les doses bronchodilatrices ont un effet antitussif chez des patients non asthmatiques, il est improbable que ceci soit dû à un effet sur la sensibilité du réflexe de toux.

Eur Respir Rev, 1991, 4, 1076-1079.