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Efficacy and Safety of Budesonide/Formoterol Combination Therapy in Asthma Patients

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ABSTRACT

Budesonide/formoterol as single inhaler was developed for treating asthma patients who are not adequately controlled on glucocorticoides alone. The aim of this study was to evaluate efficacy, safety and patient/physician satisfaction of budesonide/formoterol therapy. Total of 268 asthma patients (120 men, mean age $38,8 \pm 37,2$ years, and 148 women, mean age $42,2 \pm 32$ years) were included in the study. All patients received budesonide/formoterol bid (640 mcg of budesonide and 18 mcg of formoterol daily) during run-in period for three weeks. Patients were followed during 14 weeks at 5 visits. At each visit lung function (FEV_1 and PEF) was measured, presence of side effects was recorded and questionnaire was given to patients and physicians to estimate the level of satisfaction with budesonide/formoterol therapy (1 very unsatisfied to 5 very satisfied). Significant improvement was noticed in FEV_1 , from 76,25% of predicted value to 86,94% ($p < 0,01$); and in PEF from 380,84 L/min to 442,29 L/min ($p < 0,01$) in all patients. At the end of the study patients' satisfaction with budesonide/formoterol therapy was significantly improved comparing with satisfaction with previously taken therapy, in average grade, from 2,94 to 4,56 ($p < 0,01$), and similar results were noticed with physicians' satisfaction, from 2,60 to 4,41 ($p < 0,01$). Budesonide/formoterol in single inhaler, significantly improved lung function in patients with asthma.

Key words: asthma, asthma control, budesonide/formoterol

Introduction

Asthma is a chronic inflammatory disease of the airways. The underlying inflammation leads to hyperresponsiveness of the airways which results in reversible bronchial obstruction. Fluctuations in symptoms and airway inflammation are major characteristics of asthma. Asthma can not be cured, although it is a disease that can be managed effectively with combination of trigger avoidance, education and pharmacotherapy¹. Effective control of asthma symptoms and maintenance of optimal lung function are crucial for the long-term management of patients with asthma. Asthma control is defined to achieve and maintain control of the symptoms and best possible lung function, and at the same time to prevent worsening and exacerbations of asthma and to achieve best possible quality of life^{2,3}. Despite available and precise treatment guidelines, in many patients asthma

is under treated and control of the diseases is not achieved⁴.

Current asthma treatment guidelines recommend a stepwise approach to the treatment of asthma in adults based on the severity of the disease^{2,3}. Inhaled corticosteroids (ICS) are accepted for the first-line management of moderate to severe persistent asthma, but do not always provide sufficient control of the disease in all patients. For patients who are not well controlled by ICS alone, as first line add-on treatment are recommended long-acting β_2 -agonists (LABA), like formoterol and salmeterol. First study that gave rationale for adding LABA to ICS as first-line option was published by Greening and colleagues and showed that adding LABA to ICS is more effective than increasing the dose of ICS in treating asthma patients⁵. Further studies, using bu-

desonide and formoterol confirmed that adding LABA to low dose of ICS in patients previously treated with ICS is superior in improving lung function compared to two – folds or even four – folds increase in the dose of ICS^{6,7}. Price and colleagues showed that adding formoterol to low dose budesonide results in faster and more effective asthma control than budesonide alone in patients with mild asthma⁸.

However, there is a need to simplify the asthma treatment, particularly when patients are using more than one medication for the treatment of their disease. Patients would prefer as less as possible medications to control their disease, and would prefer as less as possible inhalers for drug delivery⁹. In the last years, two fixed combination of inhaled corticosteroid and long – acting β_2 – agonists were developed: combination of fluticasone propionate and salmeterol (Seretide™/ Advair™, Glaxo-SmithKline) and combination of budesonide and formoterol (Symbicort®, AstraZeneca).

Since then, several studies established efficacy and safety of budesonide and formoterol fixed combination in the treatment of asthma in adults, as well as in children^{10–12}.

The aim of this 14 – week open – labeled study was to estimate efficacy and safety of fixed budesonide/formoterol combination (Symbicort® Turbuhaler®, AstraZeneca) in patients with persistent asthma. Primary end point of this study was improvement in lung function, and secondary end points were to estimate patients' and physicians' satisfaction with the budesonide/formoterol treatment.

Methods

Patients

Male and female asthma patients aged = 11 years were eligible for the inclusion in the study in if:

- 1) They were newly diagnosed asthma patient with moderate to severe persistent asthma according to GINA guidelines (2) previously not treated; or
- 2) They were using inhaled corticosteroids at daily dose ≥ 400 mcg of budesonide propionate or equivalent daily; or
- 3) They were using ICS and LABA in separate inhalers; or
- 4) They were inadequately controlled on fixed fluticasone/salmeterol combination; or
- 5) They were inadequately treated with ICS and short – acting β_2 – agonist as needed; or
- 6) They were using oral corticosteroids for more than 10 days in the last three months; or
- 7) They were hospitalized due to asthma in the last 12 months.

The study was conducted in accordance with the Declaration of Helsinki. The local ethics committees approved the study protocol. All patients gave written informed consent before entering the study.

Study Design

This was open – labeled, controlled study conducted at 10 outpatient centers in Croatia. At the initial visit patient underwent physical examination and their medical histories were recorded. Patients then entered a 3 – week run – in period during which they received budesonide/formoterol (Symbicort Turbuhaler®, AstraZeneca) 160/4.5 mcg two inhalations twice daily plus short – acting β_2 – agonist salbutamol (Ventolin) as needed. Patients returned to the centers for follow – up visits after 3, 6, 10 and 14 weeks of the treatment.

Assessments

At each visit lung function was tested by spirometry (Erich Jaeger, Master Lab Body) in accordance to European Respiratory Society guidelines (13). The highest value for FEV₁ from at least three acceptable attempts was recorded with no reliever medication being used within the 6 hours before the performance of the lung function tests.

At each visit also peak expiratory flow (PEF) was also recorded, again using the highest value from at least three acceptable attempts with no reliever medications being used within the 6 hours.

At each visit patients also recorded symptoms (cough, dyspnea, chest tightness, night awakening due to asthma) in a period of time from the last visit.

At each visit patient and physician graded their satisfaction with therapy: from very unsatisfied (grade 1), unsatisfied (grade 2), moderately satisfied (grade 3), satisfied (grade 4) and very satisfied (grade 5).

Patients were recording their symptoms on daily base and symptoms were graded as mild, moderate and severe,

Safety was assessed by recording spontaneously reported adverse events or in response to question asked by the investigator at each visit.

The budesonide/formoterol dose 160/4.5 two inhalations bid was reduced by the physicians to one inhalation bid if there was normal lung function measured and no symptoms or need for reliever therapy occurred since the last visit.

Statistical analysis

The data were presented in absolute and relative frequencies of various answers. Changes from baseline were analyzed by analysis of variance (ANOVA). The results considered statistically significant for p values less than 0.05. Statistical analyses were performed using the SPSS software.

Results

A total of 268 patients were enrolled in the study with slight female predominance (148 females, 115 males) with mean age 40.8 years. Only 16% of patients were newly diagnosed. More than half of patients (145 patients, 54.2%) had every day symptoms. All patients had

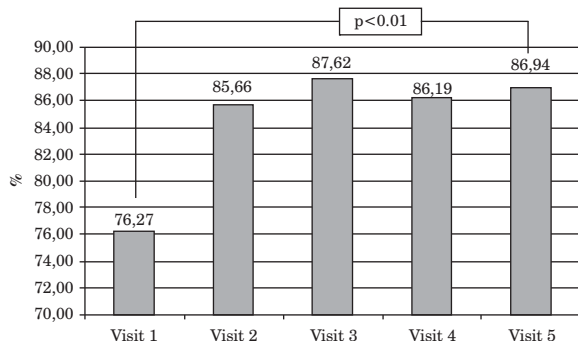
TABLE 1
PATIENTS DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Mean age (range)	40,8 y (11–76)
Previous asthma	225 (84%)
Newly diagnosed asthma	43 (16%)
Prestudy medication	
Seretide	88 (39%)
fluticasone and salmeterol	16 (7%)
fluticasone	25 (11%)
budesonide	27 (12%)
other	69 (31%)
Frequency of symptoms	
every day	145 (54,2%)
weekly	94 (35,2%)
monthly	29 (10,6%)
Asthma severity	
mild	27 (10%)
moderate	214 (80%)
severe	27 (10%)
Mean FEV ₁	76,27 %
Mean PEF	380.84 L/min
Average grade of satisfaction with previous therapy	
patients	2.94
physicians	2.60

persistent asthma, with majority of them (80%, 214 patients) had moderate persistent asthma. Patients were receiving various previous medications: 39% were not well controlled on fluticasone/salmeterol, 11% of patients were using fluticasone alone, 12% of patients were using budesonide alone and 7% of patients were using salmeterol and fluticasone in separate inhalers; the rest of the patients used various medications (short acting β_2 – agonists alone, teophyllins, montelukast). Patients baseline characteristics and demographics are shown in Table 1.

Lung function

Significant improvement in FEV₁ was seen in all patients (76.27% to 86.94%, $p < 0.01$) after 14 weeks of treatment. Improvement in FEV₁ was seen all ready af-

Fig. 1. Improvement in FEV₁ after 14 weeks.

ter three weeks of treatment and then remained stable during the follow – up period (Figure 1).

Significant improvement was also noticed in peak expiratory flow (PEF) after 14 weeks (380.84 to 442.29 L/min, $p < 0.01$). The improvement was noticed already after 3 week of treatment (Figure 2).

Satisfaction with treatment

At the start of the study only 4.4% of patients were very satisfied with previous treatment (grade 5); 24.4% were satisfied (grade 4); 36.8% were moderately satisfied (grade 3); 32% were unsatisfied (grade 2); and 2.4% were very unsatisfied with previous treatment. Average grade of satisfaction at the start of the study was 2.94. At the end of the study 63.5% of patients were very satisfied with the budesonide/formoterol in single inhaler (grade 5); 31.2% were satisfied (grade 4); 4.2% were moderately satisfied (grade 3) and 1.1% of patients were unsatisfied (grade 2) with the new treatment at the end of the study. There were no very unsatisfied patients at the end of the follow – up period. Average grade improved, from 2.94 to 4.56. This improvement was statistically significant ($p < 0.01$). (Figure 3)

At the start of the study 3.6 % of physicians were very satisfied with previous treatment of their patients (grade 5); 15.3% were satisfied (grade 4); 35.5% were moderately satisfied (grade 3); 31.9% were unsatisfied (grade 2); and 13.7% were very unsatisfied with previous treatment. Average grade of satisfaction at the start of the study was 2.60. At the end of the study 59.6% of physicians were very satisfied with their patients' treatment (grade 5); 26.6% were satisfied (grade 4); 11.2% were moderately satisfied (grade 3) and 2.7% of patients were unsatisfied (grade 2) with the treatment at the end of the study. There were no very unsatisfied (grade 1) physicians at the end of the follow – up period. Average grade improved, from 2.60 to 4.41. This improvement was statistically significant ($p < 0.01$) (Figure 4).

Safety

Only small number of side effects was recorded during the study period. Dysphonia was noticed in 8 patients (3%); headache in 6 (2%); meteorism in 5 (2%); tremor in 5 patients (2%); oral candidiasis in 2 patients (1%); tachy-

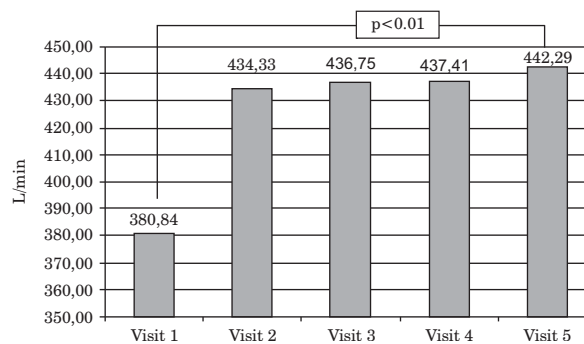


Fig. 2. Improvement in PEF after 14 weeks.

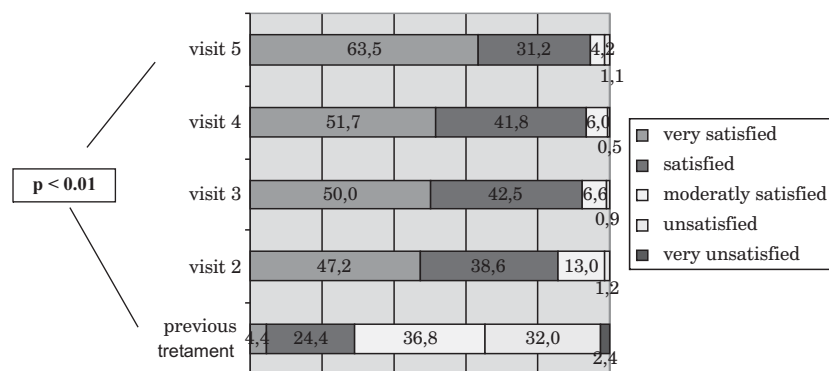


Fig. 3. Patients satisfaction with the budesonide/formoterol treatment. (percentage of patients in each group of satisfaction at each visit).

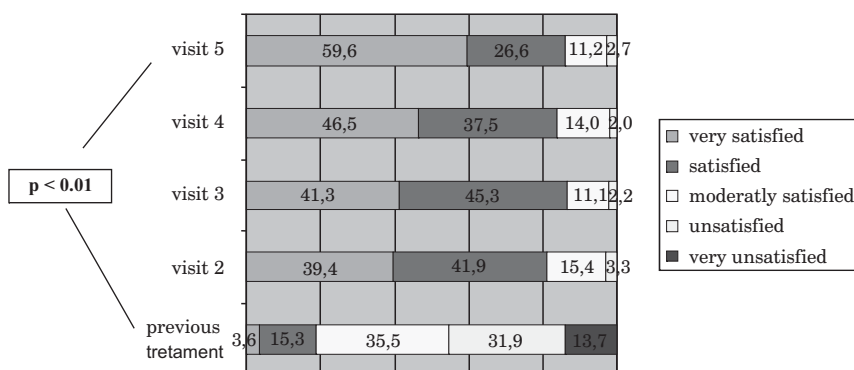


Fig. 4. Physicians satisfaction with the budesonide/formoterol treatment. (percentage of physicians in each group of satisfaction at each visit).

cardia in 1 patient (0.3%); vomitus in 1 (0.3%); and rash in 1 patient (0.3%).

Discussion

In this 14 – week, open – label study we tried to estimate the efficacy and safety of fixed combination of budesonide/formoterol in asthma patients with persistent asthma. Our primary end point was improvement in lung function. In all patients we noticed significant improvement in lung function measured by FEV₁ and PEF after 14 weeks of treatment. Thus, this improvement was already noticed after three weeks of treatment. In this study we also tried to estimate patient and, what is rarely done, physicians satisfaction with their patients' treatment. We found significant improvement in satisfaction, both patients and physicians with budesonide/formoterol fixed combination treatment compared with previous therapy. Only small number of adverse events was reported during the study.

Asthma treatment approach used in this study was in accordance with previous studies which showed efficacy of fixed combination and fixed dosing of budesonide/formoterol combination^{6,7,10}.

Majority of patients in the study were patients with moderate persistent asthma², and small percentage of

our patients were those with other categories of persistent asthma. In our study there were 10% of patients with mild persistent asthma, which were also included in the study, although, current guidelines do not recommend inhaled corticosteroids and long – acting β_2 – agonist combination in the treatment of such patients. Thus, all patients with mild asthma were not well controlled on high doses of inhaled corticosteroid alone, so they were included in the study.

We demonstrated in our study that budesonide/formoterol quickly improved lung function, already after three weeks of treatment and than maintained this improvement throughout the study period. This result is supported by several studies which showed that budesonide/formoterol combination quickly gains asthma control in patients with mild, moderate and severe persistent asthma^{10–12}.

Interesting point was that 39% of patients were not well controlled on fluticasone/salmeterol combination before entering the study. All those patients improved their lung function and satisfaction with the budesonide/formoterol treatment after 14 weeks. However, this study was not design to compare efficacy and safety of budesonide/formoterol and fluticasone/salmeterol combination, although, this observation was in favor of SUND study which showed better asthma control in patients

who were treated with budesonide/formoterol than fluticasone/salmeterol¹⁴.

Budesonide/formoterol has rapid onset of action, even within minutes^{15–17}. This rapid onset of action may be important factor for good compliance of patients to the budesonide/formoterol, so this can partially explained improvement in satisfaction of our patients with the treatment compared with previous one.

Limitation of this study was that there was no control group. We used as primary end point improvement in lung function. Using only isolated parameters, like lung function, for estimation of asthma control can overestimate control of the disease¹⁸. Asthma control should not

only be estimated according to isolated parameters. It should be estimated according to lung function, presence of day and night symptoms, reliever usage, exacerbations and presence of treatment adverse events².

Budesonide/formoterol (Symbicort Turbuhaler®, AstraZeneca) is an effective and well tolerated treatment option for patients with persistent asthma. The ability to administer both anti-inflammatory and bronchodilatory drugs in one inhaler improves adherence of patients. Budesonide/formoterol fixed combination could be reasonable choice for first line treatment in patients with moderate to severe persistent asthma.

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UČINKOVITOST I SIGURNOST KOMBINACIJE BIDEZONIDA I FORMOTEROLA U BOLESNIKA S ASTMOM

SAŽETAK

Kombinacija budezonida i formoterola u jednom inhalatoru koristi se u bolesnika koji nemaju dobru kontrolu astme uz inhalacijske kortikosteroide. Cilj ovog rada je procijeniti učinkovitost i sigurnost fiksne kombinacije budezonida i formoterola te procijeniti zadovoljstvo bolesnika i liječnika navedenom terapijom. U studiju je uključeno ukupno 120 ispitanika. Svi bolesnici su koristili budezonid/formoterol dva puta na dan u ukupnoj dozi 640 mcg budezonida i 18 mcg formoterola kroz tri tjedna. Bolesnici su praćeni tijekom 14 tjedana u 5 posjeta. Na svakoj posjeti mjerena je plućna funkcija, bilježeno prisustvo nuspojava, te su bolesnici i liječnici ispunjavali upitnik o zadovoljstvu liječenjem. Tijekom praćenja nađeno je značajno poboljšanje u plućnoj funkciji (FEV₁ i PEF). Također, na kraju studije značajno veće zadovoljstvo liječenjem pokazano je i među ispitanicima i među liječnicima. U konačnici, budezonid i formoterol u jednom inhalatoru značajno poboljšava plućnu funkciju, te zadovoljstvo liječenjem u bolesnika s astmom.