A CLINICAL STUDY OF COLCHICINE IN CHILDHOOD ASTHMA

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SUMMARY : A double-blind, randomized, crossover study was done to determine the efficacy of colchicine in 30 atopic children with moderately severe asthma. A constant dose of sustained-release theophylline and salbutamol as needed, was administered by inhalation, to all patients. Compared to placebo, colchicine, 0.05 mg twice daily, significantly reduced morning tightness from 0.50 ± 0.38 to 0.32 ±0.29 ($p<0.05$) and nocturnal asthma score from 0.44 ± 0.34 to 0.23 ± 0.25 ($p<0.01$) but there was no significant difference between colchicine and placebo for cough, daytime asthma and daily combined symptom scores for each patient. Colchicine did not significantly decrease beta-2 agonist inhaler use when compared with placebo. Similarly, there was no statistically significant difference between placebo and colchicine therapy as far as pulmonary function tests and peak flow reversibility were concerned.

Thus, colchicine administered for 4 weeks duration demonstrated insufficient antiasthma activity.

Key Words : Asthma, Colchicine.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways. There have recently been important advances in understanding the components of this inflammatory reaction which have implications for future approaches to therapy (2).

Colchicine is an anti-inflammatory and immunomodulating agent which has been used for years with few side effects to treat various inflammatory disorders (9, 10). It has recently been shown to be effective in the treatment of mild bronchial asthma (16).

The purpose of this study was to determine the efficiency of colchicine in moderately severe asthma. To assess this, a double blind, randomized, crossover study was designed in chronic moderately severe perennial childhood asthma.

MATERIALS AND METHODS

Subjects

Thirty children, 7 girls and 23 boys managed in our outpatient asthma clinic were recruited for the study. Their ages ranged from 7 to 12 (mean 8.9) years. The duration of their asthma was from 4 to 11 (mean 7.1) years. All patients had positive skin test responses to two or more common allergens and they suffered from moderately severe perennial asthma. All the children were taking continuous slow release oral theophylline and inhaled anti-inflammatory therapy (21 of the 30 patients were receiving cromolyn sodium via MDI, 9 were receiving

inhaled steroid medication). In addition, they were using inhaled beta-2 agonist as needed. At the onset, the forced expiratory volume of one second (FEV1) was at least 65 % of the predicted value. Subjects were required to demonstrate an increase in FEV1 of more than 15 % after two inhalations of salbutamol after discontinuing bronchodilatator medications. Subjects were maintained on their individual medical regimens for at least 2 weeks prior to entry into our study. Afterwards, inhaled anti-inflammatory therapy was stopped and oral theophylline was continued at the same dosage. There were no patients taking oral glucocorticosteroids or medications interacting with theophylline.

Protocols

We conducted a double - blind, crossover and placebo controlled study. All patients were subjects receiving sustained release theophylline (Theo-Dur, 100, 200, 300 mg tablets, Azim Pharmaceuticals Inc, İstanbul, Turkey). The mean serum theophylline steady-state level was 11.82 ug/ml. Inhalations of salbutamol (Ventolin, Glaxo Inc, İstanbul, Turkey) were taken, as needed, and recorded in a daily diary. Tablets of colchicine (0.5 mg) or placebo were each taken orally, b.i.d. for 4 weeks during either the third to sixth weeks or during the ninth to twelfth weeks, as determined by a randomized table. The first 2 weeks were the run in, and the seventh and eighth weeks were the washout periods.

Inhaler use, morning and evening peak flow rates (PEFR am, pm) and scores for day time asthma, cough, nocturnal asthma, and morning tightness were documented daily (Fig 1) (7). PEFR readings were taken with a mini-Wright peak flow meter using the best of three measurements. The mean for each patient's PEFR was calculated for weeks 3 to 6 and for weeks 9 to 12. At the end of each regimen (drug or placebo at week 6 or 12), pulmonary function tests (Vitalograph S spirometer, Buckingham, UK) were conducted and diary cards were reviewed.

The results were evaluated statistically according to Student's t test.

Diary Card Symptom Scores

NIGHT - TIME ASTHMA

0 = None.
1 = Awoke once for less than an hour because of asthma and / or cough.
2 = Awoke for less than an hour because of asthma and/or cough. Needed to use Ventolin aerosol to get back to slepp.
3 = Awoke once for longer than an hour or awoke more than once because of asthma and / or cough.
4 = Awake most of the night because of asthma and/or cough.

DAY- TIME ASTHMA

0 = No symptoms during the day.
1 = Occasional wheeze or breathlessness, quickly relieved.
2 = Wheezing or short of breath most of the day. Did not interfere with usual activities.
3 = Wheezing or short of breath most of the day. Some interference with usual activities.
4 = Asthma very bad. Could not go to work or school or do usual activities at all.

NIGHT - TIME ASTHMA

0 = None.
1 = Awoke at usual times. Chest tight. Did not use Ventolin aerosol..
2 = Awoke at usual times. Chest tight. Used Ventolin aerosol.
3 = Awoke earlier than usual due to asthma. Used the Ventolin aerosol once between waking and getting up.
4 = Awake earlier than usual due to asthma. Used the Ventolin aerosol more than once between waking and getting up.

DAY- TIME ASTHMA

0 = No cough at all.
1 = Occasional coughing. Not troublesome.
2 = Frequent coughing. Did not interfere with usual activities.
3 = Frequent coughing. Some interference with usual activities.
4 = Distressing cough most of the time.

Fig - 1 : Score used for day and night asthma severity and morning tightness and cough.

RESULTS

Compared to placebo, colchicine, 0.5 mg twice daily, significantly reduced morning tightness from 0.50 ± 0.38 to 0.32 ± 0.29 ($p<0.05$) and nocturnal asthma score from 0.44 ± 0.34 to 0.23 ± 0.25 ($p<0.01$)However, there were no significant differences in symptom scores for cough ($p>0.05$) and day time asthma ($p>0.05$). Furthermore, a combined respiratory symptom score for each patient (induced day time asthma, cough, morning tightness and nocturnal asthma scores) for colchicine and placebo did not show a significant difference ($p>0.05$) (Table 1).

	Placebo (Mean+SD)	Colchicine (Mean+SD)	P
Day-time Asthma	0.41 ± 0.39	0.27 ± 0.28	> 0.05
Morning Tightness	0.50 ± 0.38	0.32 ± 0.29	< 0.05
Day-Time Cough	0.61 ± 0.44	0.49 ± 0.28	> 0.05
Night-Time Asthma	0.44 ± 0.34	0.23 ± 0.25	< 0.01
Daily Combined Symptom Score	0.49 ± 0.36	0.39 ± 0.28	> 0.05

Table 1 : Effect of colchicine on symptom scores.

There was no significant ($p>0.05$) difference in the number of inhalations of salbutamol per day during colchicine administration (5.88 ± 1.33) when compared to placebo administration (5.94 ± 1.50).

No significant ($p>0.05$) difference was observed during placebo or colchicine administration for daily PEFR (192.60 ± 51.97 and 205.62 ± 55.92) or pulmonary function tests measured at the end of 4 weeks of placebo or colchicine administration (Table 2).

No major side effects were noted.

	Run-in (Mean+SD)	Placebo (Mean+SD)	Colchicine (Mean+SD)	P
FVC (l)	1.46 ± 0.57	1.41 ± 0.67	1.54 ± 0.68	> 0.05
FEV1 (l)	1.09 ± 0.42	1.10 ± 0.57	1.20 ± 0.54	> 0.05
FEV1 / FVC (%)	0.74 ± 0.10	0.78 ± 0.08	0.78 ± 0.07	> 0.05
FMEF (l /sn)	0.99 ± 0.40	1.04 ± 0.69	1.10 ± 0.63	> 0.05

FVC. Forced vital capacity, FEV1. Forced expiratory volume of one second, FMEF. Forced midmaximal expiratory flow.

Table 2 : Effect of colchicine on pulmonary function tests.

DISCUSSION

Our current understanding of the pathogenesis of asthma suggest that long term suppression of inflammation is the goal of asthma treatment (2, 8). Chronic colchicine treatment changes the course of various inflammatory disorders such as gout, familial Mediterranean fever (FMF), liver cirrhosis, scleroderma, leukocytoclastic vasculitis, psoriatic arthritis and Behçet's disease (10-16, 12-17). The drug has been shown to bind microtubuler proteins and to interrupt cellular mitosis. Examples of diverse phenomena induced by colchicine and considered to be modulated by micro tubules include effects on cyclic AMP, prostaglandin release from rat peritoneal macrophages, leukocyte chemotaxis, platelet aggregation and secretion (13). More recently, several studies disclosed an inhibitory effect of colchicine on the cellular immune response, contact sensitivity and delayed hypersensitivity (14). It can block alveolar macrophage release of the two mediators associated with the development of fibrosis in interstitial lung diseases, fibronectin and the alveolary macrophage derived growth factor (15). Suppression of these mediators associated with fibroblast proliferation and collagen deposition could contribute desirable antifibrotic properties. Because of these effects, colchicine had been advocated for treatment of many diseases in which there is prominent inflammation or fibrosis.

Danon et al (5) demonstrated that the incidence of asthma was significantly lower in FMF patients than the age matched adolescent population in Israel. Investigators suggested that the decreased inci-

dence of asthma in FMF patients might be attributed to chronic colchicine treatment. Schwarz et al (16) have recently demonstrated that oral colchicine 0.5 mg. twice daily together with oral theophylline administration for 4 weeks, completely corrected the deficiency of conconavalin-A induced suppressor T cell function in patients with mild asthma. Investigators suggested that, oral colchicine may be synergistic with oral thophylline for correcting the conconavalin-A induced suppressor T cell function. T lymphocytes may play a provital role in the asthmatic process (11), as evidenced by their involvement in many stages of the allergic response. In this study, there was an improvement of asthma symptoms such as wheezing and cough. The number of inhalations of albuterol was reduced. Although the mode of action of colchicine in asthma is largely unknown, its effects are likely to be due to its anti-inflammatory and especially immunomodulatory activity. These investigators' results are in favor of colchicine therapy in mild asthma.

These findings suggest that colchicine may be helpful in asthmatic patients who require anti-inflammatory prophylactic therapy. In our present study, the nocturnal asthma score was the mostly improved parameter. The ability of colchicine to significantly attenuate nocturnal asthma in our subjects directs attention to the role of inflammation in the pathogenesis of this phenomenon. But, there was no significant difference from placebo in the daily combined symptom scores for each patient. Also the improvement of nocturnal asthma did not induce a simultaneous reduction in beta-2 agonist inhaler usage. Furthermore colchicine had no significant effect on pulmonary function tests. Treatment of bronchial asthma must be aimed at maximizing prophylaxis (2, 8), it is critical therefore to monitor the response to therapy by objective parameters of assessment, such as the home peak flow monitoring (6). This test can provide valuable objective information than the perception of symptoms by helping to monitor the course of the disease and its response to medication (4). The patients in this study had moderately severe, chronic asthma as indicated by their unmedicated pulmonary functions which were at or just below the predicted normal values. Airway inflammation and increased airway responsiveness are important characteristics of such asthmatic patients, and the clinical severity of asthmais related to the extent of inflammation (3). The anti-inflammatory effect of colchicine was not sufficient in impairing the symptoms in our chronic asthmatic patients. This point may explain the absence of significant improvement in sequential pulmonary function tests and the combined mean symptom scores during the study. Asthma severity can be reduced only with realistic anti-inflammatory therapy quided by the clinicians' close correlation of clinical responses to the patients' enhanced peak flow performance (2, 6, 8). More effective inhaled anti-inflammatory therapy is required in achieving optimal effectiveness in the prophylactic management of such asthmatic patients.

COMMENT

The results of this study suggest that usage of the minimal therapeutic dose of colchicine for a 4 weeks-short-time period, cannot be justified in moderately severe asthmatic patients.

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REFERENCES

1. Aram H : Colchicine in dermatologic therapy. Int J Dermatol 1983; 22 : 566-569.
2. Barnes PJ : Pharmacology of airway inflammation mechanisms and therapy. Eur Respir Rev 1991; 1 : 68-71.
3. Barnes PJ : New concepts in the pathogenesis of bronchial hyperresponsiveness and asthma. J Allergy Clin Immunol 1989; 83 : 1013-1026.
4. Cross D, Nelson HS : The role of the peak flow meter in the diagnosis and management of asthma. J Allergy Clin Immunol 1991; 87 : 120-128.
5. Danon YL, Laor A, Shlezinger M, Zemer D : Decreased incidence of asthma with familial Mediterranean fever. Isr J Med Sci 1990; 26 : 459-460.
6. Guidelines for the diagnosis and management of asthma. National Heart, Lung , and Blood Insitute, National Asthma Education Program Expert Panel report. Pediatr Asthma Allergy Immunol 1991; 5 : 73-84.
7. Harper GD, Neil P, Vathenen AS, Cookson JB, Ebden P. A comparison of inhaled beclomethasone dipropionate and nedocromil sodium as additional therapy in asthma. Resp Med 1990; 84 : 463-469.

8. Holgate S : Mediator and cytokine mechanisms in asthma. Thorax 1993; 48 : 103-109.
9. Ilfeld D, Kuperman O : Correction of a suppressor cell deficiency in four patients with familial Mediterranean fever by in vitro or in vivo colchicine. Clin Exp Immunol 1982; 50 : 99-106.
10. Insel PA : Analgesic-antipyretics and anti inflammatory agents, drugs employed in the treatment of rheumatoid arthritis and gout. In : A.G Gilman, TW Rall, AS Nies, P Taylor, editors. The pharmacological basis of therapeutics. New York : Pergamon Press 1990; 638-681.
11. Kay AB : Lymphocytes in asthma. Respir Med 1991; 85 : 87-90.
12. Kershenobich D, Rojkind M, Quirega A, Varela JA : Effect of colchicine on lymphocyte and monocyte function and its relation to fibroblast proliferation in primer bilier cirrhosis Hepatology 1990; 11 : 205-209.
13. Mekori YA, Baram D, Goldberg A, Klajman A : Inhibition of delayed hypersensitivity reactions in mice by colchicine. Mechanisms of inhibition of contact sensitivity in vitro. Cell Immunol 1989; 120 : 330-340.
14. Mekori YA, Chovers Y, Drucker I, Klajman A : Inhibiton of delayed hypersensitivity reactions by the colchicine. Colchicine inhibits interferon-gamma induced expression of HLA-DR on gut epithelial cell line. Clin Exp Immunol 1989; 78 : 230-231.
15. Peters SG, MacDougall JC, Douglas WW, Douglas TC, DeRemee RA : Colchicine in the treatment of pulmonary fibrosis. Chest 1993; 103 : 101-104.
16. Schwarz YA, Kivity S, Ilfeld DN, et al : A clinical and immunologic study of colchicine is asthma. J Allergy Clin Immunol 1990; 85 : 578-582.
17. Segovia AD, Niembro RD, Kaper ID : Long term evaluation of colchicine in the treatment of scleroderma. J Rheumatol 1979; 6 : 705.