Original Articles

Comparison of four-times-a-day and twice-a-day dosing regimens in subjects requiring 1200 µg or less of budesonide to control mild to moderate asthma

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The aim of this study was to compare the efficacy, compliance and side-effects of budesonide administered twice daily (b.d.) and four times a day (q.d.) with a Turbuhaler® device in asthmatic subjects requiring $\leq 1200\,\mu g$ daily. The randomized, parallel group study design included a 2-week baseline period followed by a 6–12-month treatment period. Subjects were assessed at regular intervals in hospital through FEV_1, PC_{20} methacholine, adrenal function and throat swabs. They were asked to record their symptoms and PEF values morning and evening at home. An asthmatic flare-up, which was the main outcome resulting in a patient's termination of the study, was defined beforehand as (a) 25% or greater diurnal variability in PEF for 2 consecutive days, and/or (b) nocturnal awakenings due to asthma symptoms 2 days or more in the same week and/or (c) an increase (doubling or more) in the need for inhaled bronchodilator 2 days in the same week.

Fifty-eight adult asthmatic subjects (20 males and 38 females) entered the study, one-half being randomly assigned to the b.d. regimen and one-half to the q.d. regimen. Fourteen subjects were on $400\,\mu g$, 15 subjects on $800\,\mu g$ and 29 subjects on $1200\,\mu g$ of budesonide daily. Seventeen flare-ups were recorded in the b.d. regimen group as opposed to 11 in the q.d. regimen ($P=0.05$), significant differences being found in the 800 and $1200\,\mu g$ groups (a total of 13 flare-ups in the b.d. group and eight flare-ups in the q.d. group for the two doses, $P=0.01$). Kaplan–Meier survival analysis yielded similar results. There was no significant difference in FEV_1, PC_{20} or cortisol levels during the study on either regimen. Throat symptoms and growth of *Candida albicans* were more common in the q.d. group. Compliance assessed by the number of times the Turbuhaler® device was actuated was significantly better in the b.d. group (95%) as compared with the q.d. group (83%). To conclude, administering inhaled budesonide with a Turbuhaler® device on a q.d. basis results in fewer flare-ups in spite of less satisfactory compliance and more common, local side-effects than on a b.d. regimen at daily doses of 800 and $1200\,\mu g$.

Introduction

Anti-inflammatory medication is currently the cornerstone in the treatment of asthma (1). In adults, inhaled steroids is the preferred anti-inflammatory medication. Their use is advocated in international guidelines whenever inhaled β_2-adrenergic agents are used on a regular basis (2,3). Although the conventional dose frequency is four times a day (q.d.), dose frequency is often reduced in an attempt to improve patient compliance while maintaining the efficacy of the drug. A previous study showed that budesonide, administered with a conventional metered dose inhaler device, was more efficient when administered on a q.d. basis as opposed to a twice-daily (b.d.) basis (4). However, one-half of the 36 patients who completed the study were on high doses of budesonide ($1600\,\mu g\,day^{-1}$) and it was unknown whether the results would hold if budesonide was administered in powder form. Inhaled β_2-adrenergic agents and anti-inflammatory preparations are now available in powder form. The advantages were summarized recently (5). Budesonide has been made available in

powder form. The Turbuhaler® is a multiple-dose powder inhaler that is easier to use than the standard metered dose inhaler (6).

This study was designed in an attempt to test the hypothesis that inhaled budesonide given at daily doses $\leq 1200\,\mu g\,day^{-1}$ would show greater efficacy in the context of a q.d. regimen, and that there would be equivalent side-effects but better compliance with a b.d. regimen.

Materials and Methods

SUBJECTS

Fifty-four adult subjects who fulfilled the criteria of the American Thoracic Society for a diagnosis of asthma were included in the study (7). Four subjects were randomized twice, once in each of the two regimens (see below) after a 3-month washout period. All were in a clinically steady state (no nocturnal awakenings due to asthma, no recent modification in their need for bronchodilators) at the time they entered into the study. All showed a $\geq 20\%$ improvement in FEV_1 30 min after inhalation of 0·5 mg terbutaline sulphate on entry into the trial. Fifty-two subjects underwent methacholine inhalation challenges and the provocative concentration causing a 20% fall in FEV_1 (PC_{20} was $\leq 16\,mg\,ml^{-1}$, indicating significant bronchial hyper-responsiveness (8) in all of them. None had required oral steroids in the 3 months preceding the study and none had been hospitalized for asthma in the previous year. All gave informed written consent and the protocol was approved by the Ethics Committee of the Hospital.

STUDY DESIGN

The study was of a randomized, open-label, parallel design consisting of a 2-week baseline period followed by a 6–12-month treatment period. After the 2-week run-in period in which a clinically stable asthmatic state was ensured (no nocturnal awakenings due to asthma; no recent modification in the need for bronchodilators or inhaled steroids, no viral infections), eligible patients were randomly assigned to receive b.d. dosing with budesonide Turbuhaler® or q.d. dosing with budesonide Turbuhaler®, at a dose considered to be equivalent to their usual dose of inhaled steroids (equivalent doses of 400, 800 or 1200 μg of budesonide). Subjects on 400 μg daily had to take either 200 μg b.d. or 100 μg q.d. from one of the two different inhalers (one containing 100 μg puff^{-1} and the other, 200 μg puff^{-1}), those on 800 μg were asked to take 400 μg b.d. or 200 μg q.d., and, finally, those on 1200 μg, 3 puffs of 200 μg b.d. or 3 puffs of 100 μg q.d. The study was an open-label design; however, patients were randomized to treatment by a nurse not involved in the study to prevent possible bias in treatment assignment. In addition, this nurse was responsible for dispensing and collecting all study medications. Patients were advised not to discuss their treatment assignment with the study personnel. So, every attempt was made to keep the study single-blind, despite being open-label. Patients were also not informed that their compliance was being monitored, so this aspect of the study was also single-blind, albeit open-label. An open-label design was chosen in order to assess patient compliance with the two dosing regimens more accurately. Using a double-blind design would have meant inconveniencing the patients whether they were on a b.d. or q.d. regimen, since they would then have had to use two separate inhalers – one q.d. and one b.d. With such a study design, it would have been impossible to properly evaluate if subjects were more compliant with one or other of the dosing regimens. A difference in the degree of compliance with the two dosing regimens could also have had considerable impact on the overall efficacy of the dosing regimens.

Subjects were instructed on how to use the Turbuhaler® with a deep inspiration, not too slow as to generate a sufficient flow rate ($>30\,l\,min^{-1}$), and a post-inspiratory breath-hold of 10 s. They were advised to wash their mouth after using the device. Suggested timings for taking the medication were on awakening, at noon and supper time, and before going to bed. The instructions were similar in the two treatment groups and subjects were reminded at each visit. Subjects were followed for 6 months ($n=8$) or 12 months ($n=18$) if they experienced no flare-ups. Clinical assessments were completed at weeks 2, 4, 8, 12, 16, 20, 24 (this was the final visit for subjects who decided not to continue with the study because they were no longer interested), 30, 36, 42 and 48 weeks. At each visit, spirometry was performed, and throat swabs for *Candida albicans* were taken every second visit. Assessment of bronchial responsiveness to methacholine as well as serum cortisol levels and response to an injection of 25 IU synthetic ACTH were performed on entry and at the end of the study period. Subjects were asked to fill in daily diary cards throughout the study, answering the following questions:

(1) Did you have asthma during the . . . day/night?
(2) If asthma was present at night, how many times were you awakened by it?
(3) If asthma was present at night, did you need an inhaled β_2-adrenergic agent?

(4) During the day, how severe was the asthma? (answer on a seven-mark scale from absence of symptoms to symptoms so severe that the subject could not go to work or perform normal daily activities)

(5) Did you cough during the . . . day/night?

(6) Was your throat sore or hoarse today (answer on a four-mark scale)

(7) How many puffs of inhaled β_2-adrenergic agents and inhalations of study medication did you take?

Peak expiratory flow rates (PEF) were recorded b.d., upon awakening and at bedtime, before any medication scheduled for that time was taken. Subjects were asked to take three readings and record them in their diaries.

TESTING

Spirometry was assessed according to American Thoracic Society standards (7). The best of two reproducible ($\pm$ 20 l min^{-1}) PEF values was kept for analysis. Bronchial responsiveness to methacholine was assessed using Cockcroft *et al.*'s method at tidal volume breathing for 2 min with a Wright's nebulizer (output=0·14 ml min^{-1}) (9). Throat swabs were cultured for *Candida*, using commercially prepared Sabouraud's and Dextrose Agar plates as the medium for yeast growth. Blood was taken for cortisol at the same time of day (morning) for each patient, and 30 min after the injection of synthetic ACTH.

ANALYSIS OF RESULTS

An asthmatic flare-up, which was the main outcome that resulted in the termination of the study, was defined beforehand as: (a) 25% or more changes in morning and/or evening PEF values over 2 consecutive days, and/or (b) nocturnal awakenings due to asthma symptoms 2 days in the same week, and/or (c) an increase (doubling or more) in the need for inhaled bronchodilators 2 days in the same week.

Compliance was measured by continuing to turn the dosing grip of the used, returned Turbuhaler® devices until the last dose had been selected. By counting the remaining doses and subtracting this number from 200 (the total number of doses in Turbuhaler®), the number of doses taken by the patient was calculated. Patients were not informed that their compliance was being monitored.

The confidence interval test, χ^2-test, unpaired *t*-test, analysis of variance with orthogonal contrasts, and Kaplan–Meier survival curve were used in the analysis of results, with the SYSTAT statistical

Table 1 Reasons for flare-ups in the b.d. and q.d. groups

	b.d. group	q.d. group
1. Fall in PEF>25% on 2 days	3	1
2. Nocturnal awakening on 2 days	5	2
3. Increase in the need for inhaled		
β_2-adrenergic agent on 2 days	4	2
Combination of criteria		
1+2	0	2
2+3	3	4
1+3	2	0
Total	17	11

package (SYSTAT, Inc., Evanston, IL). A *P* value $\leq 0\cdot05$ was considered significant.

Results

Of the 58 subjects, 20 were male and 39 female. One-half of the subjects were randomized to the b.d. regimen and one-half to the q.d. regimen. Four of the 58 subjects participated in the study twice, being included in the b.d. and the q.d. groups after a washout period of 3 months. The mean age was 50 ± 13 (SD) years. The duration of asthma was 18 ± 17 (SD) years. The mean baseline FEV$_1$ was 75 ± 16 (SD) %predicted. There were no significant differences in the clinical (number of days with asthmatic symptoms), physiological (serial PEF, FEV$_1$, PC$_{20}$) or laboratory (oral candidiasis, cortisol level results) when comparing the b.d. and the q.d. groups on entry to the trial and during the baseline period, except for the frequency of throat symptoms. This was higher in those who later entered in the b.d. group (37·2% of days with throat symptoms) in comparison with the q.d. group (20·9% of days with throat symptoms) (χ^2=28, P<0·001).

Four subjects (one in the b.d. group and three in the q.d. group) were excluded after being entered into the study because of poor compliance in terms of hospital visits. There were four flare-ups in the 400 μg b.d. group and three flare-ups in the q.d. group, four flare-ups in the 800 μg b.d. group and two flare-ups in the q.d. group, and nine flare-ups in the 1200 μg b.d. group and six flare-ups in the q.d. group. The number of flare-ups was therefore slightly but significantly greater in the b.d. group (*n*=17) than in the q.d. group (*n*=11) (confidence interval test, P=0·05). This difference was more marked taking into consideration subjects on the 800 and 1200 μg daily doses (13 as opposed to 8) (confidence interval test, P=0·01). The reasons for the flare-ups are listed in Table 1.
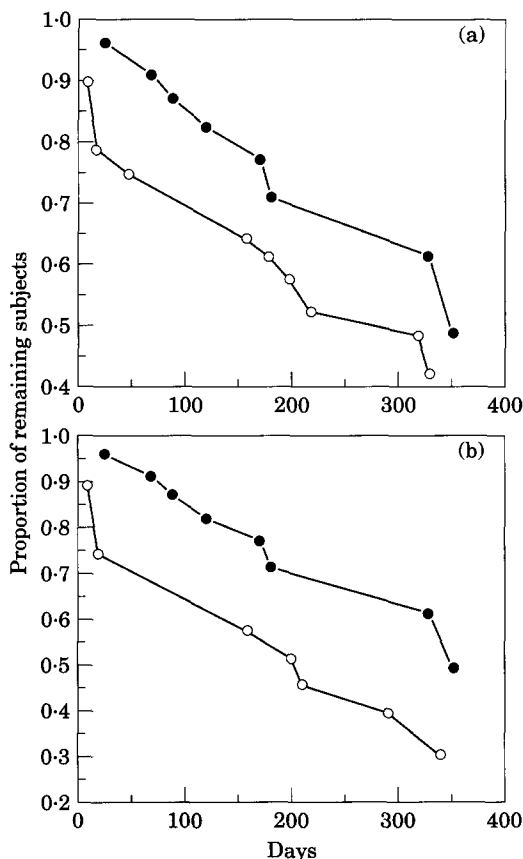
Fig. 1 Curves relating time in days to the proportion of
subjects who did not have a flare-up (a) for all subjects,
$n=58$; (b) for subjects on 800 and $1200\,\mu g\,day^{-1}$, $n=44$.
Curves were analysed by survival analysis and showed a
borderline difference for the whole group but definite differ-
ences for subjects on 800 and 1200 μg of budesonide day^{-1}
(see text for details of Kaplan–Meier survival analysis).
Each point represents the time interval at which the cumu-
lative proportion surviving at end (as obtained from
the survival analysis) changed. ●, q.d. regimen; ○, b.d.
regimen.

Clinical symptoms (nocturnal awakenings due to
asthma and/or increase in the need for inhaled
β_2-adrenergic agents) were more often responsible for
flare-ups than were significant changes in PEF.
Curves relating the proportion of subjects not
affected by flare-ups and time from entry in the
trial are shown in Fig. 1. Survival analysis showed
borderline differences in the q.d. and b.d. curves
(Mantel, $P=0.15$, Breslow–Gehan, $P=0.07$, Tarone–
Ware, $P=0.1$) when all subjects were included,
whereas it reached statistical significance when
analysing the 44 subjects taking 800 and 1200 μg
of budesonide (Mantel, $P=0.03$, Breslow–Gehan,

$P=0.02$, Tarone–Ware, $P=0.02$). Approximately
one-half of the flare-ups in the b.d. group occurred
within 1 month of entry into the study. There were no
significant differences in terms of age, atopic status,
sex and duration of asthma in those who had early
flare-ups (in the first 2.5 months after entry), those
with flare-ups at a later stage and those who had no
flare-up. Four subjects were included in the b.d. and
q.d. regimens in order to balance the number in each
group. Even after eliminating those four subjects, the
survival analysis remained significant for the 800 μg
and 1200 μg groups (Mantel, $P=0.05$, Breslow–
Gehan, $P=0.04$, Tarone–Ware, $P=0.05$) and border-
line for the whole group ($P=0.1$). Table 2 shows the
differences in clinical and functional results between
the two groups. Although the number of nights with
awakenings due to asthma and the total number of
awakenings were significantly more frequent in the
b.d. group, the number of days with asthmatic symp-
toms only tended to be significantly greater in the
same group although the number of days in which a
β_2-adrenergic agent was used was similar in the two
groups. Morning (and to a lesser extent, evening)
PEF values were higher in the q.d. group, and there
were many fewer days with significant ($>25\%$ or
$>20\%$) fluctuations. FEV_1 and PC_{20} values were not
significantly different from the beginning to the end
of the study.

Throat symptoms were more common and oral
candidiasis was more than twice as common in the
q.d. group (Table 2), although an equivalent number
of subjects had candidiasis at one time or another
during the study (five subjects in the b.d. group and
six subjects in the q.d. group). Cortisol level and the
response to cortisol after synthetic ACTH injection
remained unchanged throughout the trial.

Compliance was significantly better in the b.d.
group as compared to q.d. group ($83 \pm 16\%$ in the
q.d. group and $95 \pm 16\%$ in the b.d. group, $P=0.006$).

Discussion

This study shows that administering budesonide
on a q.d. basis instead of a b.d. basis has the
advantage of controlling asthma better at the expense
of more local (throat) side-effects in subjects who
require a low to moderate dose of the preparation. A
previous study at our centre showed that a q.d.
regimen was superior to a b.d. regimen in terms of
relapses and several clinical and functional indices
(4). However, that study (4) (a) included 18 of a total
of 36 subjects (50%) who were on 1600 μg of budes-
onide, which can be considered a high dose, (b) tested
budesonide with the standard metered dose inhaler

Table 2 Comparison of clinical and functional results and side-effects according to regimen

	b.d. group	q.d. group	χ^2	P value
Number of nights with awakenings due to asthma	46	20	10·4	0·001
(% of total number of nights in the study)	(0·08%)	(0·03%)		
Number of awakenings due to asthma	53	32	5·4	0·02
(% of total number of nights in the study)	(0·09%)	(0·05%)		
Number of days in which β_2-adrenergic agent was used	189	175	0·6	ns
(% of total number of days in the study)	(0·3%)	(0·3%)		
Number of days with asthmatic symptoms	1392	1318	3·05	0·09
(% of total number of days in the study)	(23·6%)	(22·2%)		
Peak flow rates			*t* value	P value
Morning value				
(l min^{-1})	396 (±97)	423 (±97)	1·0	ns
Mean within-subject variability (SD)	23 (±12)	21 (±9)	0·7	ns
Evening value				
(l min^{-1})	411 (±91)	434 (±90)	1·0	ns
Mean within-subject variability (SD)	20 (±8)	20 (±7)	0	ns
Daily fluctuations				
(maximum–minimum values in % of maximum)	3·8 (±9·5)	3·1 (±6·8)	0·3	ns
Number of days with daily fluctuations			χ^2	P value
≥25%	438	273	42	<0·001
(% of total numbers of days in the study)	(7·4%)	(4·6%)		
≥20%	490	362	21	<0·001
(% of total number of days in the study)	(8·3%)	(6·1%)		
FEV$_1$			*t* value	P value
End of the study (% predicted)	76 (±17)	75 (±15)	0·2	ns
Changes (% value at entry into the study)	4·5 (±2·2)	4·8 (±2·3)	0·5	ns
PC$_{20}$				
End of the study (mg ml^{-1})	1·9	2·5	0·7	ns
			χ^2	P value
Changes (number of subjects >2-fold)	8	8	0·1	ns
			t value	P value
Number of days with throat symptoms	938	1570	198	<0·001
	(15·9%)	(26·5%)		
Oral Candidiasis				
(number of positive/total throat swabs, %)	5/81	13/85	3·6	0·05
	(6·2%)	(15·3%)		
Cortisol level				
End of the study (nmol l^{-1})	309 (±151)	290 (±196)	0·4	ns
Changes (% value at entry into the study)	−63 (±94)	3·7 (±170)	1·9	ns

The total number of nights/days was 5899 in the b.d. group and 5928 in the q.d. group. Mean ± SD value are given. ns, not significant.

while budesonide is now available in powder form and (c) did not assess compliance.

The difference in the number of flare-ups was significant in the 800 and 1200 μg groups but not among subjects taking 400 μg. In the 800 μg group (15 subjects), four of six subjects (67%) on the b.d. regimen experienced flare-ups as compared with only two subjects out of nine (22%) in the q.d. regimen group. In the 400 μg group which included 14 subjects, it was not possible to document superior efficacy of the q.d. regimen over the b.d. regimen. Although the possibility that there would have been differences if a larger number of subjects had been included cannot be excluded, this suggests that a b.d. regimen may be just as good as a q.d. regimen in subjects taking small doses of inhaled steroids. Most studies that have used small doses of budesonide or beclomethasone failed to demonstrate any difference in efficacy of a b.d. or q.d. regimen. Meltzer *et al.* showed no difference when comparing b.d. and q.d. regimens in a group of 52 children and 37 young adults who required 336 μg of beclomethasone daily, which is comparable to 400 μg dose of budesonide (10). Nyholm *et al.* also failed to demonstrate the superior efficacy of a q.d. regimen in 24 adults who were on a daily dose of 400 μg of budesonide (11). Field *et al.* showed that 400 μg of budesonide administered b.d. (200 μg each time) had the same efficacy

as beclomethasone administered q.d. (100 μg each time) (12). Willey et al. had similar results in 30 adult patients using a similar design (13). Toogood et al. found advantages in using the q.d. regimen over the b.d. regimen in 37 subjects who were given 400, 800 and 1600 μg of budesonide, although the dose by itself was the major determinant of efficacy (14). The inclusion of clinically unstable subjects (pollen sensitive patients studied during the pollen season) in the study by Toogood et al. could have enhanced the potential difference in efficacy (14). Dahl and Johansson also found advantage in terms of PEF values but not in terms of clinical efficacy in using a q.d. as opposed to a b.d. regimen (15). However, this included patients taking 400 and 800 μg of budesonide daily. The authors did not mention if these differences hold for both the 400 and 800 μg daily doses.

In a previous study, the number of relapses was found to be equivalent in subjects on a high dose of budesonide (1660 μg), regardless of the regimen (b.d. or q.d.) (4). This was explained by the fact that one-half of the subjects were on oral steroids as well, which could have masked the difference. Satisfactory control of asthma was also more difficult in this group, which could explain why it was impossible to detect differences. The evidence, therefore, is that in the low (400 μg) and high (1600 μg) dose ranges, administering budesonide on a b.d. or a q.d. regimen results in no significant influence on its efficacy. Differences can only be detected in the middle dose range (800 and 1200 μg daily).

Although the efficacy of budesonide was better in the q.d. group, throat symptoms and the proportion of positive throat swabs for Candida albicans were also higher, a difference from a previous study (4). However, Toogood et al. also found that the frequency of oropharyngeal candidiasis correlated strongly with the daily dose of budesonide and dosing frequency, a b.d. treatment abolishing the effect of increasing the dose of budesonide on candidiasis (16). This different type of comparison (graded dose) used by Toogood et al. (14) indicated that (a) to achieve equivalent levels of anti-asthmatic response, a higher and more toxic dose of budesonide is required if the total daily dose is administered in two rather than four divided doses, (b) that the difference is potentially clinically important, i.e. to achieve an equivalent anti-asthmatic response, a low and non-toxic dosage would have to be increased to high and potentially toxic levels (17), and (c) the difference may only be demonstrable when the asthma has been destabilized immediately prior to making the comparison. Adrenal function as

assessed by cortisol levels before and after administering synthetic ACTH was equivalent in the two groups.

Although the q.d. regimen was more effective than the b.d. regimen in the 800 and 1200 μg range doses, compliance was significantly better in the b.d.group, as expected. Compliance was assessed in an indirect way by counting the number of puffs which were not actuated. No direct and more precise means to assess timing of actuation and whether patients really took the inhalation was available. The statistically significant difference in compliance which favoured the b.d. over the q.d. regimen proved clinically inconsequential since it was more than offset by the potency-reducing effect of b.d. treatment. The fact that compliance was on the whole very good, even in the q.d. group, can be explained by the fact that more compliant subjects are more likely to be included in clinical trials. This is also reflected by the fact that only four subjects had to be withdrawn due to poor compliance in terms of hospital appointments.

To conclude, the efficacy of budesonide administered with a Turbuhaler® device is better when administered on a q.d. basis than on a b.d. regimen. Although compliance was less satisfactory, a difference in efficacy favouring the q.d. regimen was detected. These results hold for the moderate daily doses of 800 and 1200 μg. Although efficacy was better in the q.d. group, this was at the expense of more local side-effects in terms of throat symptoms (16% as opposed to 27% of days) and growth of Candida albicans. Advising patients to take their medication on a q.d. basis is valuable in terms of better efficacy but one should expect less compliance and more throat side-effects. It would appear to us particularly relevant to recommend a q.d. regimen in those requiring 800 μg or more of budesonide, considering that this dose can lead to some systemic absorption.

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