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Comparative study of budesonide as a nebulized suspension *vs* pressurized metered-dose inhaler in adult asthmatics

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The study objective was to compare the effect of budesonide administered as a nebulized suspension as compared to a spray with a spacer in adult asthmatics. In a double-blind, double-dummy crossover study, 26 adult patients with moderately severe unstable asthma were randomized to three 4-week treatment periods with budesonide 0·8 mg b.i.d. administered by a pressurized metered-dose inhaler (pMDI) with spacer (Nebuhaler®) and budesonide 1 mg and 4 mg b.i.d. administered by a Pari Inhalier Boy® jet nebulizer. The nebulizer was activated only during inspiration. The total mass output was similar from the two devices but their fraction of small particles differed by a factor of 2 in favour of pMDI. Effect was evaluated from daily home measurements of peak expiratory flow (PEF), need of β_2-agonist and symptom scores. Plasma cortisol and budesonide levels were measured in a subgroup of 10 patients.

A consistent trend showed the nebulizer treatment to be at least as efficient as the pMDI plus spacer treatment. In actual fact, the apparent order of effect was: 4 mg nebulized suspension treatment $\geq$1 mg nebulized suspension treatment $\geq$0·8 mg pMDI with spacer treatment. Plasma budesonide and plasma cortisol also exhibited dose-related levels independent of device. The adverse effects reported appeared to be related to the dose rather than delivery device. Accordingly, the effect was related to total mass output, rather than to the small particle fraction of the budesonide aerosol.

These results attest to the efficiency of jet-nebulized budesonide suspension, and indicate nebulized budesonide to be equipotent to standard budesonide therapy delivered by pMDI with Nebuhaler®, provided nebulization is synchronized with inspiration and no loss of aerosol occurs during expiration.

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Introduction

Inhaled corticosteroids are becoming established drugs in the treatment of chronic asthma. The inhaled corticosteroids attenuate bronchial inflammation and responsiveness to various trigger factors, improve the patient's clinical status and reduce the number of asthma attacks.

The inhaled corticosteroid budesonide has traditionally been administered using pressurized metered-dose inhalers (pMDI), often with spacers, or using a dry powder inhaler. Recently, a water suspension of budesonide has become available for jet nebulization. This inhalation form has been considered supplemental to the more common and simple inhaler devices, but may be of value in some infants, young children (1–3) and older children or adults with particularly poor inhalation technique.

A number of single-dose studies have compared the airway response to β_2-agonist delivered via a nebulizer and a pMDI, with (4–6) or without (7,8) a spacer. Despite the fact that, in most of these studies, the nominal dose of drug tested with the pMDI was four- to eight-fold lower than that used with the nebulizer, airway response was shown to be comparable. From these single-dose studies, it has been suggested that to attain equipotency with a β_2-agonist, a nominal dose ratio of between 4:1 and 8:1 is required when the drug is delivered from a nebulizer as compared with a pMDI plus spacer (4,6,9). However, the inhaled mass of drug, i.e. the amount of drug inhaled by the patient from any of the devices used in these studies, was not defined. Therefore, it would seem to be difficult to draw any reliable conclusions from these studies regarding potency. Long-term crossover studies comparing bronchodilators administered via pMDIs and nebulizers (10,11) did not support the results of the single-dose studies. The crossover studies

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demonstrated equivalent clinical efficacy with terbutaline sulphate (10) and ipratropium bromide (11) when equal nominal doses were administered by each device. Further in-depth investigation of both methods of drug delivery has demonstrated a similar dose-response with the two devices (12). The inhaled mass of drug was not determined in these studies.

Isotope studies indicate that the lung dose may be comparable for the nebulizer and the pMDI (13,14) without spacer. It would appear, therefore, that data are equivocal, that the relatively large recommended nominal dose for nebulization requires re-evaluation and that a definition of the inhaled mass of drug is necessary in order to provide a sound basis for a device comparison.

The present study was undertaken to assess the relative efficiency of budesonide administered from a pMDI with large-volume spacer and from a jet-nebulizer to adult patients with asthma, as measured by lung function, symptom response and requirement for additional p.r.n. medication.

The study was designed as a three-way, double-blind, crossover study comparing the standard dose of budesonide pMDI with the large-volume spacer (Nebuhaler®) 0·8 mg b.i.d. with 1 mg and 4 mg budesonide suspension b.i.d. administered by a Pari Inhalier Boy® jet nebulizer, each given for 4 weeks. In an attempt to standardize the inhaled mass of drug from the nebulizer, intermittent nebulization was applied which synchronized the nebulization with the inspiration.

Patients and Methods

Twenty-six patients (17 women) were selected for the study and started randomly on each treatment. Mean age was 45 years (range 27–62 years), mean height 169 cm (range 154–185 cm), mean weight 74 kg (range 51–118 kg) and mean FEV_1 63% (range 36–93%) in percent of predicted normal. The patients had moderately severe asthma that was inadequately controlled despite continuous treatment with a combination of inhaled steroids (0·4–1·0 mg daily) and β_2-agonists. Inadequate control was defined as the persistence of symptoms and/or the presence of one or more measures of pulmonary function below 80% of the predicted value. Patients were excluded from entering the study if they had significant bronchopulmonary disease other than asthma, any other disease or disability likely to interfere with drug evaluation, or infection requiring antibiotic therapy. Patients who had been taking oral glucocorticosteroids during the month prior to the study were also excluded, as were those known to have a poor inhalation technique.

Plasma budesonide and cortisol were measured in a subgroup of 10 patients. Mean age was 42 years (range 31–57 years), mean height 169 cm (range 158–183 cm), mean weight 72 kg (range 56–97 kg) and mean FEV_1 in percent of predicted of 65% (range 38–90%). The study was performed in accordance with the Guidelines of the Declaration of Helsinki, and was approved by the Ethics Committee of the Danish Board of Health. All patients gave informed consent prior to entry.

STUDY DESIGN AND TREATMENT

The trial was performed as a double-blind, double-dummy, crossover study with treatment periods of four weeks for each regime:

(a) budesonide pMDI with Nebuhaler® 0·8 mg;
(b) budesonide nebulized suspension 1 mg; and
(c) budesonide nebulized suspension 4 mg.

All treatments were administered b.i.d. To achieve blinding, all patients received a 4 ml suspension for nebulization accompanied by 4 puffs from a pMDI with Nebuhaler®, a 750 ml spacer during each period. Every 4 weeks, the active ingredients of the regimens changed, although patient handling was the same. There was no washout period between treatments and no placebo-only period. Rescue medication of β_2-agonist was allowed as required.

DELIVERY DEVICES

Budesonide suspension was nebulized with a Pari Inhalier Boy® jet nebulizer (Pari Werke GmbH, Germany) fitted with a mouthpiece and driven by a CR60 air compressor (Medic-Aid Ltd, U.K.) with a dynamic flow of 8 l min^{-1}. A 4 ml suspension of budesonide was used for nebulization. Patients were instructed: (a) to inhale tidally from the nebulizers; (b) to activate the nebulizer only during inspiration, using the finger-operated interrupt valve, to reduce the waste of the substance during expiration; and (c) to run the nebulizers to dryness but not to tap them. The budesonide pMDI was fitted with a large-volume spacer (Nebuhaler®) for inhalation. Patients were instructed to inhale slowly from the spacer with tidal breathing for five cycles after each puff.

The budesonide droplet size characteristics of the Pari Inhalier Boy® jet nebulizer driven by a CR60 compressor were determined by connecting the jet nebulizer outlet to the glass inlet of a cascade impactor operating at 28 l min^{-1}. The nebulizers were run constantly until no aerosol was generated (approximately 4 min), and the amount of budesonide on the different impactor stages was determined using liquid chromatography. Budesonide suspension (2 ml, 0·5 mg ml^{-1}) was used for the tests. The *in vitro* tests included one run with each of two Pari Inhalier Boy® jet nebulizers.

The total output of budesonide from Pari Inhalier Boy® jet nebulizer (eight individual devices) driven by a CR60 compressor was further assessed in a fume cupboard, where the nebulizer was run to dryness. The nebulizer parts were washed after nebulization, the amount of budesonide washed out assayed by liquid chromatography and the measured amount of budesonide subtracted from the nebulizer charge of budesonide. In this set-up, no suction pump was connected to the nebulizer mouthpiece.

The budesonide particle size characteristics from pMDI with Nebuhaler® were determined in three Nebuhaler® spacers which were primed with 15 doses of a budesonide pMDI the day before the test. A 200 μg budesonide puff was subsequently fired into Nebuhaler®, and after 2 s, the dose was sampled for 10 s through an Anderson sampler

with a USP inlet and a flow of 28 l min $^{-1}$. This procedure was repeated five times.

The budesonide aerosol output from the budesonide pMDI with Nebuhaler® was defined by using five doses of 200 μg each, which were collected on filters placed at the mouthpiece of the Nebuhaler®, and emptying the spacer through a constant flow immediately after actuation of the spray.

ASSESSMENT

Patients were asked to measure peak expiratory flow (PEF) at home using a mini-Wright Peak Flow Meter (Clement Clarke International Ltd, U.K.). The best of three measurements was recorded every morning and evening before aerosol treatment. Patients also kept a diary of coughing, wheezing, breathlessness, nocturnal asthma and normal activity (each recorded as yes or no). The number of puffs of concomitant β_2-agonist administered and the occurrence of adverse events were also recorded. Compliance was encouraged by telephoning each patient weekly.

Clinic visits were made by all patients on entering the trial, and after each of the three treatment periods. Spirometry was performed during these visits. In addition to standard clinical assessments, plasma budesonide and cortisol levels were determined in a subgroup of 10 patients. These patients attended the clinic between 6.00 a.m. and 7.00 a.m., and the morning budesonide inhalation was performed under supervision. Venous blood was taken for cortisol analysis before drug administration and 1 and 2 h afterwards. Additional samples were collected for plasma budesonide assay 9 min after the start of drug inhalation, on completion of nebulization and 10, 20, 50 and 110 min later.

Plasma was analysed utilizing a high-performance liquid chromatography–radioimmunoassay (HPLC-RIA) method. The integrated plasma budesonide concentrations were utilized to generate a 2-h area under the curve (AUC).

STATISTICAL ANALYSIS

All treated patients were included in the analyses. Data from the last 2 weeks of each treatment phase were analysed; both diary card information and clinical determinants were assessed.

The statistical analyses are based on an ANOVA model:

$$\text{Effect} = \text{patient} + \text{treatment} + \text{period} + \text{error}.$$

The three treatments were compared pairwise using this model. P values of <0·05 were considered to be statistically significant and all tests were two-sided. P values of <0·05 was designated by * and P values of <0·01 by **.

Results

Twenty-one of the 26 enrolled patients (81%) satisfactorily completed the trial protocol. One patient was excluded at the start of the study due to non-compliance. Two patients interrupted the study during the budesonide pMDI regimen; one because of pregnancy and the other as a consequence of a deterioration in asthma. Two other patients withdrew from the study during the budesonide nebulization (1 mg b.i.d.) treatment phase due to non-compliance and deteriorating asthma.

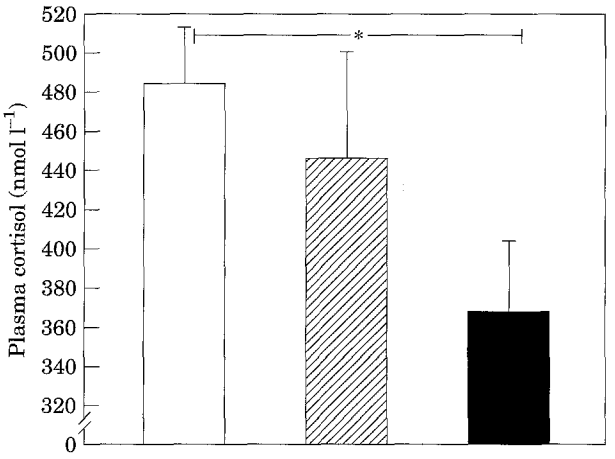

FIG. 1. Plasma cortisol *vs* the nominal dose of budesonide. Open bar, 0·8 mg × 2 pressurized metered-dose inhaler plus spacer; hatched bar, 1 mg × 2 nebulizer; solid bar, 4 mg × 2 nebulizer.

IN VITRO MEASUREMENTS

Thirty-three percent of the delivered dose from the nebulizer was contained in the fraction less than 4·7 μm in diameter, and the droplet mass median aerodynamic diameter (MMAD) was estimated as 6·5 μm. The total *in vitro* output was 58% (SD 5·3%) of the nebulizer charge, i.e. the dose of budesonide poured into the nebulizer.

Sixty-nine percent (SD 5·3%) of the delivered doses from the pMDI with Nebuhaler was contained in the fraction less than 4·7 μm, and the particle MMAD was estimated as 3·9 μm. The total output was 61% (SD 4·5%) of the nominal dose.

CLINIC ASSESSMENTS

Spirometry at the clinic revealed no statistically significant difference between the treatments.

Plasma cortisol level determined prior to the morning administration of the drug regimens for the subgroup of 10 patients exhibited a dose-related suppression (Fig. 1). The plasma cortisol level was significantly lower during the treatment with 4 mg budesonide suspension b.i.d. as compared to pMDI 0·8 mg b.i.d. The 2-h AUC obtained from pooled plasma budesonide concentrations after treatment with the specified drug regimens showed a similar dose-effect relationship (Fig. 2). The mean AUC after administration of 4 mg nebulized budesonide was significantly higher than that obtained after the 1 mg nebulized dose

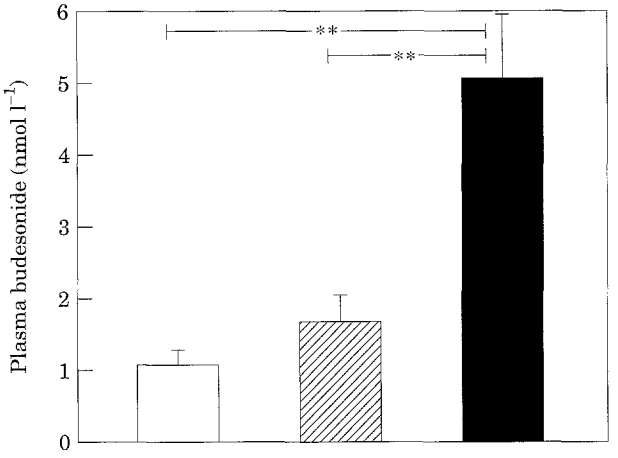

FIG. 2. Plasma budesonide *vs* the nominal dose of budesonide. Open bar, 0·8 mg × 2 pressurized metered-dose inhaler plus spacer; hatched bar, 1 mg × 2 nebulizer; solid bar, 4 mg × 2 nebulizer.

($P<0·01$) and that obtained after the 0·8 mg pMDI dosing ($P<0·01$).

HOME ASSESSMENTS

Symptom score, PEF and p.r.n. use of β_2-agonist from the last 2 weeks of each treatment period are depicted as mean ± SEM in Figures 3–5. The consistent trend in all effect variables demonstrates the nebulizer regimes to be as efficient or more efficient than the pMDI plus spacer treatment. The high-dose regime was significantly more effective for PEF morning ($P<0·01$) and evening ($P<0·01$), use of β_2-agonist ($P<0·05$) and for three out of five symptoms ($P<0·05$). The low-dose regime was significantly more effective for PEF evening ($P<0·01$) and for two of five symptoms ($P<0·05$). The 4 mg budesonide nebulizer suspension appeared to be equally or more effective than 1 mg budesonide nebulizer suspension. However, the apparent difference between nebulizer dosages did not reach significance. Opposite trends were never observed.

CONCOMITANT MEDICATION

Five patients required concomitant anti-asthma medication whilst receiving 1 mg b.i.d. of budesonide by nebulization, as did four whilst receiving the 0·8 mg b.i.d. dosage by pMDI, and two whilst receiving the 4 mg b.i.d. nebulized dosage. A short course of prednisolone rescue was given three times during nebulization with 1 mg budesonide and once during nebulization at 4 mg and with pMDI at 0·8 mg.

One patient needed additional bronchodilators and another required nasal beclomethasone dipropionate (BDP) during treatment with the 1 mg nebulized dosage. BDP was taken by two patients during the pMDI regimen. One patient used Becotide Rotacaps® (4 capsules b.i.d.) and the other used Becloforte® pMDI 4 puffs b.i.d.

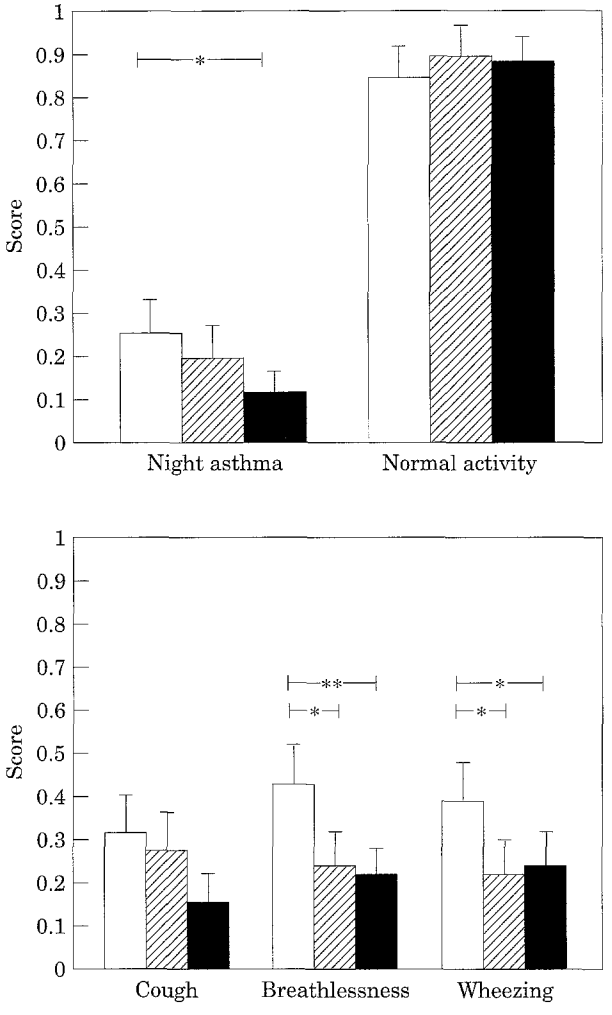

FIG. 3. Symptoms scores *vs* the nominal dose of budesonide. Open bar, 0·8 mg × 2 pressurized metered-dose inhaler plus spacer; hatched bar, 1 mg × 2 nebulizer; solid bar, 4 mg × 2 nebulizer.

ADVERSE EVENTS

Clinical signs of oral candidiasis occurred in five patients receiving 4 mg of nebulized budesonide compared with three patients receiving 1 mg and two patients receiving 0·8 mg by pMDI.

Discussion

The results presented here suggest equipotency between budesonide pMDI administered via a large-volume spacer and nebulized budesonide suspension administered synchronized with inspiration in adult asthmatics. The effect variables consistently showed the nebulizer regimes to be equal to or more efficient than the pMDI and spacer treatment in this group of adult asthmatics. None of the outcome variables ever exhibited any trend in opposite direction. This attest to the efficiency of the budesonide suspension used for the jet nebulization. It should be

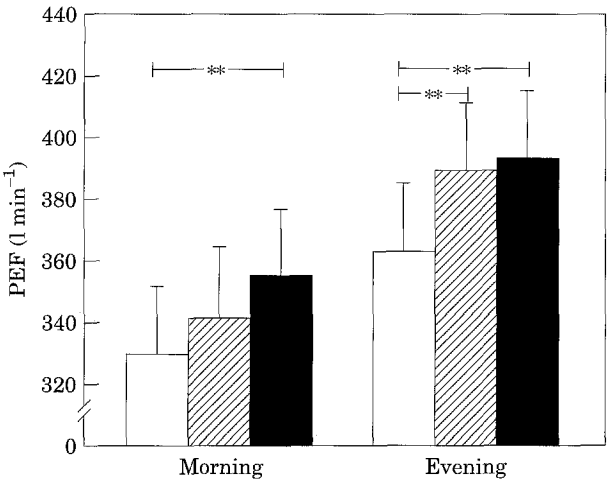

FIG. 4. Peak expiratory flow (PEF) morning and evening *vs* the nominal dose of budesonide. Open bar, 0·8 mg × 2 pressurized metered-dose inhaler plus spacer; hatched bar, 1 mg × 2 nebulizer; solid bar, 4 mg × 2 nebulizer.

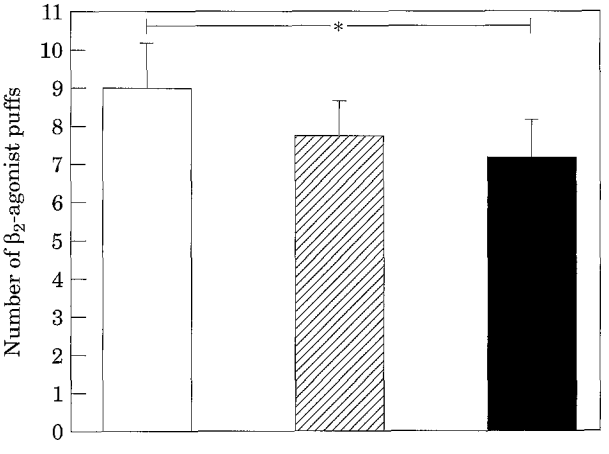

FIG. 5. Use of p.r.n. β_2-agonist *vs* the nominal dose of budesonide. Open bar, 0·8 mg × 2 pressurized metered-dose inhaler plus spacer; hatched bar, 1 mg × 2 nebulizer; solid bar, 4 mg × 2 nebulizer.

emphasized that intermittent nebulization was used to assure optimal delivery of the aerosol in synchrony with the inhalations. During continuous nebulization, a loss of aerosol will occur during the exhalation reducing the potency of the nebulizer treatment by a fraction similar to the I:E ratio.

Dose-related effects from topical corticosteroids are seldom documented. The dose-relation found in the present study is probably related to the inclusion of patients with unstable asthma (15,16). These dose-related effects are also reflected in the plasma budesonide and cortisol levels.

The systemically available dose of budesonide is mainly attributable to the lung deposition, from which budesonide is completely absorbed, whereas efficient first-pass metabolism assures only marginal systemic bioavailability of the swallowed fraction of budesonide. Furthermore, the swallowed fraction of budesonide is probably not increased from nebulizer administration as compared to pMDI with spacer administration (14). The dose-related plasma levels of budesonide and cortisol regardless of device, therefore, point to comparable lung deposition from the two delivery systems.

In vitro measurements showed the two methods of drug delivery used in this study to be equivalent in terms of total drug output; the mean budesonide dose leaving the devices was approximately 60% of the nominal dose from either device. However, the MMAD differed between devices, from 3·9 μm with the pMDI with spacer to 6·5 μm with the nebulizer. Accordingly, the pMDI with spacer conveyed 69% of the delivered dose in particles less than 4·7 μm, whereas with the nebulizer, only 33% of the delivered dose had a particle size of less than 4·7 μm.

The clinical outcome indicate that a defined inhaled total mass of drug for the devices tested is a better predictor for the dose of drug delivered to the lungs of the patient than the estimated dose of fine particles. This was supported by the cortisol and AUC budesonide in plasma. This is in contrast to the traditional concept, that only particles with a MMAD less than approx. 5 μm are likely to reach the lower airway. However, the clinical data presented here suggest that a fraction of the dose that is contained in particles larger than 5 μm provides active anti-asthmatic corticosteroid therapy. Several explanation, though purely speculative, may explain this apparent paradox.

LUNG TARGET AREA

It seems likely that the target area in the lung varies between drugs, and the relevant target area for topical corticosteroids is not known. Central deposition with subsequent intrapulmonary redistribution may be sufficient, in which case particles larger than 5 μm may reach the relevant target.

SYSTEMIC ACTIVITY

The unique feature of topical corticosteroids is assumed to be a high local activity in relation to low systemic activity. However, the need for a systemic anti-asthmatic effect of topical corticosteroids may be underestimated. In this case, the comparable systemic bioavailability from either delivery system may explain the apparent clinical equipotency despite unequal lung distribution.

DOSE DELIVERY BY PMDI

The apparently favourable dose output from the pMDI with spacer system was measured 2 s after activation of the spray. The volume needed to empty an aerosol from a spacer is several-fold that of the spacer, due to exponential dilution of the aerosol by fresh air substituting the volume inhaled. The passive half-life of the aerosol in a plastic spacer is short due to the electrostatic attraction between plastic and particles (17). During tidal breathing, the delay in emptying the aerosol from the spacer may cause a loss of

aerosol within the spacer, thus reducing the actual dose obtained.

BUDESONIDE DISTRIBUTION

The micronized budesonide particles do not distribute evenly throughout the aerosol droplets, thus the overall aerosol droplet profile may differ from the budesonide-containing particle profile. This is due to the fact that budesonide in suspension is available in particles of approx. 3 μm. Accordingly, the fine particle mass less than that is unlikely to contain any drug.

IMPORTANCE OF PARTICLE SIZE

The concept that only particles with MMAD less than 5 μm can provide therapeutic benefit in the lower airway is mainly based on studies of artificial monodisperse aerosols, which may not extrapolate to the polydisperse aerosols found in clinical practice. Lung deposition of nebulized budesonide appeared independent of droplet size within the range of 3–7 μm (18). Further, recent evidence questioned the importance of particle size in determining therapeutic response, at least with regard to the bronchodilator therapy (19–21).

In any case, the present data illustrate that nebulization can efficiently deliver budesonide to the lungs. Nebulized regimens were well tolerated, and the occurrence of objective adverse events and subjective discomfort was comparable with that of the pMDI regimen. The techniques may be comparable in clinical response in adults, provided intermittent inhalation of the nebulized suspension is used. Further research is, however, required before any recommendation or re-assessment of current dosing policy for either device may be advocated.

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