

Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough

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Background: Chronic cough often lasts for more than 1 year and is associated with airway inflammation. The effect of inhaled corticosteroids on symptom severity and inflammatory mediator levels in these patients is unknown.

Objective: We sought to determine whether inhaled corticosteroids reduce cough severity and sputum mediator concentrations in patients with chronic persistent cough.

Methods: We performed a double-blind, randomized, placebo-controlled crossover study with inhaled fluticasone, 500 µg twice daily, and placebo for 14 days in 88 patients with cough for more than 1 year, with normal chest radiography and spirometry results. Outcome measures were a daily cough visual analogue scale and induced sputum concentrations of eosinophilic cationic protein (ECP), myeloperoxidase, leukotriene B₄ (LTB₄), leukotrienes C₄/D₄/E₄ (cysteinyl leukotrienes [Cys-LTs]), prostaglandin E₂ (PGE₂), IL-8, and TNF-α. Sputum cell counts, exhaled nitric oxide levels, and carbon monoxide levels were also measured.

Results: There was a significant improvement in the cough visual analogue scale after inhaled fluticasone compared with placebo (mean difference, 1.0; 95% CI, 0.4-1.5; *P* < .001). LTB₄, Cys-LT, and PGE₂ levels were increased in all causes of cough. Sputum ECP counts, exhaled nitric oxide levels, and carbon monoxide levels decreased significantly after inhaled fluticasone. There was no change in sputum cell counts and other mediator concentrations.

Conclusion: Cough severity and sputum ECP levels are modestly reduced by inhaled corticosteroids in patients with chronic cough persisting for more than 1 year. LTB₄, Cys-LT, PGE₂, IL-8, myeloperoxidase, and TNF-α levels are unaltered by this therapy. This raises the possibility that drugs targeted to reduce the effects of these mediators might be of benefit in chronic persistent cough. (*J Allergy Clin Immunol* 2004;113:1063-70.)

Abbreviations used

CO: Carbon monoxide
COPD: Chronic obstructive pulmonary disease
CVA: Cough variant asthma
Cys-LT: Cysteinyl leukotriene
ECP: Eosinophilic cationic protein
eNO: Exhaled nitric oxide
GERD: Gastroesophageal reflux disease
LTB₄: Leukotriene B₄
MPO: Myeloperoxidase
PGE₂: Prostaglandin E₂
PNDS: Postnasal drip syndrome
VAS: Visual analogue scale

Key words: Chronic persistent cough, inflammation, mediators, inhaled corticosteroids

Chronic cough has a reported prevalence of between 14% and 23% and is associated with considerable morbidity, including sleep loss, impaired performance of daily activities, and considerable social disability.¹⁻³ The diagnosis and management of chronic cough is often unsatisfactory. In nonsmokers with a normal chest radiograph, the most frequent causes identified are postnasal drip syndrome (PNDS), gastroesophageal reflux disease (GERD), and cough variant asthma (CVA).⁴⁻⁶ Several algorithms have been developed for investigating the cause of chronic cough, involving a series of investigations, trials of empiric treatments, or both.⁵⁻⁷ However, despite these attempts, in a significant proportion of patients (12% to 31%), the specific cause of the cough is not established.^{4,7,8} Patients presenting with chronic cough have often had symptoms for many years.^{7,8} In clinical practice inhaled corticosteroids are often used empirically when patients first present with a chronic cough. The value of inhaled corticosteroids in patients with chronic cough that has persisted for more than 1 year is not known.

Airway inflammation is usually a common underlying feature of all the main causes of cough, such as asthma, rhinosinusitis, GERD, or angiotensin-converting enzyme inhibitor-induced cough.⁹⁻¹² Eosinophil numbers, neutrophil numbers, or both in the airways can be increased in patients with chronic cough.^{10,11} The type of airway

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inflammatory cell present in an individual patient presenting with chronic cough might help to predict the response to corticosteroids,¹³ as occurs in patients with asthma¹⁴ and chronic obstructive pulmonary disease (COPD).¹⁵ Inflammatory mediators within the airways are increased in specific groups of patients with cough, such as IL-8 and TNF- α in nonasthmatic patients with chronic dry cough⁹ and cysteinyl leukotrienes (Cys-LTs) and eosinophilic cationic protein (ECP) in patients with eosinophilic bronchitis.¹⁶ Recently, Birring et al¹⁷ demonstrated increased levels of mast cell–derived mediators in all causes of cough, where the main groups of subjects had CVA, eosinophilic bronchitis, and idiopathic cough. The effect of inhaled corticosteroids on proinflammatory mediators in cough is unknown. Exhaled nitric oxide (eNO) and exhaled carbon monoxide (CO) have been used as markers of airway inflammation in various respiratory conditions, especially asthma, and have been shown to be responsive to corticosteroids.^{18,19}

The aims of this study were to determine the efficacy of inhaled corticosteroids in patients with chronic cough that has persisted for more than 1 year and to assess the effect of this treatment on induced sputum inflammatory mediators, cell counts, eNO levels, and carbon monoxide levels.

METHODS

Subjects

Adults with a cough for more than 1 year were recruited from hospital respiratory clinics and from responses to an advertisement in a local newspaper. No subject had evidence of any other lung disease on the basis of history, clinical examination, chest radiography, and spirometry. Exclusion criteria were treatment with inhaled or oral corticosteroids within 3 weeks of inclusion, upper respiratory tract infection within 6 weeks of inclusion, angiotensin-converting enzyme inhibitor treatment, and smoking within the past year. The study was approved by the West Glasgow University Hospitals Ethics Committee, and informed consent was obtained from all subjects.

Study design

In a double-blind, randomized, placebo-controlled crossover study, subjects were treated with inhaled fluticasone (Accuhaler), 500 μ g, or matching placebo twice daily for 14 days, with a 2-week washout phase in between. All other treatment for cough was omitted. A daily cough diary was maintained by the patient to chart the cough severity. A computer-generated randomization sequence was used, with random numbers allocated consecutively. The randomization code was withheld from the investigators until completion of the study. The study medication was packed by the central pharmacy according to the randomization code and was identical in appearance and taste.

On completion of the crossover study, to achieve a final diagnosis for the cause of the cough, all subjects were offered sequential trials of specific therapy depending on the likely clinical diagnoses for their cough. Specific first-line therapy used for GERD was oral omeprazole, 20 mg twice daily, for a month, followed by 20 mg daily for a second month along with advice on lifestyle alterations to reduce acidity, including elevation of the head end of the bed and alterations in diet. Second-line treatment was a combination of metoclopramide and ranitidine for 2 months. For CVA and

eosinophilic bronchitis, an inhaled corticosteroid (budesonide Turbohaler) was prescribed at a dose of 400 μ g twice daily for 2 months along with a short-acting β_2 -agonist, as required, for asthma. For PNDS, first-line therapy was a combination of a local nasal decongestant (pseudoephedrine drops, 2 to 3 drops to each nostril 3 times daily) for a week, along with 2 months of intranasal corticosteroid (mometasone, 50 μ g/d, 2 sprays daily) and an oral non-sedating antihistamine (loratadine, 10 mg daily). Second-line therapy was 3 weeks of an oral decongestant (pseudoephedrine) and a first-generation antihistamine (brompheniramine maleate).

Final diagnosis or diagnoses of the cause of the cough were based on defined pretreatment criteria²⁰ and accepted only when the cough significantly improved or disappeared with specific therapy.⁶

Measurements

The primary outcome measure for improvement in the cough was a cough severity visual analogue scale (VAS; a linear scale with 0 cm indicating no cough and 10 cm indicating worst cough). Patients were asked to enter the number of puffs administered of the study inhalers into their daily diary card (as 1 or 0) morning and night. The number of inhalations left in the Accuhaler device used for fluticasone and placebo were recorded as an indicator of adherence to medication. FEV₁ values before and after inhaled albuterol were measured according to American Thoracic Society guidelines.²¹ Total serum IgE levels and IgE levels to common allergens (house dust mite, grass pollen, and cat dander) were measured by means of enzyme immunoassay (Unicap System; Pharmacia UK Ltd, Milton Keynes, United Kingdom). Total IgE levels of greater than 120 IU/L and specific IgE levels of greater than 0.35 IU/L were considered positive. The total and differential white blood cell counts were measured by using an automated cell counter (SE9500; Sysmex UK Ltd, Milton Keynes, United Kingdom), with our standard laboratory values used as control values. Bronchial challenge testing with methacholine was undertaken by using the technique of Cockcroft et al²² to identify those with hyperreactivity and to aid in the final diagnosis of the cough. Bronchial hyperreactivity was defined as a PC₂₀ FEV₁ value of 8 mg/mL or less. Exhaled NO and CO were measured at all visits with a chemiluminescence analyzer (LR2000; Logan Research Ltd, Rochester, Kent, United Kingdom).²³ Sputum induction with 3% hypertonic saline was performed at all visits by using a modification of the method described by Pin et al²⁴ and Chalmers et al.²⁵ The sputum was processed, and the dispersed cell total and differential counts were obtained according to the technique described by Popov et al.²⁶ The supernatant was frozen at -70°C for subsequent mediator measurements. Normal values for the induced sputum cell counts and exhaled gases were based on reference values obtained from large cohorts of healthy individuals^{23,27} and confirmed to be similar to our laboratory values by measuring them in 50 healthy control subjects before this study. Cutoff values at the upper limits of normality were as follows: total sputum cell count, 8×10^6 ; sputum eosinophils, 2%; sputum neutrophils, 53%; and sputum lymphocytes, 3%. Exhaled NO levels were considered increased at greater than 9 ppb, and exhaled CO levels were considered increased at greater than 4 ppm. Mediators measured by using RIA were ECP and myeloperoxidase (MPO; Pharmacia UK Ltd, Milton Keynes, United Kingdom). The other mediators were measured by their immunoreactivity in sandwich enzyme immunoassay: IL-8 and TNF- α (IDS, Boldon, Tyne and Wear, United Kingdom), prostaglandin E₂ (PGE₂) and leukotriene B₄ (LTB₄; R&D Systems, Abingdon, United Kingdom), and cysteinyl leukotrienes (LTC₄/D₄/E₄; Amersham Pharmacia Biotech, Buckinghamshire, United Kingdom). Typical sensitivities of the assays were as follows: IL-8, 25 pg/mL; TNF- α , 10 pg/mL; PGE₂, 36.2 pg/mL; LTB₄, 19.5 pg/mL; ECP, 2 μ g/mL; MPO, less than 8 μ g/mL; and Cys-LT, 10 pg/mL. The precision of the assays was described by using the within-plate and between-plate coefficients of

variation, which across the concentration ranges of the study were as follows: TNF- α , less than 1.0% and less than 3.1%; IL-8, less than 2.1% and less than 6.2%; Cys-LT, both less than 8.6%; LTB₄, less than 6.9% and less than 16.7%; ECP, less than 11% and less than 9.2%; MPO, less than 8.4% and 12.4%; and PGE₂, less than 5.2% and less than 17.6%, respectively. The cross-reactivity of the prostanoid assays was as follows: Cys-LT assay, 100% for LTC₄, 115% for LTD₄, and 62.7% for LTE₄ (the cross-reactivity with the other main prostanoids was <1.2%); LTB₄ assay, 5.5% for 6-trans-12-epi-LTB₄ and 4.9% for 6-trans-LBT₄ (the cross-reactivity with the other main prostanoids was <0.2%); and PGE₂ assay, 70% for PGE₁ and 16.3% for PGE₃ (the cross-reactivity with the other main prostanoids was <1.0%). Healthy volunteers were recruited from hospital staff to perform induced sputum for control mediator measurements.

Statistical methods

The baseline characteristics of patients with cough were compared with those of either a normal comparator group or cutoff values by using appropriate tests. Correlation among the baseline factors was examined by means of Spearman rank correlation coefficients. The response to inhaled steroids was calculated for each variable in turn by first removing the effect of baseline from the posttreatment and postplacebo periods. The differences of these differences were then calculated by subtracting the placebo effect from the treatment effect. The responses were analyzed by means of 1-sample *t* tests, and the corresponding 95% CIs were calculated. This method was used because many of the underlying variables were not suitable for ANOVA because of nonnormality. The study was adequately powered, as with a sample size of 68, the study would have 90% power to detect a within-subject change of 1 unit on the VAS, assuming an SD of 2.5 and using a 2-tailed test at the 5% significance level. The treatment difference for the cough VAS was modeled by means of regression analyses to see whether any of the baseline factors could predict steroid responsiveness. All analyses were carried out with SAS version 8.02 software.

RESULTS

Baseline subject characteristics and investigations

We screened 120 subjects with cough, 93 of whom met all the inclusion criteria and were randomized; 88 completed all study visits. Of these, 52 were recruited from the community (general practitioner referrals and advertisement in a newspaper), and 36 were referred from hospital clinics. Five subjects dropped out because of inability to attend all study visits.

A final diagnosis for the cough was obtained in 78 (89%) of the 88 patients; 74% had a single diagnosis, 24% had 2 diagnoses, and 2% had 3 diagnoses. The pattern of primary diagnoses was PNDS (*n* = 30), GERD (*n* = 18), CVA (*n* = 13), bronchiectasis (*n* = 9), eosinophilic bronchitis (*n* = 5), habitual cough (*n* = 2), and bronchitis (*n* = 1). In 10 subjects the cough was termed idiopathic. Baseline characteristics of the patients are shown in Table I. Individual data for the smaller diagnostic subgroups are not depicted because the numbers were too small for meaningful analysis.

An adequate sample of sputum for differential cell counts was obtained in 70 (80%) subjects with chronic cough. All were able to perform the eNO and CO tests adequately. The results of the noninvasive tests are

depicted in Table II. The total sputum cell count, sputum neutrophil proportion, and eNO level were increased in subjects with chronic cough compared with cutoff values. The sputum eosinophil proportion correlated significantly with the eNO levels ($r = 0.43$; $P < .001$), and the total cell count correlated with the neutrophil proportion in sputum ($r = 0.48$; $P < .001$). There was no significant correlation between neutrophils in induced sputum and the age of the patient ($r = 0.249$; $P = .225$) or the duration of the cough ($r = -0.013$; $P = .916$). The total and differential blood cell counts were within the normal ranges.

Mediators at baseline were measurable in 61 of 88 patients and 12 of 17 control subjects. The mean age of the control subjects was 41 (SD, 11) years. LTB₄, Cys-LT, and PGE₂ levels were significantly increased in patients with all causes of cough. IL-8, MPO, and TNF- α levels were increased only in patients with bronchiectasis.

Response to inhaled corticosteroids

There was a significant difference in the cough VASs before and after fluticasone compared with before and after placebo (difference of differences, 1.0; 95% CI, 0.4–1.5; $P < .001$; Fig 1). The mean percentage change in VAS was 22.3% (95% CI, –3.5% to 48.2%). There was no carryover effect of active treatment. Compliance was greater than 90% with fluticasone and placebo inhalers. Sputum ECP, eNO, and CO levels showed a significant reduction after inhaled corticosteroids. The mean difference was –2.1 (95% CI, –3.56 to –0.64; $P = .005$) for eNO, –0.34 (95% CI, –0.6 to 0.04; $P = .025$) for CO, and –396 (95% CI, –753 to 39; $P = .031$) for ECP (Fig 2). For all causes of cough, there was no significant change in sputum cell counts, Cys-LT levels, LTB₄ levels, PGE₂ levels, IL-8 levels, TNF- α levels, and MPO levels after treatment (Table III), except for a reduction in sputum eosinophils in patients with CVA and IL-8 levels in patients with bronchiectasis.

Predictors of inhaled corticosteroid responsiveness

Exhaled NO levels ($R^2 = 0.152$; $P < .001$), sputum eosinophils ($R^2 = 0.08$; $P = .019$), sputum ECP levels ($R^2 = 0.064$; $P = .05$), Cys-LT levels ($R^2 = 0.07$; $P = .039$), and total IgE levels ($R^2 = 0.07$; $P = .022$) were significant predictors of corticosteroid responsiveness. The other mediators and cell counts had no predictive value for this response. Factors unrelated to corticosteroid responsiveness were age, sex, duration of cough, baseline cough VAS level, specific IgE positivity, FEV₁ percent predicted, previous smoking history, and whether the patient entered the study through the community or hospital clinics. Only one subject had received a course of oral corticosteroids in the past. Forty-eight subjects had previously received inhaled corticosteroids in varying doses and durations of treatment. There was no significant difference in response to fluticasone in those who had received inhaled corticosteroids in the past compared with those who had not received this treatment earlier ($R^2 = 4\%$; $P = .069$).

TABLE I. Baseline characteristics of patients with chronic cough

	All causes	PNDS	GERD	CVA	Bronchiectasis	Idiopathic cough
No.	88	30	18	13	9	10
Age, y*	59.0 (12.7)	58.8 (12.4)	67.7 (4.4)	48.5 (17.3)	64.0 (9.6)	57.7 (8.7)
Sex, male/female	32/57	12/18	8/10	2/11	3/6	4/6
Duration of cough, y	16.2 (16.1)	18.6 (17.4)	14.9 (15.8)	13.6 (9)	17.8 (19.4)	13.9 (18.6)
Baseline cough VAS, cm	4.1 (2.0)	3.9 (2.3)	3.9 (1.9)	4.7 (2.1)	4.3 (1.7)	4.4 (2.2)
Exsmokers, n	35	13	8	4	4	4
Years quit smoking	19.7 (12.9)	20.7 (13.7)	21.6 (13.9)	7.1 (8.9)	20.3 (6.9)	25.8 (16.4)
Pack-years smoked	14.8 (15.8)	10.0 (13.1)	24.7 (19.9)	14.6 (24.4)	20.3 (8.7)	7.4 (7.0)
Previous inhaled corticosteroids, n (%)	48 (55)	15 (50)	8 (44)	6 (46)	6 (67)	6 (60)
FEV ₁ , L	2.6 (0.8)	2.7 (0.8)	2.4 (0.6)	2.4 (1.0)	2.1 (0.8)	2.9 (0.9)
FEV ₁ , % predicted	94 (16)	96 (12)	94 (15)	86 (24)	88 (12)	101 (13)
Total serum IgE, IU/L	96 (195)	61 (72)	110 (162)	32 (35)	75 (99)	168 (419)
Positive specific IgE level, n (%)	18 (21)	4 (13)	4 (22)	4 (33)	1 (14)	4 (13)

Data are listed as means (SDs) unless stated otherwise.

*ANOVA, $P < .001$ between the subgroups.**TABLE II.** Baseline values of exhaled gases, sputum cell counts, sputum mediators, and blood counts in subjects with chronic cough

	Normal/ cutoff	All causes	PNDS	GERD	CVA	Bronchiectasis	Idiopathic cough
No.		88	30	18	13	9	10
Exhaled NO, ppb	9	10.4* (5.7)	8.9 (3.5)	10.0 (3.8)	12.6 (7.6)	11.2 (3.7)	8.6 (4.3)
CO, ppm	4	3.7 (1.1)	3.6 (1.0)	3.7 (1.4)	3.4 (0.9)	3.5 (1.2)	4.1 (0.9)
Induced sputum							
Total cell count, $\times 10^6$	8	10.4* (9.1)	10.1 (7.0)	6.1 (5.6)	7.9 (4.9)	21.3* (12.1)	14.6 (12.9)
Neutrophils, %	53	62 (22.9)†	60.4 (25)	58.1 (20.6)	68.1* (21.2)	81.2 (13)†	62.7 (26.9)
Eosinophils, %	2	1.0 (2.3)	0.3 (0.4)	0.4 (0.5)	2.4 (4.3)	1.4 (3.3)	0.3 (0.8)
Lymphocytes, %	3	0.2 (0.4)	0.3 (0.6)	0.2 (0.4)	0.2 (0.5)	0.1 (0.2)	0.1 (0.2)
ECP, ng/mL	363 (249)	1082* (891)	1055 (931)	1182* (966)	895 (904)	1479* (812)	661 (305)
MPO, $\mu\text{g/mL}$	5.2 (4.1)	17.8 (24.6)	11.6 (19.0)	16.6 (23.0)	14.7 (15.8)	57 (32.2)†	8.8 (6.0)
PGE ₂ , ng/mL	0.1 (0.2)	16.0 (10.7)†	10.2 (6.5)†	21.0 (14.2)†	11.5 (7.1)†	17.5 (8.0)†	27.9 (10.7)†
LTB ₄ , ng/mL	4.58 (5.4)	28.2 (12.7)†	35.3 (13.7)†	25.3 (14.3)†	25.9 (10.7)†	32.7 (8.4)†	33.3 (6.6)†
Cys-LT, ng/mL	0.3 (0.8)	1.4 (1.0)†	1.3 (0.9)*	1.4 (1.3)*	1.5 (1.2)*	1.2 (0.6)*	1.7 (1.6)*
IL-8, ng/mL	4.8 (2.1)	29.7 (65.4)*	9.0 (6.9)	25.1 (47)	14.6 (23.1)	142 (126)†	12.9 (18.6)
TNF- α , ng/mL	0.02 (0.02)	1.3 (4.1)	0.04 (0.1)	1.0 (2.8)	0.05 (0.1)	6.0 (8.1)*	0.01 (0.0)
Blood cell counts, $\times 10^9/\text{L}$							
Total white cells	4.0-11.0	7.9 (1.7)	8.1 (1.4)	7.7 (1.5)	7.9 (2.3)	8.5 (2.2)	7.5 (1.7)
Neutrophils	2.0-7.5	3.97 (1.3)	3.98 (1.0)	4.2 (1.1)	3.6 (1.2)	4.6 (2.0)	3.8 (1.7)
Eosinophils	0.04-0.4	0.09 (0.1)	0.09 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.07 (0.1)
Lymphocytes	1.5-4.0	3.43 (1.01)	3.7 (0.9)	3.1 (0.9)	3.8 (1.4)	3.3 (1.1)	3.3 (1.1)

Data are depicted as means (SDs) unless stated otherwise.

* $P < .05$.† $P \leq .001$ compared with healthy control values.

DISCUSSION

This is the first randomized, placebo-controlled study to demonstrate an improvement in cough severity after inhaled fluticasone compared with after placebo in patients with chronic cough for more than 1 year. The decrease in cough severity score was accompanied by a decrease in sputum ECP, eNO, and CO levels, but there was no reduction in sputum mediator levels of LTB₄, Cys-LT, PGE₂, IL-8, MPO, and TNF- α .

Although there was a statistically significant decrease in the cough VAS, this corresponded to a mean improvement of 22.3% (95% CI, -3.5% to 48.2%) in the cough. There are several possible explanations for the modest improvement in cough severity score for most subjects in this study.

First, the baseline sputum samples demonstrated a predominant airway neutrophilia rather than eosinophilia. Neutrophilic inflammation of the airways is relatively insensitive to corticosteroid therapy.²⁸ The association

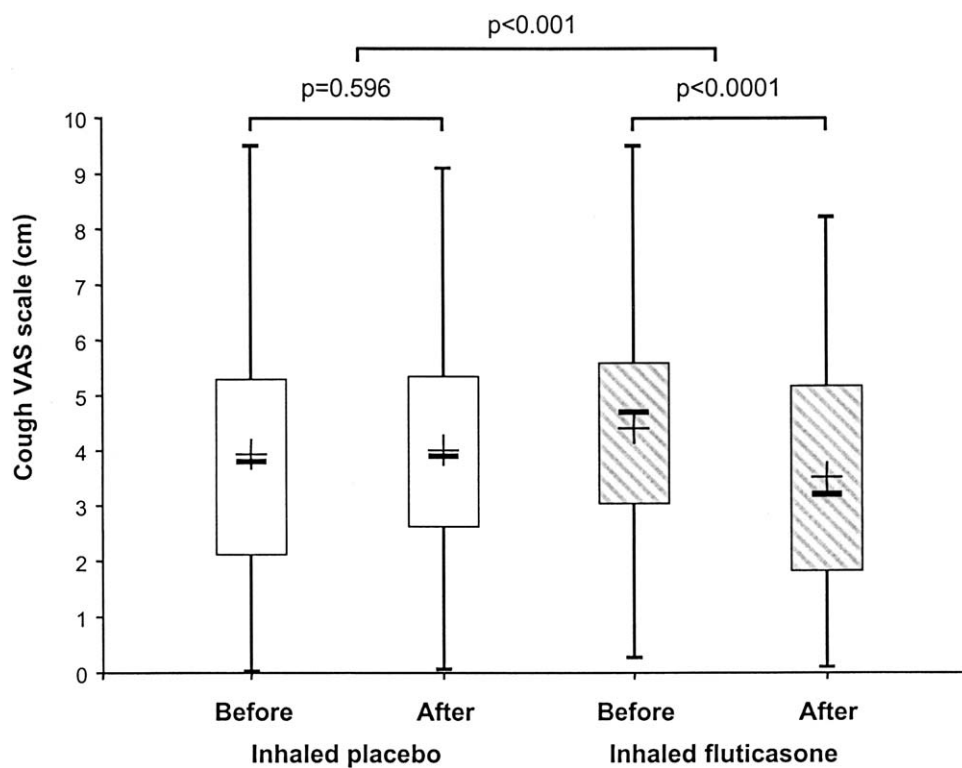


FIG 1. Mean VAS for cough severity measured on a 10-cm scale after inhaled fluticasone compared with placebo. The *boxes* represent the interquartile range, with the *extended lines* representing the maximum and minimum values. The mean (+) and the median (–) values of the VAS are depicted in the figure.

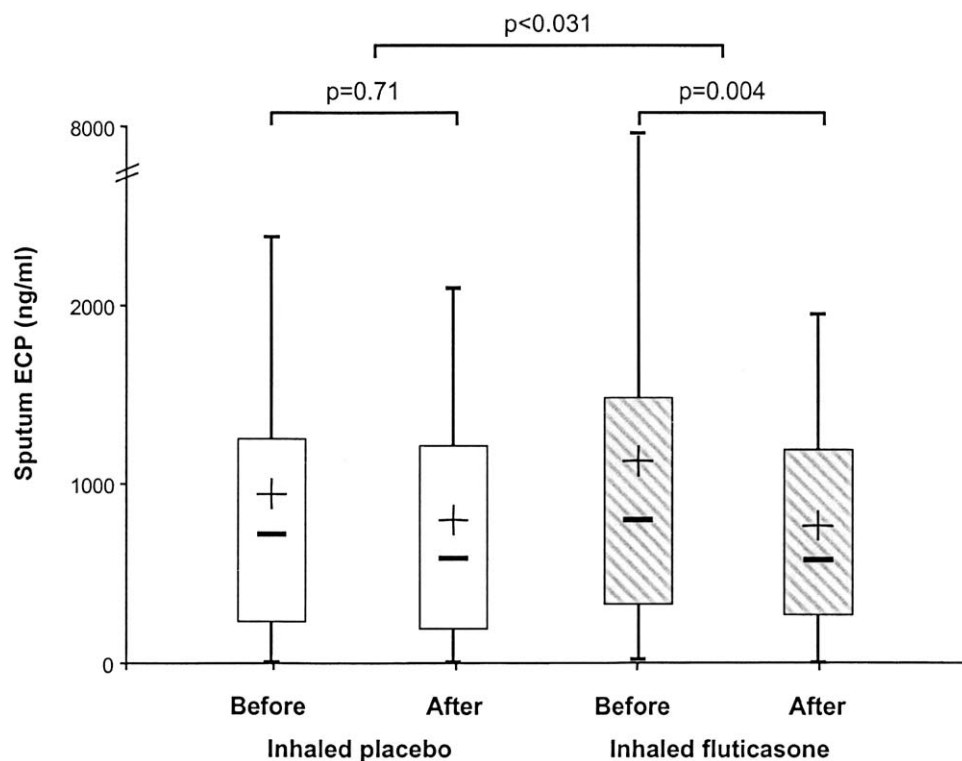


FIG 2. Induced sputum ECP levels after inhaled fluticasone compared with placebo. The *boxes* represent the interquartile range, with the *extended lines* representing the maximum and minimum values. The mean (+) and the median (–) values of ECP are depicted in the figure.

TABLE III. Change in cough VAS, noninvasive tests of inflammation, and sputum cells and mediators after inhaled corticosteroids compared with after placebo

	All causes	PNDS	GERD	CVA	Bronchiectasis	Idiopathic cough
No.	88	30	18	13	9	10
Δ Cough VAS, cm	1.0† (0.4 to 1.5)	0.9* (−0.0 to 1.8)	1.2 (0.0 to 2.3)	1.4* (−0.0 to 2.7)	0.7 (−0.9 to 2.4)	0.5 (−1.0 to 2.1)
Δ eNO, ppb	−2.1* (−3.6 to −0.6)	0.0 (−2.0 to 2.0)	−3.1* (−5.8 to −0.5)	−3.3* (−6.5 to −0.2)	−0.9 (−4.5 to 2.7)	−1.4 (−4.8 to 2.1)
Δ Exhaled CO, ppm	−0.3* (−0.6 to −0.0)	−0.1 (−0.6 to 0.4)	−0.3 (−1.0 to 0.4)	−0.3 (−1.1 to 0.5)	−0.7 (−1.6 to 0.2)	−0.1 (−1.0 to 0.7)
Induced sputum						
Δ Total cells, × 10 ⁶	−1.0 (−7.4 to 7.7)	−1.5 (−11.9 to 9.0)	−4.6 (−12.3 to 3.1)	3.4 (−7.0 to 13.9)	5.1 (−6.3 to 16.4)	−2.8 (−15.2 to 9.6)
Δ Neutrophils, %	1.1 (−7.5 to 9.7)	−1.2 (−18.6 to 16.2)	−13.8 (−29.8 to 2.1)	0.9 (−19.9 to 21.7)	0.6 (−20.2 to 21.4)	5.3 (−14.2 to 24.8)
Δ Eosinophils, %	−0.7 (−1.8 to 0.3)	−0.0 (−2.0 to 2.1)	−0.1 (−2.0 to 1.8)	−4.6† (−7.1 to −2.1)	1.5 (−1.0 to 3.9)	0.1 (−2.2 to 2.4)
Δ Lymphocytes, %	−0.1 (−0.2 to 0.1)	0.0 (−0.3 to 0.4)	0.1 (−0.3 to 0.4)	−0.3 (−0.7 to 0.1)	−0.1 (−0.5 to 0.3)	−0.1 (−0.5 to 0.3)
Δ ECP, ng/mL	−396* (−753 to 39)	−506 (−1160 to 148)	62 (−554 to 679)	80 (−1227 to 1387)	−142 (−969 to 684)	−248 (−1316 to 820)
Δ MPO, μg/mL	10.7 (−29.5 to 51.1)	−34.0 (−113.3 to 45.3)	−17.7 (−97.1 to 61.6)	70.0 (−98.3 to 238.3)	133.5* (27.0 to 239.9)	9.1 (−128.3 to 146.5)
Δ PGE ₂ , ng/mL	−1.9 (−9.0 to 5.3)	4.9 (−10.3 to 20.1)	−4.7 (−20.9 to 11.4)	12.1 (−10.7 to 34.9)	−11.6 (−30.2 to 7.1)	−9.8 (−32.7 to 13.0)
Δ LTB ₄ , ng/mL	2.3 (−13.2 to 17.8)	5.1 (−32.8 to 43.1)	1.7 (−36.3 to 39.7)	25.6 (−18.3 to 69.4)	−15.7 (−49.7 to 18.2)	−9.2 (−53.1 to 34.6)
Δ Cys-LT, ng/mL	−0.4 (−1.2 to 0.4)	0.1 (−1.5 to 1.7)	−0.2 (−1.8 to 1.5)	−0.6 (−2.9 to 1.6)	−1.4 (−3.3 to 0.4)	0.3 (−2.3 to 2.9)
Δ IL-8, ng/mL	−21.5 (−48.3 to 5.2)	−3.5 (−61.9 to 55.0)	−27.0 (−88.9 to 35.0)	1.5 (−86.1 to 89.1)	−74.7* (−146.3 to −3.1)	−20.9 (−122.1 to 80.3)
Δ TNF-α, ng/mL	0.3 (−4.9 to 5.4)	−3.9 (−17.7 to 9.9)	3.6 (−8.4 to 15.6)	0.0 (−13.8 to 13.8)	0.4 (−10.3 to 11.1)	ND (0 to 0)

Data are depicted as mean differences (95% CI).

Δ, Change in value after inhaled fluticasone compared with after placebo; ND, not detectable.

**P* < .05.†*P* ≤ .001.

between airway eosinophilia and corticosteroid responsiveness has been demonstrated in patients with chronic cough.²⁹ Corticosteroids are very effective at reducing eosinophils in the airways,³⁰ and sputum eosinophilia has been shown to predict a clinical benefit from corticosteroids in asthma and COPD.^{14,31} A study by Pizzichini et al,³² which included subjects with chronic cough in whom asthma, PNDS, and GERD were excluded as possible causes, found none of the subjects had increased sputum eosinophil counts, and there was no response to a trial of inhaled corticosteroids.

Second, we included subjects with a cough duration of greater than 1 year because it represented the most problematic patients with cough in the community. It is possible that cough of a shorter duration might be more corticosteroid responsive.

Third, it is possible that a longer duration of treatment with inhaled corticosteroids could increase the number of responders. In some studies response to inhaled corticosteroids was seen within 2 weeks,^{13,33} and in others, extending treatment to 4 weeks did not improve the

response rate.^{32,34,35} We believe that 2 weeks of high-dose inhaled corticosteroids should have identified a change in cough severity in the vast majority of subjects who are likely to respond to this treatment.

In this study patients had a history of cough for a mean duration of 16.2 years. Most of the subjects had previously received some form of treatment for chronic cough, details of which they were unable to accurately recall. Because we had no record of response to previous therapy, we included all subjects provided they had not been taking inhaled or oral corticosteroids in the previous 3 weeks. There was no significant difference in response to inhaled fluticasone in those who had received a prior course of inhaled corticosteroids compared with those who had never received this treatment. Hence there was no bias toward selecting subjects who were unlikely to respond to inhaled corticosteroids.

We have shown that airway inflammation is present in patients with cough persistent for more than a year regardless of cause, with an increase in induced sputum neutrophils, airway mediators, and eNO levels. Jatakanon

et al⁹ selected patients with nonasthmatic chronic cough and demonstrated a marked neutrophilia in induced sputum. We have shown that this neutrophilia extends across the spectrum of causes of chronic persistent cough, with the highest levels found in patients with bronchiectasis. Although the reasons for this are not known, speculation has included the effect of mediators, such as TNF- α and IL-8, promoting the neutrophil influx, which might be perpetuated by the act of coughing itself. In contrast, Birring et al¹⁷ noted increased sputum eosinophils in a subgroup of patients and normal neutrophil counts. They included subjects with a cough duration of greater than 3 weeks, as opposed to 1 year in our study, and the mean duration of cough was about 3 years compared with 16 years in our study. Hence although the trend of inflammation in induced sputum in persistent cough appears to be neutrophilic, further work on this subject is required.

Because the inflammatory pattern can vary in cough, we chose to measure 7 mediators to assess activation of different inflammatory cells. ECP and MPO are indirect markers of eosinophil and neutrophil activity, respectively. IL-8 is a neutrophil chemoattractant and activator and can also induce the release of histamine and Cys-LTs from human blood basophils.^{36,37} TNF- α is a pro-inflammatory cytokine produced by macrophages and mast cells and might be an important mediator in initiating chronic inflammation by activating the secretion of cytokines from a variety of cells in the airways.³⁸ Leukotrienes are produced by mast cells, eosinophils, and neutrophils and are implicated in the inflammation of asthma and COPD. PGE₂ can increase cough sensitivity.³⁹

In our study we noted increased levels of Cys-LTs, LTB₄, ECP, PGE₂, and IL-8. After 2 weeks of inhaled fluticasone, 1000 μ g daily, exhaled NO, CO, and ECP were significantly suppressed compared with placebo, with no change in sputum cell counts and other mediators. Responsiveness of ECP to corticosteroids has been noted in asthma,^{40,41} as well as in COPD.⁴² Leukotriene and IL-8 levels were increased at baseline but did not respond to corticosteroids, which is similar to findings in patients with asthma and COPD.^{42,43} Choudry et al³⁹ demonstrated that the cough reflex is increased in the presence of PGE₂ in the airways, and Birring et al¹⁷ found increased PGE₂ levels in the induced sputum of subjects with cough. We have demonstrated that induced sputum levels of PGE₂, Cys-LT, and LTB₄ are significantly high in patients with all causes of chronic persistent cough and persist after inhaled corticosteroid treatment.

Exhaled NO has been shown to be increased in inflammatory lung conditions, such as asthma, and has been used as a predictor of oral corticosteroid responsiveness.⁴⁴ In this study eNO levels were mildly increased in patients with chronic cough. We found a strong correlation between eNO and sputum eosinophils, which is similar to that seen in patients with asthma.⁴⁵ Regression analysis revealed eNO to be the most useful predictor of corticosteroid responsiveness. Exhaled CO has been

shown to be increased in asthmatic patients¹⁹ and patients with cystic fibrosis.⁴⁶ The level of CO was not increased at baseline in patients with chronic persistent cough but did reduce significantly after inhaled corticosteroid treatment.

In conclusion, chronic cough persistent for more than 1 year partially responds to inhaled corticosteroids, regardless of the cause of the cough. The inflammation is complex, with sputum neutrophilia and increased PGE₂, LTB₄, and Cys-LT levels in patients with all causes of cough. ECP was the only mediator to decrease after corticosteroid treatment. This result raises the possibility that alternative drugs targeted to reduce the production-action of these proinflammatory mediators might be of therapeutic benefit in chronic cough.

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