Allergy 1998: 53: 20–23
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ALLERGY
ISSN 0105-4538

Additive effects of inhaled formoterol and budesonide in reducing asthma exacerbations

Pauwels R. Additive effects of inhaled formoterol and budesonide in reducing asthma exacerbations.
Allergy 1998: 53: 20–23. © Munksgaard 1998.

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The place of the long-acting β-adrenergic agonists in the long-term management of chronic asthma is still controversial. It is still not clear when long-acting β-adrenergic agonists should be introduced into therapy. Many international guidelines for the treatment of asthma advise the use of long-acting β-adrenergic agonists only when high doses of inhaled corticosteroids are already prescribed (1). However, recent studies have shown that long-acting β-adrenergic agonists can be used effectively in combination with low doses of inhaled corticosteroids (2). In addition, there remain concerns over safety with the long-term use of long-acting β-adrenergic agonists, as short-acting β-agonists have been linked to the worsening of asthma symptoms and an increase in asthma mortality (3). This review will detail the formoterol and corticosteroids establishing therapy (FACET) study that was specifically designed to address these two questions (4).

Study population

The FACET study was based on the hypothesis that the addition of regular treatment with formoterol to inhaled corticosteroids (budesonide) will result in improved control of asthma symptoms and lung function without long-term deterioration of asthma. The study was double-blind, randomized, of parallel-group design, and performed at different centres in nine countries. The study population included patients with moderate to severe asthma aged 18–70 years who had been regularly taking inhaled corticosteroids for at least 3 months. Patients had an FEV_1 of more than 50% predicted and displayed at least 15% reversibility after the inhalation of 1 mg terbutaline. Severe asthmatics were excluded from the study. This included patients on very high doses of inhaled corticosteroids, such as 2000 μg BDP or 1600 μg budesonide per day delivered via a pMDI, patients on more than 800 μg budesonide delivered via Turbuhaler®, and those on more than 800 μg fluticasone per day. Patients regularly taking oral corticosteroids, or who had had more than two courses of oral corticosteroids over the last 6 months, or who were hospitalized in the last month before the study were also excluded. Hence, patients who relied heavily on corticosteroids to control their asthma were not allowed to enter the study. This was required for safety reasons, as very low doses of inhaled corticosteroids were administered during the study.

Study design

The study consisted of a 4-week run-in period, during which 852 patients received 800 μg b.i.d. of budesonide via Turbuhaler. Terbutaline Turbuhaler was also used as rescue medication during this period. The run-in period was designed to stabilize the patients' asthma before randomization, and only patients who were stable during the last 10 days of this 4-week period were allowed to enter the study. Unstable patients were defined as those who had a variation in PEF of ≥20% on two consecutive days, or who used more than three inhalations of terbutaline over 24 h on two consecutive days, or who had nocturnal asthma on two consecutive nights; patients who required oral corticosteroids were also defined as unstable.

Patients who were well controlled were randomized to receive 12 months of treatment in one of four treatment groups:

1) low dose of inhaled corticosteroids
2) low dose of inhaled corticosteroids plus formoterol (delivered via Turbuhaler)
3) moderate dose of inhaled corticosteroids
4) moderate dose of inhaled corticosteroids plus formoterol.

Terbutaline Turbuhaler was provided as rescue medication in all four groups (Table 1). Each treatment arm consisted of more than 200 patients with a mean age of 42 years. Before entry into the study, the patients were taking, on average, 800 μg of inhaled corticosteroids per day, and they had a mean FEV_1 of 76% predicted.

Table 1. Four treatment arms in FACET study

Budesonide 100 μg b.i.d.	Placebo b.i.d.	Terbutaline 0.25 mg p.r.n.
Budesonide 100 μg b.i.d.	Formoterol 9 μg b.i.d. (delivered dose)	Terbutaline 0.25 mg p.r.n.
Budesonide 400 μg b.i.d.	Placebo b.i.d.	Terbutaline 0.25 mg p.r.n.
Budesonide 400 μg b.i.d.	Formoterol 9 μg b.i.d. (delivered dose)	Terbutaline 0.25 mg p.r.n.

Outcome measures

Severe asthma exacerbations

The primary outcome variable was the number of severe asthma exacerbations over the study period. A severe asthma exacerbation was defined as an exacerbation that was treated with oral corticosteroids. This was determined by the investigating physician, who could make a clinical decision to prescribe oral corticosteroids. The treatment course was standardized, and each patient received 10 days' treatment with prednisolone. A treatment course of oral corticosteroids was also administered if, on two consecutive days, the patient's morning PEF had decreased by more than 30% when compared with baseline measurements. Baseline was defined as a mean PEF determined over the last 10 days of the run-in period when patients were considered to be optimally controlled. Measurements of PEF were self-administered, and patients could contact their physician if treatment was required.

The absolute number of severe asthma exacerbations was reduced in patients treated with a moderate dose of budesonide or in the presence of formoterol (200 μg budesonide, 153 exacerbations; 200 μg budesonide plus formoterol, 125 exacerbations; 800 μg budesonide, 90 exacerbations; 800 μg budesonide plus formoterol, 57 exacerbations). The severe exacerbation rate (the number of exacerbations per patient per year) is shown in Fig. 1. Increasing the dose of budesonide from 200 to 800 μg decreased the exacerbation rate by 49%, and the addition of formoterol to either dose of budesonide decreased the exacerbation rate by 26%. Hence, the effect of increasing the dose of budesonide was significantly higher than the effect of adding formoterol. However, the effects of each drug were independent of each other; overall, the combination of 800 μg budesonide with formoterol gave the lowest incidence of severe asthma exacerbations.

The total number of severe asthma exacerbations can also be expressed according to the criteria used to initiate oral corticosteroid treatment. In all groups, the physician made a clinical judgement to initiate treatment in 70% of cases, irrespective of the patients' own PEF measurements. Interestingly, the characteristics of the severe exacerbations were the same in all treatment groups, even when identified by the physician or by PEF measurements.

The percentage of patients with no severe exacerbations over the study period also followed the same pattern. Some 81% of patients treated with 800 μg budesonide and formoterol had no severe exacerbations compared with 61% in the 200 μg budesonide treatment group. Finally, patients could be withdrawn from the study if, over a period of 3 months, they had three or more severe exacerbations. The number of patients withdrawn from each group was highest in the 200 μg budesonide group, and this decreased with increasing therapy. No withdrawals were observed in the 800 μg budesonide and formoterol treatment group over the study period.

Mild asthma exacerbations

A mild exacerbation was defined as a day when the morning or evening PEF fell more than 20% below the baseline measurement at run-in, or a day when the patient used four or more inhalations of terbutaline above the level at the end of the run-in or the occurrence of nocturnal asthma. These signs of deterioration had to exist for 48 h before a mild exacerbation was recorded.

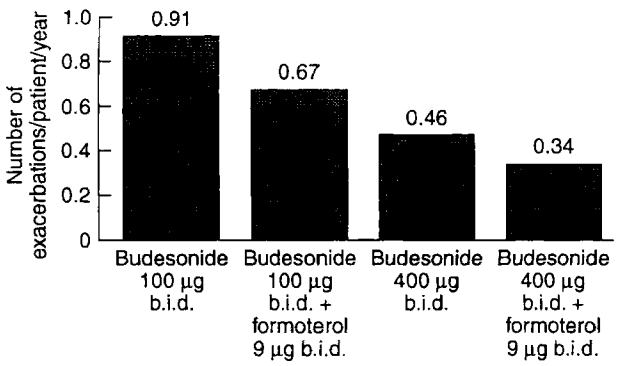

Fig. 1. Severe exacerbation rate in four treatment arms of FACET study.

An analysis of the rate of mild exacerbations over the study period showed that increasing the dose of inhaled corticosteroids to 800 μg decreased the number of mild exacerbations by 37%. Adding formoterol to the low dose or moderate dose of budesonide decreased the number of mild exacerbations by 40%. Hence, both treatment changes had a similar efficacy, and the lowest number of moderate exacerbations was recorded in the 800 μg budesonide- and formoterol-treatment group. Furthermore, the number of patients with no mild exacerbations over the whole year reached 51% in this group. This can be compared with 29% in the 200 μg budesonide-treatment group.

PEF

The addition of formoterol to inhaled corticosteroid therapy increased morning PEF by 30–40 l/min above the values obtained at the end of the run-in period. This response was maintained for 2 days, but dropped slightly by day 3 of the study. The response to formoterol was then maintained throughout the study period with no further significant drop in measured PEF. Moreover, this response was significantly higher than that observed with inhaled corticosteroid therapy alone. A moderate dose of 800 μg of budesonide increased the PEF measurement above that seen with 200 μg budesonide, either with or without formoterol. This indicates a dose-dependent response for budesonide treatment.

FEV_1

A highly significant increase in FEV_1 was observed when patients were switched to 1600 μg of budesonide during the run-in period. The addition of formoterol further increased the measured FEV_1, and this remained constant over the study period. A small, dose-dependent decrease in FEV_1 was observed after the run-in period in patients placed on 200 and 800 μg budesonide alone.

Asthma symptom score

At the end of the run-in period, patients had a mean asthma symptom score of 0.5, on a scale of 0–3. This reflected the effective control of their asthma obtained with a daily dose of 1600 μg inhaled budesonide. During the study period, there was a further decrease in the symptom score with the addition of formoterol, during both the day and the night. This was reflected by a decrease in the use of terbutaline as rescue medication in the formoterol treatment groups. Moreover, the use of rescue medication remained constant in the budesonide-treatment groups (0.6 applications per day). The occurrence of nocturnal asthma symptoms increased with low-dose budesonide, and this resulted in a higher number of awakenings in this group compared with the other treatment groups. Nocturnal symptoms were lowest in the formoterol-treatment groups.

The number of days in which asthma was well controlled was also recorded. These were defined as days with no symptoms, where patients did not require rescue medication, had a PEF of at least 80% of their baseline value, and did not experience an adverse event. A low dose of budesonide with formoterol resulted in 163 well-controlled days compared with 153 days for 800 μg budesonide alone and 179 days for 800 μg budesonide with formoterol. Therefore, the addition of formoterol increased the number of symptom-free days in this study.

Conclusions

Increasing the dose of budesonide, or adding a regular treatment with formoterol to inhaled budesonide, decreased the severe exacerbation rate. Therefore, the hypothesis that adding formoterol would not lead to deterioration in disease was reversed, showing that adding formoterol results in better control of the disease. However, increasing the dose of budesonide was more effective in decreasing severe exacerbations than the addition of formoterol. Secondly, adding regular treatment with formoterol to inhaled budesonide or increasing the dose of budesonide decreased the mild exacerbation rate in a similar manner. Furthermore, formoterol improved asthma symptoms and lung function to a greater extent than an increased dose of budesonide.

The effects of adding formoterol or increasing budesonide on asthma control were independent of each other. Hence, formoterol had a similar effect when combined with a low or high dose of budesonide. These effects were constant over the whole study except for a small decrease in the bronchodilating effect of formoterol after the first 2 days of treatment. Finally, all treatments were very well tolerated, and no safety implications were identified.

Discussion

S. Durham: What is your own view about the place of formoterol in asthma management at the present time?

R. Pauwels: Based on these results and the findings of Greening et al. (2) and Woolcock et al. (3), we should not be afraid of adding regular treatment

with long-acting β-agonists at an earlier stage. A new place for long-acting β-agonists should be found in the international guidelines. For example, a patient who is on a low dose of inhaled corticosteroids and still has symptoms of asthma, e.g., nocturnal asthma, or who has a peak flow that is less than optimal, should be given a long-acting β-agonist as regular treatment. This will improve the control of asthma in that patient. However, in a patient with a history of severe exacerbations or who has had a severe exacerbation, you should increase the dose of inhaled corticosteroid before adding a long-acting β-agonist.

Audience: What percentage of patients did not respond to formoterol?

R. Pauwels: I do not know; however, the majority of patients did respond.

Audience: When you compared the severe exacerbation rates in the different treatment groups, did you correct your data for the occurrence of upper respiratory tract or viral infections?

R. Pauwels: Data on viral infection were not collected. However, we did collect data on symptom scores for the days before and after an exacerbation. Peak flow measurements were also recorded, as was the use of rescue medication. If you compare these parameters between the four treatment groups, they are exactly the same at each exacerbation.

Audience: A deterioration in the peak flow, from baseline, was recorded in the 200 and 800 μg budesonide groups over the study. Does this mean that those patients were not well controlled?

R. Pauwels: The baseline peak flow was measured when the subjects were on 1600 μg of budesonide. Therefore, with a decrease in the dose of budesonide from 1600 to 200 μg, you would expect a slight decrease in PEF corresponding to a dose-response curve for budesonide.

Audience: If you have a patient whose asthma is not completely controlled, should you add a high dose of inhaled corticosteroids, and then add formoterol before reducing the corticosteroid dose?

R. Pauwels: If a patient is not controlled on a symptom basis or lung function measurement, then the first step is to add formoterol. If, on the other hand, your patient is not controlled and has had a severe exacerbation, then you have to increase the dose of inhaled corticosteroid first.

Audience: Professor Selroos, you showed two, 3-day studies with high doses of formoterol; 12 patients in the first one and 15 patients in the second. You draw the conclusion that the drug is safe when given in high doses, but are 3 days enough and is the number of patients large enough to draw such a conclusion?

O. Selroos: The doses were approximately 10 times higher than those normally used. Patients were exposed to these high doses for 3 days and no serious effects were observed. This is reassuring in a clinical situation where a patient may take an additional dose of formoterol by mistake. This was the purpose of the study, and it has demonstrated a wide safety margin.

Audience: Professor Pauwels, is treatment with formoterol cost-effective?

R. Pauwels: Cost-efficacy analyses are being done on the FACET study, but I do not have the results. However, there is clearly a difference in the number of symptom-free days with formoterol use, and we had very few severe exacerbations. If you look at the number of severe exacerbations and multiply that by the associated costs, then you have a good argument in favour of formoterol use.

S. Durham: It remains for me to thank all of the speakers for their excellent presentations and also to thank Astra Draco for making this symposium possible.

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