Original article

THE SAFETY PROFILE OF INHALED CORTICOSTEROIDS (BECLOMETASONE DIPROPIONATE) APPLIED IN CONVENTIONAL AND HIGH DOSES IN PREVENTION OF CHILDHOOD ASTHMA

Milica Martinovic

Asthma is the most widespread childhood chronic disease. The most recent findings about the nature of pathophysiological action in asthma have led to a wide application of anti-inflammatory agents and inhaled corticosteroids in the prevention of this disease. It is considered that these medications, taken in conventional doses, have a very good safety profile. Increasing the dose increases the risk of causing undesired side effects. The application of very high doses should be reserved for cases of persistent and severe asthma with intensive monitoring of these patients, and "stepping down" the dose as soon as it is possible, with the aim to reduce the danger of undesired side effects.

In a group of 50 patients from different regions of Montenegro, of both sexes, aged between 7 and 14 years, ten were diagnosed with mild asthma, thirty with moderately severe asthma and eight with severe persistent asthma, according to international standards of diagnosis. All respondents had allergic asthma (a serum IgE concentration statistically significantly higher than in healthy children from the control group, results from specific IgE and allergy tests).

With the aim to prevent the occurrence of asthma attacks, beclometasone dipropionate was used in conventional doses (200-400 μg) in cases of children suffering from mild and moderately severe persistent asthma, and in high doses (1000μg) in cases of those suffering from severe persistent asthma, over a twelve-month period. The evaluation of the appearance of undesired side effects was undertaken by regular clinical check-ups and in the laboratory (daily cortisol profile at the beginning and end of the treatment with these medications, and urinary excretion of 17-OH corticosteroids). The control group comprised 20 healthy children.

During the application of the aforementioned doses of beclometasone dipropionate, suppression of hypothalamus-pituitary-adrenal functions was not observed either in patients taking conventional doses or subjects taking high doses of this medication. Other authors' data are similar. *Acta Medica Medianae 2008;46(4):13-18.*

Key words: *childhood asthma, inhaled corticosteroids, side effects*

Institute for Pathological, Physiological and Laboratorial Medicine of the Faculty of Medicine in Podgorica

Contact: Milica Martinovic
Faculty of Medicine
Nn Krusevac Street, Podgorica
Phone: 069/473-772; 083/ 234-320
E-mail: dmartinovic@cg.yu

Introduction

Asthma is a chronic lung disease which can appear at any age. It is the most common chronic childhood disease. The prevalence of asthma in children varies across different ethnic groups and different geographical areas (1,2,3,4,5). In some populations (Australia, New Zealand), it is as high as 30%. Similarly, severe clinical forms of asthma are on the rise.

According to figures of the AAFP (American Academy of Family Physicians) from 2001, the prevalence of childhood asthma has risen by 160% since 1980. Then, about 5 million children in the USA suffered from asthma, more than 5% of the population younger than 18 (6).

There are no reliable epidemiological data about the prevalence of asthma in Montenegro.

According to some researches, about 5-7% of school children in Podgorica suffer from asthma. In recent years, new findings about the nature of the pathophysiological processes in asthma have come to light. The understanding of asthma as a chronic inflammatory disease has led to the modification of the approach to the treatment these patients. Considering the fact that chronic inflammation of the airways plays the most important role in the pathogenesis of asthma, priority importance in the treatment of these patients is given to anti-inflammatory medications, which is pointed in all current guidelines for treating this disease (7,8,9,10).

Anti-inflammatory agents, corticosteroids taken in vapour form, are today the most effective medications for achieving and maintaining control of this disease. The long-term application of these medications with the aim of preventing the

occurrence of asthma attacks, when they are taken in conventional doses (mild and severe forms of persistent asthma), according to a large number of authors is safe for everyday use over a long period of time (11,12,13). They restore lung functioning, reduce bronchial hyperreaction, lower and prevent the occurrence of symptoms and reduce the frequency and severity of attacks.

Inhaled corticosteroids (ICS) are incomparably safer than oral corticosteroids for long-term use. Undesired side effects with long-term use of oral corticosteroids include: hypertension, osteoporosis, hypothalamus-pituitary-adrenal suppression, diabetes, cataracts, obesity and thinning of hair and muscle fibres.

Inhaled corticosteroids (ICS) are the main preventative therapy for children and adults with moderate and severe persistent asthma. The early introduction of ICS significantly improves the prognosis for childhood asthma. Today, it is considered that timely introduction and prevention of these medications (14,15,16) also prevents the appearance of severe, irreversible anatomical changes to the walls of the airways (remodelling of the bronchial walls).

The use of facilitative equipment, valve chambers, and nebulisers has significantly lowered the age limit of children who can use inhaled glucocorticoids. This has increased the interest in their undesired side effects. Inhaled corticosteroids are safe and efficient in the prevention of asthma, whether prescribed long-term in small doses or for a shorter period in high doses. Long-term treatment with inhaled corticosteroids in high doses is useful in the treatment of severe persistent asthma because it reduces the need for long-term use of corticosteroids in the form of tablets and syrups and has significantly less frequent undesired side effects.

There is a large amount of data about the risks associated with the use of ICS, but it is nevertheless inconclusive. However, it is considered that long-term treatments of high doses, greater than 400 μg/m^2 per 24 hours for beclometasone and greater than 250 μg/m^2 per 24 hours for fluticason, can be linked to undesired side effects. For example, children's growth can be impeded, although severe asthma itself can cause delayed growth, especially in late childhood and early adolescence. The risk of undesired side effects depends on the dosage; however, one group of authors considers that there also exists a particular individual oversensitivity towards the effect of inhaled corticosteroids. The relative advantages and risks for each patient should be determined individually. Continued therapy with doses of less than 400 μg/m^2 per 24 hours for beclometasone and less than 250 μg/m^2 per 24 hours for fluticason, according to general opinion, carries a minimal risk of causing undesired side effects. It is considered that if the doses are increased above the above-mentioned levels, the likelihood of causing undesired side effects becomes progressively greater (17,18).

Fortunately, only a small number of children have severe persistent asthma and therefore the need for high doses of ICS and excessive use of systemic corticosteroids.

Estimates of the severity and classification of asthma in childhood is complicated, more so when the child is younger. A good estimate of the severity of asthma is essential so that a good therapy can be chosen. Most authors advise a highly individual approach for each patient, particularly taking into account all diagnostic criteria. Children up to the age of two are put into a group of their own, while amongst older children, adolescents make up a special, high risk group. Because of many distinct influences applying to that age group (such that they often refuse to take the medications), particular patience and tactfulness is necessary in the approach to these patients.

Asthma can be very diverse. It can be intermittent (having mild, moderate, or severe symptoms) or persistent (mild, moderate, or severe). The severity of asthma also changes in some patients over time. For example, asthma can be moderate in childhood and mild in adulthood, or can be severe only at particular times of the year.

Table 1: Classification of asthma in children over two years of age

	Clinical signs prior to treatment		
	Symptoms	Nocturnal symptoms	Lung functions
Mild, intermittent	-symptoms either appear <twice a week, and/or; -no symptoms and normal PEF between attacks, and/or; -short attacks of varying intensity	none	FEV1 or PEF >80%, PEF coefficient variance <20%
Severe, intermittent	Severe attacks between which lung functions are regular, but there are no symptoms	none	
Mild, persistent	-symptoms appearing > twice a week or <once daily	> twice a month	FEV1 or PEF>80% PEF variance 20-30%
Moderate, persistent	Symptoms appearing every day, as well as β_2-agonists Attacks > twice weekly	> once a week	FEV1 or PEF 60-80% of predicted level PEF variance >30%
Severe, persistent	-constantly present symptoms; -limited physical activity; -frequent attacks	frequent	FEV1 or PEF <60% of predicted level PEF variance >30%

Notes:
FEV1: Forced Expiratory Volume)
PEF: Peak Expiratory Flow
The presence of any one of these indicators of severity is sufficient for the patient to be placed in that category
Patients in each of these groups can have attacks of varying intensity

Aims

The aim of the paper was to describe the safety profile of treatment lasting several months with inhaled glucocorticoids (beclometasone dipropionate) prescribed for the prevention of childhood asthma in its mild and moderately severe forms in conventional doses, and in a small number of patients with severe persistent asthma in high doses.

Study Sample and Methodology

Diagnoses were made in 50 children from different areas of Montenegro (over several years of monitoring and working with these patients) in those suffering from mild persistent asthma (ten patients), moderate persistent asthma (thirty-two) and severe persistent asthma (eight) according to the criteria of the International Consensus of Diagnosis and Management of Asthma from 1992. All had allergic asthma which was determined on the basis of data from personal anamnesis (atopic dermatitis), family anamnesis, determining the total IgE (by ELISA method, Institute for Nuclear Medicine, Zemun), the specific IgE for Detrmatophagoides Pteronyssinus, pollen from grass, trees and weeds and undertaking skin prick tests to determine the allergic reaction.

There are certain benefits to the use of a Forced Expiratory Volume (FEV1) test with a spirometer before the beginning of ICS treatment, but there should also be daily monitoring of peak expiratory flow (PEF) undertaken with Ferrari peak expiratory flow gauges in home conditions.

Beclometasone dipropionate is normally prescribed in conventional doses of 400μg (by means of a metered-dose inhaler connected to a Glaxo Volumatic expansion chamber for young patients with mild and moderately severe asthma). In 8 children with severe persistent asthma, beclometasone dipropionate was prescribed in doses of 1000μg after first making a detailed check of their technique and reliability in taking the medication; the duration of taking the therapy to date and their existing Asthma action plan.

The control group included 20 healthy children. Before the start of this therapy, a daily cortisol profile (ELISA, Institute of Nuclear Medicine, Zemun) and urinary excretion of 17-OH corticosteroids (Photometrics S300 camera) were taken of all the subjects, which was also repeated 12 months after the beginning of treatment.

The children had compulsory clinical check-ups (monitoring changes in body weight and height and blood pressure by non-agressive methods) monthly or more often if needed. The data were compared with standards for healthy children and the results of healthy children from the control group.

Results

In the test of serum IgM, IgG and IgA concentrations, there was no statistically significant difference between children suffering from asthma and healthy children from the control group; however, in the test of serum IgE concentration the difference was significant. In Table 3, the serum IgE concentration of children with asthma and children from the control group is shown.

Table 2 - Distribution of respondents by severity of asthma

Age	Asthma test group (Total Sample=50)		
	Mild persistent	Moderate persistent	Severe persistent
7-10	6	7	2
10-14	4	25	6

Table 3 - Comparison of total IgE of children with asthma in children from the control group

IgE-children with asthma	n_1	50
	X_1	181,14
	SD_1	63,42
IgE-children from control group	N_2	20
	X_2	73,80
	SD_2	20,37
	T	6,98
	p	0,01
		VS

Legend :
n_1 – number in test group (asthma sufferers)
n_2 – number in control group (non-sufferers)
X_1 – arithmetical mean of IgE for n1
X_2 – arithmetical mean of IgE for n2
SD_1 – standard deviation of X1
SD_2 - standard deviation of X2

Serum concentrations of specific IgE were obtained for a mixture of springtime pollens, house dust and D. pteronyssinus. Results are shown in Table 4.

Table 4. Serum concentration of specific IgE

IgE Specific	0,7	0
	3,5	0
	17	15
	>17	18
IgE PPM	No increase	0
	Moderate increase	5
	Marked increase	3
IgE KP	No increase	0
	Moderate increase	12
	Marked increase	15
IgE D.pter.	No increase	0
	Moderate increase	12
	Marked increase	16

Legend:
IgE MSP – IgE specific to mixed spring pollens
IgE HD – IgE specific to house dust
IgE D.pter. – IgE specific to Dermatophagoides pteronyssinus

When skin tests were being carried out on inhaled allergens, the most prevalent allergens were house dust and D. Pteronyssinus (in earlier research this was revealed in a much larger sample of children suffering from asthma in Montenegro, in both the inland and coastal regions). Findings obtained by skin testing show a very good correlation with the serum concentration of specific IgE. This is shown in Table 5.

Table 5. Results obtained from skin tests of inhaled allergens

Bed dust	Negative Slightly positive Positive	0 1 0
Grass pollen	Negative Slightly positive Positive	0 1 5
Tree pollen	Negative Slightly positive Positive	0 2 4
Weed pollen	Negative Slightly positive Positive	0 1 5
Feathers	Negative Slightly positive Positive	0 1 2
Tobacco	Negative Slightly positive Positive	0 1 1
Mould	Negative Slightly positive Positive	0 0 0
Bacterial allergens	Negative Slightly positive Positive	0 1 1
House dust	Negative Slightly positive Positive	0 15 25
Dermatophagoides pteronyssinus	Negative Slightly positive Positive	0 5 25

In the test of serum concentration of cortisol before the start of the therapy, there was no statistically significant difference between children suffering from asthma and healthy children. The daily cycle of cortisol secretion remained constant. This is shown on Table 6.

After 12 months of taking beclometasone dipropionate in conventional doses in the first two groups of patients and in high doses in patients with severe persistent asthma, the daily profile of cortisol was constant, but the serum concentration was within expected limits. There was no statistically significant difference between those suffering from different severities of asthma, nor compared to healthy children, which is shown in Table 7.

Table 6. Serum concentration of cortisol in children with asthma before the start of beclometasone dipropionate treatment compared with children from the control group

		Cortisol	
		8 h	20 h
Children with asthma	n_1	50	50
	X_1	320,0	151,5
	SD_1	80,0	50,0
Children from control group	N_2	20	20
	X_2	348,5	162,0
	SD_2	76,0	40,0
	T	1,55	3,65
	p	0,01	0,01
		NS	NS

Legend:
n_1 – cohort of children with asthma on beclometasone dipropionate therapy
X_1 – arithmetic mean of asthma sufferers
SD_1 – standard deviation of X_1
n_2 – set of children from control group
X_2 – arithmetic mean of control group
SD_2 – standard deviation of X_2

Table 7. Serum concentration of free cortisol in children suffering from asthma after 12 months of undergoing preventative therapy with beclometasone dipropionate

		Cortisol	
		8 h	20 h
Asthmatic children after 12 months of treatment with Becotide 400μg	n_1	42	42
	X_1	320,0	151,5
	SD_1	80,0	50,0
Asthmatic children after 12 months of treatment with Becotide 1000μg	N_2	8	8
	X_2	314,5	163,0
	SD_2	68,0	53,0
	T	0,96	1,25
	p	0,05	0,05
		NS	NS

Legend:
n_1 – asthmatic children receiving a standard dose of Becotide over 12 months
X_1 – arithmetic mean n_1
SD_1 –standard deviation X_1
n_2 –children treated with the higher Becotide dose for 12 months
X_2 – arithmetic mean n_2
SD_2 – standard deviation X_2

Discussion

Fortunately, among children suffering from asthma, only a small number have severe uncontrolled asthma; therefore, the indications for the application of ICS in high doses are rare.

Note – In comparison, major and minor criteria for adult sufferers (19) are:

Major criteria:

- use of oral corticosteroids 50% of the time or more;

- continued use of high doses of inhaled corticosteroids, >1200 μg/day of beclometasone or equivalent medications;

Minor criteria:

- daily treatment with dual-action β2-agonists, theophylline or leukotriene antagonists;
- persistent obstruction of the airways;
- FEV1<80% of the predicted value;
- daily PEF variance of 20% or more;
- at least one visit to the emergency service in the previous year;
- at least three treatments of oral or inhaled corticosteroids in the previous year;
- rapid worsening of symptoms with a reduction of the dose of oral or inhaled corticosteroids of 25% or more;
- life-threatening asthma attacks in personal anamnesis.

Whenever asthma seems to be "uncontrolled" one should first check whether the patient is using the medication properly in terms of the regularity of taking medications, how carefully the patient is following their given Plan for Curing Asthma, and thus for any need to reinforce the instruction. Only then should one consider if it is appropriate to prescribe higher doses of ICS.

In our patients, beclometasone dipropionate did not cause any side-effects or suppression of hypothalamus-pituitary-suprarenal functions, whether in conventional or other controlled doses.

Clinical improvement and decreased use of oral and parenatal corticosteroids were achieved simultaneously.

Conclusion

The application of these medications (and other inhaled corticosteroids) in high doses should be reserved for strictly assessed patients. Particular care is essential in children, even more so among younger children. During the therapy, it is necessary to perform regular clinical and laboratory monitoring of the patients. As soon as the patient's condition allows, it is necessary to step down the treatment and decrease the dosage, which at the same time reduces the risk of causing undesired side effects of these medications.

References

1. Global initiative for Asthma, NHLBI/WHO Workshop report, national Institutes of Health, National Heart, Lung and Blood Instutute, Publication 1995; 95:659-61.
2. Global Initiative for Asthma. Global Strategy for Asthma Menagement and Prevention NHLBI/WHO Workshop Report. 2002.
3. The International Study of Asthma and Allergies in Childhood (ISAAC) Sreering Committee. Worldwidw variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies. Eur Resp J 1998, 12:315-35.
4. Europian Community Respiratory Health Survey. Variations in the prevalence of respiratory sym-ptoms, self-reported asthma attacs, and use of asthma medications in the Europian Community Respiratory Health Study (ECRHS). Eur Resp J 1998;12:315-35.
5. Kemp J, Kemp J, Am Fam Physicians 2001; 63:1341-8.
6. Strachan DP, The epidemiology of childhood asthma, Europian Journal of Allergy and Clinical Immunology. 1999;54: Suppl 49,7-11.
7. Djordjević D. Bronhijalna astma- inflamacija, opstrukcija i hiperreaktivnost. Niš 2001.
8. Nestorović B. Pedijatrijska pulmologija, Beograd 2001;226-45.
9. Barnes PJ. Pathophysiology of Asthma. In: Astma. Chung F, Fabbri LM eds. Europian Respiratory Monograph 2003;8: 84-114.
10. Jenkins AJ, Cool C, Czefler SJ, Covar R, Brugman S, Gelfand EW at al. Histopatology of severe childhood asthma. Chest 2003;124:32-41 (Medline).
11. Global strategy for asthma menagement and prevention. Bethesda (MD) : National Institutes of Health / National Heart, Lung , and Blood Institute; 2002.NIH publication 02-3659.
12. Kaye PO, Sullivan I. BTS asthma guide. Thorax 2001;56(8):666.
13. Asthma menagement handbook 2002.5th ed. Melbourne: National Asthma Council;2002.
14. Recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Volume 41, Issue 09, September 2005.
15. Guidelines for the Diagnosis and Menagement of Difficult-to-Control Asthma, Arch. Bronchoneumol 2005;41:513-23.
16. Chung KF, OByrne PM. Pharmacological agents used to treat asthma. In :Asthma. Chung F, Fabbri LM,eds. Europian Respiratory Monograph 2003; 8:339-75.
17. McGhan, Macdonald C, James DE, Naidu p, Wong E, Sharpe H, Hessel PA, Befus AD,Factors associated with asthma control in children aged five to 13 years; Can respir J 2006;13(1):23-9.
18. Zeiger RS, Szefler SJ, Phillips BR et al. Response profiles to fluticason and montelukast in mild-to-moderate persistent childhood asthma. J Allergy Clin Immunol 2006;117(1):45-52.
19. Bel EH, Severe asthma, Breathe, December 2006;3(2):129-38.

SIGURNOSNI PROFIL INHALACIONIH KORTIKOSTEROIDA (BECLOMETHASON DIPROPIONAT) PRIMIJENJENIH U KONVENCIONALNIM I VISOKIM DOZAMA U PREVENCIJI DEČJE ASTME

Milica Martinović

Astma je najrasprostranjenija hronična bolest u detinjstvu. Novija saznanja o prirodi patofizioloških zbivanja kod astme dovela su do široke primene antiinflamatornih agenasa i inhalacionih kortikosteroida u prevenciji ove bolesti. Smatra se da primenjeni u konvencionalnim dozama, ovi lekovi imaju dobar sigurnosni profil. Porast doze povećava rizik od ispoljavanja sistemskih neželjenih dejstava. Primjena vrlo visokih doza treba da bude rezervisana za slučajeve teške perzistentne astme uz intenzivno praćenje takvih bolesnika i prelazak «korak dalje» čim je to moguće, u cilju smanjivanja opasnosti od ispoljavanja sistemskih neželjenih dejstava.

Kod 50 bolesnika iz raznih krajeva Crne Gore, oba pola, uzrasta 7-14 godina, primenom međunarodnih standarda postavljena je dijagnoza blage (desetoro), umereno teške (trideset dvoje) i teške perzistentne astme (osmoro). Svi ispitanici su imali alergijsku astmu (serumska koncentracija IgE statistički značajno veća nego kod zdrave dece iz kontrolne grupe, nalaz specifičnih IgE, alergo-test).

U cilju prevencije javljanja napada astme, primenjen je beclomethason dipropionat, u konvencionalnim dozama (200-400 mcg) kod dece obolele od blage i umereno teške perzistentne astme i u visokim dozama (1000 mcg) kod obolelih od teške perzistentne astme u toku 12 meseci. Procena ispoljavanja sistemskih neželjenih efekata vršena je ponavljanim kliničkim pregledima i laboratorijski (dnevni profil kortizola na početku i na kraju primene ovih lekova i urinarna ekskrecija 17-OH-kortikosteroida). Kontrolnu grupu činilo je 20 zdrave dece.

U toku primene navedenih doza beclomethason dipropionata, klinički a ni laboratorijski, nije uočena supresija hipotalamo-hipofizno-adrenalne osovine bilo kod bolesnika koji su primali konvencionalne bilo kod onih koji su primali visoke doze ovog leka. Podaci drugih autora su slični. *Acta Medica Medianae 2008;47(1):13-18.*

Ključne reči: *dečja astma, inhalacioni kortikosteroidi, neželjena dejstva*