EFFECTS OF INHALED BUDESNIDE AND NEDOCROMIL SODIUM ON EXHALED NITRIC OXIDE LEVELS IN MILD ASTHMATIC PATIENTS

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SUMMARY :

***Purpose** : In this study we compared the short-term antiinflammatory effects of budesnide and nedocromil sodium, by exhaled nitric oxide (eNO) levels, pulmonary function tests and symptom scores in mild asthmatic patients. **Methods** : 19 of the 37 newly diagnosed mild asthmatics (with mean age of 40; 33 female, 4 male) received 8 mg nedocromil sodium and 18 patients received 800 (g budesnide (n: 18) daily as a routine antiinflammatory therapy. eNO and forced expiratory volume during first second (FEV1) were measured before and on the fifteenth day of the treatment. Peak expiratory flow (PEF), PEF variation, day and night time symptom scores, and bronchodilator consumption were recorded daily during the treatment period. **Results** : Our data indicate that in the budesnide group there was a significant increase in FEV1 ($p<0.005$), PEF ($p=0.01$); day time symptom scores ($p<0.005$) and night time symptom scores ($p<0.05$), and a significant fall in PEF variation ($p<0.01$) and eNO levels ($p=0.01$). In the nedocromil sodium group, the only significant changes were in eNO levels ($p=0.01$) and PEF variation ($p<0.005$). **Conclusion** : When comparing the two antiinflammatory agents, there was no significant difference between their efficacy on study parameters.*

***Key Words:** Asthma, Nitric Oxide, Budesnide, Nedocromil Sodium.*

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways. This inflammation is multicellular, composed mainly of activated eosinophils, mast cells and lymphocytes. Lymphocytes also aid in the establishment and persistence of the chronic inflammatory state. In the presence of the multiple risk factors in asthmatics, CD4+ lymphocytes differentiate as Th2. The cytokines produced by these Th2 cells are responsible for this specific inflammation in asthma. (1-3).

Nitric oxide (NO) is produced by many cells within the respiratory tract and can be detected in the exhaled air of human subjects. It is known that exhaled nitric oxide (eNO) concentrations are significantly higher than normal in patients with asthma (2, 4). Endogenous NO is generated from L-arginin by the enzyme NO synthase (NOS). NOS has three distinct isoforms: two constitutive isoforms are found in endothelial cells (eNOS) and neurons (nNOS). They are activated by a rise in intracellular calcium. The third isoform, inducible NOS (iNOS), is induced in several cell types by exposure to proinflammatory cytokines and endotoxin. It has been shown that inhaled

glucocorticoids decrease NO in exhaled air of asthmatic patients by blocking iNOS induction. This suggests that exhaled NO may be a useful marker of chronic inflammation in the airways and may also be useful in monitoring the response to antiinflammatory treatment (4-7).

Corticosteroids are currently the most effective antiinflammatory medications for the treatment of asthma. Several studies have demonstrated that treatment with inhaled corticosteroids for at least one month reduces the pathological signs of airway inflammation in asthma. They reduce microvascular leakage, inhibit cytokine production and secretion, prevent the directed migration and activation of inflammatory cells (3). Glucocorticoids prevent the induction of inducible NO synthase by cytokines in epithelial cells (5).

Nedocromil sodium was introduced as a prophylactic treatment for asthma in the mid 1980's. It has proven antiinflammatory effects in vitro (8). It has been shown to inhibit mediator release from inflammatory cells. It improves asthma control and some clinical trials and clinical research data show that it has an antiinflammatory activity in vivo (9).

In this study we compared the short term antiinflammato y effects of an inhaler corticosteroid, budesnide and nedocromil sodium by eNO levels, pulmonary function tests, symptom scores and bronchodilator consumption in mild asthmatic patients.

MATERIAL AND METHODS

Subjects

Thirty-seven mild asthmatics (4 males and 33 females) with a mean age of 40 (range 16-65) years were included in the study. All had the clinic features of asthma for more than six months and met the diagnostic criteria of National Heart, Lung and Blood Institute (NHLBI) (3). None of the patients had had any antiinflammatory therapy previously.

All subjects had symptoms of variable wheezes and dyspnoea. All were stable for at least 2 weeks before the study. Patients did not consume any caffeinated beverage, inhaled or took oral medication including beta agonists for 8 hours before each study visit. None of the patients had sinopulmonary infection, bronchiectasis or a pulmonary disease other than asthma.

Study design

As a routine treatment 19 of the subjects received 4 mg inhaled nedocromil sodium (Tilade®, Fisons Plc, UK) via metered dose inhaler and compact open spacer (OS Synchroner, Fisons, UK) and 18 received 400 (g inhaled budesnide (Pulmicort, Astra) via a multiple-dose dry power delivery system (Turbohaler®, Astra); twice daily.

eNO and FEV1 were measured before and on the fifteenth day of the treatment, PEF, PEF variation, day and night time symptom scores, and bronchodilator consumption were recorded daily during the treatment period.

Pulmonary function tests and Nitric oxide measurement

FEV1 was measured with Sensor Medics Vmax 20 spirometer. The best value of three manoeuvres was expressed as a percentage of the predicted value and as absolute value.

eNO was measured on a chemiluminescence analyzer (Sievers 280 NOA™, Sievers Instruments, Inc., USA) sensitive to NO from <1 to 500 parts per billion (ppb, by volume). Subjects wore Sievers Accurate NO™ Exhaled Breath Kit that applies resistance to the exhaled breath circuit. Resistance creates positive pressure in the mouth, forces the subject's soft palate shut and eliminates nasal NO from the measurement. NO was sampled at a rate of 100-300 ml/min. During a 3 min tidal breathing period, the program displays the NO concentration and flow signals in real time, and calculates minimum, maximum average NO for each breath. The median value of the averages was considered as the eNO level. The zero calibration was performed and ambient air NO was recorded before each test.

Symptoms, maximal diurnal variability, bronchodilator consumption

Diary cards were given to all patients to record beta agonist use, PEF and asthma symptoms every morning and evening during the treatment period. The symptom enquiry included assessment of symptoms during the day and night, using four point scale (0=no symptoms; 3=severe symptoms) (7).

Diurnal variability of PEF was calculated as fol-

lows (3):

$$\frac{\text{Maximum PEF-Minimum PEF}}{\text{1/2 (Maximum PEF+Minimum PEF)}} \times 100\ \%$$

Statistical analysis

Values of FEV1, PEF, eNO, PEF variation, symptom scores and bronchodilator consumption after the treatment were compared with the values obtained before the treatment using Wilcoxon test separately for each study group. Comparisons between the groups were made by Mann-Whitney rank sum test. Results were expressed as the mean (SEM). A p value of less than 0.05 was considered significant.

RESULTS

19 patients (51.4) were in the nedocromil group, 18 patients (%48.6) were in the budesnide group. Eight patients (%21.6) used a beta agonist when needed, before the study. Five patients (% 13.5) are current smokers. Patient demographics were shown in Table 1.

eNO, FEV1, PEF, PEF variation, symptom scores and bronchodilator consumption values before and after the therapy is shown in Table 2. In the nedocromil sodium group the only significant changes were in eNO levels (p=0.01) and PEF variation (p<0.005). In the budesnide group there was a significant improvement in all the parameters except bronchodilator consumption. eNO levels before and after the treatment in two study groups are shown in Fig. 1.

When comparing the effects of two antiinflammatory agents no significant difference was found between their efficacy on study parameters. Current smokers were too few to compare the eNO levels of smokers and nonsmokers.

DISCUSSION

The aim of the asthma therapy is to reverse and prevent symptoms and airflow limitation by controlling the airway inflammation. Controller medications include corticosteroids, sodium cromoglycate, nedocromil sodium, sustained release theophylline and long acting beta agonists. Nedocromil sodium is an antiinflammatory pyronoquinoline that has been shown to inhibit activation of, and mediator release from

Table 1 : Demographic data of the patients.

	Nedocromil s. group	Budesonide group
Number (%)	19 (%51.4)	18 (%48.6)
Male / Female (%)	2 / 17 (%10.5/89.5)	2 / 16 (%11.1/88.9)
Mean age (yr.)	39.6±11.3 (20-65)	41±12.6 (16-6:)
Asthma history (yr.)	4.3±0.9	6.3±1.3
Current smokers (%)	2 (10.5)	3 (16.6)

Table 2 : Effect of two drugs on study parameters.

	Nedocromil sodium			Budesonide		
	Baseline values	After treatment	p	Baseline values	After treatment	p
eNO (ppb)	24.98±4.67	10.94±1.74	<0.05	35.88±6.94	15.38±3.00	<0.05
FEV1 (L)	2.59±0.18	2.62±0.17	NS	2.35±0.19	2.52±0.18	<0.005
PEF (L)	5.22±0.31	5.74±0.44	NS	4.97±0.33	5.68±0.37	<0.05
PEF variation (%)	17.21±3.6	5.53±1.36	<0.005	7.56±1.86	2.06±1.19	<0.05
Night time symp. score (n)	0.89±0.19	0.37±0.19	NS	0.67±0.23	0.06±0.06	<0.05
Day time symp. score (n)	0.84±0.19	0.53±0.19	NS	1.00±0.16	0.28±0.11	<0.005
Bronchodilator consumption (n)	0.26±0.10	0.05±0.05	NS	0.50±0.31	0.06±0.06	NS

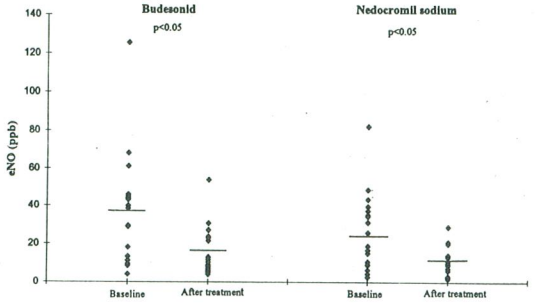

Fig - 1 : eNO levels before and after treatment (Short horizontal lines indicate the mean values).

inflammatory cells. It also inhibits neuronal pathways. Clinical trials have shown that it has a rapid effect on symptoms, improves lung function and reduces nonspecific airway responsiveness (3).

Inhaled glucocorticoids are at present the most effective antiinflammatory medications for the treatment of asthma. They inhibit cytokin production and secretion, prevent the direct migration and activation of inflammatory cells and increase the airway smooth muscle beta receptor responsiveness (3, 10).

There is now evidence that increased levels of eNO are released from the conducting airways in response to airway inflammation. The inducible isoform of the enzyme NO synthase (iNOS) has been demonstrated in the bronchial epithelium of asthmatics, and this isoform is induced in airway epithelial cells by specific cytokines (11).

Corticosteroids decrease the eNO levels by inhibiting the iNOS enzyme. Kharitonov et al. have shown that eNO concentrations are significantly higher than normal in patients with asthma who are not receiving inhaled steroids, and with steroid treatment eNO levels became normal (6). With the steroid treatment in asthmatics eNO levels decrease in parallel with clinical improvement (10). In asthmatic patients a double blind study of inhaled budesnide has shown a progressive reduction in eNO down to normal values after three weeks of treatment (12). In our study 2 weeks budesnide therapy was enough to reduce eNO levels significantly (p=0.01).

In another study by Kharitonov et al. eNO was significantly reduced after one week treatment of budesnide, with further reductions over three weeks, but there was no significant improvement in lung functions. That was explained with the almost normal baseline lung functions in mild asthmatics (5).

In our study 18 mild asthmatics who received inhaled budesnide for two weeks had improvement in FEV1, PEF, PEF variation, symptom scores and a decrease in eNO levels. We have shown that short term inhaled budesnide therapy both control inflammation and improve pulmonary functions and symptom scores.

Nedocromil sodium is classified as an antiinflammatory drug but there is little evidence that it exerts a significant inhibitory effect on airway inflammation in asthma. It is effective in controlling asthma symptoms in some patients with mild asthma, but its mode of action is uncertain (13). It is assumed that it shows its antiinflammatory effect by interfering with the mediator secretion from mast cells. There are reports that it is effective especially in asthmatics whose major symptom is coughing. The main advantage of this drug is that it has no side effects. It is used for intermittant and mild persistent asthmatics in step 1 and 2 of the asthma therapy (3, 10, 14).

In his metaanalyses about the efficacy and therapeutic position of nedocromil sodium, Holgate has mentioned the long-term antiinflammatory effects of nedocromil sodium (9). Bronchoalveolar lavage (BAL), fluid eosinophils, neutrophil and lymphocyte numbers, BAL fluid inflammatory mediators and peripheral blood circulating eosinophil cell numbers were significantly reduced in adult asthmatics after 17 weeks treatment with nedocromil.

In our study, in 19 mild asthmatics who received nedocromil, with the two weeks treatment, there was a significant decrease in eNO levels and PEF variation (Table 2). The improvement in FEV1, PEF, symptom scores were not statistically significant. We have shown that nedocromil sodium has an early antiinflammatory effect that decreases eNO levels but the two week period was not enough for the improvement of the other

parameters.

Creticos et al. could not achieve an improvement in pulmonary functions with nedocromil as in our study, but in an 8-week-period the symptomatic improvement and the decrease in bronchodilator consumption was significant (14). As mentioned the FEV1 of mild asthmatics are near normal. So the PEF variation and eNO changes can be more valid in determining the efficacy of the drug in short term.

When comparing the two antiinflammatory agents, there was no significant difference between their short-term efficacy on pulmonary functions, symptoms, eNO levels and bronchodilator consumption. It is shown that long or short acting beta agonists do not affect eNO levels (15). Thus in this study, patients were asked to use beta agonist when needed, but neither in budesnide nor in nedocromil group there was a significant decrease in bronchodilator consumption. This was because the bronchodilator consumption was very slight at the beginning of the study period.

We conclude that, in mild asthmatics treated with inhaled budesnide for two weeks, all the study parameters improved significantly. In mild asthmatics treated with nedocromil sodium, only the improvement in eNO and PEF variation was significant. However, when comparing the two agents, there was no significant difference between their efficacy on pulmonary functions, eNO levels, symptom scores and bronchodilator consumption. Inhaler budesnide has an advantage of early improvement of symptoms and FEV1.

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