

Failure of colchicine to reduce inhaled triamcinolone dose in patients with asthma

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In recent years there has been significant interest in alternative antiinflammatory agents in the treatment of asthma. However, many of these medications are limited by modest efficacy, toxicity, or cost. Colchicine is an inexpensive and safe medication, which has unique antiinflammatory properties. Although traditionally used to treat gout, it has also been used in various inflammatory disorders such as familial Mediterranean fever,¹ Behcet's syndrome, urticarial vasculitis,² and interstitial lung disease.³ Prior studies have suggested a potential role for colchicine in the treatment of asthma.⁴⁻⁷

METHODS

Patient selection

Twenty patients were recruited from the outpatient clinic of the National Jewish Center for Immunology and Respiratory Medicine. Patients had never smoked and had to satisfy the definition of asthma as stated by the American Thoracic Society.⁸ Patients received maintenance treatment with a minimum of 1600 μ g per day of inhaled steroids for at least 3 months before entering the study. The study was approved by the National Jewish Center Institutional Review Board, and written informed consent was obtained from all subjects.

Experimental protocol

Period 1: Run-in period. Subjects were instructed to keep a twice-daily diary of asthma symptoms, medication use, and peak flows. Patients receiving inhaled steroids other than triamcinolone were changed to triamcinolone with a ratio of 4 puffs of Aerobid to 5 puffs of Azmacort. A steroid reduction tapering protocol was initiated, with oral steroids being tapered by 2.5 to 5 mg every 2 weeks until one of following conditions was met: a decrease in early morning peak flow by more than 20%, an increase in symptom scores, or development of nocturnal awakenings caused by asthma. After the oral steroid dose had been reduced to zero or the lowest dose that maintained peak flows and symptoms, the dose of inhaled triamcinolone was tapered. The dose was decreased by 2 to 4 puffs every 3 weeks. When symptoms or peak flow measurements decreased accord-

ing to the above criteria, the patients increased to the immediately prior dose, and they were entered into the baseline period.

Period 2: Baseline period. For 2 weeks, the subjects received their determined minimum dosages of inhaled corticosteroid. During this period, baseline values were established for peak expiratory flows, symptoms, pulmonary function, total IgE, and β -agonist use. Baseline studies included complete blood and platelet count, hepatic transaminases, peripheral blood eosinophil count, and IgE levels.

Period 3: Colchicine initiation and steroid tapering protocol. If the subject's minimum dose of triamcinolone was ± 1600 μ g/day of canister output, then he or she continued the protocol. The subjects were randomized to receive either colchicine, 0.6 mg twice daily, or an identically appearing placebo. The triamcinolone tapering protocol was reinitiated with the described schedule for 4 months, or until attempts to taper the triamcinolone twice resulted in evidence of asthma deterioration. The subjects were seen monthly during the tapering protocol, with monitoring of pill counts, diaries, hepatic transaminases, and complete blood counts. At the end of the trial, the current inhaled corticosteroid dose, inhaled β -agonist use, and symptom scores were recorded; spirometry was performed; and the baseline laboratory studies were repeated.

Statistical analysis

Results were analyzed by using proprietary statistical packages: either SPSS (SPSS Inc., Chicago Ill.) or JMP (SAS, Cary, N.C.). Symptom scores were averaged over the last 2 weeks of the treatment period for comparison with baseline scores. Comparisons between treatment groups were made with a two-sample *t* test. The changes in blood chemistries, pulmonary function, and symptom scores were compared from the end of the study to the baseline period by using a two-sample *t* test, as well as a Wilcoxon rank-sum test.

RESULTS

Seven patients were tapered to triamcinolone use of less than 1600 μ g/day and discontinued from the study. The remaining 13 were randomized to colchicine (six subjects) or placebo (seven subjects). The demographic characteristics of the two groups are shown in Table I. One subject receiving colchicine had diarrhea and abdominal discomfort and was discontinued from the study.

The major end point, reduction in triamcinolone dosage, was not significantly different between colchicine or placebo. The average reduction was 400 μ g/day (95% confidence interval, 117 to 683 μ g) in the colchicine group and 443 μ g/day (95% confidence interval, 70 to 879 μ g) in the placebo group. Four of the five subjects

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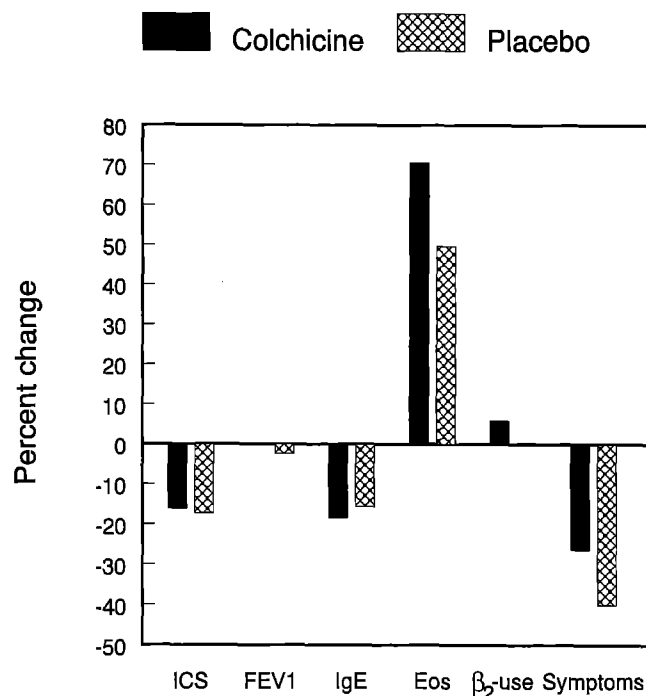


FIG. 1. The percentage change in inhaled triamcinolone dose (*ICS*) and clinical parameters, comparing the end of the study with the baseline period. Shown are FEV₁, serum IgE levels, peripheral eosinophil count (*EOS*), inhaled β_2 -agonist use, and symptom scores averaged over 2 weeks.

TABLE I. Patient characteristics at baseline

	Colchicine group (n = 6)	Placebo group (n = 7)
Age (yr)	51.2 $\pm$ 15.5	58.1 $\pm$ 13.4
Sex (M/F)	3/3	3/4
Duration of asthma (yr)	33.8 $\pm$ 18.3	19.9 $\pm$ 19.5
FEV ₁ (L)	2.41 $\pm$.9	2.15 $\pm$ 1.0
Oral steroid use (no. of subjects)	1	3
Baseline IgE (IU/ml)	109 $\pm$ 90	96 $\pm$ 146
Baseline total eosinophils (10 ⁶ /L)	165.2 $\pm$ 126	120.6 $\pm$ 97
Baseline symptom scores (/day)	1.9 $\pm$ 1.7	5.2 $\pm$ 3.0
Baseline triamcinolone dose (μ g/day)	2480 $\pm$ 715	2571 $\pm$ 420
Baseline β -agonist use (puffs/day)	6.3 $\pm$ 3.5	6.8 $\pm$ 1.8

Results are expressed as means $\pm$ SD.

Symptom scores were averaged over 2 weeks and are expressed as average score per day.

receiving colchicine reduced their triamcinolone dose as compared with five of seven control subjects. There was also no significant difference between groups in change between baseline and the end of the study in FEV₁, symptom scores, β_2 -agonist use, total IgE level, or serum eosinophils (Fig. 1).

DISCUSSION

Colchicine, in this double-blind, placebo-controlled study, failed to allow a reduction in inhaled steroid dosage greater than placebo treatment. There was also

no difference in the effect of the colchicine and placebo on pulmonary function, asthma symptoms, β -agonist use, or measures of inflammation including total peripheral eosinophils and IgE levels. This was a small study, and there was a large placebo effect. Therefore it is possible that a type II error did occur, but considering the absence of any trends in the data favoring active treatment, it is unlikely that colchicine has a role as a steroid-sparing agent.

There are a number of possible mechanisms of action of colchicine that could apply to asthma. These include

a decrease in leukotriene production from peripheral mononuclear cells,³ an increase in cyclic adenosine monophosphate production,⁹ and a correction of concanavalin A-induced suppressor cell function.⁴ Colchicine has been found to inhibit both the early and late airway responses to antigen. Kelly et al.⁵ found a 40% attenuation of the decrement in FEV₁ during a late-phase response to antigen. They proposed that this effect may, at least in part, be due to a decrease in lipoxygenase products.

However, colchicine has had mixed results in clinical trials of patients with asthma. Adalioglu et al.⁶ performed a double-blind, crossover study in 30 children with moderately severe asthma. They found no effect on symptom scores, use of β -agonist inhalers, or pulmonary function. In 1990, Schwarz and Kivity⁷ found that administration of colchicine in 10 patients with mild asthma did reduce symptom scores and β -agonist use, but without any change in pulmonary function.

In conclusion, this study would not support the use of colchicine as a steroid-sparing agent.

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