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Pulmicort® Turbohaler® once daily as initial prophylactic therapy for asthma

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In a double-blind, randomized, parallel-group clinical trial, 340 asthmatic patients aged 12–70 years received budesonide 400 μg once daily in the morning, budesonide 400 μg once daily in the evening, budesonide 200 μg twice daily or placebo, for 12 weeks in addition to inhaled short-acting β_2-agonists used as required (p.r.n.). Budesonide was given as Pulmicort Turbohaler.

Peak expiratory flow rate (PEFR) increased by 20 to 30 l min^{-1} in each of the active treatment groups, significantly more than in the placebo group ($P<0{\cdot}01$). There were no significant differences between the active treatment groups. Symptom improvement and decreased β_2-agonist use reflected the PEFR data. Incidences of adverse events in the active treatment groups were similar to those observed in the placebo group.

Budesonide 400 μg given once daily morning or evening is equieffective with the same total daily dose given twice daily in the treatment of mild to moderate stable asthmatics.

Introduction

Recent guidelines for the management of asthma emphasize the need to initiate prophylactic medication with an inhaled steroid if a patient needs to take an inhaled short-acting β_2-agonist more than three times a week (1,2) or once a day (3). It is, moreover, widely recognized that poor compliance with inhaled therapy is an important cause of persistent morbidity from asthma (4). Use of a device with high acceptability – Turbohaler (5) – coupled with a convenient once-daily regimen should favour good compliance (6). A previous study (7) showed that budesonide (Pulmicort Turbohaler, Astra) 400 μg once daily, taken in the evening, was superior to placebo in the control of mild to moderate asthma. However, the earlier study left unanswered the questions of whether 400 μg once a day was as effective as 200 μg twice a day, and whether the time of day for administration of the single daily dose was of importance. The present study addressed these questions.

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On behalf of the ACCEPT research group.

Methods

PATIENTS

Patients aged 12–70 yr with mild to moderate stable asthma and documented response to a β_1-agonist were eligible, provided their peak expiratory flow rate (PEFR: recorded with a mini-Wright peak flow meter; Clement Clarke Int. Ltd.,) was $\geq$60% of predicted when first seen and after one week's run-in. During the run-in, the patient had to have used inhaled β_2-agonist and to have had asthma symptoms (score of $\geq$1 on a 0–3 scale) on at least 2 of the last 5 days. The patients also had to demonstrate competence in the use of Turbohaler and the peak flow meter.

Patients were ineligible if they had received long-term glucocorticosteroids in the previous 6 months, short courses of glucocorticosteroids by any route in the past 2 months (except nasal steroids, where the period was 1 month), had exacerbation of asthma in the past 2 months or used cromoglycate or nedocromil in the past 2 months.

A need for nebulized β_2-agonist, a current respiratory infection or one treated in the past 6 weeks, other concomitant respiratory diseases, symptomatic allergy or a predicted seasonal allergy during the study rendered the patient ineligible.

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Table 1 Patient characteristics at receipt of randomized treatment

Pulmicort Turbohaler dose	Morning 400 μg	Evening 400 μg	Twice daily 200 μg	Placebo
Number	84	85	86	85
Males:females	44:40	42:43	42:44	50:35
Weight (kg)	71 (16)	67 (14)	68 (16)	71 (13)
Height (cm)	167 (10)	165 (10)	167 (11)	168 (10)
Age (yr)	36 (16)	36 (17)	36 (17)	40 (18)
Duration of asthma (yr)	12 (12)	11 (9)	9 (8)	11 (10)
Most recent exacerbation (yr ago)	1·0 (1·7)	1·6 (4·2)	1·6 (2·2)	1·7 (2·5)
PEFR (a.m.)* (l min^{-1})	383 (99)	376 (101)	372 (96)	386 (99)
(p.m.)† (l min^{-1})	403 (98)	391 (102)	395 (100)	404 (108)
Symptoms‡ (night)	0·87 (0·54)	0·83 (0·68)	0·89 (0·60)	0·88 (0·68)
(day)	1·11 (0·57)	1·04 (0·52)	1·03 (0·63)	1·11 (0·66)
β_2-agonist use§ (night)	1·25 (1·24)	0·96 (1·04)	1·25 (1·49)	1·17 (1·27)
(day)	3·41 (3·06)	3·37 (3·09)	3·34 (2·68)	3·33 (2·61)

Values are means (SD) 1: recorded on waking, 2: recorded on going to bed, 3: 0–3 scale, 4: actuations, 1–4 relate to diary card data during the run-in. The mean PEFR was 379 l min^{-1} (morning) which was 80% of predicted normal for these patients, and 398 l min^{-1} (84% predicted normal) for the evening diary card measurements. The mean PEFR at clinic visit 2 was 403 l min^{-1} (85% predicted).

STUDY AND DESIGN

This was a randomized double-blind, placebo controlled, multi-centre trial with four parallel treatment groups. Following a 1 week (minimum 5 days) run-in when patients continued on their current medication, they were randomized to receive budesonide 400 μg once daily in the morning ('morning' group), budesonide 400 μg once daily in the evening ('evening' group), budesonide 200 μg twice daily i.e. in the morning and evening ('twice daily' group) or placebo twice daily ('placebo' group). All patients received coded Turbohaler inhalers for morning and evening use, containing lactose as placebo where appropriate to maintain blindness. The schedule treatment duration was 12 weeks ± 7 days. Compliance was assessed from diary cards, on which patients recorded the time of administration of the study medication. All patients were treated by their General Practitioner, and all gave written informed consent to participate in this study which was approved by an Ethics Committee independent of the sponsor.

Inhaled, short-acting β_2-agonists were allowed on an as required (p.r.n.) basis, and their use recorded on diary cards. Each patient had to continue using the same β_2-agonist and inhaler device throughout. Nebulized β_2-agonists, cromoglycate, nedocromil, or any non-trial glucocorticosteroid were prescribed.

Diary cards were completed every morning and evening by all patients to record asthma symptoms (Scale: 0=none to 3=severe), PEFR, time of taking the study medication and β_2-agonist use. Data recorded in the morning related to time in bed ('night'). At clinic visits every 4 weeks, the Investigators checked the diary cards and recorded any adverse events or changes in concomitant medication.

ANALYSIS

To detect a 5% difference in PEFR between any pair of treatments assuming that the SD of a change is 10% of the predicted normal value requires 65 patients per group ($P<0·05$, 80% probability, *t*-test). This corresponds to detecting differences with regards to changes in asthma symptoms between any two groups of about 0·2 scale points assuming a standard deviation of 0·4 (on a 0–3 scale).

The primary efficacy variables were PEFRs (best of three always taken) and asthma symptoms on diary cards. Averages over time-intervals were calculated for the run-in, weeks 1 and 2, 3 and 4, 5 and 6, 7 and 8, 9 and 10 and 11 and 12. Data are presented for intention-to-treat (all patients treated) analyses with last value extended.

Statistical tests were used to compare changes from baseline in the four treatment groups (*t*-test). Absolute values are shown as means (SD) and changes as mean changes ± standard error means. The principal analyses are from the run-in to the end of the 12-week trial (Tables 2–4).

Table 2 Peak expiratory flow rate at the start and end of treatment

Pulmicort Turbohaler dose	Morning 400 μg	Evening 400 μg	Twice daily 200 μg	Placebo
PEFR measured in the morning				
Baseline	383 [80%]	376 [80%]	372 [79%]	386 [80%]
Increase	26 ± 5**	28 ± 6**	31 ± 5***	6 ± 5
PEFR measured in the evening				
Baseline	403 [85%]	391 [84%]	395 [84%]	404 [84%]
Increase	21 ± 5**	24 ± 6**	23 ± 6**	2 ± 7

Values are shown in l min^{-1} [and % predicted normal] for the run-in (start) and weeks 11–12 (after treatment). **$P<0.01$, ***$P<0.005$ compared with placebo. Increases in PEFR are mean ± SEM.

Table 3 Asthma symptoms at the start and end of treatment

Pulmicort Turbohaler dose	Morning 400 μg	Evening 400 μg	Twice daily 200 μg	Placebo
Symptoms during the night				
Baseline	0·87	0·83	0·89	0·88
Decrease	31%	16%	38%**	6%
	0·27 ± 0·08	0·13 ± 0·09	0·34 ± 0·06	0·05 ± 0·09
Symptoms during the day				
Baseline	1·11	1·04	1·03	1·11
Decrease	32%	26%	28%	17%
	0·35 ± 0·08	0·27 ± 0·09	0·29 ± 0·07	0·19 ± 0·08

Values are shown as symptom severity scores (0–3 scale) for the run-in (start) and weeks 11 and 12 (after treatment). **$P<0.01$ *vs.* placebo. Decreases are shown as % and mean ± SEM scale scores.

Table 4 β_2-agonist use at the start and end of treatment

Pulmicort Turbohaler dose	Morning 400 μg	Evening 400 μg	Twice daily 200 μg	Placebo
β_2-agonist use at night				
Baseline	1·25	0·96	1·25	1·17
Decrease	30%*	−1%	38%**	−11%
	0·37 ± 0·14	−0·01 ± 0·14	0·48 ± 0·13	−0·13 ± 0·19
β_2-agonist use during the day				
Baseline	3·41	3·37	3·34	3·33
Decrease	44%**	30%	27%	18%
	1·50 ± 0·24	1·02 ± 0·26	0·91 ± 0·23	0·59 ± 0·21

Values are shown as doses per day or per night. *$P<0.05$, **$P<0.01$ *vs.* placebo. Decreases are shown as % and doses/day, mean ± SEM.

Results

Three hundred and forty-four patients were randomized; 340 received treatment and 265 completed the 12 week study. Of the remaining 75, 14 withdrew because of adverse events and 18 because of deterioration of asthma, and 43 were lost to follow-up or withdrew for other reasons.

Patient characteristics for the 340 analysed patients at randomization are shown in Table 1. Patients received the study drugs on average for 12·8

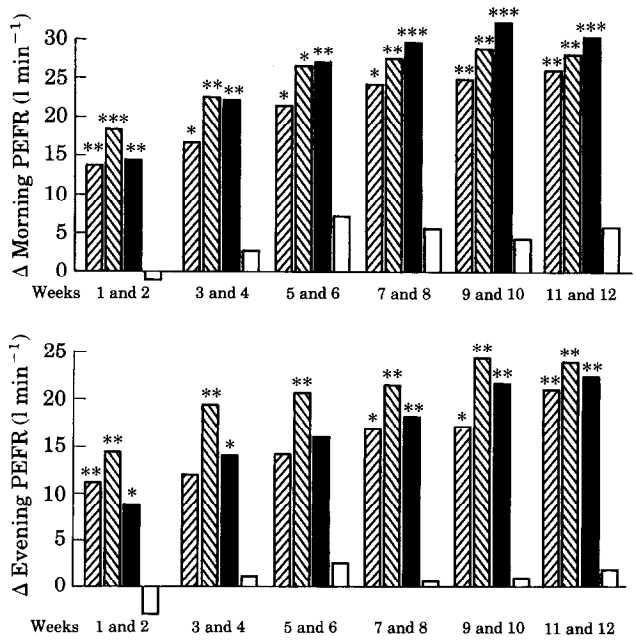

Fig. 1 Increases in peak flow (PEFR) for each treatment group from diary cards completed in weeks 1 and 2, 3 and 4, 5 and 6, 7 and 8, 9 and 10 and 11 and 12 compared with run-in. (▨) 400 μg morning, (▧) 400 μg evening, (■) 200 μg b.d., (□) placebo. *$P<0{\cdot}05$, **$P<0{\cdot}01$, ***$P<0{\cdot}001$.

(morning), 12·7 (evening), 12·8 (twice daily) and 12·6 (placebo group) weeks. The mean times of drug intake were 08.19 h and 09.23 h. Patients reported missing taking study drugs on 2·8% of scheduled occasions.

PEAK EXPIRATORY FLOW RATE

Morning and evening peak expiratory flow rates (PEFR) increased to a significantly greater extent in patients receiving each budesonide regimen than in patients receiving placebo (all $P<0{\cdot}01$). There were no significant differences between the budesonide groups (400 μg morning, 400 μg evening or 200 μg twice daily) (Fig. 1)

Mean values recorded on diary cards are shown in Table 2. Absolute and calculated % predicted PEFR increased similarly for all three active budesonide regimens, but not for placebo. The mean differences between active and placebo in the increment in PEFR measured in the morning from the run-in to weeks 11 and 12 were 20·2 l min^{-1} for budesonide 400 μg in the morning ($P<0{\cdot}005$), 22·3 l min^{-1} for 400 μg budesonide in the evening ($P<0{\cdot}005$) and 24·8 l min^{-1} for 200 μg budesonide twice daily ($P<0{\cdot}001$). The corresponding values for peak flow measured in the evening were 19·3 ($P<0{\cdot}01$), 22·2 ($P<0{\cdot}005$) and 20·9 ($P<0{\cdot}01$) l min^{-1}.

ASTHMA SYMPTOMS

Asthma symptoms improved in all treatment groups over the 12-week study. The improvements were from a relatively low level of recorded symptoms (Table 1) and although the improvements were consistently greater for the three active groups than for placebo, these differences did not generally attain statistical significance (Table 3).

β_2-AGONIST USE

In general the three groups receiving budesonide used less β_2-agonists on a p.r.n. basis than the group receiving placebo (Table 4). Although these results showed appreciable variability, daytime β_2-agonist use fell by around 1 dose per day (approximately 30%) in all budesonide groups from a starting level of about 3·4 doses per day.

In the morning and twice-daily groups nocturnal β_2-agonist use also fell by around 30%; in the evening group, β_2-agonist use at night did not change from a level which was already lower than in other groups during the run-in.

TIME COURSE OF CHANGES

Figure 2 shows the changes in the variables from run-in to weeks 3 and 4 and to weeks 11 and 12. Whilst changes in symptoms and β_2-agonist use were

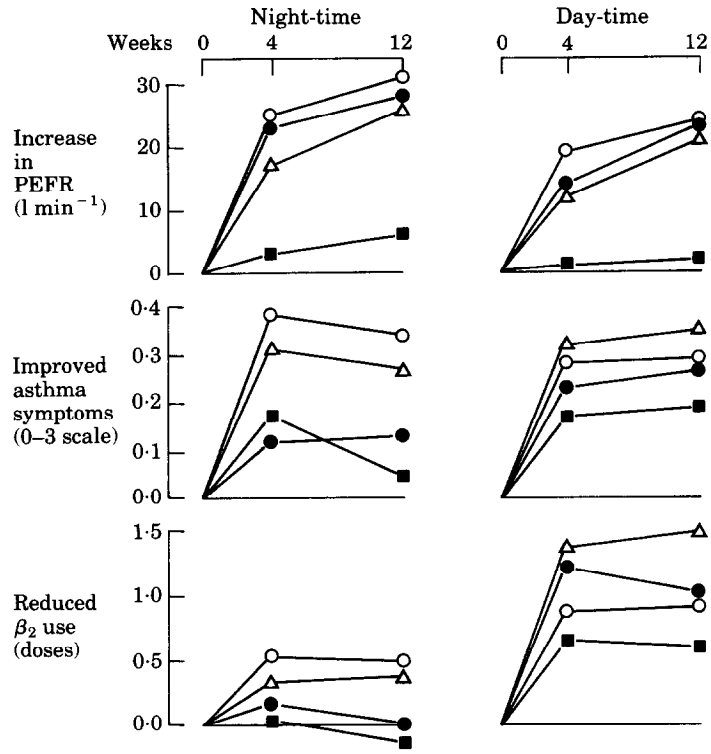

Fig. 2 Changes in PEFR, asthma symptom severity and β_2 use after 4 weeks and 12 weeks treatment with budesonide 400 μg once daily in the morning (△), 400 μg once daily in the evening (●), 200 μg twice daily (○) or placebo (■). Changes are shown separately for night-time (recorded on rising: morning peak flow) and day-time (recorded on retiring: evening PEFR).

essentially complete after 4 weeks, improvements in PEFR with budesonide were consistently greater after 12 weeks.

SAFETY AND TOLERABILITY

In all, 324 patients were evaluable for safety. Of the 16 not evaluable, 13 were lost to the treatment week 4 follow-up clinic visit, two withdrew a few days after randomization and all records were lost for one patient. The frequency of occurrence of adverse events was the same in the budesonide and placebo groups. In the three budesonide groups, 98 (40%) patients reported 152 adverse events, and in the placebo group 34 (43%) patients reported 59 adverse events.

Around 20% of the reported adverse events were identified from patients' comments on diary cards, and the remainder from clinic visit reports. Details of all serious adverse events and adverse events leading to withdrawal are given in Table 5. Other events reported with a frequency >2% were: respiratory infection (budesonide 11%, placebo 20%), aggravation of asthma (placebo 8%), coughing (placebo 4%), bronchitis (placebo 3%), headache (budesonide 7%, placebo 8%), dyspepsia (placebo 3%), accident and/or injury (placebo 5%). An extensive miscellany of other reports were found. The distribution of withdrawals was significantly different between groups ($P<0{\cdot}05$, χ^2-test) only with regard to deterioration of asthma which occurred most commonly in the placebo group (Table 5).

Discussion

Pulmicort (budesonide) Turbohaler in a total daily dose of 400 μg is equally effective and well tolerated when given once daily as when given in two divided doses for the treatment of mild to moderate stable asthma.

This study confirms and extends the observations made previously (7) that budesonide 400 μg once-daily in the evening is superior to placebo, to show that the once-daily dose may be given in the morning or evening, and that once daily administration is

Table 5 Reasons for withdrawal

Pulmicort Turbohaler dose	Morning 400 μg (*n*=84)	Evening 400 μg (*n*=85)	Twice daily 200 μg (*n*=86)	Placebo (*n*=85)
Adverse events				
Serious adverse events*	0	3***	2†	2‡
Withdrawals due to adverse events	5§	2¶	5‖	2**
Other reasons for withdrawal				
Asthma deteriorated	3	6	0	9
Others (lost to follow-up)	14 (10)	6 (1)	12 (5)	12 (9)††
Total withdrawals	22	14	17	23

*According to protocol definition. ***pleural pain; angioneurotic oedema; bleeding gastric ulcer. †Appendicitis (2). ‡Pneumonia; asthma deterioration. A causal relationship with the study medication was considered 'unlikely' by the Investigators in each case. §Lump in throat; sinusitis; chest tightness, fatigue, tremor, itching; fractured ankle; headache, coughing. ¶Vomiting, shaking; pleural pain. ‖Dizziness, nausea; rash; acne; mouth ulcers; bad dreams, bad temper, tearful. **Wheeze, cough; pneumonia. ††Includes one for whom the record book was lost.

equieffective with the same total daily dose given in divided doses. All dosage schedules for budesonide were equivalent in efficacy and superior to placebo.

The magnitudes of the increases on PEFR measured both morning (around 30 l min^{-1}) and evening (around 25 l min^{-1}) were similar in the present and the previous study (7), patient characteristics also being similar in the two studies. Patients' PEFRs were relatively high at entry (evening PEFR around 400 l min^{-1}: Table 1), reflecting the fact that relatively mild asthmatic patients were eligible for this study in General Practice; one consequence of this is that the potential for improvement in PEFR is limited. It is interesting that PEFR appeared to increase after the first 4 weeks of treatment, through improvements in asthma symptoms and bronchodilator use were apparently maximal within 4 weeks. Patients in both studies were not using inhaled corticosteroids before the start of the study, and in both studies β_2-agonist use was about 3–4 times per day on average, well in excess of the recommended frequency of use at which inhaled steroid therapy should be introduced, i.e. once a day (3) or less (1,2). Moreover, reduced bronchodilator use was a less sensitive reflection of improved PEFR or asthma symptoms. From these two studies, it appears that if PEFR is the primary end-point in a trial, a treatment period in excess of 4 weeks is mandatory, and recording β_2-agonist use as a surrogate end-point for asthma symptoms or PEFR could be misleading.

Asthma symptoms improved in all active treatment groups to a greater extent than in the placebo group; however scores were low at entry to the trial. Typical symptom scores in the run-in, before the institution of budesonide or placebo were around 1 by day and 0·9 by night out of a maximum of 3. A 'placebo effect' would be predicted on symptoms, and was found, more marked by day than by night; since the study was designed to detect a difference between changes in symptom scores of about 0·2 scale point, it is not surprising that changes from a baseline as low as 0·9–1·0, while indicating advantages for budesonide, did not always reach statistical significance especially as there were concomitant reductions in β_2 use. Use of a 0–10 scale system would not have helped (7). It may be that both 'overuse' and habitual use of β_2-agonists among these patients means that they were relatively free of symptoms, although their PEFRs were around 80% predicted, at entry.

Comparing the three active regimens (Fig. 2) does not give a clear basis for recommending use of budesonide at any particular time of day. Where apparent differences exist (e.g. in the failure of the evening dose to result in reduce β_2-agonist use: Table 4), they appear to reflect differences in baseline values, and as in this case, are not consistent with the earlier study (7). In the previous study, nocturnal administration was chosen to give the best chance of controlling nocturnal symptoms which were considered the most likely to be troublesome; however, if such an advantage exists, it is marginal (Fig. 2) over other dosage schedules. Evening administration may be less preferable on theoretical grounds, to avoid exacerbating the physiological diurnal reduction in circulating cortisol levels, though it is uncertain whether this has any relevance at dosage levels such

as 400 μg/day in adults. On balance, it seems reasonable to leave the time of dosing to the individual physician. Having established that once-daily administration of budesonide is appropriate as initial prophylactic treatment at 400 μg/day, trial study raises two issues which need further study: whether once-daily administration is appropriate for higher doses, and whether once-daily budesonide administration is an option for patients already receiving inhaled steroids – including those in whom a dose-reduction is possible.

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