A randomized, double-blind dose reduction study to compare the minimal effective dose of budesonide Turbuhaler and fluticasone propionate Diskhaler

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Background: New inhaled glucocorticosteroids and inhalers are being developed. Their clinical equipotency is difficult to assess and is often discussed.
Objective: This study was carried out to compare the effect of budesonide Turbuhaler and fluticasone propionate (FP) Diskhaler in a dose reduction study in children (ages 5 to 16 years) with asthma.
Methods: Children treated with budesonide administered through a pressurized metered-dose inhaler with a large volume spacer had their budesonide dose gradually reduced to define the minimal effective dose with this delivery system. After this period, 217 children were randomly allocated to treatment with half the dose of either budesonide Turbuhaler or FP Diskhaler for 5 weeks in a double-blind trial. If no deterioration in asthma control was seen, the dose was further reduced by 50% at 5-week intervals until deterioration in asthma control was seen. Throughout the study, morning and evening peak expiratory flow, symptoms, and use of rescue β_2-agonist were recorded in diaries. Lung function tests and a standardized exercise test were performed at the clinic at the end of each treatment period. Urine cortisol excretion (24 hours) was measured before and after the first 5-week treatment period. Standardized criteria for deterioration in asthma control, based on diary card variables and exercise testing, were used to determine the minimal effective dose for each patient; and from this, the number of dose reduction steps was calculated.
Results: No statistically significant difference was seen in number of dose reduction steps from baseline or in minimal effective dose between the two treatments; mean reduction was 1.59 dose steps for budesonide Turbuhaler and 1.65 dose steps for FP Diskhaler ($p = 0.52$), and minimal effective dose was 188 μg for budesonide Turbuhaler and 180 μg for FP Diskhaler. After these dose reductions, the same level of asthma control was observed in the budesonide Turbuhaler and FP Diskhaler groups. Furthermore, no statistically significant differences between the two inhaler-drug combinations were seen in daytime or nighttime symptoms, morning and evening peak expiratory flow, use of rescue β_2-agonist, lung functions at the clinic, exercise-induced fall in lung function, or 24-hour urinary cortisol excretion during the first 5-week period.
Conclusion: Microgram for microgram, budesonide Turbuhaler and FP Diskhaler are equally effective in treatment of children with moderate asthma. (J Allergy Clin Immunol 1997;99:773-80.)

Key words: Children, asthma, inhaled steroids, efficacy, safety

Inhaled corticosteroids have become established as a very effective asthma therapy, and this treatment is now increasingly being used as first-line therapy in both children and adults with chronic asthma. Consequently, new potent inhaled corticosteroids with somewhat different and perhaps improved pharmacokinetics are being developed. These new drugs are normally compared with the established corticosteroids. The majority of these comparisons are performed in laboratory studies (receptor binding, receptor affinity, potency, lipophilicity, retention time in the airways, and pharmacokinetics).[1,2] The clinical relevance of significant differences between the various drugs observed in such studies is not clear. Only carefully conducted clinical trials can provide this information. However, clinical trials are complicated by the fact that the various inhaled corticosteroids are delivered from inhalers, which may differ markedly in output characteristics and drug delivery to the intrapulmonary airways.[3] Therefore in clinical practice it is not possible to compare two drugs only. The comparison must be between two drug-inhaler combinations. Such comparisons are clinically relevant and very important for therapeutic decisions, but they do not always answer the question of how laboratory findings relate to the clinical situation.

The newest inhaled glucocorticosteroid on the market is fluticasone propionate (FP). So far, the majority of studies with this drug have been done in adults; the designs and patient groups have varied, and so have the conclusions. The range of conclusions include: clinical equipotency between FP Diskhaler and budesonide Turbuhaler[4] and between FP and beclomethasone pressurized metered-dose inhalers (pMDIs),[5] twice the potency of FP pMDI compared with all other currently available inhaled corticosteroids delivered by pMDI,[6-8] no systemic effects at all,[7,9] sytemic effects similar to those of beclomethasone pMDIs[6] or budesonide Turbuhaler,[10,11] and two to four times the systemic effect of budesonide pMDI.[12-16] The most relevant clinical parameter, the clinical effect/systemic effect ratio, assessed in the same group of patients, has not yet been thoroughly studied or compared with other corticosteroids.

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Abbreviations used

FEF_{25-75}:	Forced expiratory flow rate 25% to 75%
FP:	Fluticasone propionate
MED:	Minimal effective dose
PEFR:	Peak expiratory flow rate
pMDI:	Pressurized metered-dose inhaler

The aim of this dose reduction study in children with asthma was to compare the minimal effective dose (MED) and the clinical and systemic effects of the two newest inhaled corticosteroids, budesonide and FP, both administered through their respective dry powder inhalation devices (Turbuhaler and Diskhaler) to determine whether important differences exist between these two drug-inhaler combinations in their clinical effect/systemic effect ratio.

METHODS

Patients

Children with asthma, who were well known from our outpatient clinic, entered an evaluation period before the trial. To be evaluated, their asthma had to be well controlled for at least 2 months by treatment with budesonide (≥400 μg/day) administered through a pMDI with a large volume spacer (Nebuhaler). During the evaluation period, the budesonide dose was gradually reduced until clinical deterioration or unacceptable control, determined by preset criteria (see below), was seen. Patients, who after this period were found to require either 800 μg or 400 μg of budesonide per day from pMDI Nebuhaler for good control of asthma, were eligible for the study. With a Turbuhaler output of 200 μg and 100 μg, these doses could be achieved with one dose given twice daily in all children at study entry when the steroid dose was halved (see below). During the evaluation period, the children measured peak expiratory flow rate (PEFR) in the morning and in the evening. In addition, asthma symptoms during the day, during the night, and during exercise and use of rescue β_2-agonist (terbutaline sulfate administered through Turbuhaler) were recorded in diaries. Lung function measurements were performed at the clinic. After the evaluation period, children who fulfilled the following criteria were included in the study.

Inclusion criteria

- Boys and girls between 5 and 16 years of age
- Requirement of 400 μg or 800 μg budesonide from pMDI with a large volume spacer (Nebuhaler) daily assessed during the evaluation period
- Competence in use of Nebuhaler, Turbuhaler, and Diskhaler according to package inserts
- Informed consent given

Exclusion criteria

- Acute severe exacerbation of asthma within 2 months before the evaluation period
- Symptomatic respiratory tract infection during the month before the evaluation period
- Treatment with systemic glucocorticosteroids, anticholinergic agents, theophylline, or disodium cromoglycate during the month before the evaluation period
- Other respiratory diseases of dominating nature such as chronic bronchitis, emphysema, or interstitial lung disease
- Past or present cardiovascular, renal, liver, or endocrine disease, which might interfere with the study
- Poor compliance

Furthermore, patients with a significant degree of seasonal variability in their asthma symptoms only entered the study during a stable period when it would be most unlikely that a seasonal change would occur during the next 3 months. Treatment with anticholinergic agents; theophylline; disodium cromoglycate; and oral, inhaled, or injected glucocorticosteroids (other than study medication) was not permitted during the study. Nasal glucocorticosteroids were to be avoided, if possible. Occasional use of inhaled long-acting β_2-agonists was permitted, if needed, when participating in sporting activities. Such patients were asked not to use their long-acting β_2-agonist during the 24-hour period before all clinic visits. Otherwise, use of β_2-agonists (except for rescue medication) was not allowed during the study.

The inhaled steroid treatment was always carried out in the morning and in the evening. The patients were advised to take the medicine just before brushing their teeth to ensure effective mouth rinsing after each treatment. All children used rescue β_2-agonist on an as-needed basis. No other anti-asthma drugs were allowed.

PEFR was measured every morning and evening on a Vitalograph peak flow meter (Vitalograph, Buckingham, U.K.) with a nonlinear scale. The measurements were performed at the same time of day, before intake of study medication and preferably at least 6 hours after any intake of β_2-agonist. Patients were requested to measure PEFR three times while standing and to record the highest reading. Asthma symptoms (daytime, nighttime, and during exercise), use of study medication (yes or no), and β_2-agonist (daytime and nighttime) were recorded daily in diaries throughout the study. Asthma symptoms were scored according to the following definitions.

Daytime. A scale of 0 to 3 was used for rating daytime symptoms: 0 = none (very good day, activities not restricted); 1 = mild wheezing or breathlessness (e.g., when exercising or in a hurry but activities not restricted); 2 = moderate (some discomfort but able to carry out most of daily activities); 3 = severe or incapacitating (inability to attend school or do usual activities).

Nighttime. A scale of 0 to 3 was used for rating nighttime symptoms: 0 = none (peaceful night, slept well); 1 = mild (peaceful night but woke once or woke early because of asthma symptoms); 2 = moderate (woke two or three times because of asthma symptoms); 3 = severe (awake most of the night because of asthma symptoms).

During exercise. A scale of 0 to 3 was used to rate symptoms during exercise: 0 = none (can walk, run, and participate in sports or play with no problems); 1 = mild (no problems when walking but a little wheezing and breathlessness when running, participating in sports/playing or when in a hurry; otherwise, activities not restricted); 2 = moderate (breathlessness and wheezing when walking, which worsens when running or participating in sports/playing); 3 = severe or incapacitating (difficulties when walking and inability to run or participate in sports/play).

The study was approved by the ethics committee, and informed consent was obtained from all children and their parents.

Study design

After the clinical condition had stabilized after the evaluation period, 219 children, whose minimal effective budesonide dose was 400 μg (n = 85) or 800 μg (n = 134) per day (mean, 640 μg) entered a 2-week run-in period (baseline) of a randomized double-blind, double-dummy, parallel-group study. During this period the children continued treatment with 400 or 800 μg budesonide administered through pMDI Nebuhaler per day. After run-in, 217 children were randomly allocated to treatment with half their baseline dose of either budesonide Turbuhaler or FP Diskhaler for 5 weeks. A block randomization generated by a computer program was used. Of the 217 children allocated to treatment, one was considered ineligible for randomization (respiratory tract infection) and was thus excluded from analysis. If no deterioration in astma control was seen and asthma control was not reduced to "acceptable control" (see below) during these 5 weeks, the steroid dose was further reduced by 50% at 5-week intervals until deterioration in asthma control or "acceptable asthma control" was seen or until 5 weeks of treatment with 100 μg/day had been completed without any of these conditions being reached (Fig. 1).

The patients were seen at the outpatient clinic at the beginning and at the end of run-in and after each 5-week treatment period or in case of deterioration. At each visit, pulmonary functions were measured on a Vitalograph compact. Forced vital capacity, FEV_1, PEFR, and forced expiratory flow rate 25% to 75% (FEF_{25-75}) were used for analysis. Careful tuition and control of inhaler use and inhalation technique according to the manufacturer's pamphlets were done at each visit, and at the time of entry, all children demonstrated correct inhaler use and optimal inhalation technique with both dry powder devices. Furthermore, at the end of run-in and at the end of each 5-week treatment period, the children performed a standardized exercise test as follows. The exercise test was a 6-minute treadmill test. The workload was adjusted to produce a pulse rate of 170 or more during the last 3 minutes of exercise. Each child wore a nose clip during the test, and the temperature and air humidity were recorded. FEV_1 (in liters), forced vital capacity (in liters), FEF_{25-75} (in liters per second), and PEFR (in liters per minute) were measured before the test and at 1, 3, 5, 8, 10, 15, and 20 minutes after the test, or until a maximum fall had occurred. Two reproducible lung function measurements were to be obtained at each time. The one with the highest FEV_1 was used for calculations. The maximum percent fall in the various pulmonary function parameters was analyzed.

MED

Deterioration of asthma. Patients were to be discontinued if deterioration of asthma occurred, defined as:

- The need for an alteration in asthma therapy, as judged by the investigator.
- A fall in morning PEFR of more than 20% (compared with the average over the last 7 days of baseline) on each of any 3 consecutive days since the previous visit.
- Use of five or more inhalations of rescue medication (terbutaline sulfate through Turbuhaler) on each of any 3 consecutive days since the previous visit.
- More than a one-step worsening in either day, night, or exercise symptom score (compared with the average score during the last 7 days of baseline rounded to the nearest integer (i.e., from 0 to 2 or 3, or from 1 to 3) on each of any 3 consecutive days since the previous visit.

MED for these patients was the dose before deterioration.

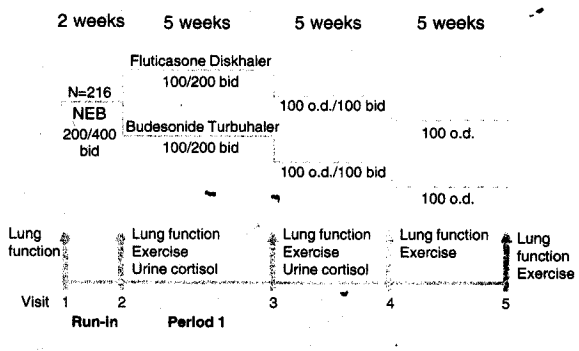

FIG. 1. Study design. After a 2-week run-in period of budesonide treatment delivered by pMDI and a large volume spacer (Nebuhaler) at a daily dose of 400 μg or 800 μg (individually tailored), children were randomly allocated to treatment with half their run-in dose of either budesonide Turbuhaler or FP Diskhaler for 5 weeks in a double-blind, double-dummy trial. If no deterioration in asthma control was seen, the dose was further reduced by 50% at 5-week intervals until deterioration in asthma control was seen. *NEB,* Nebuhaler; *bid,* twice daily; *o.d.,* once daily.

Acceptable asthma control. Fulfillment of two or more of the following criteria indicated that the therapy provided acceptable asthma control but that the dose could not be further stepped down. The patient then had to discontinue the study. The criteria were as follows:

- The maximal fall in FEV_1 after an exercise test increased more than 15% compared with the maximal fall at visit 2.
- A fall in average morning PEFR of more than 10% occurred over the 7 days before clinic visits (compared with the average over the last 7 days of baseline), calculated at the clinic visit.
- A fall in FEF_{25-75} of more than 20% compared with FEF_{25-75} occurred at visit 2.
- More than a one-step worsening observed in either day, night, or exercise symptom score compared with the average score during the last 7 days of baseline rounded to the nearest integer (i.e., from 0 to 2 or 3, or from 1 to 3) on at least five occasions during the last 14 days before clinic visits, determined at clinic visits.

MED for these patients was the dose when this level of asthma control was reached.

Laboratory evaluations

Twenty-four–hour urine cortisol excretion was measured at the end of run-in and at the end of the first 5-week treatment period. When the urine samples were delivered to the clinic, the bottles were weighed. Daytime and nighttime urine specimens were carefully mixed, and two 10 ml samples were transferred to polystyrene test vials and kept at −20° C until they were analyzed. The remaining urine was discarded. Urine volume was calculated, with an assumed density of 1.02 gm/ml. The urine samples were analyzed for cortisol by using gas chromatography mass spectrometry and for creatinine by using an enzymatic method at BCO Medical Services BV (Breda, The Netherlands).

Compliance

The amount of medication used was estimated by counting the number of unused doses of budesonide by turning the grip on the Turbuhaler until the red mark on the dose indicator was

TABLE I. Baseline data for randomized patients

	Budesonide	FP
No. of patients	107	109
High-dose/low-dose	66/41	67/42
Age (yr)	9.9 (5-15)	10.1 (5-16)
Boys/girls	74/33	62/47
Height (cm)	141 ± 16	140 ± 17
Weight (kg)	37 ± 13	38 ± 14
Asthma duration (yr)	7.1 ± 3.1	7.5 ± 3.0
FEV_1 (% predicted)	91.9 ± 14.6	93.8 ± 13.3
$FEF_{25-75\%}$ (% predicted)	76.7 ± 20.6	79.6 ± 21.9
Urine cortisol (nmol/24 hr)	29.8 ± 20	27.5 ± 16
Urine cortisol (nmol/24 hr/creatinine)	4.5 ± 2.5	4.4 ± 2.3

Patient characteristics during run-in (baseline) when both groups were treated with budesonide from a pMDI Nebuhaler. Values are given as mean ± SD, except for age, for which mean and range are given.

seen. The administered number of doses was the total number of doses in the Turbuhaler (200) minus the unused doses. The administered number of doses of FP was determined by counting unused doses in the blisters. Compliance was defined as 100 times the ratio between "actual number of doses used during the study" and "required number of doses intended to be used during the study." Patients were judged compliant if between 75% and 125% of the intended number of doses were taken.

Statistics

A power calculation based on the residual standard deviation from analysis of variance (0.71 for reduction in dose steps and 23 L/min for change in morning PEFR) showed that there was 80% power to detect a difference between treatments of 0.30 dose reduction steps, or a difference of 10 L/min in change of morning PEFR, tested at 5% significance level.

When reduction in dose steps was analyzed, all doses (baseline dose and MED) were first transformed into a logarithmic scale of base two, which means that the distance between doubling doses is one dose step. Geometric means of MED were computed as back transformations to the original microgram scale of adjusted means.

The effects of the 5-week treatment on evening PEFR, asthma symptom scores, use of rescue medication, baseline lung function recorded at the clinic visits, and maximal fall in FEV_1 and FEF_{25-75} after an exercise test were also assessed. The end point for diary variables was the change from baseline (mean of the last 7 days before randomization) to end of the treatment comparison period (mean during weeks 4 and 5). For visit variables, the end point was the change from the randomization visit to the visit at the end of the first 5-week treatment period.

The effect of treatment was investigated, for all variables, by using analysis of variance with a fixed effects model with the factors of treatment, dose group, and treatment-by-dose interaction. The possible influence of sex and age was investigated by using descriptive statistics, but they were not included in the model. All tests were two-sided, and p values below 5% were considered statistically significant.

RESULTS

Characteristics for 216 randomized patients are given in Table I. Of these patients, two (both in the FP group) were unwilling to complete the first 5-week treatment period.

TABLE II. MED and reduction in dose steps from baseline to MED (main analysis, n = 214 patients)

	Budesonide Turbuhaler		FP Diskhaler	
Dose group	GM (μg)	MRDS	GM (μg)	MRDS
All*	188	1.59	180	1.65
High	232	1.79	227	1.82
Low	153	1.39	143	1.49

GM, Geometric mean of MED; *MRDS*, mean reduction in dose steps from baseline to MED.
*Adjusted for dose groups.

Only minor differences were seen between the two groups in demographic data, pulmonary function measured at the clinic, or cortisol excretion in the urine during run-in (Table I). Furthermore, within each group, there was no significant variation in any of the recorded variables from visit 1 to visit 2 during the 2-week run-in period, indicating that the patients' clinical condition was stable before entering run-in.

One patient received intranasal steroids during run-in. Otherwise, no intranasal steroids were taken during the study.

Dose reduction from baseline to MED

In the analyses, the nine patients (6 receiving FP and 3 receiving budesonide) whose asthma was not controlled at the first dose level were included, assuming that their asthma would be controlled at the double dose level (i.e., 400 μg or 800 μg). No statistically significant difference was seen in number of dose step reductions from baseline to MED between the two treatments; mean reductions were 1.59 dose steps for budesonide Turbuhaler and 1.65 dose steps for FP Diskhaler (p = 0.52). The 95% confidence interval for the difference was −0.14 to +0.26. There was a statistically significant difference between dose groups (p = 0.0004); dose reduction was approximately 0.4 steps greater in patients receiving high doses than in those receiving low doses (Table II). The interaction between treatment and dose group was not statistically significant (p = 0.74).

In an alternative analysis, the 58 patients who reached the last dose level and still fulfilled the criteria for further dose reduction were assigned an MED of 50 μg. The conclusion was the same: no statistically significant difference between treatments (budesonide = 1.83 and FP = 2.02 dose step reductions, p = 0.21).

MED

No statistically significant difference was seen in MED between the two inhaler-drug combinations, either when the 58 patients who reached the last dose level fulfilling the criteria for further dose reduction were assigned an MED of 100 μg (geometric means: budesonide = 188 μg; FP = 180 μg; p = 0.36) or an MED of 50 μg (budesonide = 159 μg; FP = 140 μg) (Table II and Fig. 2).

Finally, an analysis was made without the 58 patients who reached the last dose level and still fulfilled the criteria for further dose reduction. The results were the same: no statistically significant difference was found in MED or number of dose step reductions between the two drug-inhaler combinations.

Acceptable asthma control was the only cause of study discontinuation in seven patients. In the remaining cases discontinuation was due to "deterioration in asthma control."

Diary recordings

The mean values and differences between mean values for morning PEFR, evening PEFR, nighttime symptoms, daytime symptoms, symptoms during exercise, and the use of β_2-agonists during run-in and treatment weeks 4 and 5 are shown in Table III. The table also gives *p* values for the treatment factor and 95% confidence intervals for various differences between treatments in change from baseline. The difference between treatments was not statistically significant for any of the diary recordings. Furthermore, mean morning and evening PEFR, asthma symptoms, exercise symptoms, and use of β_2-agonists were similar for both treatment groups during the last 2 weeks of the treatment period, during which the patients were treated with their MED, indicating comparable asthma control between the two groups also after downtitration of the steroid dose.

Recordings at the clinic

Mean lung functions, maximum percent fall in lung functions after exercise, and mean changes from the end of run-in (visit 2) to the end of the first treatment period (visit 3) are shown in Table IV. No statistically significant differences were observed between the two treatments in any of the parameters.

Urine cortisol excretion

The 24-hour urine cortisol excretion values during run-in and during treatment are shown in Table V. No differences were seen between the high- and low-dose groups. The changes from run-in to the end of treatment were similar for both drug-inhaler combinations. The conclusions were the same for cortisol excretion during the night (data not presented).

Compliance

Compliance with the dose regimen was acceptable and without any statistically significant differences between the two treatment groups: 72% (FP Diskhaler) and 67% (budesonide Turbuhaler), respectively.

DISCUSSION

Clinical comparisons between different inhaled corticosteroids are difficult to perform because of the dose-response relationships seen with this treatment.[7, 17-19] Usually, marked effects on symptoms and PEFRs are seen already with daily doses of around 100 μg in children with moderate and severe asthma.[17] Increasing the dose further

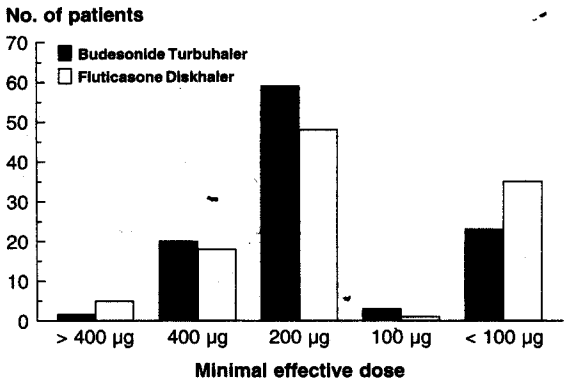

FIG. 2. Distribution of MED of budesonide delivered from Turbuhaler or FP delivered from Diskhaler in 214 children with persistent asthma. No statistically significant difference was seen between the two drug-inhaler combinations.

produces only small additional improvements in these parameters because the dose-response curve after the initial steepness is rather flat. For this reason, differences between drugs are difficult to detect unless low doses are used or a regular dose-response trial is conducted. It is difficult in single-dose comparative studies to show any differences between two drugs, two doses of the same drug, or a high dose of one drug and a low dose of another if only PEFR measurements and diary recordings are assessed. In such studies false conclusions about equieffective doses may be made on the basis of the finding of "no difference" between treatments.

It seems that increases in FEV_1, FEF_{25-75}, or protection against exercise-induced asthma are somewhat more sensitive in detecting differences between different doses of inhaled corticosteroids. Thus in an earlier study, we were able to detect statistically significant differences in these parameters, but not in symptoms or PEFR, between doubling doses of budesonide.[17] This prompted us to include lung function measurements and a standardized exercise test at each dose step in the assessment to increase the likelihood of detecting a difference between the two treatments. In addition, all patients had had their budesonide dose from pMDI Nebuhaler titrated down to the lowest dose that could control their condition before they entered the study, in order to ensure that the patients were not overtreated at study entry.

Finally, we chose a dose reduction design because it would both mimic the normal day-to-day treatment and a modified dose-response study because with this design the majority of patients would receive treatment with the two drug-inhaler combinations at the steep part of the dose-response curve at which differences are more likely to be detected. If we could not detect a significant difference in MED under these strict and controlled conditions, it would be most unlikely that there would be any clinically important differences between the two drug-inhaler combinations.

A marked difference in compliance or ability to use the two powder inhalers optimally would have compli-

TABLE III. Mean values of diary recordings

Parameters	Measured value				Change from run-in			
	BUD		FP					
	Run-in	5 wk	Run-in	5 wk	BUD	FP	95% CI	*p* Value
Morning PEFR (L/min)	263.8	265.8	253.7	261.3	1.9	7.6	−12.0, 0.7	0.06
Evening PEF (L/min)	270.0	269.3	259.6	264.7	−0.7	5.1	−12.1, 0.6	0.06
Asthma symptoms (night)	0.10	0.07	0.15	0.11	−0.03	−0.04	−0.07, 0.09	0.75
Asthma symptoms (day)	0.30	0.25	0.45	0.34	−0.05	−0.11	−0.08, 0.20	0.37
Exercise symptoms (0-3)	0.25	0.22	0.41	0.33	−0.03	−0.08	−0.07, 0.18	0.41
No. β_2-agonists (day)	0.45	0.46	0.59	0.62	0.01	0.02	−0.20, 0.18	0.87

Mean values of diary recordings during the last week of run-in (when all children received budesonide from a nebuhaler) and during the last 2 weeks of the first 5 weeks treatment with either half the run-in dose of budesonide Turbuhaler or FP Diskhaler. 95% CI (confidence intervals) refer to the difference between budesonide and FP in change from run-in to 5 weeks. *p* values refer to analysis of variance.
BUD, Budesonide.

TABLE IV. Mean lung functions and percent fall in lung functions

parameters	Measured value				Change from run-in			
	BUD		FP					
	Run-in	5 wk	Run-in	5 wk	BUD	FP	95% CI	*p* Value
FEV_1 (L)	2.02	2.07	2.06	2.12	<0.1	0.1	−0.07, 0.03	0.77
FVC (L)	2.55	2.58	2.58	2.61	<0.1	<0.1	−0.07, 0.05	0.85
FEF_{25-75} (L/sec)	2.01	2.06	2.07	2.20	<0.1	0.1	−0.18, 0.01	0.16
Fall in FEV_1 (%)	8.0	7.4	10.7	8.2	−0.7	−2.5	−0.70, 4.5	0.16
Fall in FEF_{25-75} (%)	18.1	16.9	20.4	19.5	−1.2	−1.2	−4.9, 4.9	0.97

Mean lung functions and percent fall in lung functions after exercise challenge during run-in (when all children received budesonide from a Nebuhaler) and after 5 weeks of treatment with either half the run-in dose of budesonide from a Turbuhaler or FP from a Diskhaler. 95% CI (confidence intervals) refer to the difference between budesonide and FP in change from run-in to 5 weeks. *p* values refer to analysis of variance.
BUD, Budesonide; *FVC,* forced vital capacity.

cated the interpretation of the results. Therefore a Nebuhaler was used during the evaluation and run-in periods to avoid favoring any of the two devices. All children were thoroughly trained in correct use of both powder inhalers before the study, and their inhalation technique was checked at each visit to ensure that a possible difference in efficacy would not be due to differences in the children's handling of the two inhalers or inhalation technique. Furthermore, a double-blind design and strict objective criteria for "deterioration" and acceptable asthma control minimized the risk of an investigator bias toward one of the two drug-inhaler combinations. Because compliance was found to be on the same level in the two groups, we believe that we succeeded in controlling these different confounding factors. The two groups were comparable with respect to asthma control, budesonide dose, and epidemiology at study entry. Unacceptable asthma control was demonstrated by 75% of the children during the dose reduction in both treatment groups, suggesting that they had been brought into the steep part of the dose-response curve during the study. Even so, there was no significant difference in MED, number of dose step reductions, or any other effect variable between the two drug-inhaler combinations. This conclusion was the same even in the alternative analysis in which we assigned the 58 children whose asthma did not deteriorate during the study an MED of 50 μg/day, or the analysis only included the 156 children whose asthma had deteriorated during the dose reduction. Furthermore, this held true for both the high- and the low-dose treatment groups.

It was not possible to administer a daily dose of 50 μg. Therefore we designed the study to stop at 100 μg per day. If MED is normally distributed (which we believe it is, see Fig. 2), it would be expected that the vast majority of the 58 children who stopped at 100 μg would experience deterioration if they had had their daily dose further reduced to 50 μg. They would then by definition have been assigned an MED of 100 μg. Therefore we set the MED for these children to 100 μg in the main analysis.

When no statistically significant difference between two treatments is assessed, there is always a risk of making a statistical type 2 error. However, a poststudy power calculation and the confidence intervals showed that it is most unlikely that FP Diskhaler should be twice as effective as budesonide Turbuhaler in children. This claim is sometimes made in adult studies comparing half the dose of FP Diskhaler with a full dose of budesonide Turbuhaler when no difference in asthma control has been detected between the two treatments.[20-22] However, such studies run a substantial risk of a type 2 error because of the dose-response relationships of inhaled

TABLE V. Mean 24-hour urinary cortisol

Parameters	Dose	Measured value				Change from run-in			
		BUD		FP					
		Run-in	5 wk	Run-in	5 wk	BUD	FP	95% CI	*p* Value
Cortisol (nmol)	All	29.8	31.5	27.5	34.5	1.8	6.6	−10.9, 1.3	0.13
	High	26.7	27.4	26.7	33.3	0.4	5.7	−12.9, 2.3	
	Low	34.4	37.8	28.7	36.3	3.8	7.9	−14.2, 6.0	
Cortisol/creatinine	All	4.5	5.0	4.4	5.2	0.4	0.8	−1.3, 0.5	0.50
	High	4.1	4.3	4.3	5.4	0.1	1.0	−2.2, 0.4	
	Low	5.2	6.0	4.5	5.0	0.7	0.5	−1.1, 1.5	

Mean 24-hour cortisol excretion in the urine during run-in (when all children received budesonide from a Nebuhaler) and after 5 weeks of treatment with either half the dose of budesonide from a Turbuhaler or FP from a Diskhaler. Values are given separately for high-dose (800 μg of budesonide per day from Nebuhaler during run-in) and low-dose (400 μg of budesonide per day from Nebuhaler during run-in). 95% CI (confidence intervals) refer to the difference between budesonide and FP in change from run-in to 5 weeks. *p* values refer to analysis of variance.
BUD, Budesonide.

corticosteroids described earlier.[7, 17-19] Therefore a lack of a difference in effect between two doses in such studies cannot be taken as proof of a 2:1 potency between the two drug-inhaler combinations. In agreement with this, a clinical study, which compared budesonide and FP at equal doses, indicated that the two substances are clinically equally effective.[4]

Only one other double-blind study has compared these two drug-inhaler combinations in children.[23] That study, by Hoekx and Hollingworth,[23] used a rather high daily dose of 400 μg of both drugs in children with mild and moderate asthma and therefore may not have been very sensitive in detecting a difference between the two drugs. No difference was found between budesonide and FP in any of the parameters studied except for home PEFR, which was higher during FP treatment during the middle of the study but not during the rest of the trial. The systemic effects of the two drug-inhaler combinations were also similar. So, the study by Hoekx and Hollingworth[23] seems to corroborate the findings in this study (i.e., the two drug-inhaler combinations seem to have very similar clinical effects, microgram for microgram of the nominal dose in children with asthma). This conclusion should be transferred to adults with some caution because the anatomy of the upper airway is different and because inspiratory flow rates through the dry powder inhalers differ. Furthermore, effects on PEFR, symptoms, and mild exacerbations may not reflect a treatment's ability to prevent acute severe exacerbations or hospitalizations. Such information can only be obtained from long-term studies. Finally, the conclusion cannot be extended to other inhalers such as pMDIs, which may have totally different output characteristics.[3]

The best parameter to use when comparing two inhalers or drugs is the ratio between the clinical effect and the systemic effect, preferably measured in the same patients. Therefore in addition to clinical effect assessments, comparisons of systemic effects should also be performed to define this ratio. In this study 24-hour urinary cortisol excretion, which is a sensitive measure of the systemic effect of exogenous steroids, was identical for the two treatments, suggesting that the clinical effect/systemic effect ratio is the same for the two drug-inhaler combinations. This is in accordance with other studies in children, which have shown that, microgram for microgram, nominal doses of the two drug-inhaler combinations have similar systemic effects in children.[10, 23] In contrast, studies in adults, in which sensitive methods are used to detect systemic effects of the two drug-inhaler combinations, suggest that FP may have greater systemic potency than budesonide on a microgram-to-microgram basis.[12-14] The same seems to be the case for the pMDIs of the two products, both in children and in adults.[15, 16]

Symptoms were the most sensitive parameter with which to detect deteriorations in asthma control. This is in good agreement with an earlier dose reduction trial in adults.[24] Increases in symptoms normally preceded the fall in PEFR and FEV_1. Surprisingly, exercise was not as useful as we expected before the study on the basis of earlier findings.[17] This suggests that increases in symptoms also precede a measurable increase in bronchial hyperreactivity. Further studies are needed to assess this hypothesis. Since only seven children stopped their downtitration of dose because they had acceptable asthma control, it seems sufficient for future dose reduction trials to include only deterioration criteria. This would also make the performance of the study easier.

The number of dose reduction trials is rather limited, and the optimal duration of each dose step is not known. Deterioration was most often seen during the last 3 weeks, suggesting that the periods should be longer than 2 weeks, which have been used in earlier studies.[24, 25] Increasing the duration of each period even further might have increased the MED a little, but probably to the same degree for both treatments. On the other hand, longer study periods would increase the risk of seasonal variations and drop-outs caused by too-long study periods.

It was surprising that the steroid dose could be reduced with almost two dose steps, from around 600 to 200 μg per day, even if the children had had their

budesonide dose reduced to the lowest dose from pMDI Nebuhaler, which could maintain asthma control before entry. Earlier clinical studies of a longer duration found a 2:1 potency between Turbuhaler and Nebuhaler.[26, 27] However, in these studies there was a trend (which for some parameters was significant) for a better effect of Turbuhaler at half the dose of that used with Nebuhaler, suggesting that the effect ratio between the two devices may be greater than 2:1. In agreement with this, a pharmacokinetic lung deposition study in children suggested a 2.5 times higher lung deposition from Turbuhaler compared with Nebuhaler.[28] So, the findings of both these studies are in agreement with the findings of this study. The intrabronchial deposition of FP from Diskhaler in children is not known. In vitro studies and findings in adults suggest that it is lower than that for budesonide Turbuhaler. If this is the case, it would imply that FP is more potent than budesonide because a lower dose to the lungs produces a similar clinical effect. This assumption is in agreement with some studies[29] but in disagreement with others.[30, 31]

Conclusion

The clinical effects of budesonide Turbuhaler and FP Diskhaler are very similar. Because the systemic effects are also similar, it can be concluded that budesonide Turbuhaler and FP Diskhaler have very similar clinical effect/systemic effect ratios in children with asthma.

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