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Efficacy and Safety of Inhaled Steroids in Children with Asthma: a Comparison of Fluticasone Propionate with Beclomethasone

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ABSTRACT

Background: *Inhaled corticosteroids are indicated in children who have mild persistent asthma. Fluticasone propionate is a newer corticosteroid agent with higher potency compared with previous generations. However, still few dose-ranging studies have been investigated for optimal dosing of inhaled corticosteroids particularly in children with regard to the tolerability and safety of the drug.*

The primary purpose of this study was to compare and evaluate the efficacy and safety of fluticasone with beclomethosone in the treatment of childhood asthma unresponsive to non-steroidal medications and also in persistent, moderate and severe asthma.

Materials and Methods: *Seventy children, aged 6 to 14 years were enrolled in an open randomized trial with a parallel group design. Fifty-two children with moderate, severe or persistent asthma received fluticasone 100 µg twice daily for 12 weeks compared with 18 asthmatic children on beclomethasone 200 µg daily. The outcome was assessed by data on questionnaires, changes in clinical symptoms, and results of peak flowmetery (PEFR).*

Moreover, safety was assessed by 24 hour urinary cortisol measurement at the beginning of the study and comparison of the data with urinary cortisol at the end of 12 weeks.

Results: *A total of 70 children between 6 to 14 years (33 girls and 37 boys) were randomized to start treatment with fluticasone or beclomethasone. From 70 children 13(18.6%) had a history of contact with pets during their life. At the beginning in beclomethasone group: 88.9% had cough, 88.9% had post exercise cough, 66.7% had dyspnea and 72.2% had wheezing. In Fluticasone group: 75% had cough,76.9% had post exercise cough, 46.2% had dyspnea and 59.6% had wheezing. After 3 months of therapy in beclomethasone group: cough was seen in 16.7%, post exercise cough in 11.1%, dyspnea in 11.1%, wheezing in 16.7% and in fluticasone group: cough in 15.4%, post exercise cough in 11.1%, dyspnea in 1.9% and wheezing in 3.8%.Data showed a better improvement in clinical signs of patients with fluticasone ($p<0.05$). Pulmonary function tests revealed better lung function in fluticasone group ($p<0.05$). In addition, 24 hours urinary cortisol level was measured at the beginning and after 12 weeks of therapy and it was within the normal range for both drugs.*

Conclusion: *Fluticasone produced significantly greater improvement in lung function and control of asthma symptoms compared to beclomethasone and is efficient in the treatment of persistent, moderate and severe asthma in children. In addition these improvements were achieved with no greater degree of cortisol suppression compared with beclomethasone.* ***(Tanaffos 2007; 6(1): 29-35)***

Key words: *Fluticasone propionate, Beclomethasone dipropionate, Adrenal suppression, Inhaled corticosteroids*

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INTRODUCTION

Asthma is a chronic, inflammatory and life threatening disease of the airways that affects all ages, races and ethnic groups. It is one of the few chronic diseases whose prevalence rates are increasing despite the better understanding of the disease and improved medical treatments (1). Asthma is characterized by symptoms of wheezing, cough and tightness of the chest resulting from an inflammatory reaction in the airways (2).

The prevalence and severity of asthma in different regions of the world have been studied through the International Study of Allergies and Asthma in Childhood (ISAAC) project (3, 4, 5). The self-reported 12 months prevalence of wheezing in children aged 13–14 years ranged from 2.1% in Indonesia to 32.2% in the UK (3). Similarly, parent-reported 12 months prevalence of wheezing in children aged 6–7 years ranged from 4.1% in Indonesia to 32.1% in Costa Rica. The prevalence was the highest (>20%) in English-speaking countries and in North America and some Latin American countries (3). Taken together, the data suggest that there are more cases of asthma in more westernized, affluent countries. In addition, the risk of asthma may be related to environmental factors associated with a modern, Western ways of life.

Inhaled corticosteroids (ICS) have become established as first-choice drugs in the treatment of bronchial asthma in childhood (6,7). Their main advantage is high efficacy combined with few systemic side effects, when compared to previously used systemic steroids (8). A number of ICS have been introduced over the years, presenting different pharmacokinetics, pharmacodynamics, potency, and bioavailability, and more efficient delivery systems have been developed. Recent studies have shown that treatment with inhaled corticosteroids reduces hospitalization rates and asthma related mortality in adults (9, 10). Fluticasone propionate (Flixotide/Flovent; FP) is a highly potent and topically active ICS, with an oral bioavailability of less than 1% (11, 12).

In recent years, many studies have been conducted to determine the safety of new generation of ICS such as fluticasone in adults and children (13, 14). The relative clinical efficacy and systemic effects of new inhaled corticosteroids are still under study particularly in children. This study was therefore designed to compare the effects of fluticasone on clinical symptoms and pulmonary function tests.

MATERIALS AND METHODS

Subjects

Seventy children with moderate, severe, and persistent asthma aged 6 to 14 years who referred to our center were enrolled in the study. Each subject's parents gave written informed consent and the study was approved by the National Research Institute of Tuberculosis and Lung disease Ethics Committee.

Study design

This study was an open randomized trial of parallel group. Fifty-two children with moderate, severe or persistent asthma received fluticasone 100 µg twice daily for 12 weeks and compared with 18 asthmatic children on beclomethasone 200 µg daily. The outcome was assessed by data from questionnaires, changes in clinical symptoms and results of peak flowmetery (PEFR). Data were collected in each clinical visit by a physician. Patients were asked whether to have any contact with smoking particularly in adults or any history of contact with pets.

Monitoring of Adverse Events

Safety assessments were performed by using 24 hours urinary cortisol measuring at the beginning and at the end of 12 weeks of therapy; besides, the

patients were visually examined for the presence of oral candidiasis and were asked whether asthma exacerbations occurred between clinical visits or the patient had any other problems since their previous clinical visit.

Statistical analysis

For each treatment, we report the percentage change between the mean of two placebo measurements with a 95% confidence interval using SPSS software (Release 11.05, Chicago). Wilcoxon matched pairs signed rank test was used. The percentage of plasma cortisol level was also compared with all other treatments using Wilcoxon matched pairs signed rank test.

RESULTS

A total of 70 children between 6 to 14 years (33 girls and 37 boys) were randomized to start treatment with fluticasone (n =52, range=3 to 15 years, mean age=8.85 years SD=3.030) or beclomethasone (n= 18, range=5 to 13 years, mean age=7.22 years, SD=2.074). Both groups were well matched for sex, age and race. (p>0, 05)

Out of 70 children 13(18.6%) had a history of contact with pets during their life. 32(45.7%) were passive smoker. 40(58%) were born by Caesarean section and 51(72.9%) had a positive history of asthma or allergy in the family.

Effects of administered drugs on clinical symptoms

Clinical symptoms were included in the questionnaire and compared with regard to the administered drugs in periodic clinical visits. Results revealed that after 3 months of therapy clinical signs and symptoms were improved in both groups. However, the improvement in clinical features such as cough, post exercise cough, dyspnea and wheezing in patients who were treated with fluticasone was significantly better in comparison to those in the beclomethasone group (p<0.05)(Table1).

Table 1- Clinical features of patients during 12 weeks.

Clinical signs and symptoms		cough %	Post exercise cough%	Dyspnea %	Wheezing %
Beginning	Beclomethasone	88.9	88.9	66.7	72.2
	Fluticasone	75	76.9	46.2	59.6
1st visit (4th week)	Beclomethasone	38.9	38.9	11.1	11.1
	Fluticasone	21.2	17.3	7.7	7.7
2nd visit (8th week)	Beclomethasone	16.7	16.7	5.6	11.1
	Fluticasone	3.8	12.3	3.4	3.8
3rd visit (12thweek)	Beclomethasone	16.7	11.1	11.1	16.7
	Fluticasone	15.4	9.6	1.9	3.8

Effects of administered drugs on pulmonary function tests

At the beginning and after 1, 2 and 3 months of therapy four measurements were recorded. Where possible, measurements were made at the same time of the day. During the study, the peak expiratory flow rate (PEFR) of patients was measured in the morning (8:00 A.M.) and in the evening (4:00 and 9:00 P.M.) using a standard peak flow meter. The mean PEF for the patients in the beclomethasone group was 151.4 lit/min and 186.7 lit/min for patients who were on the fluticasone treatment at the beginning. At the 4th clinical visit the beclomethasone group had an average of 157.2 lit/min and the fluticasone group had an average of 213.3 lit/min in their PEF. This result shows a greater improvement in lung function with fluticasone treatment in our patients. (p<0.05) (Figure 1).

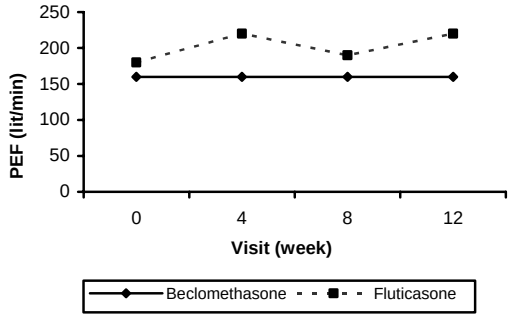

Figure 1- PEF of the patients on both drugs during 12 weeks.

Effects of administered drugs on cortisol level

Safety assessments were performed at the beginning and end of treatment by measuring 24 hours urinary cortisol level. No significant differences were observed for either treatment, when considering adverse events. No serious adverse events were seen during the study and the cortisol level was within the normal range in both groups.

DISCUSSION

This study was designed to test the hypothesis that long-term treatment of asthma with fluticasone at a similar dose to beclomethasone would result in a better anti asthma effect and a similar safety profile. The results indeed show that fluticasone, at the same dose of beclomethasone, results in a similar and even better efficacy in the control of moderate to severe asthma in children. This was evident from the PEFR, recorded at each clinical visit and from the percentage of reduction in the clinical symptoms and signs. After three months of treatment the PEFR measurements as well as the clinical improvements were significantly higher in the fluticasone group. There are other studies that reveal a better clinical and paraclinical improvements in patients treated with fluticasone with the same dose or even smaller doses in children and adults compared with beclomethasone group (15, 16, 17, 18).

The data showed that clinical signs and symptoms of patients were significantly improved better with fluticasone after 3 months of therapy. Other studies also reported a better quality of life and days and nights with no overall symptoms (19). Childhood asthma may not only interfere with the child's daily activities but can also place a considerable burden on the child's family (20, 21, 22). The responsibility of caring for a severely ill child or one whose activities are restricted can interfere with the parent/s attendance at work, ability to deal with their responsibilities at home and ability to participate in leisure activities (20). In the present study, baseline data and questionnaires filled out in the follow ups showed that the parents/guardians of the patients treated with fluticasone experienced a consistent and significant improvement in their children's general condition and asthmatic complaints such as cough, dyspnea, and post-exercise cough. In addition, the physician recorded a significant improvement in children's signs such as wheezing in the clinical visits.

This study demonstrated that 40(58%) of the studied children were born by Caesarean section. It has been hypothesized that Caesarean section might increase the risk of developing allergic diseases by depriving the fetus and newborn of being exposed to maternal micro flora. Even though there are some that claim Caesarean section delivery may be associated with an increased prevalence of atopic asthma (23, 24), there are still some studies that believe delivery by Caesarean section is not associated with the subsequent development of asthma, wheezing, or atopy in late childhood in this population (25).

We investigate the number of our children who had contact with pets to estimate the effect of pet ownership and exposure to animal allergens on childhood asthma occurrence. Thirteen (18.6%) of our children had a history of contact with pets. Childhood asthma is strongly associated with allergic sensitization. Although Studies have suggested that animal exposure during infancy reduces subsequent allergic sensitization (26).

Fifty-one (72.9%) had a family history of asthma or allergy traced in our children. Family history of asthma and allergies strongly influences the risk of asthma in children. London SJ and colleagues

showed that for children with two asthmatic parents relative to those with none, the prevalence ratio for early-onset persistent asthma was 12.1 compared to 7.51 for early-onset transient asthma and 5.38 for late-onset asthma (27).

In addition to family history 32(45.7%) of our children were passive smokers. It is well recognized that exposure to environmental tobacco smoke leads to reduced lung function, increased risk of lower respiratory tract illnesses, acute exacerbation of asthma resulting in hospitalization, increased prevalence of non-allergic bronchial hyper-responsiveness, increased risk for sudden infant death syndrome (SIDS) and possibly increased risk for asthma (28).

All mean morning cortisol levels for both ICS remained unchanged within normal upper and lower limits. No differences in cortisol levels were found between both treatments. There are other researches with similar results. Barnes and colleagues found no greater degree of cortisol suppression with fluticasone in comparison with beclomethasone (29). However the adrenal suppression and other side effects can be influenced by the prescribed dosage. Visser and colleagues showed that doses of 1,000 and 500 µg/day of fluticasone propionate are associated with marked reduction of growth velocity, bone turnover and adrenal cortical function. However, conventional doses (< or =200 µgr /day of fluticasone propionate) appear to be safe in the long-term management of childhood asthma (30).

Other studies also indicate that beclomethasone and fluticasone at doses of 400 microgram daily provide equivalent asthma control in patients with symptomatic asthma and exhibit similar safety profiles (31).

In conclusion, childhood asthma was strongly associated with a family history of asthma and rhinitis, contact with pets and smoking parents. These factors especially positive family history may have utility in targeting some individual prevention efforts. In addition, fluticasone produced significantly greater improvement in lung function and control of asthma symptoms compared with beclomethasone and was efficient in the treatment of persistent, moderate and severe asthma in children. We should mention that these improvements were achieved with no greater degree of cortisol suppression compared with beclomethasone. Thus these results highlight the need to reassess the management of asthmatic children in Iran

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