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Optimal asthma control, starting with high doses of inhaled budesonide

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ABSTRACT: The aim of this study was to determine whether outcomes in poorly controlled asthma can be further improved with a starting dose of inhaled budesonide higher than that recommended in international guidelines.

The study had a parallel-group design and included 61 subjects with poorly controlled asthma, randomized to receive 3,200 μg or 1,600 μg budesonide daily by Turbuhaler® for 8 weeks (double-blind), then 1,600 μg·day^{-1} for 8 weeks (single-blind), followed by 14 months of open-label budesonide dose down-titration using a novel algorithm, with a written asthma crisis plan based on electronic peak expiratory flow monitoring. The primary outcome variable for weeks 1–16 was change in airway hyperresponsiveness (AHR), and, for the open-label phase, mean daily budesonide dose.

By week 16, there were large changes from baseline in all outcomes, with no significant differences between the 3,200- and 1,600-μg·day^{-1} starting dose groups (AHR increased by 3.2 *versus* 3.0 doubling doses, p=0.7; morning peak flow increased by 134 *versus* 127 L·min^{-1}, p=0.8). Subjects starting with 3,200 μg·day^{-1} were 3.8 times more likely to achieve AHR within the normal range, as defined by a provocative dose of histamine causing a 20% fall in forced expiratory volume in one second (PD_{20}) of ≥3.92 μmol by week 16 (p=0.03). During dose titration, there was no significant difference in mean budesonide dose (1,327 *versus* 1,325 μg·day^{-1}, p>0.3). Optimal asthma control was achieved in the majority of subjects (at completion/withdrawal: median symptoms 0.0 days·week^{-1}, β_2-agonist use 0.2 occasions·day^{-1}, and PD_{20} 2.4 μmol).

In subjects with poorly controlled asthma, a starting dose of 1,600 μg·day^{-1} budesonide was sufficient to lead to optimal control in most subjects. The high degree of control achieved, compared with previous studies, warrants further investigation.
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Despite the fact that inhaled corticosteroids are the most effective anti-inflammatory treatment for asthma, many questions remain unanswered about their use, including the optimal starting dose. Several international asthma guidelines advocate a "step-up" approach to achieving asthma control [1–3], starting with inhaled corticosteroid doses of 200–800 μg·day^{-1} for patients with moderate asthma, with an increase in dose up to 800–2,000 μg·day^{-1} and the addition of other agents including long-acting β_2-agonists and/or long-term oral steroids for those with more severe asthma on presentation or who fail to respond to lower doses. The Global Initiative for Asthma (GINA) guidelines define control of asthma as minimal symptoms and β_2-agonist use, minimal exacerbations, near-normal peak expiratory flow (PEF) and circadian variation in PEF of <20% [1]. However, the reported outcomes of many studies indicate suboptimal asthma control despite treatment consistent with these guidelines [4–7].

More recently, it has been suggested that in order to achieve asthma control rapidly and hence enhance patient compliance, inhaled corticosteroid treatment should start at relatively high doses for all but mild asthma [8]. This recommendation has been included in some current guidelines [2, 9]. A study in subjects with newly diagnosed asthma showed no significant difference in outcomes when treatment was commenced with 4 weeks of 200 or 800 μg·day^{-1} budesonide [10], but a recent study in subjects whose inhaled corticosteroids had been withdrawn showed significantly greater improvement in sputum inflammatory marker levels and a trend to greater improvement in airway hyperresponsiveness (AHR) with 2 weeks of 2,000 μg·day^{-1} fluticasone propionate compared with 500 μg·day^{-1} [11].

In subjects with poorly controlled asthma, a short-term study has shown a dose/response relation for inhaled budesonide in the range 200–1,600 μg·day^{-1} [6], but symptom control was suboptimal even at the highest dose. The present study was designed to examine whether asthma outcomes in subjects with poorly controlled asthma could be improved by starting treatment with a higher dose of inhaled budesonide (3,200 μg·day^{-1}), compared with a conventional high-range dose for this level of asthma severity (1,600 μg·day^{-1}). Because all asthma guidelines recommend reduction of treatment once control is achieved, assessment was also made of whether the higher starting dose conferred any advantage during long-term

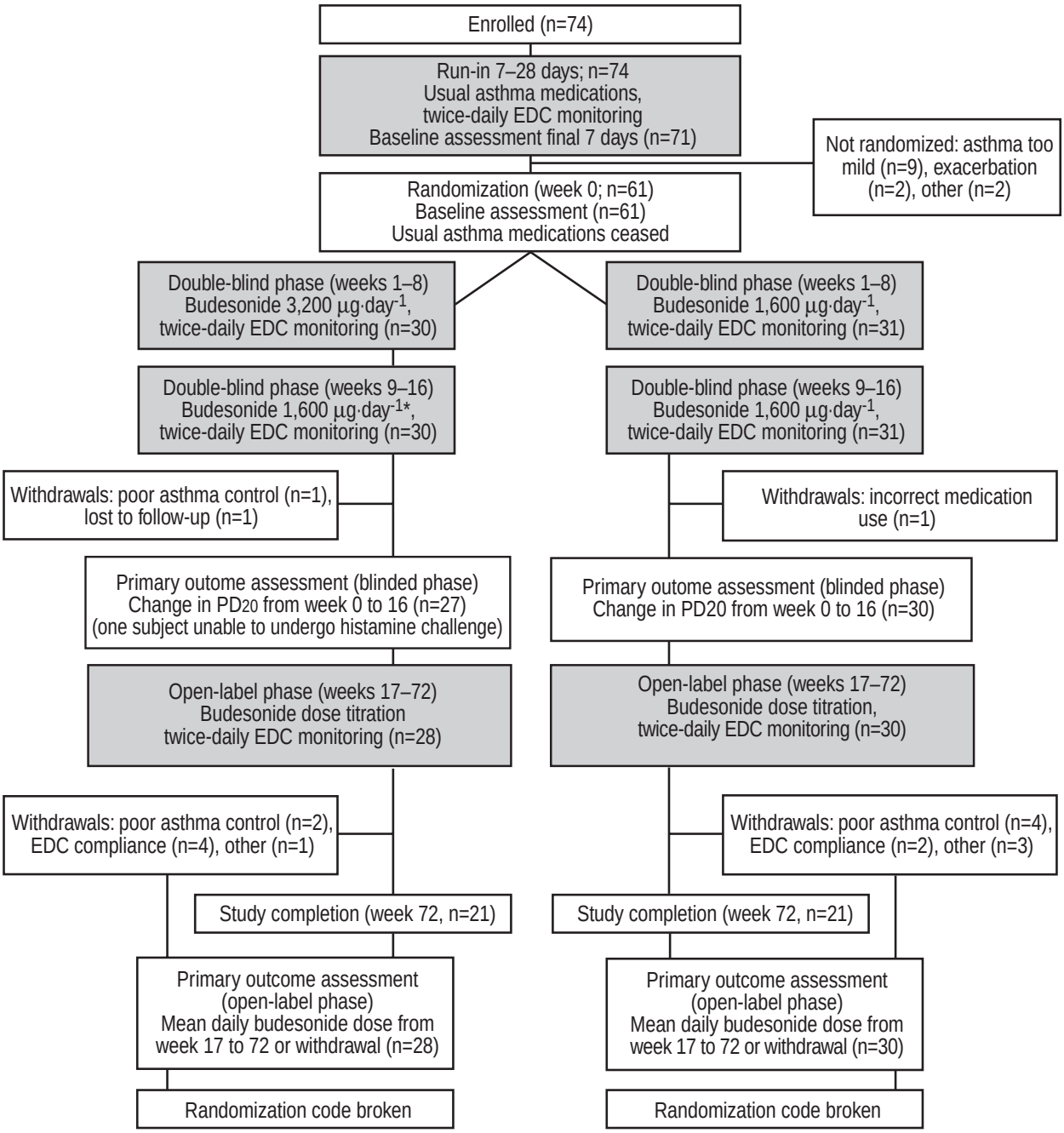

Fig. 1. – Flow chart showing study design and subject disposition. Budesonide was administered by Turbuhaler®. The four phases of the study (run-in, double-blind, single-blind and open-label dose down-titration) are indicated by shaded boxes. *: three subjects in the 3,200 mg·day^{-1} group were affected by a packing error which resulted in that dose being continued after week 8 for a further 33, 35 and 43 days; exclusion of their data did not change the primary outcome results. EDC: electronic diary card spirometer; PD_{20}: provocative dose of histamine causing a 20% fall in forced expiratory volume in one second.

(72-week) budesonide dose down-titration, using a novel algorithm to maintain optimal clinical control.

Methods

Study design and inclusion/exclusion criteria

The study was of randomized double-blind parallel-group design (fig. 1), approved by the Central Sydney Area Health Service Ethics Review Committee, and conducted in a single centre between October 1995 and October 1998. Written informed consent was obtained from all subjects. Recruitment of nonsmoking subjects aged 18–75 yrs was through radio and print advertisements for asthma research volunteers; five subjects were recruited from the Royal Prince Alfred Hospital asthma clinic. Inhaled corticosteroids were permitted prior to randomization at a constant dose of ≤1,200 μg·day^{-1}. Subjects were required to have a diagnosis of asthma [12], and to have demonstrated bronchodilator reversibility of forced expiratory volume in one second (FEV_1) of ≥15%

Table 1. – Asthma score

Asthma symptoms	Subscore	β_2-Agonist use	Subscore	Two lowest PEF* % pred	Subscore
Waking with asthma >4 (1) nights	4	≥4 occasions on >14 (≥4) days	4	<70	4
Symptoms >14 (≥4) days, or waking with asthma 1–4 (1) nights	3	1–3 occasions on >14 (≥4) days	3	70–77.5	3
Symptoms 4–14 (2–3) days	2	Used on 4–14 (2–3) days	2	77.6–85	2
Symptoms 1–3 (1) days	1	Used on 1–3 (1) days	1	85.1–92.5	1
No asthma symptoms	0	Not used	0	>92.5	0

At each visit, score components were calculated from the electronic diary card data from the preceding 4 weeks for symptoms and β_2-agonist use and 2 weeks for peak expiratory flow (PEF) data. Numbers in parentheses indicate the criteria used for the initial (end of run-in) assessment, based on the previous 7 days. The total asthma score (range 0–12) was obtained by adding the subscores for each component. *: mean of the two lowest morning PEFs in the previous 2 weeks (1 week for baseline). % pred: percentage of the predicted value [13].

in the previous 6 months, but were excluded if there had been significant clinical deterioration during the previous month, or if there was significant other illness such as emphysema or chronic bronchitis. Subjects underwent a run-in period of 28 days, which could be shortened to 7 days if necessary for patient safety. The final 7 days were used for assessment of overall asthma control using an asthma score (table 1), adapted from one reported previously [14], and based upon asthma symptoms, β_2-agonist use and PEF variation. The primary requirement for randomization was poor asthma control, as indicated by an asthma score of ≥6, plus one or more of the following: diurnal PEF variability (daily amplitude as a percentage of daily mean) ≥20%, prebronchodilator FEV1 ≤80% of the predicted value [15], mean of the two lowest morning PEFs ≤80% pred. [13], and on-demand inhaled β_2-agonist use on 5 out of 7 days. Subjects who fulfilled the inclusion criteria were randomized using a computer-generated balanced block method to receive budesonide by Turbuhaler™ (Astra Pharmaceuticals Production, Södertälje, Sweden) at a dose of either 3,200 μg·day^{-1} (4 × 400 μg twice daily) or 1,600 μg·day^{-1} (4 × 200 μg twice daily) for 8 weeks, with stratification according to inhaled corticosteroid dose on entry (0–600 μg, 600–1,200 μg) to ensure balance between randomization groups. The second 8-week period was single-blind to the subjects, with a budesonide dosage of 1,600 μg·day^{-1} (4 × 200 μg twice daily). The Turbuhaler™ inhalers used in the blinded phases were of identical appearance. All subjects then received open-label budesonide for a further 56 weeks of budesonide dose titration (see below). After enrolment, short-acting β_2-agonist (salbutamol or terbutaline) was used on-demand. Use of long-acting or oral β_2-agonists, theophylline or long-acting antihistamines was not permitted.

Assessments and outcome variables

Subjects attended the laboratory at the beginning and end of the run-in, and then every 8 weeks to 72 weeks. β_2-Agonist was withheld for 6 h and short-acting antihistamines for 3 days prior to visits. The primary outcome variable for the blinded phases of the study (weeks 1–16) was change in AHR. Histamine bronchial provocation testing was performed at weeks 0, 8, 16, 24, 48 and 72 using the rapid method [16] with calculation of the provocative dose of histamine causing a 20% fall in FEV1 (PD20). Extrapolated values were calculated when the FEV1 fell by >20% with the first histamine dose, or when the FEV1 fell by <20% at the final dose of 7.8 μmol (maximum extrapolated value 15.6 μmol). A PD20 of ≥3.92 μmol (approximately equivalent to a provocative concentration of histamine causing a 20% fall in FEV1 of ≥8 mg·mL^{-1}) is considered to represent the normal range ("remission") of AHR [17]. Electronic monitoring was carried out twice daily throughout the study, using hand-held electronic diary card (EDC) spirometers (Micro Medical Diary Card; Micro Medical, Rochester, UK) [18]. Subjects were asked to use the EDC before medication immediately upon waking and in the evening, to record symptoms and medication use and to perform three spirometric manoeuvres. At each visit, a cumulative chart showing PEF and FEV1 was shown to and discussed with the subject. From the EDC data, the mean morning and evening prebronchodilator PEF and FEV1, symptoms and night-waking, and β_2-agonist use were calculated. The primary outcome variable for the open-label phase of the study was mean daily dose of budesonide between week 17 and study completion/withdrawal. In order to assess the reliability of this measure, a *post hoc* estimate of medication use was obtained for 48 of the subjects for weeks 9–16 from analysis of the Turbuhaler™ indicator position, indicating the number of priming manoeuvres performed during that period. Spirometry was performed at each visit using a pressure differential heated pneumotachometer (Jaeger Masterscope version 4.17; Erich Jaeger GmbH Hoechberg, Germany). Measurement and calculation of FEV1, forced vital capacity and PEF were carried out according to American Thoracic Society guidelines [19]. Quality of life was assessed using the Asthma Quality of Life Questionnaire (AQLQ, University of Sydney, Sydney, New South Wales, Australia) [20]. For detection of asthma exacerbations, a trigger point was calculated at each visit as 85% of the recent best (highest morning prebronchodilator PEF in the previous 2 weeks). Mild exacerbations, defined as morning PEF <85% recent best on 2 consecutive days, were treated with an additional 800 μg·day^{-1} budesonide until 1 week after morning PEF was >85% recent best on 2 consecutive days. Severe exacerbations were defined as morning PEF <80% recent best on 2 consecutive days, with β_2-agonist use required on ≥3 occasions; a morning PEF of <70% recent best could be immediately regarded as a severe exacerbation. Severe exacerbations were treated additionally with a 5-day course of oral steroids. In the first 8 weeks, when underlying PEF

variability was still high, exacerbation medication could be withheld at the investigator's discretion. For clinical exacerbations failing to fulfil all criteria, an additional 800 μg·day^{-1} budesonide could be used at the investigator's discretion. One investigator (H.K. Reddel) was responsible for all exacerbation decisions during the study. Overall asthma control was assessed using the asthma score (table 1). Optimal asthma control was assessed on the basis of symptoms, night-waking, β_2-agonist use, PEF variation and AHR. At each visit, ecchymoses on the dominant forearm and hand, and the subject's weight, were recorded.

Budesonide dose titration

Budesonide dose titration was carried out from week 16 using an algorithm, based on the asthma score, designed to maintain optimal asthma control. The available doses were 2,800, 2,400, 2,000, 1,600, 1,200, 800, 400, 200, 100 and 0 μg·day^{-1}. A dose reduction was permitted if the asthma score had decreased since the previous visit or was the same as on the previous two visits, and a dose increase was indicated if two or more exacerbations had occurred in the previous 8 weeks. Dose reduction was not permitted if there had been an asthma exacerbation or <50% compliance with electronic monitoring during the previous 4 weeks. Subjects were withdrawn if two or more exacerbations occurred in two consecutive study periods. As budesonide dose titration was based on EDC records, subjects completing <50% of the electronic records in two consecutive study periods were withdrawn. One investigator (H.K. Reddel) was responsible for all budesonide titration decisions during the study.

Statistical analysis

Sample size determination was based on an SD for PD20 of 1.5 doubling doses. A sample size of 52 subjects was required to detect a clinically significant difference of 1.2 doubling doses with a significance level of 5% and power of 80%. Intention-to-treat analysis was carried out using the Statistical Analysis System (SAS) software package (SAS Institute Inc., Cary, NC, USA). The distribution of normally and log-normally distributed continuous data for baseline variables and changes in variables was described by mean and 95% confidence interval (CI), and of non-normally distributed variables by median and interquartile range (IQR). The distribution of AQLQ scores was skewed and included zero values, hence these scores were square-root transformed for parametric analysis. Comparison between randomization groups was by two-sample unpaired t-test (or Wilcoxon signed-rank test) and analysis of variance or covariance for change in continuous outcome variables, and by Chi-squared test and logistic regression analysis for binary outcome variables. In a *post hoc* analysis, Cox regression was used to compare the time required for AHR to reach the normal range (PD20 ≥3.92 μmol) during the first 16 weeks. A p-value of <0.05 was considered significant.

Results

Figure 1 shows the progress of subjects through the study. The mean run-in duration was 14.8 days. At baseline, the 61 randomized subjects demonstrated characteristics of poorly controlled asthma (table 2), with frequent symptoms, β_2-agonist use and waking due to asthma, morning dipping of PEF and FEV1, and moderate/severe AHR. There were no significant differences in baseline characteristics between the randomization groups, or between the beginning and end of the run-in (data not shown). Reproducibility and quality control data for the EDC data have been reported [18]. The median compliance with electronic monitoring, calculated as the proportion of scheduled sessions completed between randomization and completion/withdrawal, was 89% (IQR 69–97%). Analysis of Turbuhaler™ indicator position data for weeks 9–16 showed a median proportion of budesonide priming manoeuvres of 83% (IQR 65, 92%) of prescribed inhalations, compared with a reported medication use of 94% (IQR 72, 98%) for the same period (p=0.007, signed-rank test).

Effect of starting dose on primary and secondary outcome variables

The improvement in the PD20 during weeks 0–16 was not significantly different for the two randomization groups (starting dose 3,200 μg·day^{-1}: increased by 3.2 doubling doses, 1,600 μg·day^{-1}: increased by 3.0 doubling doses, p=0.7). The PD20 reached the normal range (≥3.92 μmol) more rapidly in the 3,200-μg group (9/30 *versus* 1/31 subjects at week 8, and 10/27 *versus* 3/31 subjects at week 16, hazard ratio 3.8, 95% CI 1.04–13.84, p=0.03). There were no significant differences between the ran-

Table 2. – Demographic and baseline data for the two randomization groups

	3,200 μg budesonide	1,600 μg budesonide
Subjects n	30	31
Male sex n (%)	14 (47)	19 (61)
Age yrs (range)	41 (18–63)	38 (18–67)
Nonsmoker/exsmoker n (%)	26 (87)/4 (13)	22 (71)/9 (29)
Atopy n (%)*	29 (97)	31 (100)
Duration of asthma symptoms n (%)		
1–5 yrs	1 (3)	0 (0)
6–10 yrs	3 (10)	4 (13)
>10 yrs	26 (87)	27 (87)
Inhaled corticosteroids on entry		
Subjects n (%)	12 (40)	15 (48)
Daily dose μg	592 (383–800)	660 (513–807)
FEV1 % pred	76.1 (69.5–82.8)	68.1 (63.0–73.2)
PD20 μmol^{+}	0.17 (0.11–0.28)	0.12 (0.09–0.18)
Asthma symptoms, days·week^{-1}‡	5.7 (3.6–6.5)	6.0 (4.0–6.5)
Waking due to asthma nights·week^{-1}‡	2.0 (1.0–3.9)	2.0 (0.0–4.0)
β_2-Agonist use occasions·day^{-1}‡,§	3.1 (1.3–4.3)	3.0 (2.0–4.6)

Data are presented as mean (95% confidence interval (CI)). $^{+}$: geometric mean (95% CI); ‡: median (interquartile range); *: one or more skin-prick test reactions ≥3 mm in diameter, and greater than the negative control; §: occasions (not inhalations)·day^{-1}. FEV1: forced expiratory volume in one second; % pred: percentage of the predicted value [15]; PD20: provocative dose of histamine causing a 20% fall in FEV1. There were no significant differences between the two groups.

domization groups for change in secondary outcome variables during weeks 0–16 (table 3), with improvement in morning prebronchodilator PEF of 134 and 127 L·min^{-1} respectively (p=0.8) and in morning prebronchodilator FEV1 of 0.7 L for both groups (p=0.9). Subsequent analysis showed that there were no significant differences in rate of improvement of diary card variables when analysed by day for the first 14 days or by week for the whole study (data not shown). There was a trend towards fewer total exacerbations (10/30 *versus* 19/31, p=0.054), but no significant difference in severe exacerbations (6/30 *versus* 11/31, p=0.3) in weeks 1–16 in the 3,200-µg group. In a *post hoc* analysis of weeks 1–16, subjects with airway responsiveness in the normal range were found to be less likely to experience an exacerbation than subjects with AHR (2/13 *versus* 27/48, p=0.02). During budesonide dose reduction, there was no significant difference between the randomization groups in mean daily budesonide dose or final prescribed budesonide dose (table 4). There were no significant differences between the randomization groups in change in secondary outcome variables between baseline and study completion/withdrawal.

Time course of change in markers of asthma control

The time course of changes in β_2-agonist use, AHR, FEV1 and PEF are shown in figure 2. The onset of improvement in diary card variables was rapid, with an increase in morning prebronchodilator PEF the morning after the first dose of budesonide of 35.0 L·min^{-1} (95% CI 19.6–50.4, p<0.0001) compared with the average in the previous week. Maximal improvements in laboratory FEV1 and AQLQ score were seen by week 8, but ambulatory PEF and FEV1 improved up to weeks 12–14. The PD20 continued to improve up to week 72 (fig. 2b), with an overall improvement between baseline and completion/withdrawal of 4.0 doubling doses (mean 16.5-fold change) to a geometric mean of 2.43 µmol (a PD20 of 0.8–3.92 µmol represents mild AHR). Altogether, 25 (41%) subjects achieved a PD20 within the normal range (≥3.92 µmol) (fig. 3). Symptoms and β_2-agonist use also continued to improve to completion/withdrawal, to 0.0 days·week^{-1} (IQR 0.0–2.8) and 0.17 occasions·day^{-1} (IQR 0.0–1.0) respectively. The characteristics of optimal asthma control are shown in table 5; there were no significant differences between the two randomization groups.

Effect of inhaled corticosteroid use prior to entry

Thirty-four (56%) subjects had not used inhaled corticosteroids in the 3 months prior to entry; all but four of these subjects had used inhaled corticosteroids for short periods in the past. Subjects using inhaled corticosteroids in the 3 months prior to entry (n=27) had similar baseline characteristics to those not using inhaled corticosteroids, apart from the former group having less severe AHR (PD20 0.25 *versus* 0.09 µmol, p=0.001) and a trend to higher morning PEF as a percentage of the predicted value (p=0.2; fig. 4). Over the first 16 weeks, although changes in symptoms and β_2-agonist use were similar in subjects using and not using inhaled corticosteroids prior to entry, there were significant differences between these groups in change from baseline for PD20 (increased by 2.4 *versus* 3.6 doubling doses, p= 0.03), and in percentage change from baseline for morning PEF (% pred) (median increase of 18 *versus* 51%, p=0.0002) and FEV1 (% pred) (median increase of 9 *versus* 23%, p=0.03). However, on cross-sectional analysis at week 16, there were no significant differences in any measured variable between these two

Table 3. – Effect of randomization group (weeks 1–8) on change in outcome variables during the first 16 weeks of treatment

	3,200 µg budesonide			1,600 µg budesonide		
	Baseline	Week 16	Change %	Baseline	Week 16	Change %
FEV1 % pred	76.1*	91.2*	19.3 (7.2–34.5)	68.1*	82.0*	14.1 (4.6–36.3)
PD20 µmol	0.17^{+}	1.55^{+}	3.2 (2.3–4.0)‡	0.12^{+}	0.96^{+}	3.0 (2.3–3.6)‡
AQLQ	0.88	0.45	-52.2 (-73.7– -18.5)	0.95	0.60	-42.1 (-62.1– -6.7)
Asthma score$^{\#}$	11.0	6.0	-45.5 (-66.8– -22.5)	11.0	7.0	-28.6 (-48.9– -10.0)
Severe exacerbations n (%)	–	–	6 (20)	–	–	11 (35)
Electronic diary card data						
Morning pre-BD PEF L·min^{-1}	347*	481*	38.5 (25.6–53.4)	332*	459*	44.1 (14.2–58.6)
Evening pre-BD PEF L·min^{-1}	401*	483*	20.8 (11.0–36.6)	371*	473*	23.7 (8.8–36.4)
Morning pre-BD FEV1 L	2.13*	2.84*	28.3 (19.2–52.8)	2.04*	2.74*	26.1 (15.3–47.7)
Evening pre-BD FEV1 L	2.36*	2.80*	20.8 (12.2–28.5)	2.26*	2.77*	18.5 (14.1–33.0)
Asthma symptoms days·week^{-1}	5.7	0.5	-90.3 (-100.0– -52.2)	6.0	1.5	-78.6 (-100.0– -3.6)
Night-waking						
Subjects n (%)	26 (87)	2 (7)	–	19 (61)	4 (13)	–
Frequency nights·week^{-1}§	2.0	0.0	-100.0 (-100.0– -100.0)	2.0	0.0	-100.0 (-100.0– -100.0)
β_2-Agonist use occasions·day^{-1}	3.1	0.3	-86.2 (-100.0– -65.4)	3.0	0.6	-83.3 (-98.9– -39.0)

Data are presented as median (interquartile range). *: mean; $^{+}$: geometric mean; ‡: doubling dose change (95% CI); $^{\#}$: range 0–12; §: in all subjects, including those not recording night-waking. FEV1: forced expiratory volume in one second; % pred: percentage of the predicted value [15]; PD20: provocative dose of histamine causing a 20% fall in FEV1; AQLQ: Asthma Quality of Life Questionnaire score (higher values represent more severe impairment of quality of life (range 0–4)) [20]; BD: bronchodilator; PEF: peak expiratory flow. All differences between baseline and week 16 were significant, p<0.0001. There were no significant differences between the 3,200-µg·day^{-1} and 1,600-µg·day^{-1} budesonide randomization groups.

Table 4. – Effect of randomization group (weeks 1–8) on budesonide dose

	3,200 μg budesonide	1,600 μg budesonide
Daily budesonide dosage μg·day^{-1}		
Weeks 17–end		
Best case	1327 (1162–1515)	1325^{+} (1143–1536)
Worst case	1082 (901–1230)	972^{+} (811–1165)
Weeks 1–end		
Best case	1690 (1541–1853)	1396$^{\#}$ (1260–1548)
Worst case	1394 (1227–1585)	1072$^{\#}$ (933–1232)
Final prescribed budesonide dose μg·day^{-1}		
Study completion		
Subjects n	21	21
Dose	981 (768–1194) (200–1600)	848^{+} (677–1018) (200–1600)
Withdrawal		
Subjects n	9	10
Dose	1778 (1362–2193) (800–2800)	1960^{+} (1582–2338) (800–2800)

Daily budesonide dosage data are presented as geometric mean (95% confidence interval (CI)) and final prescribed budesonide dose data as mean (95% CI) (range). The mean daily budesonide dose was based on the electronic diary card (EDC) record plus exacerbation budesonide. Different assumptions were made about missing EDC data; for the "best case", it was assumed that budesonide was always taken as prescribed when the EDC was not used, and, for "worst case", it was assumed that budesonide was never taken when the EDC was not used. $^{+}$: p>0.3; $^{\#}$: p=0.01.

groups. During the whole study, there was a higher rate of withdrawal because of poor asthma control in subjects using inhaled corticosteroids on entry (6/9 *versus* 1/10 withdrawals, p= 0.04). On study completion/withdrawal, subjects who had been using inhaled corticosteroids prior to entry had a lower morning PEF (% pred) (p=0.05) and a trend to a lower laboratory FEV_1 (% pred) (p=0.1). Of the 27 subjects using inhaled corticosteroids on entry, 12 were randomized to start with budesonide 3,200 μg·day^{-1}; five of these achieved a PD_{20} within the normal range by week 16, compared with none of the 15 randomized to start with 1,600 μg·day^{-1} (p=0.004). There were no other differences in outcome variables between starting doses for subjects using inhaled corticosteroids prior to entry, and no differences between starting doses for subjects not using inhaled corticosteroids prior to entry (data not shown).

Adverse events

Reported bruising was infrequent (0.7 bruises·subject-yr^{-1}), and there was no significant difference in number or area of measured ecchymoses between the 3,200-μg·day^{-1} and 1,600-μg·day^{-1} randomization groups. Change in weight was not significantly different (0.5 kg increase *versus* 0.7 kg decrease, p=0.3). Mild dysphonia was reported by three subjects soon after commencement of budesonide (3,200 μg-group: two, 1,600 μg: one), and by a further four subjects during the study, all at a budesonide dose of ≥1,600 μg. An episode of oral thrush was reported by 11% of subjects (3,200 μg group: two, 1,600 μg group: five).

Discussion

This 18-month study in subjects with initially poorly controlled asthma showed that a starting dose of inhaled budesonide of 1,600 μg·day^{-1} was sufficient to achieve optimal control of asthma, as indicated by infrequent symptoms and β_2-agonist use, no night-waking, low PEF variation and mild or normal AHR, and that this control was maintained during long-term budesonide down-titration. The high rate of achievement of optimal asthma control was in contrast with that seen in many previous studies. Airway responsiveness reached the normal range in 41% of subjects, and this was achieved more rapidly in subjects receiving 3,200 μg·day^{-1} budesonide for the first 8 weeks. The study design incorporated two novel features: long-term EDC spirometric monitoring, which provided reliable information about the time course of response to inhaled budesonide, and use of a clinical algorithm to enable long-term budesonide dose reduction while maintaining optimal asthma control.

The primary aim of the study was to establish whether a high starting dose of 3,200 μg budesonide was more effective in reducing AHR than a dose of 1,600 μg, which is in the range recommended in international "step-up" guidelines for subjects with poorly controlled asthma. AHR is a fundamental component of the definition of asthma, and has been associated with asthma exacerbations [23], airway inflammation [24] and decline in lung function [25]. Previous studies have shown a dose-dependent improvement in AHR with inhaled corticosteroid treatment [26, 27], and asthma outcomes and basement membrane thickness improved when AHR was added to a treatment algorithm [7]. A recent study by MEIJER *et al.* [11] showed that high-dose fluticasone was more effective in improving AHR than oral prednisolone. The present study showed very substantial improvement in AHR over the first 16 weeks, but there was no significant difference between the two starting dose groups in doubling dose difference, and no difference between starting doses in the magnitude of improvement in asthma control as assessed by symptoms, β_2-agonist use, lung function and quality of life. The trend to fewer exacerbations in the high-starting-dose group may have been related to more rapid achievement of remission of AHR, as previous studies have shown reduced asthma exacerbations in conjunction with reduced AHR [7, 23], but the present study had insufficient power to adequately examine exacerbation rate. The effect of starting dose of budesonide was also examined in the long term (weeks 17–72) during open-label budesonide dose titration. This commenced from a similar level of asthma control in each randomization group, so it is not surprising that no difference was seen in the mean daily dose of budesonide during this phase. Thus, overall, the findings of the study could not be considered to justify the potential risk of a greater systemic effect with a starting dose of budesonide of 3,200 μg·day^{-1} [28], particularly if patients do not return for review.

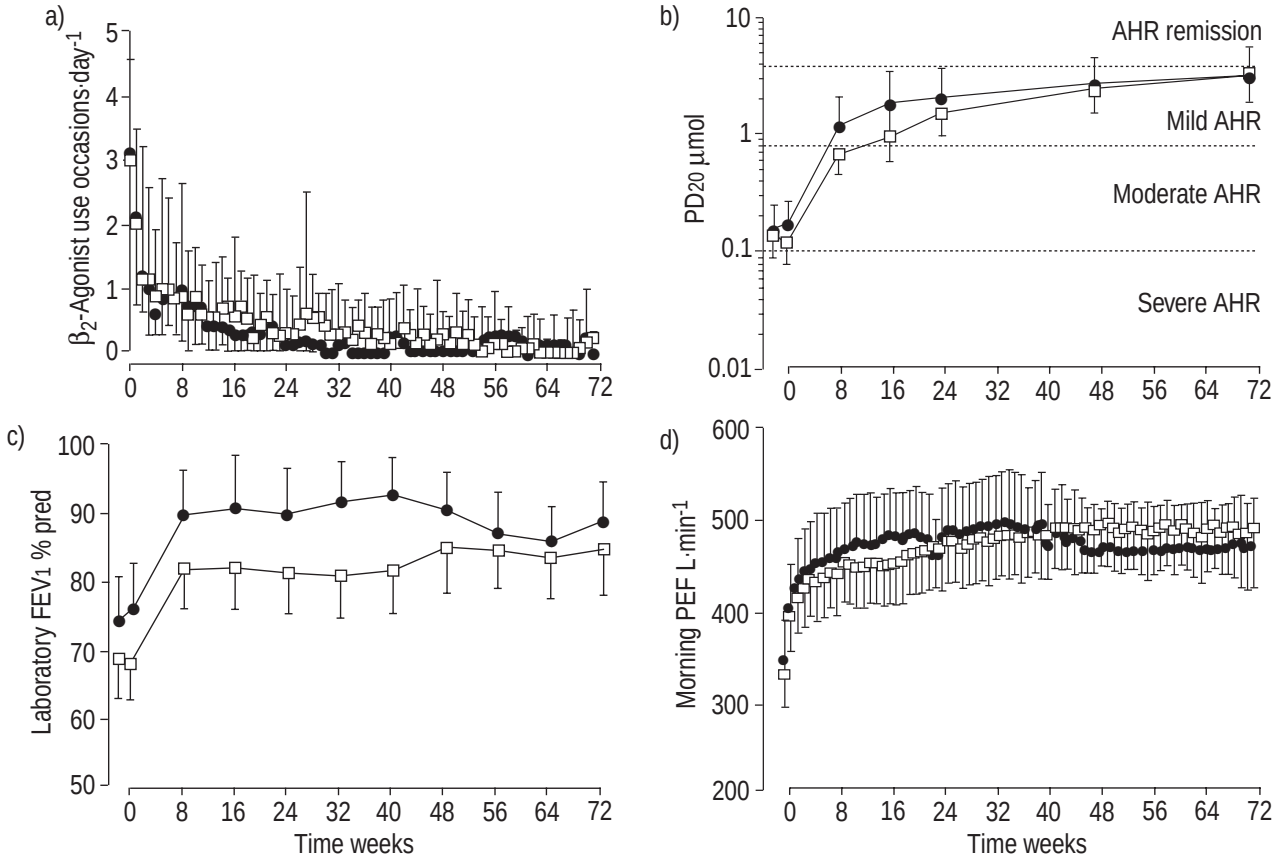

Fig. 2. – Time course of change in asthma outcome variables over 72 weeks: a) rescue β_2-agonist use (median and interquartile range; in order to allow for different formulations, occasions·day^{-1} were recorded rather than inhalations·day^{-1}); b) airway hyperresponsiveness (AHR) to histamine (geometric mean and 95% confidence interval (CI)); c) laboratory forced expiratory volume in one second (FEV1; mean and 95% CI); and d) morning pre-bronchodilator peak expiratory flow (PEF) (mean and 95% CI). Treatment commenced with 8 weeks' budesonide 3,200 µg·day^{-1} (●) or 1,600 µg·day^{-1} (□). Data from electronic monitoring were averaged for each week. There were significant differences between randomization groups in FEV1 at weeks 32 and 40 but no differences in change from baseline FEV1; there were no other significant differences between the randomization groups. PD20: provocative dose of histamine causing a 20% fall in FEV1. % pred: percentage of the predicted value [15].

Previous long-term studies have shown airway responsiveness to reach the normal range in only a small proportion of subjects [23, 29, 30], and the clinical and pathophysiological significance of this phenomenon is uncertain. In the present study, although 89% of subjects had moderate/severe AHR on entry, 41% achieved a PD20 within the normal range by completion/withdrawal. This observation has major implications for bronchial provocation testing in asthma diagnosis and epidemiology and for cross-sectional studies of asthma severity.

Most previous clinical trials of inhaled corticosteroids, including of budesonide 1,600 µg·day^{-1} [6, 7, 31, 32], have reported improvements from baseline in morning PEF of 20–40 L·min^{-1} and in AHR of 1–2 doubling doses. In the present study, the overall improvement was 135 L·min^{-1} for morning prebronchodilator PEF and 4.0 doubling doses for PD20. Subjects were selected for poor asthma control at baseline, and came from a community rather than a clinic population. They were chronically undertreated on entry and thus obviously had the potential for substantial improvement; however, most (87%) of the subjects had had asthma for >10 yrs, a feature previously associated with relatively poor response to inhaled corticosteroids [33].

Analysis according to whether the subjects were or were not using inhaled corticosteroids in the 3 months prior to

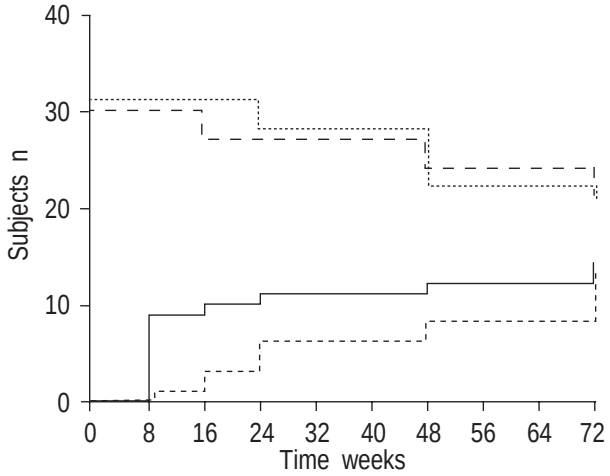

Fig. 3. – Cumulative achievement of an airway responsiveness within the normal range (provocative dose of histamine causing a 20% fall in forced expiratory volume in one second (PD20) of ≥3.92 µmol; ——: budesonide 3,200 µg·day^{-1}, ----: budesonide 1,600 µg·day^{-1}) and number of subjects remaining in the study (– – –: budesonide 3,200 µg·day^{-1}, ·····: budesonide 1,600 µg·day^{-1}). A normal PD20 by week 16 was 3.8 times more likely in subjects randomized to receive budesonide 3,200 µg·day^{-1} for the first 8 weeks ($p<0.03$). By study completion/withdrawal, 25 of 61 (41%) subjects had achieved a PD20 of ≥3.92 µmol.

Table 5. – Characteristics of optimal asthma control

Criterion	Baseline (week 0)	Week 16	Completion/ withdrawal
Symptoms less than once a week %	2	51^{+}	62
No night-waking %	26	89^{+}	93
β_2-agonist less than twice a week including before exercise %	2	49^{+}	61
Lowest morning PEF >80% best* %	3	60^{+}	69
PD_{20} >1.0 μmol %	11	56^{+}	70
All of above criteria %	0	27^{+}	28
≥4 of above criteria %	0	39^{+}	59$^{\#}$

Data are presented as a percentage of the subjects fulfilling each criterion for each week analysed (n=57). *: lowest morning peak flow expressed as a percentage of highest daily peak expiratory flow (PEF) [2, 21]. PD_{20}: provocative dose of histamine causing a 20% fall in forced expiratory volume in one second. $^{+}$: p<0.0001 *versus* baseline; $^{\#}$: p=0.05 *versus* week 16.

entry led to some unexpected observations. Levels of, and improvements in, symptoms and β_2-agonist use were similar in these two groups of subjects. However, relative to baseline, subjects previously using inhaled corticosteroids showed substantially less improvement in AHR and lung function during the study than subjects not previously using inhaled corticosteroids, with a trend to lower lung function at completion/withdrawal. One possible interpretation of these findings is that later introduction of steroids in the subjects who were not using inhaled corticosteroids on entry was not harmful, which would tend to contradict the evidence of other studies [33–35]. However, a more plausible explanation, taking into account the fact that subjects already using inhaled corticosteroids had both higher baseline AHR values and a higher rate of withdrawal due to poor asthma control during the study, is that, amongst subjects recruited largely on the basis of asthma symptoms and β_2-agonist use, there was significant heterogeneity in the underlying pathophysiology. Subjects who had previously been using inhaled corticosteroids had presumably already achieved a partial response to that treatment, so that their symptoms and β_2-agonist use on entry may have been more likely to be due, for example, to structural changes in the airway wall than to potentially steroid-responsive eosinophilic inflammation. However, optimal control of asthma was achieved by completion/withdrawal in the majority of subjects regardless of previous inhaled corticosteroid use.

There is now evidence from a systematic review that asthma self-management with regular follow-up and a written action plan results in significantly improved outcomes in asthma [36]. The present study is the first clinical asthma trial to use EDC spirometers for prolonged monitoring. Overall compliance with electronic monitoring was extremely high (median 89%), without any financial incentives to the subjects to participate or to comply with study requirements. This is in contrast with compliance rates of <50% seen in covert studies of electronic monitoring over shorter periods [37], in which subjects were also required to complete a conventional paper diary. Six subjects exhibiting poor compliance with monitoring were withdrawn as required by the study protocol, but the projected further deterioration in compliance by these subjects would not have altered the median overall compliance. The fact that the study incorporated regular review and early treatment of exacerbations using a written asthma action plan based on electronic peak flow monitoring and was associated with high overall compliance by the subjects may be relevant to the good asthma control which was achieved.

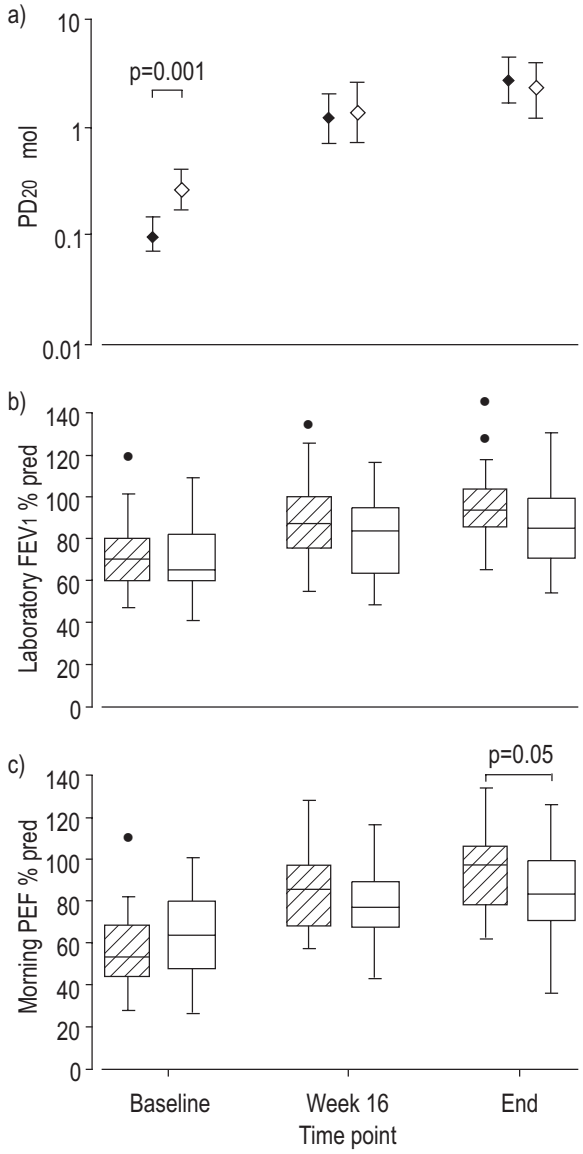

Fig. 4. – Differences at baseline (week 0), week 16 and study completion/withdrawal (end) between subjects not using (◆, ◪; n=34) and using (◇, □; n=27) inhaled corticosteroids in the 3 months prior to entry in: a) airway hyperresponsiveness to histamine (geometric mean and 95% confidence interval); b) laboratory forced expiratory volume in one second (FEV_1); and c) morning prebronchodilator peak expiratory flow (PEF). The box and whisker plots show the median, interquartile range and 1.5 interquartile range. Outliers are also shown (●). PD_{20}: provocative dose of histamine causing a 20% fall in FEV_1; % pred: percentage of the predicted value (FEV_1 [15] and PEF [22]). Within each group, all changes from baseline to week 16 and from baseline to end were significant (p<0.0001).

There is widespread agreement in international guidelines that achievement of asthma control should be followed

by down-titration of inhaled corticosteroids to reach the minimum effective dose. Several studies have provided evidence that this can be carried out in many patients [34, 35, 38], although more work is needed to establish the optimal method. In the present study, rather than using a fixed dose-reduction schedule, the budesonide dose was determined using a novel algorithm designed to maintain optimal clinical control. The algorithm was based on a simple asthma score with components for symptoms, β_2-agonist use and PEF variation, and used dose steps of $\leq$400 μg at a minimum interval of 8 weeks. The overall effectiveness of the algorithm was demonstrated by the fact that symptoms, β_2-agonist use and AHR continued to improve during budesonide dose-reduction long after maximal improvement had been achieved in lung function. This suggests the possibility that the initial marked improvement in AHR and lung function may have been associated with a reduction in the amount of inflammatory infiltrate [39], but that later improvement in AHR may have been related to reversal of airway wall remodelling [7] which, in the context of substantially reduced inflammation, may not have required such high budesonide doses.

On entry into the study, the subjects demonstrated characteristics of moderate or severe persistent asthma, for which the treatment recommended in international guidelines is high-dose inhaled corticosteroids plus long-acting β_2-agonists, with long-term oral corticosteroids also indicated for more than half of the subjects [1]. The study was designed to examine whether use of a very high starting dose of inhaled corticosteroid could lead to better asthma control than conventional high-dose treatment, and the results show that inhaled budesonide at a starting dose of 1,600 $\mu g \cdot day^{-1}$ is sufficient to achieve optimal control of asthma in most patients with initially poorly controlled asthma. However, the high degree of asthma control which was reached by the end of the study is in marked contrast with that in other trials of similar doses of inhaled corticosteroids. Further studies are needed to clarify the study design features or patient characteristics which contributed to this difference, and to assess whether substantially better improvements in asthma outcomes than have been seen in previous studies could be achieved with even lower doses of inhaled corticosteroids or with combination therapy.

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