THERAPEUTIC EQUIVALENCE STUDY OF TWO FORMULATIONS (INNOVATOR V. GENERIC) OF BECLOMETHASONE DIPROPIONATE IN ADULT ASTHMATIC PATIENTS

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Objective. To study the therapeutic equivalence of two formulations (innovator v. generic) of beclomethasone dipropionate (BDP) 400 µg twice daily administered per metered dose inhaler (MDI), in adults with moderate to severe asthma.

Methods. A double-blind randomised parallel-group trial was performed with a 2-week run-in and an 8-week treatment period. Thirty-six symptomatic adult asthmatics on a mean daily dose of 750 µg inhaled corticosteroids during run-in, a mean forced expiratory volume in 1 second (FEV_1) of 70% predicted normal and a mean histamine concentration provoking a 20% reduction in FEV_1 (histamine PC_{20}) of 0.11 mg/l were randomised to one of the two treatment groups. Primary variables were morning peak expiratory flow (mPEF), FEV_1 and histamine PC_{20}. Secondary variables were β_2–agonist use, symptom score and nocturnal awakening. The Schuirmann two one-sided tests procedure was used for the statistical analysis. Ninety-five per cent confidence intervals (CIs) were calculated for the differences in means.

Results. The mean differences end of treatment to baseline for the two formulations (Becotide and Beclate) respectively were: mPEF 5.6 l/min (CI –16.4 - 27.6) and –22.3 l/min (CI –35.6 - –9); FEV_1 –2.9% (CI –11 - 5.2) and 0.2% (CI –4.8 - 5.2); Histamine PC_{20} –0.04 mg/ml (CI –0.15 - 0.06) and 0.02 mg/ml (CI –0.37 - 0.4). Changes in clinical variables were not conclusive. The mean differences with CIs for primary variables were contained within the limits set for equivalence. The sample size was sufficient to differentiate the groups for mPEF, but this was not of clinical significance.

Conclusion. After 8 weeks of treatment the two formulations of BDP, delivered by MDI through a large-volume spacer, were therapeutically equivalent in moderate-to-severe asthmatic adults.

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An improved understanding of the pathophysiology of asthma has strengthened the case for intervention with inhaled glucocorticosteroids. Allergic inflammation underlies the clinical symptoms in even the mildest forms of asthma.[1,2] Inhaled glucocorticosteroids are the proven anti-inflammatory therapy in chronic asthma because of their remarkable efficacy and good safety profile.[2-6] This therapy is now recommended for use in the early stages of asthma, with the possibility of preventing structural changes and thereby reducing asthma mortality and morbidity.[2,7] Inhaled glucocorticosteroids, delivered by metered dose inhaler (MDI), should preferably be administered through a large-volume spacer to minimise oropharyngeal drug deposition and thereby systemic absorption and local side-effects.[5,6,8,9]

There is an increasing tendency to use generic formulations or interchangeable multi-source products with an anticipated reduction in health costs.[10-12] Well-established guidelines are available for judging equivalence between oral formulations, but determination of bio-equivalence for inhaled products remains problematic.[11,13] Equivalence for oral formulations is usually determined by clinical studies demonstrating comparable bio-availability of generic compounds with original medications.[12] An exception has been made in the case of inhaled medications because of a lack of standardised or generally accepted methods of demonstrating equivalence. The surrogate criterion usually employed is *in vitro* equivalence, without necessarily invoking comparable clinical efficacy.[11,13] This departure from standard practice has been a subject of debate.[14] According to a consensus statement by the British Association for Lung Research in 1994, the endpoint for any determination of equivalence of inhaled medications should be therapeutic equivalence.[13]

The objective of this study was to determine the therapeutic equivalence of an innovator versus a generic formulation of inhaled beclomethasone dipropionate (BDP) in adults with moderate asthma. Few studies comparing generic inhaled formulations and the original products have been reported.[15]

PATIENTS AND METHODS

Patients

Thirty-six non-smoking moderate-to-severe asthmatics diagnosed according to American Thoracic Society criteria, were recruited.[16] Patient characteristics are listed in Table I.

Table I. Baseline characteristics of study patients, mean (SEM)

	Age	Sex M/F	Atopy	Symptom score	FEV_1% of predicted normal	Histamine PC_{20}
Total group	38.6	12/24	35	1.6	70	N = 27 1.6
(N = 36)	(1.9)			(0.2)	(2.0)	(0.2)
Group 1	38.4	6/12	18	1.3	73.6	N = 15 1.3
(N = 18)	(2.7)			(0.2)	(3.0)	(0.2)
Group 2	38.8	6/12	17	1.79	66.6	N = 12 1.79
(N = 18)	(2.9)			(0.2)	(2.5)	(0.2)

SEM = standard error of mean.

Patients were symptomatic, fulfilling at least one of the following criteria before randomisation: (*i*) use of more than 6 inhalations of a short-acting β_2-agonist during the last 7 days of the run-in; (*ii*) diurnal variation in morning peak expiratory flow (mPEF) > 10% on at least 3 days during 7 days of run-in; and (*iii*) nocturnal awakening at least 2 out of 14 nights of the run-in. Forced expiratory volume in 1 second (FEV_1) was required to be more than 50% of predicted normal. No asthma exacerbation or clinically relevant respiratory infection was present during the 4 weeks before study entry. All patients were treated with stable doses of inhaled glucocorticosteroids for at least 8 weeks before enrolment, as shown in Table II. Systemic corticosteroids were not used for 8 weeks before visit 1. Long-acting inhaled or oral β_2-agonists, theophylline, ipratropium bromide and long-acting antihistamines were withdrawn before visit 1 according to accepted washout times. Nasal steroids were allowed at stable doses during the study. No concurrent diseases likely to affect the study were present in any of our patients. The patients were competent in using the inhaler and spacer devices. Approval for the study was obtained from the Stellenbosch University and Tygerberg Hospital Ethics Committee and all patients signed informed consent.

Table II. Stable dose of inhaled glucocorticosteroids for 8 weeks before study entry

	Beclomethasone dipropionate	Budesonide
Total group	N = 15	N = 21
Dose µg/d	754	747
Range	600 - 1 000	600 - 800
Group 1	N = 10	N = 8
Dose µg/d	808	743
Range	600 - 1 000	600 - 800
Group 2	N = 5	N = 13
Dose µg/d	700	754
Range	600 - 800	600 - 800

Study design and plan

A double-blind randomised parallel-group study was performed with a 2-week run-in followed by an 8-week treatment period. Patients were randomised to either group 1 (Becotide, GlaxoWellcome, 400 µg twice daily) or group 2 (Beclate, Cipla Medpro, 400 µg twice daily), using a table of random numbers. Identical labelling of the canisters ensured blinding. Study medication was delivered by metered dose inhalers and administered through large-volume spacers (Cipla Medpro).

Primary variables were changes from baseline to end of treatment in: (*i*) mPEF recorded daily in patient diaries; (*ii*) FEV_1 % of predicted normal measured at clinic visits; and (*iii*) histamine concentration provoking a 20% reduction in FEV_1 (histamine PC_{20}). Secondary clinical variables were changes from baseline to end of treatment in: (*i*) β_2-agonist use; (*ii*) symptom score (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms); and (*iii*) nocturnal awakening, recorded daily in patient diaries. Safety variables were incidents of exacerbation and other reported adverse events.

All eligible patients were entered in a 2-week run-in period during which baseline data were collected. A diary and mini-Wright peak flow meter (Clement Clarke Int., London, UK) were supplied to all patients at the first visit. Patients were asked to record twice-daily peak flow measurements, graded symptom score, β_2-agonist use and nocturnal awakening. Salbutamol 100 µg/actuation was dispensed to patients at the first and subsequent visits to standardise β_2-agonist use. Symptomatic patients complying with the randomisation criteria were randomised to an 8-week treatment period. During this period patients stopped their regular inhaled glucocorticosteroids and started using the respective study treatments. Patients were trained to use their study medication with a large-volume spacer. Five breaths at tidal volume directly followed one actuation of study medication administered into the spacer. Care of the spacer was similar for the two groups. A new diary was supplied to patients at randomisation to continue entries as before and in addition to

record the use of twice-daily study medication. A value indicating a 30% drop in average mPEF as measured during the run-in period was entered on the diary cover. This served as an indicator of deterioration in asthma control during the treatment period. A safety visit and compliance check were performed 2 weeks after randomisation. All the visits were scheduled for the same time in the morning.

Compliance was estimated from entries on use of study medication in patient diaries. Patients were discontinued for deterioration in asthma control, as well as for protocol violation and non-compliance.

Clinical assessments and lung function

Demographic details were recorded for all patients and relevant medical history, including smoking history, concomitant disease and recent airway infections as well as prescribed medication during the past 4 weeks were documented. A physical examination was done on all patients and a skin prick test was performed using a validated method.[17] Each individual kept a diary for his/her own recordings. Peak flow measurements were done in the standing position and patients were requested to record the highest of three consecutive blows. Patients were asked to avoid using rescue medication during the 6 hours before PEF measurements and clinic visits. Graded asthma symptoms, intake of rescue medication, nocturnal awakening and use of study medication were recorded.

Pulmonary function data were measured at body temperature and saturated atmospheric pressure using a spirometer that was calibrated daily. Lung function testing was done after patients had rested for 20 minutes. FEV_1 was measured and the calculation of FEV_1% of predicted was based on reference values as suggested by the European Respiratory Society.[18] The highest measured value from three acceptable efforts was chosen and recorded on each occasion.

Histamine provocation tests were done on patients with $FEV_1 > 60\%$ of predicted normal at randomisation and at the end of the treatment period. This was done using a validated method.[19] Baseline FEV_1 was measured 60 seconds post inhalation of normal saline. The patient then inhaled histamine for 2 minutes at a concentration of 0.03 mg/ml. This concentration was doubled at 5-minute intervals, until the FEV_1 dropped by 20% from the baseline FEV_1. The histamine PC_{20} was determined in mg/ml by interpolating the last 2 points of the dose response curve on a logarithmic scale.

Data management and statistical analysis

Data were entered on a spreadsheet in a blind mode and edited against the source data. The treatment groups were coded for analysis. All decisions regarding the availability of the data and the analyses were taken before breaking of the code. Graphs of the mPEF were generated for each patient to assess the within-patient and period variability. Intention-to-treat analysis was performed. To investigate the effect of outliers in the data, an analysis based on median values was compared with an analysis based on mean values. These were similar, therefore analyses based on means were used in all subsequent analyses. The Schuirmann two one-sided tests procedure was used for equivalence testing: H_o: $u_2 - u_1 \leq \theta_1$, or $u_2 - u_1 \geq \theta_2$; H_a: $\theta_1 < u_2 - u_1 < \theta_2$.[20] Ninety-five per cent confidence intervals (CIs) for the differences in means, from baseline to end of treatment, were calculated and clinical limits were set for the primary variables (20% for mPEF and FEV_1 and two doubling doses for histamine PC_{20}). Two approaches were used. Firstly, a summary value was calculated for each patient for the variables concerned. This was the mean of the last 7 days of run-in and the last 14 days of the treatment period. The mean difference from run-in to end of treatment was calculated with its CI. Secondly, an analysis of individual values in each period was done for mPEF using the linear mixed-effect model. The period effect was investigated and adjusted for sex and age as well as the time-effect in each patient. The result of the more complex linear mixed-effect model for mPEF was comparable to the analysis using the difference in mean values. The difference in mean values was therefore used in subsequent analysis.

RESULTS

Thirty-eight patients were entered in the run-in period, two of whom did not comply with randomisation criteria. Thirty-six patients were randomised to the respective treatment groups and 32 evaluable patients completed the study. Randomisation resulted in two comparable groups (Tables I and III). Moderate-to-severe asthmatics were included in the study, as suggested by significant levels of bronchial hyper-responsiveness (Table III). The transition from run-in to treatment periods was unremarkable and there was no significant period effect. The sample size was sufficient to differentiate the groups for mPEF, although this was within 10% of baseline and within the set clinical limits (Fig. 1, Table III).

The differences in effect for the primary variables, end of treatment compared with baseline, were 5.6 l/min (CI –16.4 - 27.6) and –22.3 l/min (CI –9.0 - –35.6) for mPEF; –2.9% (CI –11.0 - 5.2) and 0.2% (–4.8 - 5.2) for FEV_1 % of predicted normal; and –0.04 mg/ml (CI –0.15 - 0.06) and 0.02 mg/ml (CI –0.37 - 0.4) for histamine PC_{20}, for treatment groups 1 and 2 respectively (Table III, Fig. 1).

The decrease in mPEF in group 2 was not accompanied by an increase in bronchial hyperreactivity at the end of the treatment period. The mean differences from baseline to end of treatment, with 95% CIs, were within the clinical limits set for therapeutic equivalence for all the primary variables (Fig. 1). The null hypothesis of inequality as suggested by Schuirmann was therefore rejected and the alternative hypothesis of equality accepted.

Table III. Difference in effect — end of treatment compared with baseline

	Baseline (P_1) Mean (SEM)	End of treatment (P_2) Mean (SEM)	Difference in treatment effect ($P_2 - P_1$) Mean	95% CI
1° Efficacy variables				
MPEF l/min				
Group 1 ($N = 16$)	385.0 (14.1)	390.6 (14.4)	5.6	−16.4 - 27.6
Group 2 ($N = 16$)	384.7 (19.2)	362.4 (20.1)	−22.3	−35.6 - 9.0
FEV_1 % predicted				
Group 1 ($N = 16$)	73.6 (3.0)	70.7 (4.1)	−2.9	−11 - 5.2
Group 2 ($N = 16$)	66.6 (2.5)	68.6 (3.3)	0.2	4.8 - 5.2
PC_{20} mg/ml				
Group 1 ($N = 15$)	0.12 (0.02)	0.08 (0.04)	−0.04	−0.15 - 0.06
Group 2 ($N = 12$)	0.09 (0.16)	0.30 (0.11)	0.02	−0.38 - 0.4
2° Efficacy variables				
β-agonist use puffs/d				
Group 1 ($N = 16$)	3.36 (0.5)	3.05 (0.45)	−0.31	−1.49 - 0.87
Group 2 ($N = 16$)	2.86 (0.4)	3.23 (0.4)	0.37	−0.54 - 1.28
Symptom score/d				
Group 1 ($N = 16$)	1.3 (0.2)	1.3 (0.17)	0.0	− 0.6 - 0.6
Group 2 ($N = 16$)	1.79 (0.2)	2.27 (0.2)	0.48	−0.018 - 0.97
Nocturnal awakening /10 days				
Group 1 ($N = 16$)	2 (0.8)	3 (1.1)	1	−1.5 - 3.5
Group 2 ($N = 16$)	2 (0.9)	2 (0.7)	0	−2.0 - 2.0

SEM = standard error of mean.

The difference in effect for the clinical variables was non-conclusive, as demonstrated in Fig. 1. No serious adverse events were reported during the study. Six patients, 3 in each group, experienced deterioration in asthma control but none of them required hospitalisation. Common cold symptoms were reported in 5 patients in group 1 and 7 in group 2. (The trial was performed during the winter months.) One patient in group 2 developed pharyngeal thrush. Both formulations were well tolerated by all patients.

Discussion

We have examined the therapeutic equivalence of an innovator and a generic formulation of BDP in moderate-to-severe asthmatic adults using efficacy variables proposed in a consensus statement by the British Association for Lung Research in 1994.[12] Results of our study demonstrated that the mean differences with 95% CIs of such variables were contained within the limits set for equivalence.[20]

Expiry of patent periods for innovator formulations and changes in governmental regulations provides the opportunity for generic or interchangeable multisource products to enter the marketplace at a lower cost.[10,11] The question is whether these formulations are therapeutically equivalent to their innovator counterparts. Determination of bio-equivalence for inhaled products remains problematic.[10,13] Four principal methodologies are currently available to compare equivalence of different inhaler devices. The first of these methodologies is an *in vitro* procedure, which is based on the inertial behaviour of particle clouds emitted by inhalers. The 'respirable fraction', a standard means of evaluating inhaled products, is based on the percentage of drug contained in particles less than 5 μm in diameter. This measure of equivalence, favoured by regulatory authorities, may not correlate with efficacy in patients.[10]

Three *in vivo* methods are available to assess equivalence, namely:

1. Radio-aerosol drug deposition study (gamma scintigraphy), which assesses the pattern of delivery to the patient and quantifies distribution within the lungs.

2. Pharmacokinetic studies, which are generally of limited value in the study of inhaled medication. Drugs administered by inhalation differ from those administered by ingestion in several ways. Administration of inhaled drugs is intended for local rather than systemic deposition. This creates difficulty in the testing of inhaled products using bio-availability criteria because blood concentrations are usually very low. Furthermore, the inhaled drug in the blood is not necessarily equivalent to the dose deposited in the lungs in terms of amount or efficacy.

3. Comparative pharmacodynamic and clinical efficacy studies. These studies, including our study, are ultimately the most reliable measure of effectiveness for any medication and constitute the preferred assessment in comparisons of the performance of different medications and inhalation device combinations.[10,13]

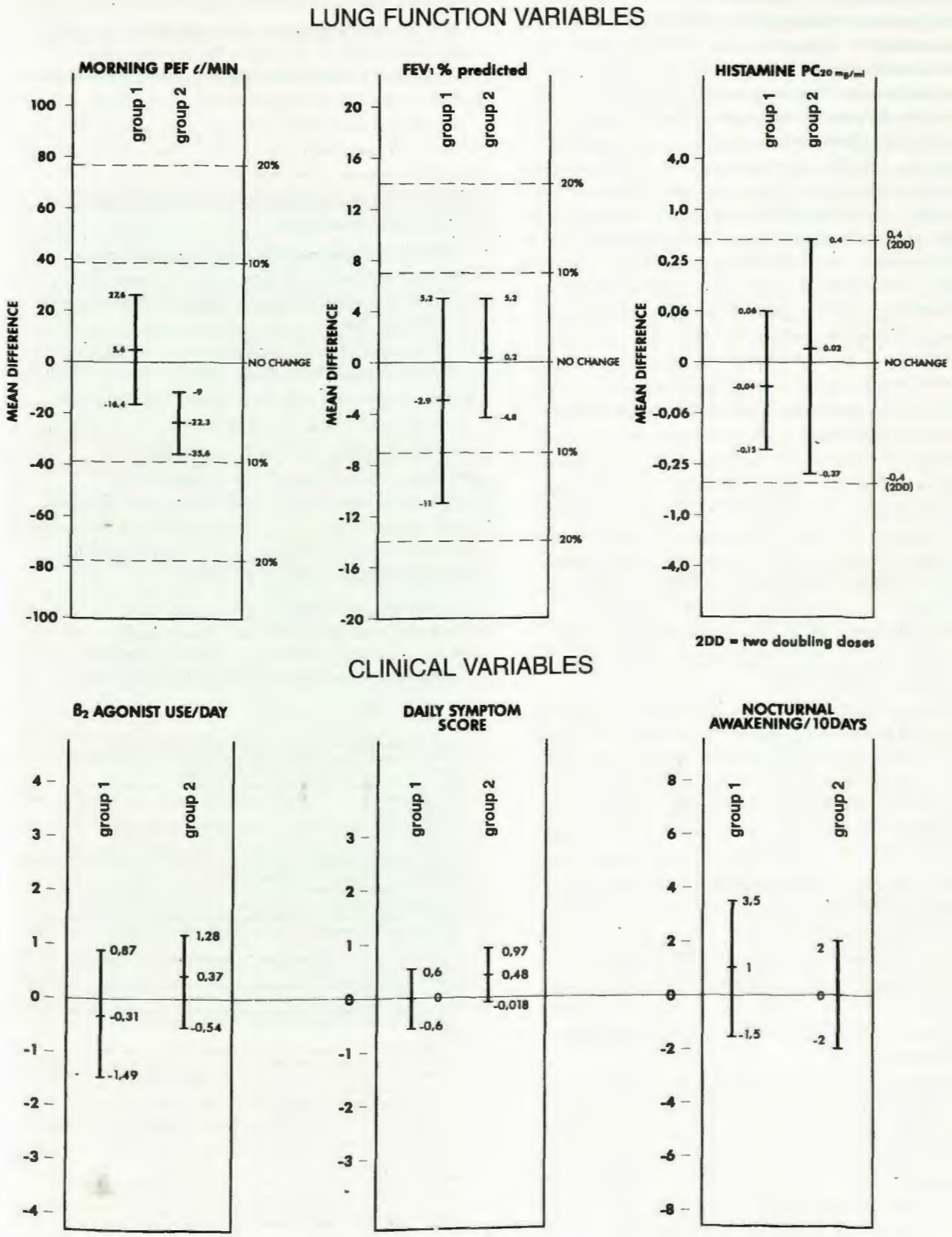

Fig. 1. Mean difference in effect, end of treatment compared with baseline, with 95% confidence intervals.