

Comparison of the antiasthmatic, oropharyngeal, and systemic glucocorticoid effects of budesonide administered through a pressurized aerosol plus spacer or the Turbuhaler dry powder inhaler

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To determine therapeutically and systemically equivalent dosages of budesonide inhaled through the Turbuhaler dry powder inhalation device (Astra Pharma Production AB, Södertälje, Sweden) or pressurized metered-dose inhaler (pMDI) plus Nebuhaler spacer (Astra Pharma Production AB), we compared these devices in a randomized, open, parallel-group trial. Adults with moderate to severe asthma inhaled budesonide (0.4, 0.8, 1.6, and 2.4 mg/day), for 2 weeks at each dose level, through the Turbuhaler (n = 30) or pMDI + Nebuhaler (n = 28). Dose-dependent effects were demonstrated on asthma symptoms (p = 0.0001), daily peak expiratory flow (p = 0.02), blood eosinophils (p = 0.0001), urinary cortisol output per day (p = 0.0001), serum cortisol (p = 0.006), serum osteocalcin (p = 0.0001), and the oropharyngeal Candida colony count (p = 0.0007, analysis of covariance). The ratio of the responses to the two inhalation devices approximated 1.0 for each index measured; that is, no significant between-device difference was found (p ≥ 0.29). However, the 95% confidence limits for the ratio of their respective systemic effects on osteocalcin production were 0.83 to 1.48. Thus in adults who use inhalation devices efficiently and have optimally controlled asthma, conversions from the pMDI + Nebuhaler to the Turbuhaler may reasonably be made at milligram equivalent doses of budesonide, then down-titrated to minimize possible systemic effects. Because earlier studies have shown that the Turbuhaler can double intrapulmonary drug delivery in comparison with a pMDI without a spacer, a 50% dose reduction may be indicated when converting from a pMDI to the Turbuhaler. (J Allergy Clin Immunol 1997;99:186-93.)

Key words: Asthma, inhaled steroids, budesonide, lung deposition, spacers, Nebuhaler, dry powder inhalers, Turbuhaler

The Turbuhaler dry powder inhalation device (Astra Pharma Production AB, Södertälje, Sweden) provides an alternative to the pressurized metered-dose inhaler (pMDI) for the treatment of chronic asthma with budesonide. The Turbuhaler eliminates the release of envi-

Abbreviations used

ANCOVA:	Analysis of covariance
CL:	Confidence limit (95%)
pMDI:	Pressurized metered-dose inhaler
MLPF:	Seven-day mean of lower of two peak expiratory flow readings
UFC ₂₄ :	Output of urinary free cortisol per 24 hours

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ronmentally undesirable fluorinated hydrocarbons; greatly simplifies the inhalation procedure, thus reducing patient error during administration of the drug¹; and can reduce or prevent the reflex cough or bronchospasm experienced by some patients with highly reactive airways when they inhale pressurized antiasthmatic drugs, such as terbutaline² or budesonide,³ directly from the pMDI or through a spacer.^{2,3}

Practicing physicians need to know to what extent the Turbuhaler may affect the delivery of inhaled budesonide to the lungs and its systemic absorption, because

TABLE I. Patient characteristics at entry

	pMDI + Neb group		TBH group	
	<i>n</i>	Mean $\pm$ SD	<i>n</i>	Mean $\pm$ SD
Male/Female	15/15		16/15	
Age (yr)		52 $\pm$ 16		57 $\pm$ 13
Weight (kg)		79 $\pm$ 17		75 $\pm$ 14
FVC (L)		96.5 $\pm$ 16.0		94.1 $\pm$ 26.6
FEV ₁ (L)	} %PN	71.4 $\pm$ 19.9		68.9 $\pm$ 23.4
FEF ₂₅₋₇₅		48.3 $\pm$ 26.1		44.9 $\pm$ 17.4
PEF (L/min)		77.6 $\pm$ 19.4		73.3 $\pm$ 22.8
FEV ₁ reversibility (%)*		26 $\pm$ 15		24 $\pm$ 19
Inhaled steroid for asthma (mg/day)		1.1 $\pm$ 0.4		1.1 $\pm$ 0.4
Intranasal steroid (puffs/day)		0.8 $\pm$ 2.1		2.1 $\pm$ 3.8
β -agonist inhalant (doses/day)		1.7 $\pm$ 2.1		1.7 $\pm$ 2.3
Nasal polyposis	1		7	
Allergic rhinitis (seasonal or perennial)	10		13	

Neb, Nebuhaler; *TBH*, Turbuhaler; *FVC*, forced vital capacity; *FEF₂₅₋₇₅*, forced expiratory flow rate between 25% and 75% of FVC; *PEF*, peak expiratory flow; *PN*, predicted normal.

*Percent change 30 minutes after 3 puffs of salbutamol inhalant.

these vary with different types of inhalers.^{4,5} Because the pMDI coupled with a large-volume Nebuhaler spacer (Astra Pharma Production AB) (pMDI + Nebuhaler) has been shown to be the most efficient way to administer budesonide from a pressurized aerosol,⁴ we elected to compare the dry powder Turbuhaler with the pMDI + Nebuhaler.

It is also important clinically to assess the effect of the Turbuhaler on the incidence of the oropharyngeal complications of budesonide, because the Turbuhaler does not possess the particle-trapping action of the Nebuhaler, which sharply reduces budesonide's oropharyngeal deposition and its associated complications.⁴

The objectives of this study were: (1) to quantify the relative antiasthmatic and systemic activities of budesonide inhaled from these two devices over a broad range of dosages, (2) to estimate a relative potency for the two devices so that their systemic effects could be compared in terms of both milligram equivalent and therapeutically equivalent doses, and (3) to use this relative potency to determine a range of efficacious and safe dosages for budesonide administered through the Turbuhaler.

A secondary goal was to compare the respective effects of these devices on the oropharyngeal deposition of budesonide and the incidence of oral complications during 8 weeks of active treatment.

METHODS

The study was a randomized, parallel-group, "open" comparison of the Turbuhaler and pMDI + Nebuhaler devices for the inhalation of budesonide. The protocol conformed with the principles of the Declaration of Helsinki and was approved by the Review Board of the University of Western Ontario for health sciences research involving human subjects.

Patients

Candidates for the study had asthma severe enough to require maintenance doses of beclomethasone or budesonide in excess of 0.4 mg/day. They were nonsmokers with a clinical history of variable wheezing and dyspnea responsive to β -agonist bronchodilator inhalant, diffuse wheezing on auscultation, and obstructive pulmonary impairment that was partly or wholly reversible by β -agonist and/or glucocorticoid treatment. Nine patients used theophylline at the time of entry to the study. None used cromolyn or nedocromil. Three patients used prednisone regularly for treatment of recurrent nasal polyposis: 10 mg on alternate days ($n = 1$), 7.5 mg daily ($n = 1$), and 5 mg daily ($n = 1$). None had used prednisone for treatment of asthma during the 30 days before recruitment. Relevant demographic characteristics at the time of entry to the study are shown in Table I.

Preliminaries

Clinic visits were scheduled at 2-week intervals. During the initial 2-week lead-in period, each of the 68 candidates continued his or her usual budesonide or beclomethasone dose and dosing frequency, whereas theophylline and inhaled β -agonist (if used) were reduced or withdrawn as feasible. Then inhaled steroid was converted to budesonide at a reduced dose of 0.2 mg, administered twice daily through the pMDI + Nebuhaler for 2 weeks. At this point seven candidates were excluded because their serum cortisol level at 8:00 am was found to be less than 200 nmol/L or because their asthma was deemed too severe for them to tolerate temporary withdrawal of the inhaled steroid during the next phase of the protocol. The remaining 61 candidates were stratified by sex and their prestudy requirement for an inhaled steroid dose above or below 1.0 mg/day. They were then randomly assigned in balanced blocks of four to either the Turbuhaler or pMDI + Nebuhaler and instructed in the use of the designated device, and the low dose of budesonide was replaced by placebo inhaled through the designated device for 2 weeks. The last week of placebo treatment provided the baseline data against which all subsequent treatment data were compared. The baseline status of the two groups with

TABLE II. Baseline values for response indices*

Response index	pMDI + Neb group (mean $\pm$ SD)	TBH group (mean $\pm$ SD)
<i>Candida</i> colony count	68 $\pm$ 201	24 $\pm$ 75
FA†	3.1 $\pm$ 2.3	2.2 $\pm$ 3.0
MLPF† (L/min)	358 $\pm$ 108	372 $\pm$ 141
FEV ₁ † (L)	1.76 $\pm$ 0.77	1.81 $\pm$ 0.75
EOS (10 ⁹ /L)	0.42 $\pm$ 0.28	0.43 $\pm$ 0.28
UFC ₂₄ (nmol)	59 $\pm$ 39	46 $\pm$ 56
Serum cortisol (nmol/L)	359 $\pm$ 158	375 $\pm$ 156
Serum osteocalcin (nmol/L)	0.29 $\pm$ 0.20	0.24 $\pm$ 0.16

Neb, Nebuhaler; TBH, Turbuhaler; FA, 7-day mean of frequency of asthma symptoms per day; EOS, peripheral blood eosinophil count.

*After 2 weeks of placebo treatment.

†See text (Results).

respect to the main response indices measured is shown in Table II.

Use of inhalation device

Immediately after randomization, a new pMDI + Nebuhaler or Turbuhaler was issued to each patient, and he or she was instructed in the procedure appropriate to the assigned device. Inspiration of the dose commenced at functional residual capacity immediately before releasing the dose, one puff at a time, into the Nebuhaler. Inspiration proceeded at 30 L/min for the pMDI + Nebuhaler or 60 L/min for the Turbuhaler, was followed by a 10-second breath-hold at total lung capacity before expiration, and finished with a mouth-wash and expectoration of any orally retained drug. At the time they were assigned to the test devices and at each subsequent clinic visit, each patient's technique for using the device was checked, and the rate of inspiration through the device was measured by a Tru-Flo sensor (Trudell Monaghan, London, Ontario, Canada), providing a read-out of inspiratory flow. Additionally, patients used a low-resistance Air_x incentive spirometer (AIRLIFE; Baxter Corp., American Hospital Supply Corp., Valencia, Calif.) to practice their inhalation technique daily at home to maintain consistency throughout the study in the desired inspiratory flow rates. Patients in the pMDI + Nebuhaler group used the same spacer throughout the study and were advised to wash the spacer if the valve began to malfunction.

Treatments

After 2 weeks of practice with the designated device, both groups converted from placebo to active treatment by using progressively increasing doses of budesonide (0.4, 0.8, 1.6, and 2.4 mg/day), taken in two divided doses at 8:00 am $\pm$ 60 minutes and 8:00 pm $\pm$ 60 minutes. All patients took each dose for the same length of time (2 weeks) and in the same sequence.

Compliance was monitored by collecting the pMDI canisters or Turbuhaler at each clinic visit, manually counting the unexpelled doses from the Turbuhaler, and measuring the change in weight of the canister.

Throughout the study, inhaled salbutamol was allowed as needed for symptom control, and oral nystatin was allowed for treatment of complicating thrush. A 24-hour on-call monitoring service was maintained to facilitate patient-physician communication. In the event of an asthma exacerbation, decisions

about the need to intervene with prednisone, and its dosage and duration, were made by one of the clinician investigators (FAW or JHT).

Response indices

Peak expiratory flow was measured morning and evening by the patient, using a mini-Wright Flow Meter, and the best of three readings was recorded in a current patient diary along with symptom frequency and severity and drug use data. Seven-day means were calculated for asthma symptom frequency each day and for the lower of the peak expiratory flow measurements each day (MLPF). Spirometry was performed at each biweekly clinic visit for measurement of forced vital capacity, FEV₁, and forced expiratory flow. At each visit the oropharynx was swabbed for *Candida* species and plated immediately to Sabouraud's dextrose agar for culture and subsequent colony counting; blood was drawn at 8:00 AM $\pm$ 60 minutes for measurement of serum cortisol, serum osteocalcin, and a blood eosinophil count; and the urine output over the previous 24 hours was collected for assay of the daily cortisol output (UFC₂₄).

Automated eosinophil counts were performed immediately after collection. Aliquots of the serum and urine specimens were stored at -70° C for batch assay after completion of the study. Serum cortisol was assayed by high-performance liquid chromatography: intraassay coefficient of variation, 1.3%; normal range, 220 to 640 nmol/L.⁶ Urinary-free cortisol was assayed by gas chromatograph mass spectrometry: intraassay coefficient of variation, 5.2%; normal range, 40 to 200 nmol/day. Serum osteocalcin was assayed by radioimmunoassay (IncStar Corp., Stillwater, Minn): intraassay coefficient of variation, 4.5%; normal range in young adults, 0.3 to 1.2 nmol/L.

Oropharyngeal complications were quantified in terms of days of huskiness or sore throat per week, nystatin use, and the *Candida* colony count. Also, the oropharynx was inspected for thrush at each visit.

Statistical analysis

Diary data from the last 7 days of each 2-week period and laboratory data from the corresponding clinic visit were analyzed. Analysis of covariance (ANCOVA) for repeated measures (General Linear Models program, SAS Institute)⁷ was used to assess the significance of the effects of dose, device, and dose-by-device interaction on changes (δ) from baseline levels. The baseline levels of the response variables were also used as covariates. The suitability of the outcomes for the parallel-line method of relative potency estimation⁸ was judged by the nonsignificance of the dose-by-device interaction ($p > 0.05$), as well as by the quadratic and cubic components of the dose effect relative to a log scale. The ratio of the mean response to the Turbuhaler treatment relative to the response with the pMDI + Nebuhaler was computed by using the adjusted means from ANCOVA. The analysis was performed on the natural log of the absolute levels with covariance adjustment for baseline levels. Confidence limits (CL) for these ratios were constructed by setting confidence intervals on the difference between the logs and inverting these limits to the ratio scale. Thus the results obtained were estimates of the ratio of geometric means.

Compliance data were tested by analysis of variance for repeated measures.

RESULTS

Compliance with the prescribed use of the drug throughout the study was 89% $\pm$ 24% (mean $\pm$ SD) in

the Turbuhaler group and $95\% \pm 30\%$ (mean $\pm$ SD) in the pMDI + Nebuhaler group ($p = 0.045$, analysis of variance).

Three patients did not receive the stepwise regimen of budesonide doses. Among these, one patient in each of the two treatment groups dropped out after being assigned to a test device but before the active budesonide treatment started, and one additional patient, assigned to the pMDI + Nebuhaler group, was terminated after 2 weeks of placebo treatment because of a severe asthma relapse plus discovery of a subnormal baseline value for serum cortisol. Data from the remaining 58 patients who completed the study (28 in the pMDI + Nebuhaler group and 30 in the Turbuhaler group) provided the basis for the primary all-patients-treated analysis with ANCOVA.

The pretrial use of budesonide or beclomethasone averaged about 1.0 mg/day and was similar in the two patient groups (Table I). The patients allocated to the Turbuhaler device had less severe asthma at baseline than those in the pMDI + Nebuhaler group (compare group means for items with daggers in Table II). Baseline status was therefore included as a covariate in the ANCOVA to account for these disparities in the analyses. Both patient groups had relatively low osteocalcin levels at baseline, indicating persisting suppression of osteoblast activity as a result of the high-dose inhaled steroid therapy used before entering the study. In the pMDI + Nebuhaler group one patient used 5 mg of prednisone daily for treatment of nasal polyposis, and seven patients required 2 to 10 days of supplemental prednisone treatment during the placebo or active budesonide treatment weeks to control exacerbations of asthma (median = 3 prednisone days). In the Turbuhaler group two patients used a stable dose of prednisone, averaging 5 mg/day, for treatment of nasal polyposis, and five patients required 2 to 13 days of prednisone treatment for asthma exacerbations (median = 4 prednisone days). Prednisone was used on 71 of 1960 scheduled treatment days in the pMDI + Nebuhaler group and 151 of 2100 scheduled treatment days in the Turbuhaler group. Inspection of scatter plots of the baseline level of UFC_{24} versus the change in UFC_{24} from baseline to the highest dosage of budesonide, separately for each treatment group, revealed no systematic difference in patient responsiveness relative to the use of supplementary prednisone, when the baseline value for UFC_{24} is taken into account (data not shown).

Dose-dependent responses to the budesonide were evident in the three areas of interest: the oropharynx, bronchopulmonary airways, and systemically (Fig. 1). These were significant ($p \leq 0.02$) for seven of the eight indices measured. There were no significant differences between the test devices for any response index, as determined by ANCOVA (Fig. 1).

Three of the primary response indices (frequency of asthma symptoms/day, MLPF, and UFC_{24}) failed to show sufficiently strong evidence of parallel responses for the two test groups to allow their comparison in

terms of relative potency (see dose-by-device interactions in Fig. 1, $p < 0.10$). The devices were therefore compared in terms of "response ratios," as shown in Fig. 2.

None of the response ratios deviated significantly from 1.0, which indicates that the deposition of budesonide at each of the target sites and systemically was similar with either inhalation device. The 95% CL of these ratios were narrow for those indices, which reflect airways deposition, but wider for the indices of systemic budesonide activity (Fig. 2). The uppermost CL among the indices of systemic activity approximated 1.5 (Fig. 2).

Similar results were found for the dose and device effects and for the response ratios and CL determined by ANCOVA in separate statistical analyses restricted to the 43 patients who had not used supplemental prednisone or to the 28 patients who complied most completely with the study protocol (data not shown).

The oropharyngeal *Candida* colony count was higher in the pMDI + Nebuhaler group at baseline (Table II) and remained so throughout the study, increasing similarly in both treatment groups as the daily dose of budesonide increased ($p = 0.0007$, Fig. 1, A). One patient in the pMDI + Nebuhaler group used nystatin for treatment of suspected thrush at the initial dose level of 0.4 mg/day, but not at higher doses. The diagnosis was not confirmed by physician examination.

Huskeness of the voice was reported during budesonide therapy on an average of 1.8 days/week in the pMDI + Nebuhaler group and 0.9 days/week in the Turbuhaler group but did not increase in either group as the budesonide doses were progressively increased. Sore throat was reported on an average of 0.99 days/week in the pMDI + Nebuhaler group and 0.39 days/week in the Turbuhaler group but did not increase in either group as the doses increased (data not shown).

DISCUSSION

The lack of conformity of the study outcome to the requirements of parallel-line assay methods and the variability between patients made it impossible to achieve a precise comparison of the systemic effects of the test devices at therapeutic equivalence over the range of doses tested. However, the absence of significant between-device differences in the results of the ANCOVA shown in Fig. 1, A, coupled with the response ratios shown in Fig. 2 indicate that, under the conditions applied in this study to optimize the use of each test device, the Turbuhaler and pMDI + Nebuhaler appeared equally efficient for the delivery of inhaled budesonide to the bronchopulmonary airways of adult patients with asthma. Furthermore, the extrapulmonary effects of the systemically absorbed fraction of budesonide were of the same magnitude on average with either device over the wide range of dosages administered (Fig. 1, B, and Fig. 2). The latter finding is consistent with the view that most of the systemically absorbed fraction of budesonide inhaled through a Turbuhaler or a pMDI + spacer (and followed by

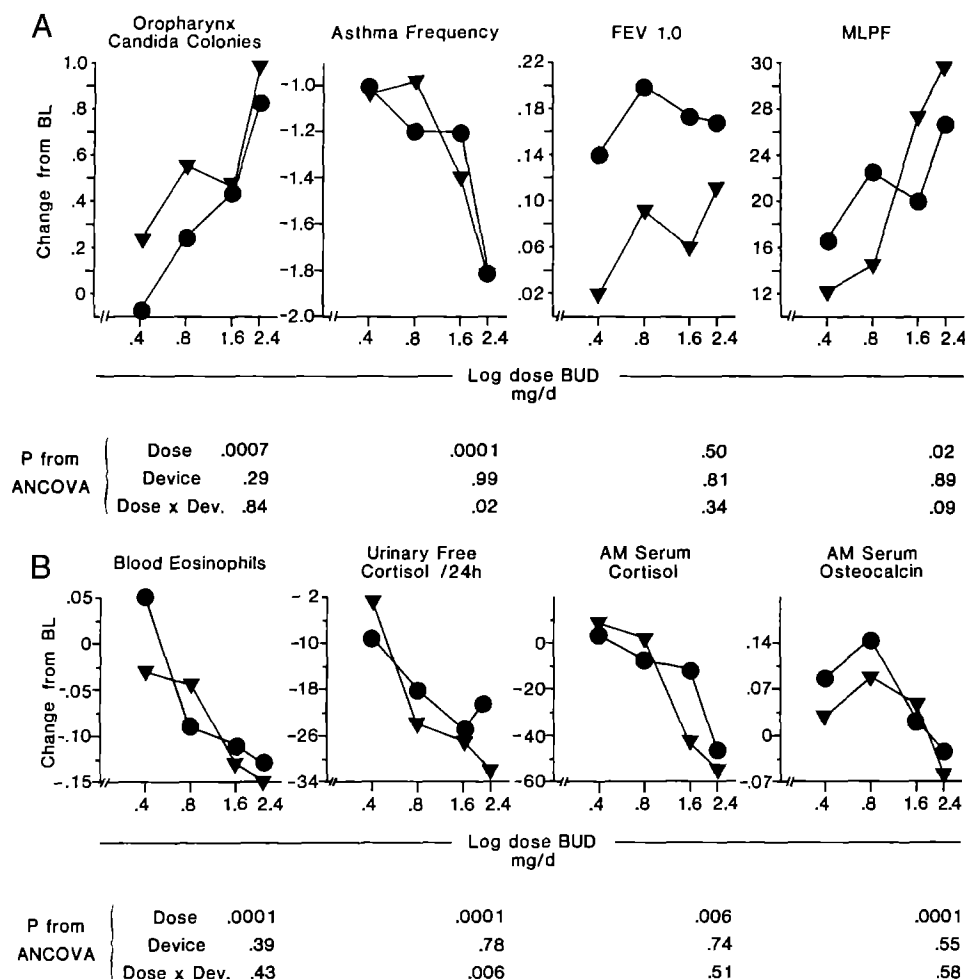


FIG. 1. Group mean responses to graded doses of budesonide inhaled through Turbuhaler (triangles) or pMDI + Nebuhaler (circles) with relevant *p* values from ANCOVA. **A**, Measures of oropharyngeal or airway deposition. **B**, Measures of systemic glucocorticoid activity. Oropharyngeal *Candida* colony counts were log-transformed for analysis. Except for FEV₁, the responses were dose-dependent. BL, Baseline; BUD, budesonide.

mouth-rinsing) comes from the lungs rather than the gut.^{1, 9-11}

The dose-dependency of seven of the eight responses (excepting FEV₁) over the range of doses shown in Fig. 1 indicates that failure to discriminate between the test devices was not attributable to abrogation of the responses at higher dosages because of a high baseline value of the response index with consequent plateauing at low dosage of the effects of the budesonide. This was ensured by destabilizing the asthma by withdrawal of inhaled steroid therapy during the 2 weeks before baseline.

The disparity between the responses of FEV₁ and other indices of the antiasthmatic effect of budesonide is in accord with the low correlation coefficients noted among these indices in earlier studies.¹² The lack of sensitivity of FEV₁ relative to frequency of asthma symptoms per day or MLPF, as measures of the dose-response (compare *p* values for dose effect in Fig. 1, A),

has also been noted previously in some studies that used the graded-dose model to assess the responsiveness of patients with moderate to severe asthma to inhaled steroid.^{13, 14} Presumably, this reflects structural remodeling of the airways by submucosal fibrosis and smooth muscle hyperplasia. Both are known to be refractory to inhaled steroid therapy.^{15, 16}

A significant quadratic effect of dose on the osteocalcin responses to budesonide is evident in Fig. 1, B (*p* = 0.006, ANCOVA).

The increases in the osteocalcin levels during administration of the two lower doses of budesonide suggest a progressive recovery of osteoblast function from a pre-existing inhibited state, presumably caused by the high-dose inhaled steroid therapy used by these patients before entering the study. This inhibited state is evidenced by the low levels of osteocalcin in both treatment groups at baseline (Table II). The subsequent dose-dependent decline in osteocalcin (δ osteocalcin) when

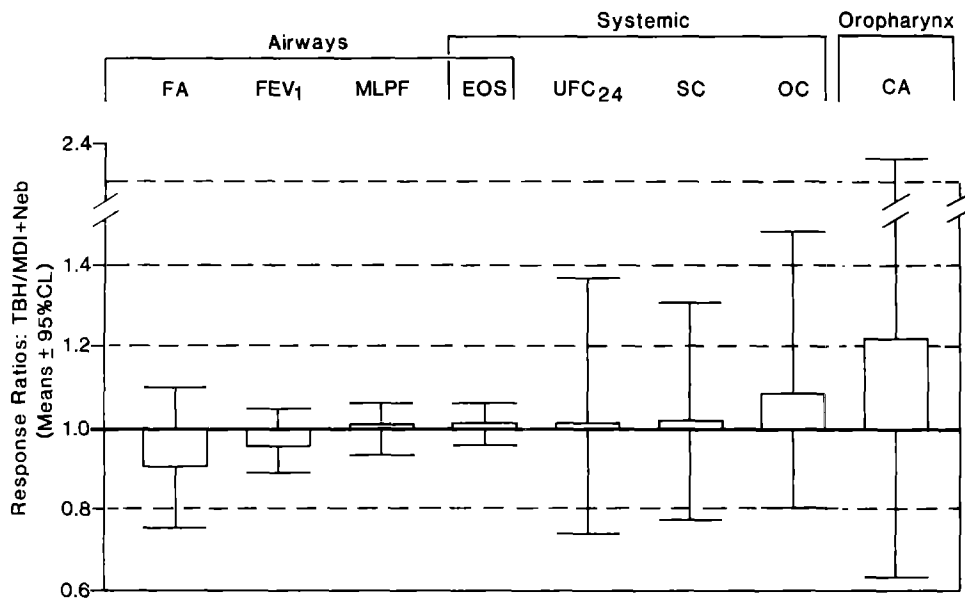


FIG. 2. Ratio of overall effects of budesonide treatment, administered by Turbuhaler or pMDI + Nebuhaler, for each of eight response indices. See text for description of method of calculating response ratios. Effects of the Turbuhaler and pMDI + Nebuhaler on budesonide delivery to the oropharynx and pulmonary airways and systemic delivery appear essentially equivalent under the conditions of this study. *TBH*, Turbuhaler; *Neb*, Nebuhaler; *FA*, 7-day mean of frequency of asthma symptoms per day; *EOS*, peripheral blood eosinophil count; *SC*, serum cortisol; *OC*, serum osteocalcin; *CA*, oropharyngeal *Candida* colony count.

higher doses of budesonide were administered, and also the threshold dose at which this decline became discernible (Fig. 1, *B*), are in agreement with previously published studies in which graded doses of budesonide were administered through the pMDI + Nebuhaler with the same optimized inhalation technique as used in this study.¹⁷⁻¹⁹ In this study the threshold dose at which the regressions of osteocalcin on budesonide dose changed from positive to negative (i.e., 0.8 mg/day) was the same with the Turbuhaler as with the pMDI + Nebuhaler (Fig. 1, *B*), indicating equivalent systemic availabilities of budesonide inhaled through either device.

The findings shown in Fig. 2 are in accord with earlier studies in which the pMDI + Nebuhaler and Turbuhaler were compared directly with one another³ or separately with the pMDI alone.^{1, 4, 5} These studies, summarized in Table III, used three different techniques for estimating drug delivery to the lungs and had concordant results, indicating that both the Turbuhaler¹ and the pMDI + Nebuhaler^{4, 5} are capable of doubling intrapulmonary drug delivery in comparison with the pMDI alone. Therefore comparisons between the pMDI + Nebuhaler and the Turbuhaler would be expected to show equivalence (i.e., a response ratio approximating 1.0), as demonstrated in this study and previously by Engel et al.³

These findings do not exclude the possibility that important differences might be demonstrable if these same inhalation devices were compared under conditions different from those that were applied in this study. If such conditions were to selectively disadvan-

TABLE III. Response and deposition ratios (B/A) from published comparisons of intrapulmonary delivery through different inhalation devices

A ▼	B ►	pMDI + Neb	TBH
pMDI		2.1*†	2.1‡
pMDI + Neb		—	1.0§

Ratios calculated as $\frac{B}{A}$, e.g., $\frac{\text{pMDI+Neb}}{\text{pMDI}} = 2.1$.

Neb, Nebuhaler; *TBH*, Turbuhaler.

Effect of devices measured by intrapulmonary deposition of radiolabeled aerosol, * FEV₁ response to budesonide, †§|| or pulmonary bioavailability of budesonide, ‡.

*Newman et al.⁵

†Toogood et al.⁴

‡Thorsson et al.¹

§Engel et al.³

||This study.

tage the pMDI + Nebuhaler relative to the Turbuhaler, the Turbuhaler would appear more efficient in achieving drug delivery to the lungs (and potentially more toxic), or the pMDI + Nebuhaler would appear less efficient (and less toxic), depending on the point of view. Observations of this sort have been reported.²⁰

Among the conditions that may reduce intrapulmonary drug delivery from the pMDI + Nebuhaler, the following are known to be important: (1) failure to shake the pMDI between each puff, which can materially

reduce the amount of drug expelled from the pressurized canister²¹; (2) variations in the amount of electrostatic charge within the Nebuhaler, which acts to trap a proportion of the aerosolized drug on its inner surfaces²²⁻²⁴ (effect may vary depending on prior use and frequency of spacer cleansing); (3) discharge of more than one puff at a time into the spacer before inhaling the drug²²⁻²⁷; (4) variations in the time lapse between expelling the drug into the spacer and the start of inspiration^{22, 24-26}; (5) whether inspiration commences at residual volume or functional residual capacity^{28, 29}; (6) rate at which the drug is inspired^{25, 28, 30, 31}; and (7) presence and duration of a postinspiratory breath-hold.²⁸

Items 1, 3, and 7 above were the most common errors identified in a recent survey of the efficiency of patients and physicians-in-training in their use of the pMDI + spacer.³² All the items listed above were addressed in the procedures used by the patients in the pMDI + Nebuhaler group in this study (see Methods).

The difference in compliance between the test groups indicates that the daily dose of budesonide might have averaged 0.06 mg more in the pMDI + Nebuhaler group than in the Turbuhaler group (i.e., about two extra puffs per week). This small disparity is unlikely to have resulted in an overestimation of the performance of the pMDI + Nebuhaler relative to the Turbuhaler. Similarly, the unscheduled "rescue" prednisone treatment used by some patients did not bias the performance of one inhalation device versus the other because the results of the ANCOVA, and also the response ratios and CL calculated for the two devices, were essentially the same with or without inclusion of the data from the prednisone users (see Results).

With respect to the relative safety of the two devices, the CL for the response ratios of Turbuhaler/pMDI + Nebuhaler indicate a small statistical possibility that the Turbuhaler might increase budesonide's systemic activity as much as 1.5 times relative to the pMDI + Nebuhaler (see upper CL for osteocalcin, Fig. 2). This could be clinically important in some patients (e.g., those receiving doses >1.0 mg/day through the pMDI + Nebuhaler). In such patients a dose reduction by 50% or less may be indicated to ensure that the systemic steroid effect of the treatment does not increase as a result of the shift to Turbuhaler use.

Oropharyngeal complications were negligible with either device (see Results). Medically diagnosed thrush did not occur during the 464 patient-weeks of budesonide treatment despite the high dosages used and their manifest effect on oropharyngeal candidiasis (Fig. 1, A). The absence of thrush may be accounted for by the twice daily dosing regimen because the use of four doses per day has been shown to be a critically important determinant of the incidence of thrush during budesonide treatment.³³ Thus these data cannot exclude the possibility that significant differences between the devices might be found if their impact on the occurrence of oropharyngeal thrush were to be compared while using a four-dose-per-day regimen.

Clinical implications

Because the mean responses to the two devices are similar in terms of their effects on the systemic activities of budesonide (Fig. 1, B, Fig. 2), the same "safe dose" threshold may be applicable with either device, providing that the conditions of use are the same as in this study. A threshold between "relatively high risk" and "relatively low risk" has been estimated to be about 2.0 mg/day for budesonide administered to adults through the pMDI + Neb³⁴⁻³⁶ (i.e., approximately 29 µg/kg/day). However, this is not a "no-effect" dose (see Fig. 1, B).

When transferring adults with well-controlled asthma treated with budesonide from the large-volume Nebuhaler + pMDI to the Turbuhaler in clinical practice, it would seem reasonable, on the basis of the findings of Engel et al.³ and the response ratios shown in Fig. 2, to do so at the same milligram equivalent daily dose. On the other hand, the same data taken in conjunction with a previously published comparison of the Turbuhaler versus pMDI alone in patients trained to use both devices optimally¹ provide a cost-benefit and risk-benefit rationale for reducing the daily dose of budesonide by half when converting patients whose asthma is well controlled with the pMDI alone to the Turbuhaler. The validity of these dosing recommendations depends on strict adherence by the patient to the approved handling instructions for each device.

A few direct comparison studies have shown small-volume spacers, such as the Inhalet (Astra Pharma Production AB) or pediatric model Aerochamber (Trudell Medical), to be equivalent to the Nebuhaler spacer with respect to the delivery of budesonide to the bronchopulmonary airways or the respirable fraction of the nominal dose emitted.^{4, 37} However, to our knowledge, no direct comparisons with the Turbuhaler have been reported. In the absence of such data, there is no objective basis for estimating the relative efficiencies of the Turbuhaler versus the Aerochamber or similar small-volume spacers.

In all cases the daily dose should subsequently be titrated to determine the minimum amount each patient requires to maintain optimum asthma control with the Turbuhaler. This is advisable in view of the dose dependency of the adverse effects that occasionally complicate inhaled steroid therapy,^{10, 38} the breadth of the CL observed in this study for the respective effects of the two inhalation devices on the systemic activities of budesonide (Fig. 2), and reports suggesting that some patients may use doses larger than necessary in ordinary clinical practice.^{20, 39, 40}

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