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Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma

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Summary Adherence to maintenance therapy is often poor in patients with asthma. Simplifying dosing regimens has the potential to improve both adherence and asthma-related morbidity. In this 12-week, randomized, double-blind, double-dummy, parallel-group study, 617 patients with mild to moderate persistent asthma (mean forced expiratory volume in 1 s [FEV_1] 78.5% predicted) who were not optimally controlled on inhaled corticosteroids (200–500 μg/day) were randomized to once-daily budesonide/formoterol (80/4.5 μg, 2 inhalations in the evening), twice-daily budesonide/formoterol (80/4.5 μg, 1 inhalation), or a corresponding dose of budesonide once-daily (200 μg, 1 inhalation in the evening). All patients received budesonide (100 μg twice daily) during a 2-week run-in. Changes in mean morning peak expiratory flow (PEF) were similar for od budesonide/formoterol (23.4 l/min) and twice-daily budesonide/formoterol (24.1 l/min), and both were greater than with budesonide (5.5 l/min; both $P<0.001$). Evening PEF, symptom-free days, reliever-free days, and asthma control days were improved with budesonide/

Abbreviations: ICS, inhaled corticosteroids; FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow

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formoterol therapy vs. budesonide ($P<0.05$ vs. budesonide for all variables). All treatments were well tolerated. Budesonide/formoterol administered once daily in the evening is a convenient treatment regimen that is as effective in improving asthma control as twice-daily dosing in patients with mild to moderate persistent asthma.

Introduction

Combination therapy with inhaled corticosteroids (ICS) and long-acting β_2-agonists is well established as maintenance treatment for patients with asthma that is not optimally controlled on ICS alone.[1,2] This may require the use of several inhalers, i.e. an ICS inhaler plus a long-acting β_2-agonist inhaler for maintenance, in addition to a short-acting β_2-agonist for reliever medication. Such regimens can be too complicated for some patients, many of whom prefer simple treatments using the minimum number of devices and less frequent dosing.[3,4] Treatment regimens that address these issues have the potential to improve adherence and reduce the morbidity associated with asthma.

The co-administration of an ICS and a long-acting β_2-agonist in the same inhaler is an important advance in asthma medication that simplifies drug administration. The combination of budesonide and formoterol (Symbicort® Turbuhaler®) has been shown to be effective and well tolerated in a range of patient populations.[5–8] In addition, greater efficacy of a lower dose of ICS in conjunction with a long-acting β_2-agonist (budesonide/formoterol 80/4.5 μg twice daily), compared with a higher dose of ICS alone, has been demonstrated in patients with mild to moderate asthma.[9] Budesonide/formoterol used as maintenance plus as needed for symptom relief has also been shown to be efficacious and well tolerated.[10]

Another factor that affects patients' adherence to prescribed medication is dosing frequency. Adherence to asthma therapy increases with less-frequent dosing regimens[11] and once-daily dosing may thus aid adherence. Buhl et al.[12] have shown once-daily dosing with budesonide/formoterol (160/4.5 μg, 2 inhalations in the evening) to be an effective treatment for patients with moderate persistent asthma. Morning and evening peak expiratory flow (PEF), night-time awakenings, symptom-free days, reliever-free days, and asthma control days were all improved compared with a corresponding dose of budesonide alone and the improvements were comparable with twice-daily budesonide/formoterol (160/4.5 μg, 1 inhalation in the morning and evening). Once-daily budesonide/formoterol provided sustained efficacy over 24 h that was comparable with twice-daily dosing and was superior to budesonide alone.

Once-daily dosing may be particularly suitable for patients with mild to moderate asthma. Patients with mild asthma can be reluctant to use their maintenance medication, especially when they are relatively symptom-free. Indeed, many consider their asthma to be a minor condition that can be treated using reliever medication alone.[3,4] Therefore, minimizing the burden of treatment is particularly important in these patients. We compared the efficacy and safety of a low dose of budesonide/formoterol (80/4.5 μg, 2 inhalations) administered once daily with that of twice-daily budesonide/formoterol (80/4.5 μg, 1 inhalation administered in the morning and the evening) and a corresponding once-daily dose of budesonide (200 μg, 1 inhalation in the evening) in patients with mild to moderate asthma.

Methods

Patients

Men or women aged ⩾18 years of age were eligible to enter this study (study code SD-039-0665) if they had a diagnosis of asthma (minimum duration: 6 months) that was not optimally controlled despite a daily ICS dose of 200–500 μg for at least 30 days before study entry. Patients had a baseline forced expiratory volume in 1 s (FEV_1) of 60–90% of predicted normal and demonstrated reversibility of FEV_1 of at least 12% upon inhalation of terbutaline sulfate 1 mg (Bricanyl® Turbuhaler®; AstraZeneca, Lund, Sweden) or salbutamol 0.4 mg.

Patients were excluded if they had: used any systemic corticosteroids within the previous 30 days; seasonal asthma (defined as asthma exacerbated by seasonal increases in aeroallergens); a respiratory infection in the 4 weeks before study entry; a severe cardiovascular disorder or any other significant disease; used β-blocker therapy (including eye drops) or had a history of heavy smoking (⩾10 pack-years). Women of child-bearing

potential who were pregnant or who failed to use acceptable contraceptive measures were also excluded from the study. Patients who were unable to use a peak flow meter or who did not complete the daily diary card during 7 or more of the last 10 days of the run-in period were not permitted to enter the randomized treatment period.

Study design

This was a randomized, double-blind, double-dummy, active-controlled study with a parallel-group design. It was conducted at 61 centers in eight countries (Finland, Germany, Mexico, New Zealand, Norway, Poland, Russia, and Sweden). The study protocol was approved by local ethics committees and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Before entering the study, each patient provided written informed consent.

Patients entering the study underwent a physical examination and provided a complete medical and respiratory history at Visit 1. Patients then entered a 2-week run-in period during which they received budesonide 100 μg twice daily (Pulmicort® Turbuhaler®; AstraZeneca, Lund, Sweden). At the end of the run-in period (Visit 2), patients were randomized to receive 12-weeks' treatment with budesonide/formoterol (Symbicort® Turbuhaler®; AstraZeneca, Lund, Sweden) 80/4.5 μg 2 inhalations once daily in the evening, budesonide/formoterol 80/4.5 μg 1 inhalation twice daily, or a corresponding dose of budesonide 200 μg 1 inhalation once daily in the evening. The budesonide doses in each group were comparable; differences are explained by labeling changes for new inhaled drugs, which require the delivered dose rather than metered dose to be reported.

To ensure treatment blinding, a double-dummy design was used so that patients received four successively numbered Turbuhalers, with the corresponding placebo inhalers being identical in appearance to those containing active medication. Patients were instructed to inhale once from the first inhaler in the morning upon rising and to inhale once from each of the other three inhalers in the evening just before going to bed. They were asked to rinse their mouths after inhaling from all inhalers. Patients returned for clinic visits at Weeks 4, 8, and 12 of randomized treatment (Visits 3, 4, and 5). All clinic visits took place between 07:00 and 10:00, i.e. within 1 h of the time that Visit 1 occurred.

Patients were given terbutaline sulfate (Bricanyl® Turbuhaler®) or another preferred short-acting β_2-agonist for as-needed reliever medication. The same reliever was used throughout the study. No other concomitant asthma medication was allowed during the study. Patients who required a change in their asthma therapy as a result of asthma deterioration were withdrawn from the study.

Assessments

PEF measurements, severity of asthma symptoms, reliever medication use, intake of study drug, and awakenings caused by asthma symptoms were recorded by patients on diary cards. Morning and evening PEF were measured while standing using a Mini-Wright® peak flow meter (Clement Clark, Harlow, UK) before intake of study medication. On each occasion, the highest of three readings was recorded. Patients recorded day-time and night-time asthma symptoms (on a 4-point scale: 0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe), together with any night-time awakenings due to asthma symptoms and the number of reliever medication inhalations taken during the day and night. Patients recorded intake of their study medication on the diary card and these data were used to assess treatment adherence.

Lung function tests were performed at all clinic visits. Patients were asked not to take their morning dose of study medication before attending the clinic and to refrain from taking any reliever medication during the 6 h prior to lung function testing at the clinic. Spirometry was performed according to the European Respiratory Society recommendations[13] at each clinic visit and the highest FEV_1 values were recorded.

The following composite measures were used: symptom-free days; reliever-free days; and asthma control days. A symptom-free day was defined as a day and a night with no asthma symptoms and no night-time awakenings due to asthma. A reliever-free day was defined as a day and a night with no reliever medication use. These measures were combined to determine asthma control days, which were defined as a day and a night with no asthma symptoms or night-time awakenings and no reliever medication use.

Safety was assessed by recording adverse events at Visits 2–5. Adverse events were either reported spontaneously by the patient or in response to a standard question asked by the investigator. All adverse events were classified by the patient in terms of intensity (mild, moderate, or severe). The investigator assessed the causal relationship between all serious adverse events and study

medication (probable, possible, unlikely). Deterioration of asthma and asthma-related signs and symptoms (wheeze, cough, chest tightness, dyspnea, breathlessness, or phlegm) were only recorded as adverse events if they were serious adverse events or resulted in discontinuation of study medication.

Analysis

All efficacy variables were analyzed on an intention-to-treat basis. The primary efficacy variable was the mean change in morning PEF from baseline to the end of the 12-week treatment period. It was estimated that 130 patients were required in each treatment group in order to detect an 18 l/min difference between the treatments with a power of 80% at the 5% significance level using pairwise comparisons, assuming a standard deviation of 50 l/min.

Secondary efficacy variables included evening PEF, asthma symptoms, use of reliever medication, night-time awakenings, and FEV_1. Comparisons between treatments were performed using analysis of variance, with treatment and country as factors and baseline values as covariate.

For PEF measurements and other diary card variables, data were reduced to one baseline value and one value on treatment (treatment mean). Baseline values were defined as the average over the last 10 days of the run-in period and the treatment value was the average over the entire treatment period. FEV_1 measurements obtained at Visit 2 were taken as the baseline value, while the treatment value was that obtained at the last clinic visit. The percentages of symptom-free days, reliever-free days, and asthma control days were calculated using an additive model.

Results

A total of 658 patients were enrolled in the study, of whom 617 were randomized to treatment with once-daily budesonide/formoterol ($n = 202$), twice-daily budesonide/formoterol ($n = 208$) or once-daily budesonide ($n = 207$). One patient in the twice-daily budesonide/formoterol group did not receive any study medication; therefore, the intention-to-treat population comprised 616 patients. A total of 61 randomized and treated patients withdrew from the study: 26 as a result of asthma deterioration (once-daily budesonide/formoterol $n = 10$, twice-daily budesonide/formoterol $n = 5$, once-daily budesonide $n = 11$); 10 as a result of other adverse events (once-daily budesonide/formoterol $n = 5$, twice-daily budesonide/formoterol $n = 3$, once-daily budesonide $n = 2$); and 25 for other reasons (once-daily budesonide/formoterol $n = 6$, twice-daily budesonide/formoterol $n = 8$, once-daily budesonide $n = 11$).

The three treatment groups were comparable with regard to demographic and baseline characteristics (Table 1). Self-reported adherence to study medication was high, with a mean medication use of $>97\%$ in all three treatment groups.

Table 1 Baseline characteristics of patients.

Patient characteristic	Once-daily budesonide/formoterol ($n = 202$)	Twice-daily budesonide/formoterol ($n = 207$)	Once-daily budesonide ($n = 207$)
Age (years)	45.8 (18–80)	43.9 (19–80)	45.1 (18–78)
Male/female (*n*)	81/121	78/129	91/116
Asthma duration (years)	11.5 (1–63)	12.2 (0–50)	10.6 (1–58)
Inhaled corticosteroid dose (μg/day)	363 (200–500)	371 (200–500)	368 (200–500)
FEV_1 (% predicted normal)	79.3 (37–115)*	77.9 (23–123)*	78.3 (38–119)*
Reversibility (%)	23.5 (12–91)	23.4 (12–75)	23.2 (12–95)
Morning PEF (l/min)	356 (115–684)	351 (173–692)	358 (98–740)
Evening PEF (l/min)	366 (112–670)	362 (181–738)	371 (112–753)
Night-time awakenings due to asthma (%)	15.8 (0–100)	14.6 (0–100)	17.9 (0–100)
Symptom-free days (%)	37.8 (0–100)	36.1 (0–100)	38.1 (0–100)
Asthma control days (%)	33.9 (0–100)	32.5 (0–100)	35.1 (0–100)

FEV_1, forced expiratory volume in 1 s; PEF, peak expiratory flow. Values are presented as absolute numbers or as mean (range).
*Deviations from inclusion criteria not sufficient to warrant excluding the patient from the study.

Efficacy

Lung function

The mean increase in morning PEF from baseline was significantly higher in the once-daily budesonide/formoterol group (23.4 l/min) and the twice-daily budesonide/formoterol group (24.1 l/min) compared with the once-daily budesonide group (5.5 l/min; $P<0.001$ for both comparisons; Table 2). There was no significant difference between the two budesonide/formoterol groups with regard to the change in morning PEF. The daily mean morning PEF values before and during treatment with budesonide/formoterol and budesonide are shown in Fig. 1. The difference in effect on morning PEF between the two budesonide/formoterol groups compared with the once-daily budesonide group was apparent from early in the study period. The curves for both budesonide/formoterol groups show a rapid and large increase in morning PEF that was maintained for the duration of the study; as expected, the budesonide group remained at approximately the same level throughout the study. Evening PEF also increased significantly in the once- and twice-daily budesonide/formoterol groups compared with once-daily budesonide ($P<0.01$ for both comparisons; Table 2).

Once- and twice-daily budesonide/formoterol both resulted in increases in FEV_1 (mean on-treatment period) from baseline that were significantly greater than the increase from baseline seen with once-daily budesonide: there was a 3.8% difference between the two budesonide/formoterol groups and budesonide (both $P<0.05$) (Fig. 2). Geometric means at baseline were 2.36, 2.32, and 2.36 l for once-daily budesonide/formoterol, twice-daily budesonide/formoterol, and once-daily budesonide, respectively, and the corresponding 12-week values were 2.44, 2.44, and 2.35 l.

Asthma symptoms

The percentages of symptom-free days, reliever-free days and asthma control days, increased in all three treatment groups compared with baseline, with significantly larger increases in both once- and twice-daily budesonide/formoterol groups compared with the budesonide group (Table 2). Once- and twice-daily budesonide/formoterol were comparable for these efficacy parameters. In particular, once- or twice-daily budesonide/formoterol treatment resulted in about 7% more asthma control days than treatment with once-daily budesonide ($P<0.01$) (Fig. 3). This is equivalent to 26 more days per year without day-time or night-time asthma symptoms and without the use of reliever medication.

Night-time awakenings during the treatment phase were comparable between the three treatment groups (Table 2) and less frequent than during the run-in period. Although even with this improvement, the patients were only completely free of symptoms on about 50% of days.

Table 2 Effect on diary card efficacy variables of 12 weeks' treatment with once-daily budesonide/formoterol, twice-daily budesonide/formoterol, or once-daily budesonide.

Efficacy variable	Once-daily budesonide/formoterol ($n=202$)	Twice-daily budesonide/formoterol ($n=207$)	Once-daily budesonide ($n=207$)
Increase in morning PEF[a] (l/min, 95% CL)	23.4*** (18.1, 28.6)	24.1*** (19.0, 29.2)	5.5 (0.3, 10.6)
Increase in evening PEF[a] (l/min, 95% CL)	9.6** (4.4, 14.8)	18.3***, # (13.2, 23.4)	−1.7 (−6.8, 3.5)
Night-time awakenings due to asthma[b] (%, 95% CL)	11.3 (9.0, 13.6)	9.9 (7.7, 12.2)	12.0 (9.8, 14.3)
Symptom-free days[b] (%, 95% CL)	50.0* (46.0. 54.0)	50.3* (46.3, 54.3)	43.4 (39.4, 47.3)
Reliever-free days[b] (%, 95% CL)	61.8* (58.1, 65.4)	66.3*** (62.7, 69.9)	55.5 (52.0, 59.1)
Asthma control days[b] (%, 95% CL)	47.3** (43.4, 51.3)	47.3** (43.4, 51.1)	40.0 (36.2, 43.9)

*$P<0.05$, **$P<0.01$, ***$P<0.001$ versus once-daily budesonide; #$P<0.05$ versus once-daily budesonide/formoterol. CL, confidence limit; PEF, peak expiratory flow.

[a]Mean change from baseline.

[b]Treatment mean.

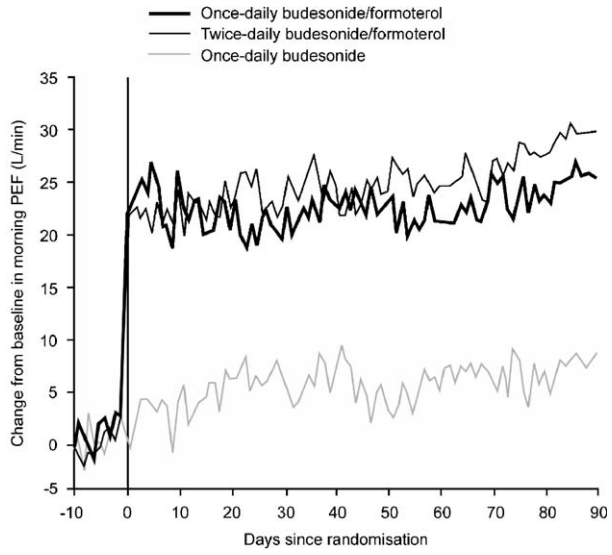

Figure 1 Mean change from baseline in morning peak expiratory flow (PEF) during 12-weeks' treatment with budesonide/formoterol 80/4.5 μg 2 inhalations once daily in the evening, budesonide/formoterol 80/4.5 μg 1 inhalation twice daily, or a corresponding dose of budesonide 200 μg 1 inhalation once daily in the evening. The solid vertical line at Day 0 represents the start of the treatment period.

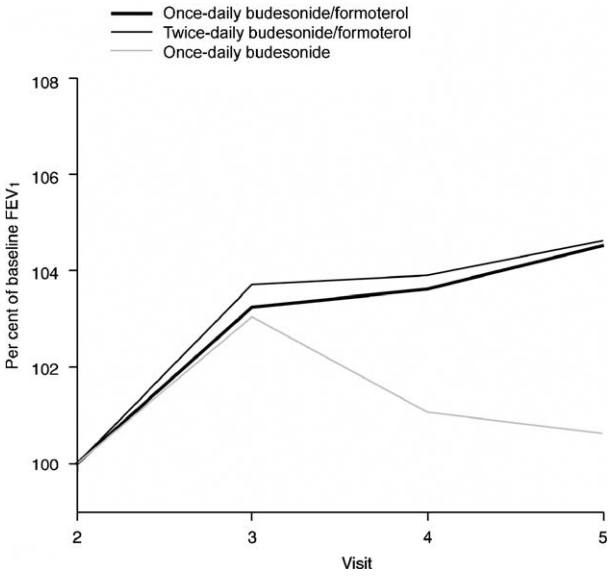

Figure 2 Forced expiratory volume in 1 s (FEV_1), expressed as a percentage of the baseline value, during 12-weeks' treatment with budesonide/formoterol 80/4.5 μg 2 inhalations once daily in the evening, budesonide/formoterol 80/4.5 μg 1 inhalation twice daily, or a corresponding dose of budesonide 200 μg 1 inhalation once daily in the evening. FEV_1 was measured at clinic visits (Visit 2 = randomization visit [Week 0]; Visit 3 = Week 4; Visit 4 = Week 8; Visit 5 = Week 12). The solid vertical line at Day 0 represents the start of the treatment period.

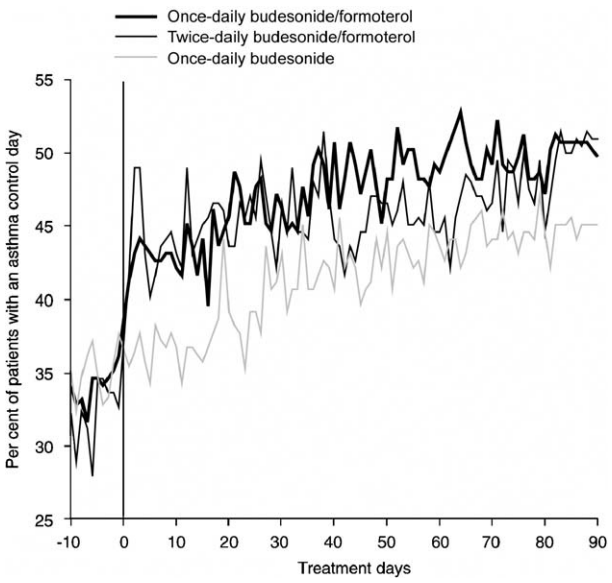

Figure 3 Mean change from baseline in asthma control days during 12-weeks' treatment with budesonide/formoterol 80/4.5 μg 2 inhalations once daily in the evening, budesonide/formoterol 80/4.5 μg 1 inhalation twice daily, or a corresponding dose of budesonide 200 μg 1 inhalation once daily in the evening. An asthma control day was defined as a day and night with no asthma symptoms, no night-time awakenings, and no reliever medication use. The solid vertical line at Day 0 represents the start of the treatment period.

Safety

All treatments were well tolerated. Seventy-six patients (38%) in the once-daily budesonide/formoterol group, 78 patients (38%) in the twice-daily budesonide/formoterol group, and 74 patients (36%) in the once-daily budesonide group experienced at least one adverse event. The number and nature of the adverse events were similar across all three treatment groups. The most frequently reported adverse events are presented in Table 3.

Seven serious adverse events were reported: two in the once-daily budesonide/formoterol group, one in the twice-daily budesonide/formoterol group, and four in the once-daily budesonide group. These were asthma aggravated ($n = 3$), acute vertigo ($n = 1$), lung carcinoma ($n = 1$), chest pain ($n = 1$), and thyroiditis ($n = 1$). None was considered to be related to study treatment.

Discussion

In this study, we have shown that once-daily budesonide/formoterol provides a rapid and sus-

Table 3 Most frequently reported adverse events (occurring in ⩾2% of patients in any treatment group).

Adverse event	No. of patients (%)		
	Once-daily budesonide/formoterol ($n = 202$)	Twice-daily budesonide/formoterol ($n = 207$)	Once-daily budesonide ($n = 207$)
Respiratory infection	23 (11.4)	32 (15.5)	25 (12.1)
Asthma aggravated	12 (5.9)	6 (2.9)	10 (4.8)
Viral infection	6 (3.0)	7 (3.4)	5 (2.4)
Pharyngitis	4 (2.0)	7 (3.4)	5 (2.4)
Rhinitis	4 (2.0)	4 (1.9)	4 (1.9)
Bronchitis	2 (1.0)	6 (2.9)	3 (1.4)
Headache	4 (2.0)	4 (1.9)	2 (1.0)
Pharynx disorder	4 (2.0)	2 (1.0)	1 (0.5)

tained improvement in lung function measured as morning PEF, similar to twice-daily budesonide/formoterol, in patients with mild to moderate asthma who were not fully controlled on ICS alone. This was achieved using a low dose of ICS/long-acting β_2-agonist (80/4.5 μg budesonide/formoterol, 2 inhalations in the evening). Patients treated with once-daily budesonide/formoterol also showed improvements in FEV_1, symptom-free days, reliever medication use, and the composite measure of asthma control days, compared with budesonide. These changes were comparable with the improvements observed in patients treated with twice-daily budesonide/formoterol, and were significantly better than for patients treated with once-daily budesonide alone.

We used the composite measure of asthma control days in order to capture the effect of treatment on a variety of outcomes relevant to patient quality of life. All patients had an increase in asthma control days, which can be attributed in part to the improved adherence and more intensive clinical care that result from being in a clinical trial. The increase in asthma control days per year was equal in patients treated with once- and twice-daily budesonide/formoterol and translates into 26 additional days of asthma control compared with patients receiving budesonide alone. This is an important benefit that patients can perceive and has the potential to improve adherence to treatment.

Improvements in morning PEF were observed earlier in both the once- and twice-daily budesonide/formoterol groups, compared with the budesonide group. This is in line with results from the study by Zetterström et al.,[5] who reported that improvements in morning PEF were significantly greater on Day 1 of the study in patients treated with budesonide/formoterol compared with budesonide alone ($P < 0.001$). This is likely to be due to the bronchodilatory effect of the formoterol component.[14] It should be acknowledged that the patients were required to have at least 12% bronchodilator reversibility in order to take part in the study. This inclusion criterion was necessary to confirm the diagnosis of asthma, but may have increased the likelihood that patients would respond to the addition of inhaled formoterol as part of their treatment regimen.

Once-daily budesonide/formoterol showed sustained efficacy that was comparable with that of twice-daily budesonide/formoterol. Although improvements in morning PEF were very similar in the two budesonide/formoterol groups, patients in the twice-daily budesonide/formoterol group had greater improvements in evening PEF than those in the once-daily dosing group. However, symptoms, reliever medication use, and night-time awakenings were similar for the once-and twice-daily budesonide/formoterol groups, indicating that control was maintained throughout the day with once-daily treatment.

While many studies have demonstrated the safety and efficacy of once-daily dosing with ICS,[15,16] once-daily dosing with the combination of an ICS and a LABA is less well investigated. To the best of our knowledge, ours is only the second study to examine the safety and efficacy of once-daily ICS/LABA, the other being the study by Buhl et al.[12] The participants in our study had less severe asthma than those in the Buhl et al. study as demonstrated by the lower dose of inhaled steroid that they were using prior to entry into the study (367, vs. 610 μg, respectively) and we were able to demonstrate the benefits of once-daily budesonide/formoterol with half the dose of inhaled steroid that was used in the study by Buhl et al. Taken together, these studies demonstrate that once-daily dosing with budesonide/formoterol is an effective treatment for patients with a range of asthma severities.

Once-daily dosing with budesonide/formoterol is possible because of the pharmacologic properties of the two components. Formoterol (24 μg) has been shown to have a protective effect against the late-phase asthmatic response to allergen challenge that is maintained for 32 h.[17] A standard dose of formoterol (12 μg via metered-dose inhaler corresponds to 9 μg via Turbuhaler) was found to have a 24-h duration of bronchodilation and attenuation of airways hyperresponsiveness.[18] The duration of action of formoterol therefore appears to be in excess of the 12 h reported previously.[19,20] Budesonide has a prolonged antiinflammatory effect compared with other ICS as it undergoes esterification in the lung and bronchial cells, which increases drug retention in the airways.[21,22] After saturation of the glucocorticoid receptor in airway cells, excess budesonide is converted to an inactive intracellular ester pool in a rapid, reversible esterification reaction. As intracellular concentrations of budesonide decline, the reaction is reversed and active budesonide is released. This prolongs the local effects of budesonide and so may explain why once-daily budesonide has been shown to be effective in adults and children with mild to moderate asthma.[23–29]

Achieving optimal frequency of dosing has important implications for adherence to prescribed medication, as compliance is reduced with increased frequency and complexity of treatment.[11,30,31] Most of the evidence for improved adherence with once-daily dosing comes from studies with oral medication but the importance of reduced dosing frequency should not be underestimated in patients with mild asthma, who may perceive their condition to be a minor one and consequently may not adhere to ICS regimens during periods of good control.[32] Indeed, patients with mild asthma showed a significant preference for a once-daily dosage regimen of budesonide compared with twice-daily fluticasone, and 61% said they would prefer to use a once-daily regimen given the choice.[28] This is supported by results of a recent market research survey, in which 85% of those questioned said they would prefer simpler regimens using fewer drugs for their asthma.[4] These findings suggest that once-daily dosing with a combination of an inhaled steroid and a long-acting inhaled β_2-agonist will improve adherence but there have been few studies that have looked directly at this question and we hope that our findings will promote more research in this area. Patients' safety concerns may also affect their adherence to ICS[33] and many patients tend to rely on their reliever medication to treat their asthma symptoms,[3] while neglecting to treat the underlying inflammation. Providing patients with a convenient to use, effective medication may contribute to improved adherence and better long-term asthma control.

In conclusion, once-daily low-dose budesonide/formoterol (80/4.5 μg, 2 inhalations) in the evening is as effective in improving asthma control and as well tolerated as the same daily dose of budesonide/formoterol administered twice daily in patients who were not optimally controlled on ICS alone. The simplicity of this treatment strategy—one inhaler used once daily—may have the potential to improve adherence to therapy.

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References

1. Pauwels RA, Löfdahl C-G, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;**337**:1405–11.
2. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;**164**: 1392–7.
3. Haughney J, Barnes G, Partridge M, Cleland J. The Living & Breathing Study: a study of patients' views of asthma and its treatment. *Primary Care Respir J* 2004;**13**:28–35.
4. Hyland ME, Ståhl E. Asthma treatment needs: a comparison of patients' and health professionals' perceptions. *Clin Ther* 2004;**26**:2141–52.
5. Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. *Eur Respir J* 2001;**18**:262–8.
6. Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Ståhl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. *Int J Clin Pract* 2002;**56**:427–33.
7. Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol* 2002;**34**:342–50.
8. Bateman ED, Bantje TA, Gomes MJ, Toumbis MG, Huber RM, Naya I, et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone

propionate alone in patients with moderate persistent asthma. *Am J Respir Med* 2003;**2**:275–81.
9. Lalloo UJ, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroids in adults with mild-to-moderate asthma. *Chest* 2003;**123**:1480–7.
10. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;**171**:129–36.
11. Cochrane GM. Compliance in asthma. *Eur Respir Rev* 1998;**8**:348–50.
12. Buhl R, Creemers JPHM, Vondra V, Martelli NA, Naya IP, Ekstrom T. Once-daily budesonide/formoterol in a single inhaler in moderate persistent asthma. *Respir Med* 2003; **97**:323–30.
13. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J- C. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;**16**:5–40.
14. Schreurs AJM, Sinninghe Damasté HEJ, de Graaf CS, Greefhorst APM. A dose-response study with formoterol Turbuhaler® as maintenance therapy in asthmatic children. *Eur Respir J* 1996;**9**:1678–83.
15. Boulet LP. Once-daily inhaled corticosteroids for the treatment of asthma. *Curr Opin Pulm Med* 2004;**10**:15–21.
16. Radzik D, Pavanello L. Inhaled steroids in the treatment of mild to moderate persistent asthma in children: once or twice daily administration? *Arch Dis Child* 2002;**87**: 415–6.
17. Brusasco V, Crimi E, Gherson G, Nardelli R, Oldani V, Francucci B, et al. Actions other than smooth muscle relaxation may play a role in the protective effects of formoterol on the allergen-induced late asthmatic reaction. *Pulm Pharmacol Ther* 2002;**15**:399–406.
18. Rabe KF, Jörres R, Nowak D, Behr N, Magnussen H. Comparison of the effects of salmeterol and formoterol on airway tone and responsiveness over 24 h in bronchial asthma. *Am Rev Respir Dis* 1993;**147**:1436–41.
19. Ringdal N, Derom E, Wahlin-Boll E, Pauwels R. Onset and duration of action of single doses of formoterol inhaled via Turbuhaler®. *Respir Med* 1998;**92**:1017–21.
20. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients:onset of actions, duration of effect and potency. *Eur Respir J* 1997;**10**:2484–9.
21. Miller-Larsson A, Mattsson H, Hjertberg E, Dahlback M, Tunek A, Brattsand R. Reversible fatty acid conjugation of budesonide. Novel mechanism for prolonged retention of topically applied steroid in airway tissue. *Drug Metab Dispos* 1998;**26**:623–30.
22. Thorsson L, Thunnisen FBJM, Korn S, Carlshaf S, Edsbäcker S, Wouters EFM. Formation of fatty acid conjugates of budesonide in human lung tissue in vivo. *Am J Respir Crit Care Med* 1998;**157**:A404.
23. Mintz S, Alexander M, Li JHS, Mayer PV. Once-daily administration of budesonide Turbuhaler® was as effective as twice-daily treatment in patients with mild to moderate persistent asthma. *J Asthma* 2002;**39**:203–10.
24. McFadden ER, Casale TB, Edwards TB, Kemp JP, Metzger WJ, Nelson HS, et al. Administration of budesonide once daily by means of Turbuhaler® to subjects with stable asthma. *J Allergy Clin Immunol* 1999;**104**:46–52.
25. Herjavecz I, Blomqvist P, Serrano A. Efficacy of once- and twice-daily administration of budesonide via Turbuhaler® as initial therapy in patients with mild persistent asthma. *Respir Med* 1999;**93**:230–5.
26. Campbell LM, Gooding TN, Aitchison WR, Smith N, Powell JA. Initial loading (400 μg twice daily) versus static (400 μg nocte) dose budesonide for asthma management. PLAN Research Group. *Int J Clin Pract* 1998;**52**:361–70.
27. Chisholm L, Dekker FW, Knuistingh Neven A, Petri H. Once-daily budesonide in mild asthma. *Respir Med* 1998;**92**:421–5.
28. Venables TL, Addlestone MB, Smithers AJ, Blagden MD, Weston D, Gooding T, et al. A comparison of the efficacy and patient acceptability of once daily budesonide via Turbuhaler and twice daily fluticasone propionate via disc-inhaler at an equal daily dose of 400 μg in adult asthmatics. *Br J Clin Res* 1996;**7**:15–32.
29. Jones AH, Langdon CG, Lee P, Lingham SA, Nankani JP, Follows RM, et al. Pulmicort® Turbohaler® once daily as initial prophylactic therapy for asthma. *Respir Med* 1994; **88**:293–9.
30. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990;**150**:1881–4.
31. Campbell LM. Once-daily inhaled corticosteroids in mild to moderate asthma. *Drugs* 1999;**58**(Suppl. 4):25–33.
32. Global Initiative for Asthma GINA. *Global strategy for asthma management and prevention (NIH publication No. 02-3659)*. Washington, DC: National Institutes of Health, National Heart, Lung, and Blood Institute; 2002.
33. Boulet L-P. Perception of the role and potential side effects of inhaled corticosteroids among asthmatic patients. *Chest* 1998;**113**:587–92.