

Chronic non-asthmatic cough is not affected by inhaled beclomethasone dipropionate

A controlled double blind clinical trial

T. EVALD, E. P. MUNCH & A. KOK-JENSEN

The Chest Clinic and Medical Department P, Bispebjerg Hospital, Copenhagen, Denmark

Thirty-one patients with a dry cough for at least 1 h duration in more than half of the last 30 days and with no recent respiratory infection participated in a clinical trial to evaluate the effect of inhaled beclomethasone dipropionate (BDP). Lung function was normal and reversibility was excluded by spirometry before and after bronchodilator and by no diurnal variation in home peak flow monitoring. Only one had significant eosinophilia and only three were mildly hyperreactive by bronchial provocation with histamine. After a 1-week run-in period the patients were randomly allocated to receive either BDP 4 puffs of 50 µg b.i.d., or placebo. After 2 weeks the patients were crossed over and received the alternative treatment for another 2-week period. The degree of cough, disturbance of night sleep and peak expiratory flow morning and evening were recorded daily in a diary. Spirometry was performed at each control visit. A significant period effect from run-in to period 1 and/or from period 1 to period 2 was demonstrated for cough and disturbance at night but not for peak flow or spirometry. However, no significant treatment effect was found for any of the measured variables.

Key words: asthma; cough; inhaled steroid; placebo controlled study.

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Chronic cough is a symptom of many different diseases. During recent years it has been shown that some patients with chronic cough have bronchial hyperreactivity and eosinophilia (5, 6, 11). These patients benefited from treatment with β_2 -agonist in a controlled trial (6). Many patients with chronic cough might have an "asthmatic" inflammatory reaction in the respiratory tract. Thus, treatment with inhaled steroid could be of value, since steroids have an unspecific antiinflammatory effect and diminish bronchial hyperreactivity (1, 18).

We studied treatment with inhaled corticosteroid for patients with chronic cough. The aim was to study the therapeutic effect and to characterize the patients who had benefited.

MATERIAL AND METHODS

Patients

Trial candidates were patients referred to the chest clinic at Bispebjerg Hospital with a daily dry cough for at least 1 h duration in more than half of the last 30 days. Further criteria were: 1) no sign of obstructive lung function (ratio between the forced expiratory volume in the 1st s (FEV₁) and the forced vital capacity (FVC) should be more than 70%), 2) no significant reversibility after bronchodilating treatment (the increase in FEV₁ 30 min after 3 inhalations of salbutamol (300 µg) and 3 inhalations of ipratropium (60 µg) should not exceed 20% or 500 ml), 3) no diurnal variation above 20% in morning and evening peak flow (PEF) during

home monitoring for 1 week calculated at visit 2 after the run-in period, 4) no treatment with anti-asthmatic drugs, 5) normal chest X-ray, 6) no recent respiratory infection, 7) no other chest disease, and 8) no pregnancy.

At the first visit anamnesis was taken with special emphasis on the following: smoking, respiratory symptoms, duration of cough before attending the clinic, disposition for asthma and atopic diseases.

Design

The trial was a double blind cross-over study. After a run-in period of 1 week the patients were randomly allocated to receive either beclomethasone dipropionate (BDP) 4 puffs of 50 µg b.i.d. or placebo 4 puffs b.i.d. After 2 weeks the patients were crossed over and received the alternative treatment for another 2-week period.

The patients were instructed according to Newman (17) to inhale with the canister being actuated during a slow, deep inhalation followed by a breath-holding pause for 10 s, and their inhalation technique was checked at each visit.

Table 1

Characteristics of the 31 patients who completed period 1 of the study

Number of patients	31
male/female	7/24
age - median (range)	35 years (15-64)
Duration of cough	
> 15 days	3
> 1 month	6
> 3 months	10
> 1 year	9
> 5 years	3
Cough attacks/day	
1-5	10
6-10	10
> 10	11
FVC % pred. (10, 15)	84
FEV ₁ % pred. (2, 15)	85
Smoker/nonsmoker	22/9
Eosinophilocytes - median (range)	$0.13 \times 10^9/l$ (0.04-1.15)
IgE - median (range)	38 (10-430)
Prick test positive (not tested)	6 (29)
PC ₂₀ < 2 mg/ml (not tested)	3 (21)

Before the run-in period, spirometry (FEV₁, FVC and PEF) and reversibility test after bronchodilator were performed. Measurements were made on a Vitalograph dry-wedge spirometer and on a Wright Peak Flow Meter. FEV₁ was recorded using the best of three acceptable manoeuvres, and FVC values were taken from the same measurement. Blood was drawn for determination of total IgE and eosinophilocytes, and skin prick tests with nine common allergens (pollen, animal dander, housedust mite, molds) were performed according to the nordic guidelines (19). After the trial the concentration of inhaled histamine precipitating a fall in FEV₁ of 20% was determined. The patient-operated Pari Inhaler Boy was used for the bronchial provocation test. The output was measured to 0.25 ml/min and the procedure described by Hargreave (12) applied. Unbuffered histamine dichloride in the concentration range 0.03-8.00 mg/ml was used. A provocation concentration that caused a 20% fall in FEV₁ (PC₂₀) of 2 mg/ml discriminated hyper-reactive from normal persons (16).

Effect monitoring

Spirometry was performed at each visit to the clinic and the patient's subjective effect of the treatment recorded (1: much worse, 2: worse, 3: the same, 4: better and 5: much better). PEF measured with a Mini-Wright peak flow meter morning and evening (best of 3 efforts) was recorded daily in a diary. The degree of cough was also recorded: 1) number of days with cough, 2) number of cough attacks a day (1, 2, 3, 4 or 5 attacks = score, while more than 5 attacks scored 10), 3) duration of cough attacks estimated for the whole day (1-29 min = 1, 30-59 min = 2, more than 1 h = 3), 4) number of awakenings each night because of cough, 5) duration of insomnia at night because of cough (< 1 h = 1, 1-3 h = 2 and > 3 h = 3).

Statistics

Most of the data were not normally distributed and were therefore analysed by non-parametric

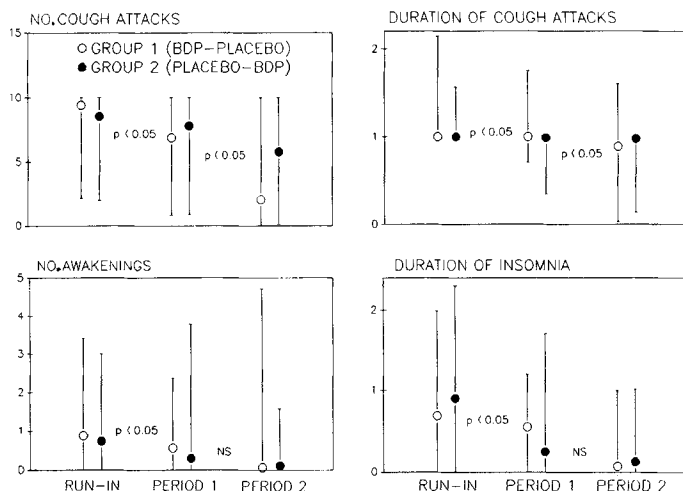


Fig. 1. Paired group median values and ranges during run-in (1 week), period 1 (2 weeks) and period 2 (2 weeks) for number of cough attacks each day, total duration of cough each day, number of awakenings because of cough each night and duration of night insomnia because of cough.

methods (Mann Whitney U test, Wilcoxon matched-pairs signed-rank test). The median values were calculated for each 2-week period for each patient and each variable. Significance tests were performed on group median values for each period and variable. The tests for period effect were done on paired group median values (13).

RESULTS

Forty patients were included in the trial. Seven were later excluded during the run-in period: four because their cough disappeared spontaneously and three because they failed to attend the control visit. Two patients were excluded during period 1: one because his cough disappeared and he did not want to continue the trial and one did not attend the control visit.

Thirty-one patients completed period 1 and their descriptive data are shown in Table 1. Of these, one patient did not record symptoms during run-in, one only recorded some of the variables during period 2, and four patients did not complete period 2: two because the cough disappeared (1 on placebo, 1 on BDP) and two did not come for further control.

There was a very low incidence of blood eosinophilia (4 of 29 patients had $> 0.45 \times 10^{-9}/l$), of prick test positive patients (6 of 29 patients), of increased IgE (3 of 29 patients), and of patients with hyperreactive airways (3 of 21 patients).

The paired median values during run-in, period 1 and period 2 for morning PEF, evening PEF, number of days with cough/monitored days, number of cough attacks per day, duration of cough attacks, number of nights awake because of cough, and duration of insomnia at night because of cough, are shown in Fig. 1. Regardless of treatment a significant period effect from run-in to period 1 and/or from period 1 to period 2 was demonstrated for these variables, while morning/evening PEF and number of cough attacks were unaffected. Testing for treatment effect is therefore restricted to data from period 1. No significant difference during run-in was found between the two groups, nor between BDP and placebo during period 1 in any of the seven variables. Supplementary analysis of data from the final week in each period showed no significant treatment effects either.

Further, during the control visits there was no significant change in subjective effect, PEF or FEV_1 (Table 4).

DISCUSSION

Cough can be an expression for an allergic condition or a dominating symptom in asthma as Colmes & Rackemann wrote nearly 60 years ago (4). However, not until Corrao in 1979 documented that cough can be the sole presenting manifestation of bronchial asthma (5), it was generally accepted, that mono-symptomatic cough can be an asthmatic equivalent.

This type of chronic cough has been successfully treated with β_2 -agonist (6) and theophylline (11). It is believed that a high degree of hyperreactivity and a long duration of cough is a predictor for subsequent development of "real" asthma (3), but a recent retrospective study in children with chronic cough indicates that these variables are of no predictive value (9).

For some years it has been a routine in our chest clinic to treat presumed asthmatic cough with inhaled steroid. Apparently the treatment is effective and the effect is correlated to the presence of eosinophilia in the blood (not published).

When we planned this study, our intention was to exclude patients with manifest asthma, but we expected to include patients with cough and "hidden" asthma. The very low incidence of positive nonspecific bronchial provocation, and of eosinophilia, and the stable lung function that was not influenced by BDP treatment, clearly shows that we were not successful in selecting the intended type of patients.

It might be preferable to perform bronchial provocations before BDP treatment, but the effect of a short-term BDP treatment on bronchial hyperreactivity is small (18) and can not convert a hyperreactive group of patients into a non-hyperreactive group.

The significant period effect on cough symptoms in our study indicates that in some patients their cough diminished spontaneously, and therefore the etiology could have been infectious. We made no immunologic investigations or sputum cultures in the present study to investigate this. Temporary hyperreactivity has been demonstrated in patients recently infected in the airways (7) but was not found in another

study (14). It has recently been shown, however, that symptoms from acute infections of the respiratory tract, are not alleviated by inhaled steroid (8). Thus, our study confirms these findings.

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Address:
Erik Munch
 Department Y
 Copenhagen County Hospital in Gentofte
 DK-2800 Hellerup
 Denmark