ORIGINAL ARTICLE

Once-daily budesonide/formoterol in a single inhaler in adults with moderate persistent asthma

R. Buhl*, J.P.H.M. Creemers†, V. Vondra‡, N.A. Martelli§, I.P. Naya¶ and T. Ekström¶

*Pulmonary Division, University Hospital, Mainz Germany, †Pulmonary Department, Catharina Hospital, Eindoven, The Netherlands, ‡Plicní Ambulance, Pneumonology Department, Prague, Czech Republic, §Neumonology Hospital, Buenos Aires, Argentina and ¶AstraZeneca R&D, Lund, Sweden

Abstract Patients with moderate persistent asthma ($n = 523$; mean FEV_1 77.4%) not fully controlled with inhaled corticosteroids (ICS; 400–1000 μg/day) were randomized to receive either once-daily budesonide/formoterol (160/4.5 μg, two inhalations); or twice-daily budesonide/formoterol (160/4.5 μg, one inhalation); or budesonide (400 μg) once-daily for 12 weeks. Once-daily dosing was administered in the evening and twice-daily dosing was administered in the morning and evening. All patients received twice-daily budesonide (200 μg) during a 2-week run-in. Compared with budesonide alone, change in mean morning and evening peak expiratory flow was greater in the once-daily budesonide/formoterol group (27 and 17 l min^{-1}, respectively; $P < 0.001$) and twice-daily budesonide/formoterol group (23 and 24 l min^{-1}, respectively; $P < 0.001$). Night awakenings, symptom-free days, reliever-use-free days and asthma-control days were all improved during once-daily budesonide/formoterol therapy *vs.* budesonide ($P \leq 0.05$). Similar improvements were also seen with twice-daily budesonide/formoterol ($P \leq 0.05$). The risk of a mild exacerbation was reduced after once- and twice-daily budesonide/formoterol *vs.* budesonide (38% and 35%, respectively; $P < 0.002$). All treatments were well tolerated. Budesonide/formoterol, once- or twice-daily, in a single inhaler improved asthma symptoms and exacerbations compared with budesonide. In the majority of patients with moderate persistent asthma requiring ICS and long-acting β-agonists, once-daily formoterol/budesonide provided sustained efficacy over 24 h, similar to twice-daily dosing.

doi:10.1053/rmed.2002.1427, available online at http://www.sciencedirect.com

Keywords budesonide; formoterol; asthma; once-daily; Symbicort®.

INTRODUCTION

The role of combined therapy with inhaled corticosteroids (ICS) and long-acting β_2-agonists in the management of moderate-to-severe asthma is well established (1–3). Until recently, combination therapy with ICS and long-acting β_2-agonists was administered via two inhalers, and in addition, patients needed a third inhaler for reliever medication. This multiple inhaler approach to asthma treatment is potentially confusing for the patient and is associated with reduced treatment compliance and poor inhaler technique (4). In recent years, a concerted effort has been made to simplify asthma treatment. The first step in simplifying asthma treatment was to combine both controller treatments (ICS and inhaled long-acting β_2-agonist) in a single inhaler. The next step, when appropriate, is to reduce the dosing frequency to the minimum necessary to maintain asthma control.

The efficacy of budesonide and formoterol in a single inhaler administered twice-daily has already been reported (5). In that study, budesonide/formoterol 160/4.5 μg, two inhalations twice-daily quickly gained asthma control and was at least as effective as budesonide and formoterol given via two separate inhalers in patients with moderate-to-severe asthma (5). In a second single-dose study (6), budesonide/formoterol 160/4.5 μg was shown to have a rapid onset of effect with the majority of patients (> 73%) achieving a 15% increase in forced expiratory volume in 1 s (FEV_1) after 1 h. Another study in

Received 15 July 2002, accepted in revised form 29 July 2002
Correspondence should be addressed to: Prof. Roland Buhl, Pulmonary Division, Mainz University Hospital, Langenbeckstrasse 1, D-55131 Mainz, Germany. Fax: +49 6131175545;
E-mail: R.Buhl@3-med.klinik.uni-mainz.de

patients with persistent atopic asthma has also highlighted the 24-h efficacy of once-daily budesonide or formoterol given alone or in combination via two separate inhalers (7). These factors support the once-daily administration of budesonide and formoterol in a combined treatment regimen.

Here we present the first study to examine the efficacy of budesonide/formoterol 160/4.5 μg, two inhalations administered once-daily. The aim of the study was to compare the efficacy of once-daily budesonide/formoterol with that of once-daily budesonide (400 μg) alone and twice-daily budesonide/formoterol and to show that a simple treatment regimen (i.e. one inhaler, once a day) is effective even in patients with moderate persistent asthma.

METHODS

Patients

Adults (aged at least 18 years) with asthma (minimum duration 6 months) were eligible for inclusion in this study if they had been using any inhaled corticosteroid (irrespective of the specific drug) at a constant daily dose of 400–1000 μg for at least 30 days before entry and still had sub-optimal asthma control. At enrolment, patients had baseline FEV_1 of 60–90% of predicted normal and a reversibility from baseline FEV_1 of at least 12% at 15 min after inhalation of a short-acting β_2-agonist. Patients were excluded if in the 4 weeks before the run-in period, they required treatment with systemic corticosteroids or had a respiratory tract infection. Other exclusion criteria included any severe cardiovascular disorders, use of β-blocker therapy or a history of heavy smoking ($\geq$10 pack-years). All patients gave their written, informed consent prior to commencing the study.

Study design

This was a randomized, double-blind, double-dummy, active-controlled study with a parallel-group design conducted at 56 centres in nine countries (Argentina, Belgium, Czech Republic, Germany, Mexico, Russia, Spain, The Netherlands and the United Kingdom). 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.

At the initial visit, patients underwent a physical examination and a complete medical and respiratory history was taken. Patients then entered a 2-week run-in period during which they received budesonide Turbuhaler® (200 μg) twice daily. At the end of the run-in period, patients were randomized to receive either: once-daily budesonide/formoterol (160/4.5 μg, two inhalations); or twice-daily budesonide/formoterol (160/4.5 μg, one inhalation); or once-daily budesonide (400 μg) for 12 weeks. When asthma medication was administered once daily, the doses were taken in the evening. All patients received an equivalent daily dose of budesonide; apparent differences in dose levels are due to the doses being expressed as delivered dose for budesonide/formoterol and as metered dose for budesonide alone. To ensure treatment blinding, patients inhaled once from a numbered inhaler in the morning upon rising and then from three consecutively numbered inhalers in the evening just before going to bed, with the corresponding placebo inhalers being identical in appearance to those containing active medication. Patients returned for clinic visits 4, 8 and 12 weeks after randomization. All clinic visits took place between 07.00 and 10.00 h.

No concomitant asthma medication was allowed during the study, with the exception of the inhaled short-acting β_2-agonist medication terbutaline sulphate (Bricanyl® Turbuhaler 0.5 mg/dose), which was to be taken as needed. The need for oral corticosteroids or any other change in asthma therapy led to withdrawal of the patient from the study.

Efficacy assessments

Peak expiratory flow (PEF) measurements and severity of asthma symptoms were recorded each morning and evening by the patients on daily diary cards for the duration of the study. Morning and evening PEF were measured, with the patient standing, using a Mini-Wright® peak flow meter (Clement Clark, Harlow, UK) before the intake of study medication. On each occasion, the highest value of three readings was recorded. Daytime and night-time asthma symptoms were graded on a scale of 0–3 (0=no symptoms; 1=mild; 2=moderate; 3=severe) and the total daily asthma symptom score (on a scale of 0–6) was the sum of the daytime and night-time symptom scores. Patients also recorded any night-time awakenings due to asthma and use of reliever bronchodilator medication during the day and night. The percentages of symptom-free days, reliever-use-free days, asthma-control days and asthma-control weeks were calculated. A symptom-free day was defined as a day and night with a total asthma symptom score of zero. A reliever-free day was a 24-h period with no reliever medication use. An asthma-control day was defined as a day and night with no asthma symptoms, no reliever medication use and no night-time awakening due to asthma. Asthma-control weeks were study weeks during which patients experienced no symptoms, had no awakenings due to their asthma and used minimal reliever medication ($\leq$4 inhalations/week on a maximum of 2 days).

A mild exacerbation was defined as 2 consecutive mild exacerbation days (for the same criterion), the latter being defined as night-time awakening due to asthma;

$\geq$20% decrease in PEF from baseline; or $\geq$4 inhalations of reliever medication over a 24-h period. Severe exacerbations were defined as asthma deterioration requiring oral corticosteroid treatment; or a $\geq$30% decrease in PEF from baseline on 2 consecutive days; or discontinuation due to worsening of asthma.

Lung function tests were performed at all clinic visits. Spirometry was performed according to European Respiratory Society recommendations (8). Patients were requested 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. After a 15 min rest, patients performed at least three forced expiratory manoeuvres. The highest of three FEV_1 values obtained was recorded at each visit.

Safety assessments

Safety was assessed by recording adverse events at all clinic visits. Adverse events were either reported spontaneously by the patient or in response to standard questions asked by the investigator. All adverse events were classified in terms of intensity (mild, moderate or severe) and causal relationship to study medication (probable, possible, unlikely). Deterioration of asthma and asthma-related signs and symptoms were only recorded as adverse events if they were serious adverse events or resulted in discontinuation of study medication.

Statistical analysis

The primary efficacy variable was the change in morning PEF from baseline to the end of the 12-week treatment period.

All efficacy variables were analysed on an intent-to-treat basis and all randomized patients with data were included in the analysis. For PEF measurements and other diary-card variables, 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. Comparisons of the treatments were performed using analysis of variance (ANOVA) with treatment and country as factors; average baseline values were used as covariates. The FEV_1 value obtained at randomization was considered as the baseline, and baseline *vs*. treatment values were analysed in a multiplicative ANOVA model. The time to first mild exacerbation was analysed with a log-rank test and further described with a Cox's proportional hazards model. For asthma control weeks' data could be viewed as a binary correlated observation series, and this was analysed in a generalized estimation equation (GEE) with a logistic link function, an exchangeable dependency model and patient as cluster. The factors were treatment and asthma control during the last week of run-in. The estimated log-odds were used in the comparisons giving odds ratios which were interpreted as risk factors. A significance level of 5% was assumed.

RESULTS

Study populations

A total of 549 patients were enrolled into the study. During the 2-week run-in period, all patients received budesonide 200 μg bid, a dose chosen because of the very flat nature of the dose–response curve of budesonide. Patients who deteriorated during the run-in period were not entered into the study. At visit 2, 523 patients (199 men, 324 women) were randomized to treatment with once-daily budesonide/formoterol (n = 176), twice-daily budesonide/formoterol (n = 176), or once-daily budesonide (n = 171). All randomized patients were included in the efficacy and safety analyses. At baseline, the three treatment groups were well matched with regard to lung function, symptoms, reliever medication use and pre-study ICS dose (Table 1).

Four hundred and eighty patients completed the study. The three treatment groups were comparable with respect to numbers and reasons for patients discontinuing treatment. A total of 43 patients (14 in the once-daily budesonide/formoterol group, 15 in the twice-daily budesonide/formoterol group and 14 in the once-daily budesonide group) discontinued the study. The number of patients discontinuing as a result of asthma deterioration was similar in the once-daily budesonide/formoterol group (n = 5), twice-daily budesonide/formoterol group (n = 4), and once-daily budesonide group (n = 5). Nine patients in the once-daily budesonide/formoterol group, 11 patients in the twice-daily budesonide/formoterol group and nine patients in the once-daily budesonide group did not complete the study for other reasons.

Lung function

Compared with the run-in period, morning PEF remained stable in the group of patients switched from twice-daily to once-daily budesonide [change (Δ); $-0.95\,l\,min^{-1}$]. There was, however, a significant increase in morning PEF in both the once-daily budesonide/formoterol group (Δ; $27.4\,l\,min^{-1}$) and the twice-daily budesonide/formoterol group (Δ; $22.8\,l\,min^{-1}$) compared with the budesonide-alone group ($P < 0.001$). These treatment benefits were apparent on the first day after randomization and were maintained throughout the 12-week treatment period (Fig. 1). The difference between the once- and twice-daily budesonide/formoterol groups was not significant. The percentage of patients in each treatment group with a clinically relevant increase in morning PEF ($> 15\,l\,min^{-1}$) from run-in was 64% in the once-daily

Table 1. Mean baseline characteristics

Patients' characteristics	Budesonide/ formoterol qd (n = 176)	Budesonide/ formoterol bid (n = 176)	Budesonide only qd (n = 171)
Age (years) [range]	42.7 [18–77]	44.8 [18–74]	45.5 [18–78]
Men/women	67/109	64/112	68/103
Asthma duration (years)	12.7 [0–62]	12.3 [1–63]	14.5 [0–62]
Nonsmoker/current smoker/past smoker	140/10/26	124/16/36	127/14/30
Inhaled corticosteroid dose (μg/day)	592	626	612
FEV_1 (l) [range][a,b]	2.32 [1.1–4.5]	2.25 [0.8–5.0]	2.28 [1.1–4.5]
FEV_1 (% predicted) [range][b]	77.1 [44–126]	77.6 [43–111]	77.6 [33–132]
Reversibility (%) [range][c]	21.5 [12–99]	21.2 [11–77]	22.6 [12–78]
Morning PEF ($l\ min^{-1}$) [range][d]	350 [143–728]	351 [167–707]	344 [142–659]
Evening PEF ($l\ min^{-1}$) [range][d]	359 [154–724]	362 [174–773]	354 [146–674]
Total symptom score (0–6 scale)[d]	1.0	1.1	1.1
Nights with awakenings (%) [range][d]	14.5 [0–100]	10.0 [0–100]	15.5 [0–100]
Symptom-free days (%)[range][d]	44.3 [0–100]	43.5 [0–100]	39.4 [0–100]
Asthma-control days (%)[range][d]	37.4 [0–100]	38.6 [0–100]	34.0 [0–100]
Use of reliever medication (inhalations/ day) [range][d]	1.1 [0–6]	1.1 [0–8]	1.2 [0–8]

[a]Geometric mean.
[b]Measurements taken at the end of run-in period (i.e. at randomization).
[c]Measurements taken at enrolment.
[d]Average values over the last 10 days of the run-in period.
qd: once daily; bid: twice daily; FEV_1: forced expiratory volume in 1s; PEF: peak expiratory flow.

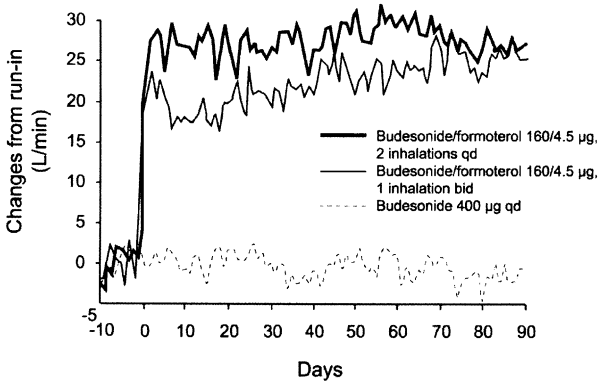

Fig. 1. Daily change in mean morning peak expiratory flow (PEF) from run-in with once-daily budesonide/formoterol (160/4.5 μg, two inhalations), twice-daily budesonide/formoterol (160/4.5 μg, one inhalation) and once-daily budesonide (400 μg) alone. All patients received budesonide 200 μg twice daily during run-in.

budesonide/formoterol group, 55% in the twice-daily budesonide/formoterol group and 27% in the budesonide-alone group.

Evening PEF was greater in the once- and twice-daily budesonide/formoterol groups compared with the group treated with budesonide alone, and there was a mean treatment difference of 16.6 and 23.6 l min^{-1} for the once- and twice-daily budesonide/formoterol groups, respectively, *vs*. budesonide ($P < 0.001$; Table 2). Moreover, the percentage of patients with a clinically relevant increase in evening PEF (> 15 l min^{-1}) from run-in was significantly greater after budesonide/formoterol administration, once- and twice-daily, compared with budesonide alone.

Mean FEV_1 was also significantly greater in the once-daily budesonide/formoterol group (2.32 l) and twice-daily budesonide/formoterol group (2.37 l) than in the budesonide group (2.22 l; $P < 0.001$). The difference between the once- and twice-daily budesonide/formoterol groups was not statistically significant.

Symptom control and use of reliever medication

As expected, once- and twice-daily budesonide/formoterol treatment resulted in consistently greater improvements in symptom measures compared with budesonide alone in terms of total asthma symptom score, nighttime awakenings, symptom-free days and asthma-control days. In addition, total daily reliever use and reliever-use-free days were significantly improved in the once- and twice-daily budesonide/formoterol groups compared with the budesonide-alone group (Table 2). There were no significant differences between once- and twice-daily budesonide/formoterol with respect to

Table 2. Effect of 12-weeks' treatment with once-daily budesonide 400 μg, once-daily budesonide/formoterol 160/4.5 μg, two inhalations or twice-daily budesonide/formoterol 160/4.5 μg, one inhalation on patient-reported secondary variables

Efficacy variable	Treatment	Treatment mean	Mean treatment difference	95% confidence limit
Δ in evening PEF (l min^{-1})	Bud only qd	−4.8		
	Bud/form qd	11.8	16.6***	9.6, 23.6
	Bud/form bid	18.8	23.6***	16.6, 30.6
Total asthma symptom score (0–6 scale)	Bud only qd	0.90		
	Bud/form qd	0.76	−0.14*	−0.27, 0.00
	Bud/form bid	0.78	−0.12	−0.25, 0.01
Symptom-free days (%)	Bud only qd	51.3		
	Bud/form qd	58.6	7.3*	1.5, 13.1
	Bud/form bid	58.2	6.9*	1.1, 12.7
Asthma-control days (%)	Bud only qd	47.6		
	Bud/form qd	55.2	7.6*	1.7, 13.5
	Bud/form bid	53.5	5.9*	0.0, 11.7
Nights with awakenings (%)	Bud only qd	14.1		
	Bud/form qd	9.9	−4.2**	−7.3, −1.1
	Bud/form bid	12.1	−2.1	−5.3, 1.0
Reliever-use-free days (%)	Bud only qd	59.7		
	Bud/form qd	68.6	8.9**	3.2, 14.7
	Bud/form bid	70.7	11.0***	5.3, 16.8
Δ in relief medication use (inhalations/day)	Bud only qd	−0.10		
	Bud/form qd	−0.37	−0.27**	−0.45, −0.09
	Bud/form bid	−0.45	−0.35***	−0.56, −0.17

Bud: budesonide. Bud/form: budesonide/formoterol. qd: once daily. bid: twice daily.
Δ: mean change from run-in. PEF: peak expiratory flow.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ *vs.* budesonide alone;

any of these parameters. The proportion of patients with an asthma control day during the 12-week treatment period is shown in Fig. 2. Treatment with once- and twice-daily budesonide/formoterol increased the number of asthma-control days by 7.6% and 5.9%, respectively, giving an estimated extra 28 and 21 days $year^{-1}$ free of asthma symptoms and the need for reliever medication. In all three groups, the proportion of patients with an asthma-control week increased progressively during treatment. The percentage of patients with asthma control in the once- and twice-daily budesonide/formoterol groups and the budesonide-alone group during the last week of run-in was 17%, 19% and 17%, respectively. During the first 4 weeks of treatment, the percentage of patients with an asthma-control week in the once- and twice-daily budesonide/formoterol treatment groups and the budesonide-alone group increased to 31%, 33%, and 23%, respectively, with further increases to 42%, 41% and 29%, respectively, during the last 4 weeks of treatment. Over the whole study period, compared with the budesonide-alone group, the average chance of achieving an asthma-control week during the study was 99% higher [odds ratio 1.99; 95% confidence limit (CL) 1.39–2.84; $P < 0.001$) in the once-daily budesonide/formoterol group and 80% higher (odds ratio 1.80; 95% CL 1.25–2.60; $P < 0.001$) in the twice-daily budesonide/formoterol group. Throughout the study, no difference in symptom control as measured by asthma-control days was observed between once- or

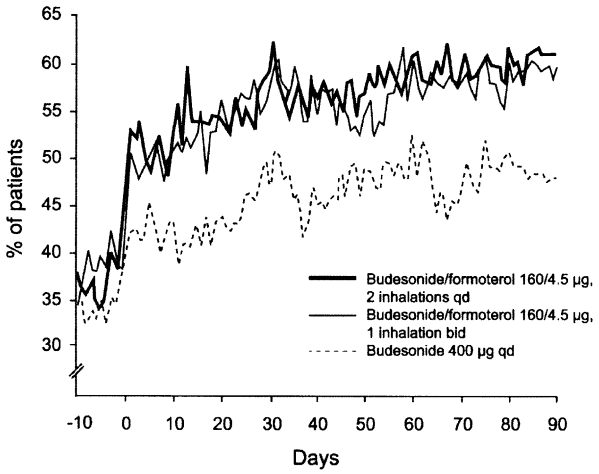

Fig. 2. Percentage of patients with an asthma-control day (no night-time awakening, no asthma symptoms and no relief medication use) during treatment with once-daily budesonide/formoterol (160/4.5 μg, two inhalations), twice-daily budesonide/formoterol (160/4.5 μg, one inhalation) or once-daily budesonide (400 μg) alone. All patients received budesonide 200 twice daily during run-in.

twice-daily dosing with budesonide/formoterol (Table 2; Fig. 2).

Exacerbations of asthma

The Kaplan-Meier survival curves for time to first mild exacerbation for each treatment group are shown in Fig. 3. Two or more consecutive nights with disturbed sleep due to asthma was the most common reason (63% of all cases) defining a mild asthma exacerbation. Patients remained exacerbation-free for a median time of 80 days in the once-daily budesonide/formoterol group, 78 days in the twice-daily budesonide/formoterol group and 42 days in the budesonide-alone group ($P < 0.001$ *vs*. budesonide alone; log-rank test). Cox's proportional hazards model revealed that in comparison to the budesonide-alone group, the relative risk of having a mild exacerbation was 38% lower in the once-daily budesonide/formoterol group (hazard ratio 0.62; 95% CL 0.46–0.84; $P < 0.001$) and 35% lower in the twice-daily budesonide/formoterol group (hazard ratio 0.65; 95% CL 0.49–0.88; $P < 0.002$).

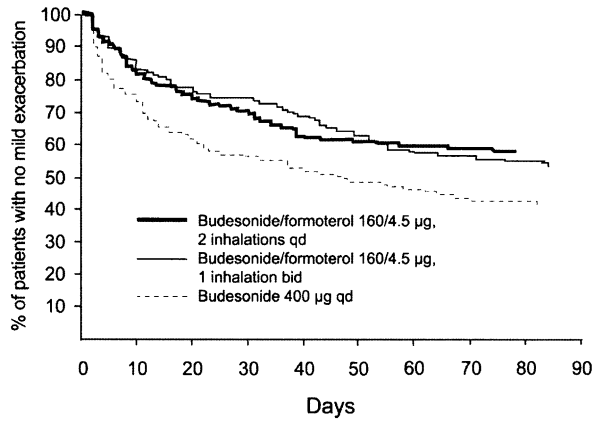

Fig 3. Kaplan–Meier survival curves of the time to first mild asthma exacerbation during 12 weeks' treatment with once-daily budesonide/formoterol (160/4.5 µg, two inhalations), twice-daily budesonide/formoterol (160/4.5 µg, one inhalation) or once-daily budesonide (400 µg) alone.

The incidence of severe exacerbations was comparable across the treatment groups, with a pattern similar to that observed for mild exacerbations. A total of 8% of patients in the once-daily budesonide/formoterol group and 9% of patients in the twice-daily budesonide/formoterol group experienced a severe exacerbation compared with 11% of patients in the budesonide-alone group. Overall, the incidences of mild and severe asthma exacerbations were numerically lower in the once-daily budesonide/formoterol group (42% and 8%, respectively) than those observed in the twice-daily budesonide/formoterol group (45% and 9%, respectively) with no significant difference between the groups.

Safety

Budesonide monotherapy and once- and twice-daily budesonide/formoterol were well tolerated. Seventy-one patients (40%) in the once-daily budesonide/formoterol group, 60 patients (34%) in the twice-daily budesonide/formoterol group, and 78 (46%) in the budesonide-alone group experienced at least one adverse event during the study. The number, nature and intensity of the adverse events were similar across all three treatment groups. The most frequently reported adverse event was respiratory infection as shown in Table 3. There were five serious adverse events: one in the once-daily budesonide/formoterol group and two each in the other two treatment groups. They included one death due to cardiac arrest and four other serious adverse events (ectopic pregnancy, aggravated asthma, tachycardia and attempted suicide). None of these events was considered related to the study medication.

DISCUSSION

This is the first study to demonstrate that once-daily budesonide/formoterol in a single inhaler (160/4.5 µg, two inhalations) provides sustained improvement in asthma control in patients with moderate persistent asthma who were not previously fully controlled on ICS alone. Compared with once-daily budesonide, in terms of lung

Table 3. Most frequently reported (≥3%) adverse events experienced by patients in any of the three treatment groups

Adverse event	Budesonide/formoterol qd (*n* = 176)	Budesonide/formoterol bid (*n* = 176)	Budesonide only qd (*n* = 171)
Respiratory infection	12 (6.8%)	14 (8.2%)	15 (8.5%)
Bronchitis	9 (5.1%)	4 (2.3%)	10 (5.7%)
Viral infection	6 (3.4%)	5 (2.9%)	9 (5.1%)
Aggravated asthma	6 (3.4%)	6 (3.5%)	7 (4.0%)
Rhinitis	6 (3.4%)	7 (4.1%)	6 (3.4%)
Pharyngitis	7 (4.0%)	3 (1.8%)	3 (1.7%)

function and asthma symptoms, once-daily budesonide/formoterol showed improved efficacy, sustained throughout the 24-h dosing interval. In addition, the improvements in asthma symptoms and asthma exacerbation control shown with once-daily budesonide/formoterol were comparable with those seen with twice-daily budesonide/formoterol.

The sustained 24-h effect of once-daily budesonide/formoterol, as shown in our study, was not unexpected given that residual 24-h activity after a standard dose of formoterol (9 μg) has been reported previously (9). Other studies using a standard dose of formoterol (4.5 or 9 μg) have demonstrated similar bronchodilatory effects to salmeterol (50 μg) for up to 12 h (10,11). A high dose of formoterol (equivalent to 18 μg delivered dose) has been reported to protect against significant falls in FEV_1 due to allergen provocation for up to 32 h (12). The duration of action of formoterol is, therefore, in excess of 12 h at the lowest recommended dose and potentially greater than 24 h at the upper recommended daily dose (equivalent to 18 μg delivered dose).

The dosing frequency of asthma treatment, particularly for an ICS such as budesonide, has been evaluated extensively in order to determine the optimal frequency for maximum efficacy and safety. Early studies conducted with budesonide aerosol in patients with severe asthma in relapse showed that asthma control was more rapidly re-established with more frequent dosing of ICS (e.g. up to four-times daily) (13,14). Toogood and colleagues (13) also showed that increasing the dosing frequency above twice-daily had no discernible benefit in patients with stable asthma. It has long been recognized that adherence to prescribed chronic therapy is reduced with increasing complexity and frequency of treatment (4,15,16). Thus, when appropriate, once-daily administration of prescribed medication should be the treatment goal. Once-daily dosing of ICS has been assessed in mild-to-moderate asthma (15,17). In these studies, once-daily budesonide was found to be as effective as twice-daily budesonide (17) and twice-daily fluticasone (15). In this study, we have demonstrated that budesonide administered once-daily maintains asthma control in many patients who were previously well controlled with twice-daily dosing and this finding supports that of previous studies (17,18).

Asthma is widely recognized as a disease with large circadian variations both in lung function and symptoms, frequently characterized by nocturnal and early morning worsening (19). Thus, the view that chronotherapy (i.e. the timing of dosing) is important to asthma treatment has received increased emphasis. Because airway inflammation is worse in the evening and early morning, it is logical to maximize the concentration of ICS in the airways at these times (20) and this can be achieved by administering the prescribed medication during the second half of the day. In studies comparing once-daily morning and once-daily evening budesonide administration, no significant differences in efficacy have been observed; however, trends towards superior efficacy were observed with evening dosing (21,22). In another study of nocturnal asthma, once-daily prednisone (50 mg) administered at 15.00 h was more effective in improving FEV_1 at 04.00 h than dosing at either 08.00 h or 20.00 h (23). Thus, several lines of evidence support the concept that the timing of the dose is important, and that a late afternoon or early evening dose tends to be superior to morning dosing. For these reasons, in the current study only evening administration of once-daily therapy was investigated.

Previous studies with once-daily budesonide (400–800 μg administered in the evening) in moderate persistent asthma have shown similar efficacy to equivalent or higher daily doses of budesonide administered twice daily (22,24), or equivalent daily doses of twice-daily fluticasone propionate (15). Indeed, in the current study, morning PEF remained stable and the number of asthma-control days improved when patients switched from twice-daily budesonide (run-in) to a once-daily regimen (Figs. 1 and 2). Despite ICS treatment, many patients with moderate persistent asthma still experience nocturnal symptoms, early morning dyspnoea and diminished quality of life. Thus, for these patients it would be more logical to have a long-acting bronchodilator, such as formoterol, administered in the evening rather than in the morning, or alternatively a single higher dose in the evening rather than lower doses in the morning and evening. In our study population, two out of every three patients in the budesonide group who experienced a mild exacerbation reported consecutive nights with nocturnal awakenings and this finding further supports the concept of a need for once-daily evening dosing.

Once-daily evening dosing with budesonide/formoterol met all the key goals of asthma management, in particular reducing daytime and nocturnal symptoms, improving morning and evening PEF, reducing the need for reliever medication and decreasing the incidence of asthma exacerbations *vs*. budesonide alone. Once-daily evening dosing with budesonide/formoterol provides equivalent efficacy to twice-daily budesonide/formoterol on asthma-control variables such as asthma-control days, asthma-control weeks and risk of asthma exacerbations. This finding further suggests that a single high dose of budesonide/formoterol in the evening could be a logical and realistic treatment option in moderate persistent asthma.

The acceptance of once-daily budesonide/formoterol in a single inhaler is likely to be higher than for once-daily budesonide alone given the greater efficacy and more rapid symptom relief provided by formoterol—a long-acting bronchodilator with a rapid onset of action (10,11). Consequently, the once-daily budesonide/formoterol single inhaler delivers the additional efficacy patients

require whilst encouraging optimal adherence to long-term inhaled corticosteroid therapy with the simplest of dosing options (i.e. one inhaler once daily) (25).

In conclusion, once-daily budesonide/formoterol in a single inhaler was as effective as twice-daily budesonide/formoterol in improving asthma control, and both regimens were more effective than budesonide alone. In the majority of patients with moderate persistent asthma requiring therapy with ICS and long-acting β_2-agonists, once-daily budesonide/formoterol provided sustained efficacy over 24 h, similar to twice-daily dosing. This study indicates that it is possible to reduce the dosing frequency with budesonide/formoterol to once daily in patients with moderate persistent asthma, without loss of asthma control. The simplicity of this treatment regimen (i.e. one inhaler, once a day) may help to improve patient adherence to treatment.

Acknowledgements

This study was supported by AstraZeneca, Lund, Sweden.

REFERENCES

1. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994; **344:** 219–224.
2. Woolcock AJ. The combined use of inhaled salmeterol and inhaled corticosteroids. *Eur Respir Rev* 1995; **5:** 142–145.
3. Pauwels RA, Lofdahl C-G, Postma DS, *et al.* Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997; **337:** 1405–1411.
4. Horn CR, Clark TJH, Cochrane GM. Compliance with inhaled therapy and morbidity from asthma. *Respir Med* 1990; **84:** 67–70.
5. Zetterström O, Buhl R, Mellem H, *et al.* Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. *Eur Respir J* 2001; **95:** 1–7.
6. Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation of budesonide/formoterol *vs* salmeterol/fluticasone in single inhalers. *Pulm Pharmacol Ther* 2001; **14:** 29–34.
7. Aziz I, Wilson AM, Lipworth BJ. Effects of once-daily formoterol and budesonide given alone or in combination on surrogate inflammatory markers in asthmatic adults. *Chest* 2000; **118:** 1049–1058.
8. Quanjer PhH, 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* 1993; **6:** 5–40.
9. 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 hours in bronchial asthma. *Am Rev Respir Dis* 1993; **147:** 1436–1441.
10. 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:** 1017–1021.
11. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lötvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J* 1997; **10:** 2484–2489.
12. Brusasco V, Crimi E, Gherson G, Nardelle R, Oldani V, Fabbri L. Protective effect of formoterol against the late-phase asthmatic response to allergen. *Eur Respir J* 1997; **10:** 474S.
13. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol* 1982; **70:** 288–298.
14. Malo JL, Cartier A, Merland N, *et al*. Four-times-a-day dosing frequency is better than a twice-a-day regimen in subjects requiring a high-dose inhaled steroid, budesonide, to control moderate to severe asthma. *Am Rev Respir Dis* 1989; **140:** 624–628.
15. Venables TL, Addlestone MB, Smithers AJ, *et al.* A comparison of the efficacy and patient acceptability of once daily budesonide via Turbuhaler and twice daily fluticasone propionate via a disc-inhaler at an equal dose of 400 μg in adult asthmatics, *Br J Clin Res* 1996; **7:** 15–32.
16. Simons FE. Inhaled glucocorticoids in children: a favourable therapeutic index. *Can Respir J* 1999; **6:** 175–178.
17. McFadden ER, Casale TB, Edwards TB, *et al.* Administration of budesonide once daily by means of Turbuhaler® to subjects with stable asthma. *J Allergy Clin Immunol* 1999; **104:** 46–52.
18. Chisholm L, Dekker FW, Knuistingh Neven A, Petri H. Once-daily budesonide in mild asthma. *Respir Med* 1998; **92:** 421–425.
19. Silkoff PE, Martin RJ. Pathophysiology of nocturnal asthma, *Ann Allergy Asthma Immunol* 1998; **81:** 878–883.
20. Martin RJ. Small airway and alveolar tissue changes in nocturnal asthma. *Am J Respir Crit Cure Med* 1998; **157:** S188–S190.
21. Jones AH, Langdon CG, Lee P, *et al.* PDI. Pulmicort® Turbuhaler® once daily as initial prophylactic therapy for asthma. *Respir Med* 1994; **88:** 293–299.
22. Campbell LM, Gunn SD, Sweeney D, *et al.* Once daily budesonide: effective control of moderately severe asthma with 800 μg once daily inhaled via Turbuhaler when compared with 400 μg twice daily. *Eur J Clin Res* 1995; **7:** 1–14.
23. Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1992; **146:** 1524–1530.
24. 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:** 361–370.
25. Chapman KR, Walker L, Cluley S, Fabbri L. Improving patient compliance with asthma therapy. *Respir Med* 2000; **94:** 2–9.