

The output of budesonide from spacer devices assessed under simulated breathing conditions

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Background: Spacer devices are increasingly used to aid inhalational therapy, and many different devices are available. Patient and spacer size and spacer static charge may affect drug delivery, but the optimum spacer size and method of reducing static charge is not certain.

Objective: We sought to determine the output of budesonide from 3 different spacer devices when assessed by using simulated breathing at different tidal volumes and to assess the effect of washing and handling the spacer on drug output.

Methods: Three spacer types were assessed: 2 polycarbonate spacers, the Aerochamber and the Nebuhaler, and the metal Nebuchamber or Non-Electrostatic-Spacer. Breathing was simulated by using a sinus flow pump. Metered-dose inhalers of budesonide 200 µg were actuated into the spacer, which was attached to the breathing simulator for 5 simulated breathing cycles. Budesonide was collected on a filter placed between the spacer and breathing simulator and was assayed by HPLC. Spacers were assessed after they had been washed briefly in water, after they had been washed briefly in cetrimide solution in an attempt to reduce their static charge, and after they had been handled to simulate normal use. In separate experiments budesonide particle size from the spacers was measured by using a multistage liquid impinger.

Results: Drug output from the Nebuchamber was greater than that from the other 2 spacers, especially at lower tidal volumes. With 150 mL of tidal volume, the Nebuchamber delivered 36% of the nominal dose to the filter versus 13% from the Nebuhaler and 7% from the Aerochamber. The output from the Aerochamber and Nebuhaler increased linearly with tidal volume, but this was not the case with the Nebuchamber, in which output was constant at tidal volumes of 150 mL and above. Compared with washing in tap water, neither washing the spacers in 0.1% cetrimide solution nor vigorous wiping with a paper towel changed their output. Thirty-eight percent of the drug from the Nebuchamber was contained in particles smaller than 4.7 µm in diameter compared with 47% from the Nebuhaler and 53% from the Aerochamber.

Conclusions: The Nebuchamber increases *in vitro* budesonide delivery compared with the polycarbonate spacers tested but delivers a greater percentage of the drug in large particles. No

increase in delivery with tidal volume was seen with the Nebuchamber, which would deliver a higher dose of drug per kilogram of body weight to smaller patients. Briefly washing the polycarbonate spacers in water or in a weak detergent solution, simulating household washing, did not make them as effective as the metal spacer. Further research is needed to determine a practical washing and handling method to reduce static charge on polycarbonate spacers. (*J Allergy Clin Immunol* 1999;1205-10.)

Key words: Drug administration, inhalation, spacer devices, static charge, budesonide, corticosteroids

Spacer devices are becoming increasingly popular for the delivery of inhaled drugs in the treatment of asthma.¹ They reduce the problems of poor inhaler technique, which may lead to treatment failure with metered-dose inhalers (MDIs)²; largely eliminate oral absorption of inhaled steroids³⁻⁵; and can be adapted by the attachment of face masks for the treatment of young children.^{6,7}

Static charge accumulates on the walls of many polycarbonate and plastic spacers, attracting drug particles, which become charged when they are produced at the MDI valve stem. Static charge has been shown *in vitro* to reduce the output of medications administered by means of polycarbonate spacer devices,^{8,9} and highly charged spacers deliver less drug than those in which the static charge has been reduced by an antistatic lining.⁸⁻¹¹

Spacers made of antistatic materials or metals may decrease this problem, and a steel spacer (the Nebuchamber or Non-Electrostatic Spacer; a gift from Astra Draco, Lund, Sweden) has recently been released for use with budesonide and terbutaline. This device has been designed for use by small children and is claimed to optimize drug delivery by its small volume, low dead space, and antistatic properties.^{12,13} Washing the polycarbonate spacer in detergent also reduces its charge¹⁴ and has been recommended, but the optimal washing and handling regimen for polycarbonate spacers is not known.

Clinicians may also be advised to use smaller devices for administering inhaled drugs to smaller patients. Although a patient's tidal volume alters drug delivery from spacers,¹³ and different spacers have different emptying characteristics,¹⁵ the effect of spacer size on drug delivery is not clear. In this experiment we measured drug particle size from 2 polycarbonate spacers and the metal spacer and used a breathing simulator to measure the output of budesonide from each. The effect of washing and handling the spacers on drug output was also determined. The data may be used to aid clinicians in

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Abbreviations used

CI: Confidence interval
MDI: Metered-dose inhaler
MSLI: Multistage liquid impinger

their choice of spacer and their advice to patients on spacer use.

METHODS**Spacers and MDIs**

Three spacer types were assessed: the Aerochamber (Trudell Medical, Ontario, Canada), a polycarbonate spacer of 145-mL volume and 11-cm length; the Nebuhaler (Astra, Kings Langley, UK), a polycarbonate spacer of 750-mL volume and 23-cm length; and the Nebuchamber or Non-Electrostatic-Spacer (Astra Draco, Lund, Sweden), a steel spacer of 250-mL volume and 13-cm length. Before the experiments, all spacers were washed in warm water, air-dried, and then put back in their original packaging.

New MDIs of budesonide 200 µg per actuation (Pulmicort; Astra) were obtained. The first 10 actuations from each MDI were fired to waste. Immediately before each experiment, the MDI was shaken for 30 seconds and primed by firing 3 actuations to waste.

Breathing simulation

The Pari Sinus Breathing Simulator (a gift from Pari GmbH, Starnberg, Germany) was used to simulate patient breathing. The simulator consists of a sinus pump, the deflection and speed of which may be altered to simulate different rates, tidal volumes, and inspiratory fractions. The experimental apparatus is illustrated in Fig 1.

Filters and experimental procedure

Pari electrostatic filter pads were used to collect the aerosolized drug, which was held in a plastic filter assembly (dead space of 11 mL). A polycarbonate board was used to simulate the patient's face. Spacers were analyzed with the face masks provided by the manufacturer.

In each experiment the spacer under test was held horizontally up to the experimental apparatus so that a good seal was made between the face mask and board. The MDI was then shaken for 10 seconds and actuated into the spacer at the beginning of inspiration. The spacer was held in place for 5 cycles of the breathing simulator. In experiments at the lowest tidal volume (50 mL), this procedure was repeated 5 times to facilitate the drug assay.

Particle size analysis

A multistage liquid impinger (MSLI)¹⁶ was used to determine the size distribution of the budesonide aerosol. The MSLI draws aerosol at a constant flow of 60 L/min through a series of stages, each connected by progressively smaller jets. Aerosol velocity therefore increases through each jet, resulting in the deposition of smaller particles at each stage. For each experiment, the MDI was shaken for 10 seconds and actuated into the spacer. This was then attached to the MSLI. In this way a total of 10 actuations were fired into the spacer to facilitate the drug assay. The stages of the MSLI were then washed with ethanol, and the amount of drug collected in the washing liquid was determined. The particle size distribution of the aerosol cloud was measured 4 times from each spacer.

Budesonide assay

The amount of budesonide collected on the filters or on each stage of the MSLI was determined by HPLC¹⁰ by using an isocrat-

ic system with UV detection at 254 nm. Fluocinolone acetonide was used as an internal standard. Chromatograms were integrated by using dedicated computer software (Summit; Comus Ltd, Newcastle, UK).

The limit of detection of the assay was 0.1 µg of budesonide per milliliter. The system response was linear over a range of budesonide concentrations from 0.1 to 200 µg/mL. The coefficients of variation of the assay were 28% (0.1 µg/mL) and 2.6% (1 µg/mL). Pilot studies with the filters showed that the recovery of budesonide from primed filters was 100.4% (95% confidence intervals [CIs], 97.5% to 103.3%) of 200 µg of drug. The filters collected all budesonide particles, with the recovery of budesonide from the second of 2 filters in line being less than the limit of detection of the assay.

Experiments

To determine the effect of changing tidal volume, the drug output from each spacer was measured with simulated breathing at tidal volumes of 50, 100, 150, 200, and 300 mL. The rate was 20 cycles per minute, and the inspiratory fraction was 40%.

Patients are commonly advised to wash their spacers weekly. To determine the effect of typical household washing, the drug output from the Nebuhaler and Aerochamber was measured with simulated breathing after the spacers had been washed in 0.1% cetrimide solution and allowed to air dry. Tidal volumes of 50, 150, and 300 mL were used. The rate was 20 cycles per minute, and the inspiratory fraction was 40%. The experiment was then repeated with spacers washed in 0.1% cetrimide solution as before but wiped with a paper cloth before the experiment.

For each of the above experiments, each spacer type was assessed on 6 or more occasions. Results are given as the mean amount of drug recovered from the filters, and 95% CIs for the mean. Mean drug recovery for different devices was compared by using ANOVA. Where a significant difference was detected by ANOVA, recovery between individual devices was compared by using unpaired *t* tests, and *P* values are given without correction for multiple comparisons.

RESULTS**Effect of varying tidal volume**

The effect of varying tidal volume is shown in Fig 2 and Tables I and II. Drug recovery increased with increasing tidal volume for all spacers ($P < .001$, ANOVA) but was not significantly increased with the Nebuchamber at tidal volumes above 150 mL. The recovery was significantly greater for the Nebuchamber than for the Nebuhaler at all tidal volumes ($P < .001$), although the difference was least marked at 300 mL ($P = .006$, *t* test). The Nebuchamber recovery was also greater than the Aerochamber recovery at all tidal volumes ($P < .001$). Nebuhaler recovery was greater than that of the Aerochamber at all tidal volumes except 150 mL, largely because of a greater variability in the Nebuhaler recovery at this tidal volume.

Effect of washing the spacer

The effect of washing the spacer is shown in Fig 3 and Tables I and II. Washing the spacer with 0.1% cetrimide solution did not significantly increase the drug output compared with the spacers that had been washed in water. Drying the spacer with a paper towel before testing did not alter the drug output ($P = .51$).

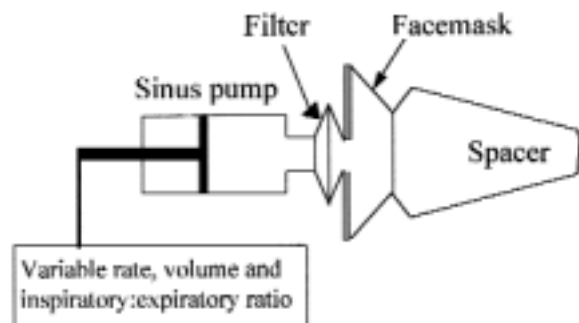


FIG 1. The experimental set up for the breathing simulator.

Particle size

Particle sizes are shown in Table III. The Nebuchamber delivered the largest amount of drug to the MSLI ($94.3 \mu\text{g}$ per $200 \mu\text{g}$ actuation; 95% CI, 93.2-95.5), but over 40% of this amount impacted in the MSLI inlet, and only 38% (95% CI, 35.5-41.1) reached the lower stages, representing particles smaller than $4.7 \mu\text{m}$. The Nebuhaler and Aerochamber delivered less total drug than the Nebuchamber ($47.6 \mu\text{g}$ [95% CI, 38.2-57.1] and $39.7 \mu\text{g}$ [95% CI, 36.5-43.0], respectively), but a higher percentage reached the lower stages (47.3% [95% CI, 45.2-49.5] and 52.7% [95% CI, 49.9-55.6], respectively). Even so, the Nebuchamber delivered a greater mass of drug to the lower stages ($36 \mu\text{g}$ vs $22.7 \mu\text{g}$ [Nebuhaler] and $21 \mu\text{g}$ [Aerochamber]). The values for mass median aerodynamic diameter given in Table III are calculated from the mass of drug progressing beyond the MSLI inlet, ignoring any ballistic aerosol component, and are thus smaller than calculated values, which include the drug deposited on the inlet.

DISCUSSION

Spacer devices are increasingly used in the treatment of asthma,¹ especially for children^{6,7} and those with poor inhaler technique.² Their use reduces the local side effects of inhaled steroids, such as oral candidiasis, and improves the therapeutic ratio of such medications by reducing nontherapeutic, extrathoracic delivery of drug.³⁻⁵

Different spacers have different characteristics and deliver a variable amount of medication.¹⁷ The ideal spacer would deliver a known, consistent, and large mass of drug to its site of action. One cause of variable dose delivery from spacers is static charge. This accumulates on the walls of many polycarbonate and plastic spacers, attracting drug particles, which become charged when they are generated by the MDI. Static charge has been shown in vitro to reduce the output of medications administered by means of polycarbonate spacer devices,^{8,9} and highly charged spacers deliver less drug than those in which the static charge has been reduced by an antistatic lining.⁸⁻¹¹

The amount of drug available for inhalation from spacer devices diminishes rapidly with time after actuation of

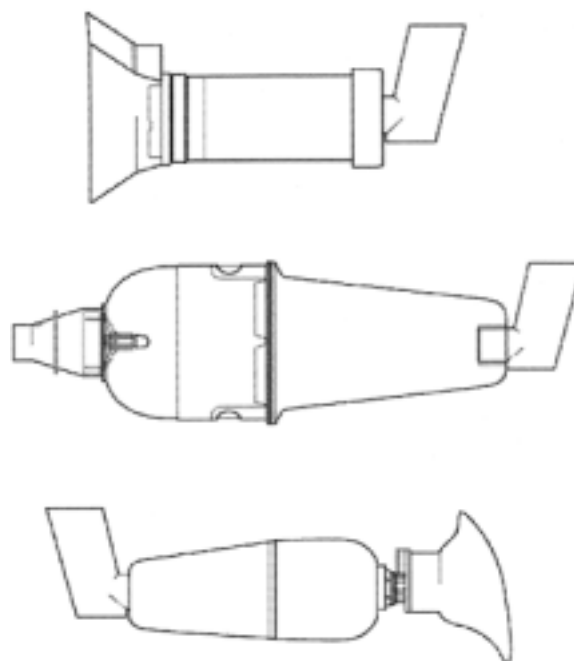


FIG 2. Schematic diagrams of the spacers.

the MDI into the spacer.^{10,18} This effect is dependent on the spacer and drug being studied,¹⁹ but for budesonide the half-life of drug within the Nebuhaler is of the order of 10 seconds.^{10,12} Treatment of the spacer with an antistatic lining considerably increases the half-life of drug,^{10,12} which may be of importance when using these devices to administer drugs to uncooperative children or those whose small tidal volumes mean that they take a longer time to inhale the available aerosol from the spacer.

The metal Nebuchamber was developed to overcome problems with static charge on spacers and is intended specifically for aerosol administration to young children¹³ because it is low volume (250 mL) and has a low dead space and low-pressure inhalation and exhalation valves. In children aged 0.5 to 7 years (tidal volume, 190-330 mL), the Nebuchamber delivers a larger and more consistent amount of drug than the Nebuhaler.^{12,13} The Nebuchamber is, however, more expensive than the polycarbonate spacers currently available. A cheaper way to overcome spacer static charge is to coat the device with drug, an antistatic lining,¹¹ or paint¹⁰ or to soak it in a detergent solution.^{8,20} However, such modifications may be temporary,¹³ and charge on polycarbonate spacers is also affected by highly charged nearby objects.⁸ Furthermore, the optimal washing and handling regimen for spacers is not known. Wildhaber et al¹⁴ have shown that rinsing spacers in water reduced the charge, although not predictably, and that the delivery of salbutamol from rinsed spacers is the same as that from highly charged new spacers. Soaking the spacers in detergent for an hour reduces charge considerably and increases the delivery of salbutamol. A questionnaire in the same study, and our own experience, suggests that parents wash the spacer by

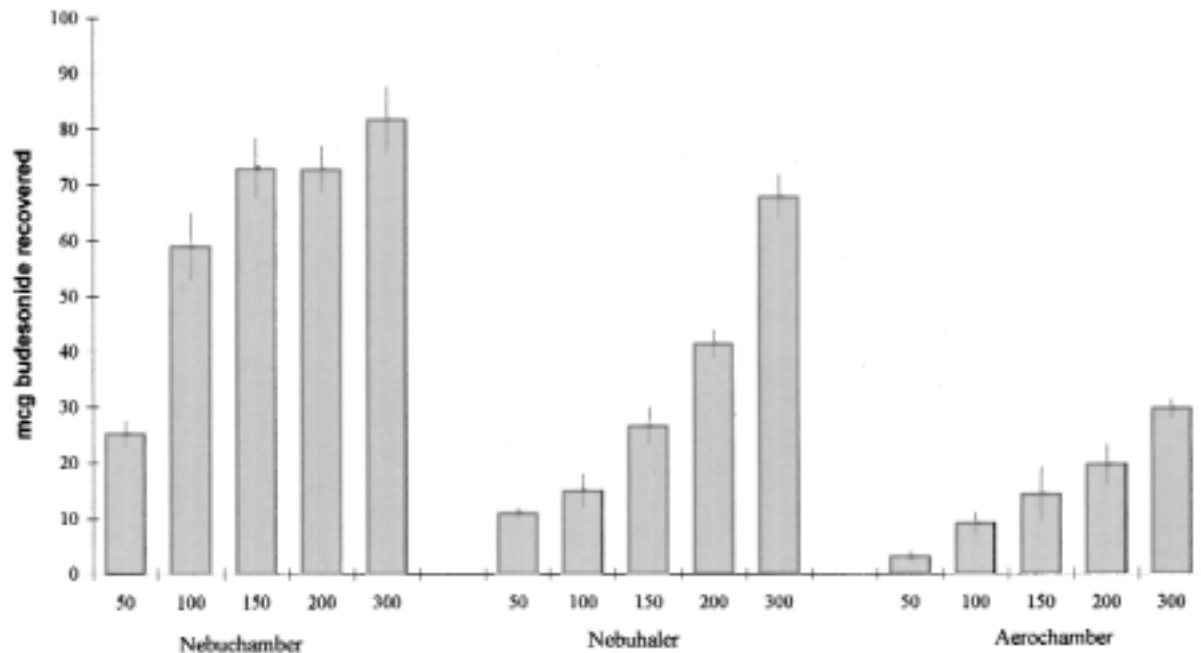


FIG 3. Amount of budesonide deposited on the filters from the different spacers at different tidal volumes. Spacers were washed in warm water and air-dried. Error bars represent 95% CIs.

TABLE I. Output of budesonide from spacers washed in water and air-dried: The effect of changing tidal volume*

Spacer	Vt 50 mL	Vt 100 mL	Vt 150 mL	Vt 200 mL	Vt 300 mL
Aerochamber	3.0 (2.2-3.8)	9.0 (7.0-11.0)	14.3 (9.4-19.2)	19.6 (16.0-23.2)	29.7 (27.9-31.5)
Nebuhaler	10.9 (10.0-11.8)	14.9 (11.9-17.9)	26.5 (23.1-29.9)	41.3 (38.7-43.9)	67.8 (63.9-71.7)
Nebuchamber	25.2 (22.9-27.5)	58.9 (52.9-64.9)	72.9 (67.5-78.3)	72.7 (68.5-76.9)	81.6 (75.7-87.5)

Values are shown as micrograms of budesonide (mean and 95% CIs).

Vt, Tidal volume.

*Rate = 20 cycles/min; inspiratory fraction = 40%.

TABLE II. Output of budesonide from spacers washed in 0.1% cetrimide: The effect of wiping the spacer dry*

Spacer	Vt 50 mL		Vt 150 mL		Vt 300 mL	
	Washed	Washed and dried	Washed	Washed and dried	Washed	Washed and dried
Aerochamber	10.3 (9.2-11.2)	8.7 (7.3-10.1)	18.8 (16.4-21.1)	16.6 (14.5-18.6)	26.0 (22.2-29.7)	38.9 (35.6-42.2)
Nebuhaler	13.2 (11.9-14.4)	12.5 (7.8-17.3)	28.2 (26.0-30.4)	29.4 (27.6-31.2)	55.3 (48.3-62.3)	49.1 (42.7-55.5)

Values are shown as micrograms of budesonide (mean and 95% CIs).

Vt, Tidal volume.

*Rate = 20 cycles/min; inspiratory fraction = 40%.

briefly immersing it in water, with or without detergent. The washing regimen in our study therefore consisted of a much briefer exposure to detergent in an attempt to reduce static charge. Unfortunately, we were not able to measure the actual level of static charge on the spacers and therefore do not know whether the washing altered this level. It is clear, however, that brief washing with 0.1% cetrimide confers no advantage over rinsing with water and that drying the spacer with a paper towel after washing does not decrease the amount of budesonide released from the spacer. Given the studies that have shown a relationship between drug output and static

charge, one explanation of our results is that spacer static charge was not altered by these washing and drying maneuvers.

There was a linear relationship between tidal volume and the output of budesonide from the Aerochamber and the Nebuhaler. Drug output from the Nebuchamber was constant at tidal volumes above 150 mL. Assuming that a child's tidal volume is approximately 10 mL/kg body weight, the dose of budesonide delivered to the patient per kilogram would be constant throughout childhood if the Aerochamber or Nebuhaler are used. In contrast, for the same nominal dose, twice as much budesonide per

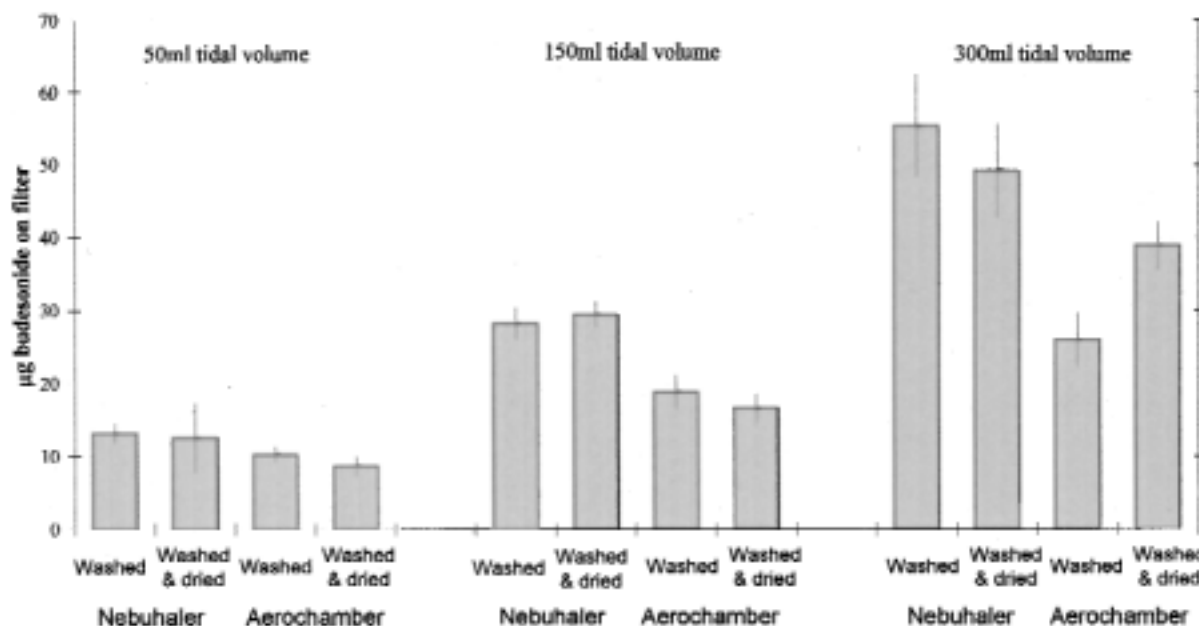


FIG 4. Amount of budesonide deposited on the filters from the spacers after washing in 0.1% cetrimide solution and either air-drying or drying by wiping with a paper towel. Error bars represent 95% CIs.

TABLE III. Particle size output of budesonide from spacers washed in water and dried (mean and 95% CIs)

Spacer	Total dose to MSLI (µg)	Amount in particles <4.7 µm (µg)	Percentage dose ex-spacer <4.7 µm	MMAD (µm)	GSD
Aerochamber	39.7 (36.5-43.0)	21.0 (18.7-23.2)	52.7 (49.9-55.6)	3.6 (3.5-3.7)	1.64 (1.60-1.68)
Nebuhaler	47.6 (38.2-57.1)	22.7 (17.4-27.9)	47.3 (45.2-49.5)	3.9 (3.3-4.6)	1.8 (1.6-2.1)
Nebuchamber	94.3 (93.2-95.5)	36.1 (33.7-38.4)	38.3 (35.5-41.1)	3.5 (3.5-3.6)	1.68 (1.66-1.70)

Values for mass median aerodynamic diameter are calculated for the drug present on stages 1 to 4 and filter, omitting the ballistic component affecting the throat. MMAD, Mass median aerodynamic diameter; GSD, geometric standard deviation.

kilogram of body weight would be delivered from the Nebuchamber to a 5-kg baby than to a 30-kg child. This suggests that for devices such as the Aerochamber and Nebuhaler, the administered dose should be kept constant to give the same received dose to the patient as he or she grows, but if the Nebuchamber is used, the administered dose should be reduced with age.

Side effects from inhaled corticosteroids are related to the dose administered,²¹ with some authors suggesting that adrenal dysfunction occurs in children at doses higher than 400 µg/d.²² Our results suggest that this nominal dose administered by means of an Aerochamber would deliver 18 µg to a 1-year-old, 10-kg child (1.8 µg/kg) and 59.4 µg to a 10-year-old sibling (2 µg/kg). If the children were instead using the Nebuchamber, they would receive 11.8 µg/kg and 5.4 µg/kg budesonide, respectively. Clearly if side effects are dose related, then the actual dose received by the patient, as well as the nominal dose emitted from the MDI, must be known. Similarly, in clinical trials of inhaled corticosteroids, standardization of the drug delivery device used by subjects is essential if meaningful results are to be obtained.²³

Measurement of drug delivery by using filter deposi-

tion is a useful noninvasive method of estimating drug delivery from different devices. The breathing simulator allows parameters, such as tidal volume and breathing frequency, to be controlled, overcoming the large intrasubject variability seen when patients are used to inhaling from the drug delivery device^{13,24,25} and which may make it difficult to determine whether there is a relationship between parameters such as age or size and drug delivery.²⁴ However, there should be some caution in inferring clinical effect from experiments with the breathing simulator, which produces a sine wave flow pattern and may not reflect real breathing patterns.²⁶ Also, the mass of drug deposited on filters represents all the medication that may be inhaled by the patient and is not the same as lung deposition, which will depend on a number of factors, such as the mode of inhalation and the aerosol particle size. In this study particle size was greatest when the budesonide MDI was used with the Nebuchamber, largely because of high deposition on the inlet of the MSLI (43% of the drug emitted from the spacer) so that only 27% of the budesonide was contained in particles smaller than 4.7 µm. Using the Anderson impactor, Bisgaard¹³ found that 60% of the budesonide from the Nebuchamber

was contained in small droplets compared with 69% from the Nebuhaler and 80% from the Aerochamber, with the latter spacers having been primed with 15 actuations of the budesonide MDI. The differences between these figures and our study may be due to this priming, to the exact method of particle sizing, or to the relatively high flow of the MSLI (60 L/min) compared with the Anderson impactor (28 L/min). The greatest mean inspiratory flow in Bisgaard's group of children, assuming an inspiratory fraction of 40%, was 17 L/min, although the peak flow may have been much higher than this, and there is great variability in typical breathing patterns in children.²⁶ However, other findings with the MSLI at 60 L/min have been subsequently confirmed by pharmacokinetic studies in vivo,²⁷ suggesting that the method does have some clinical relevance.

It may be possible to estimate lung deposition from laboratory measurements of aerosol particle size and filter collection, as has been suggested by others.²⁸ Multiplying the fraction of drug in particles smaller than 4.7 μ m from the MSLI experiments by the total filter recovery at different tidal volumes suggests that the Nebuchamber delivers 2 or 3 times as much small-particle drug at each tidal volume than the Aerochamber and twice as much as the Nebuhaler at tidal volumes below 300 mL. The problems with this approach are that it assumes that 4.7 μ m is an appropriate cut-off diameter to delineate lung and extrathoracic deposition and that the percentage of drug collected on the lower stages of the MSLI is not flow dependent because the flow through the spacer when attached to the breathing simulator is constantly changing in contrast to the constant flow in the MSLI experiments.

This study has shown large differences between the in vitro delivery of budesonide from different spacers, and in contrast to other studies with salbutamol, has failed to show an improvement in drug delivery from polycarbonate spacers from a simple washing regimen. Spacer static charge makes inhalational drug delivery less efficient and less consistent.

Further work is needed to advise patients of the best way of reducing this problem, either by a simple washing procedure or by the introduction of spacers made from materials that do not retain electrostatic charge. Spacer performance is also dependent on the patient's tidal volume, and increases in the nominal dose of drug prescribed as the patient grows may not be appropriate for all spacers. If dose-related efficacy and side effects from inhaled corticosteroids are thought to be important, the actual dose delivered to the patient should be determined. This will depend on the patient, the medication, and the actual spacer used.

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