

Inhalational drug delivery from seven different spacer devices

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Abstract

Background - A study was performed to determine *in vitro* the difference in drug output of seven currently available spacer devices when used with different inhaled medications.

Methods - A glass multistage liquid impinger (MSLI) was used to determine the amount of disodium cromoglycate (DSCG, 5 mg), salbutamol (100 µg), or budesonide (200 µg) obtained in various particle size ranges from metered dose inhalers (MDIs) actuated directly into the MSLI or via one of seven different spacer devices: the Fisonair, Nebuhaler, Volumatic, Inspirease, Aerochamber, Aerosol Cloud Enhancer, and Dynahaler.

Results - In particles smaller than 5 µm in diameter the dose of DSCG recovered from the Fisonair and Nebuhaler was 118% and 124%, respectively, of that recovered using the MDI alone. The dose recovered from the smaller volume spacers was 90% (Inspirease), 36% (Aerochamber), 33% (Aerosol Cloud Enhancer), and 21% (Dynahaler) of that from the MDI alone. The Volumatic increased the amount of salbutamol in particles smaller than 5 µm to 117% of that from the MDI, and the Inspirease and Aerochamber spacers decreased it by nearly 50%. The amount of budesonide in small particles recovered after use of the Nebuhaler, Inspirease, and the Aerochamber was 92%, 101%, and 78%, respectively, of that from the MDI alone.

Conclusions - Under the test conditions used, large volume spacers such as the Fisonair, Nebuhaler, and Volumatic delivered significantly more DSCG and salbutamol than the smaller spacers tested. The differences between spacers were less for budesonide than the other medications studied. This study shows that there are significant differences in the amount of drug available for inhalation when different spacers are used as inhalational aids with different drugs. Spacer devices need to be fully evaluated for each drug prescribed for them.

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disease. They discharge an aerosol at high speed which is inhaled by the patient. Proper use requires coordination of inhalation and MDI actuation but, even with optimum technique, less than 15% of the actuated dose reaches the lungs. Spacer devices are intended to improve the efficacy of inhaled therapy by reducing the need for coordination of MDI actuation and inhalation (acting as "holding chambers" for aerosol), and by allowing deceleration and evaporation of drug particles, decreasing extrathoracic deposition of medication (acting as "spacing devices"). They allow effective drug delivery to patients of all ages.¹

Many different devices are currently available for use in inhalational therapy. Some are intended for use with one particular product, others are marketed as being suitable for use with a variety of MDIs. Inhalation needs to be commenced before MDI actuation with "spacing devices", but not for those designed primarily as "holding chambers". There has been little published work on the comparative efficacy of different devices, and no standard methods for assessing new devices which may be marketed. Metered dose inhalers may contain different formulations with different particle size and aerosol cloud characteristics. Patients vary in size and ability to clear the spacer of medication in a single breath. Factors such as these may alter the combination of MDI, spacer, and patient required for optimum drug delivery and the ideal device for different patients and medications is not known.

We used an impaction particle sizing method to determine the amount of disodium cromoglycate (DSCG), salbutamol, and budesonide available for inhalation from different spacer devices.

Methods

A glass multistage liquid impinger (MSLI), as modified by Bell *et al.*,² was used to determine the MDI output under different conditions. The MSLI operates by drawing an aerosol at a constant flow of 60 l/min through a series of four stages, each containing a glass impaction plate. Aerosol velocity increases progressively through the device and progressively smaller particles collect at each stage. A filter after the final stage collects particles smaller than 1 µm in diameter. For DSCG, each stage of the MSLI was washed quantitatively with water. The amount of drug collected in each stage was assayed by ultraviolet spectrophotometry at a wavelength of 326 nm. For salbutamol and budesonide, each stage was washed with

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Metered dose inhalers (MDI) are a convenient way of administering medication to patients with asthma and chronic obstructive airways

Table 1 Drug/spacer combinations evaluated

Drug	Spacer
Sodium cromoglycate	Fisonair
	Nebuhaler
	Inspirease
	Aerochamber
	Aerosol Cloud Enhancer
Salbutamol	Dynahaler
	Volumatic
	Inspirease
	Aerochamber
	Dynahaler
Budesonide	Nebuhaler
	Inspirease
	Aerochamber

methanol or ethanol, respectively, and the amount of drug collected at each stage determined by high pressure liquid chromatography.

The experiments were undertaken using DSCG, 5 mg per actuation (Intal, Fisons, Loughborough, UK), salbutamol, 100 µg per actuation (Ventolin, Allen & Hanburys, Uxbridge, UK), and budesonide, 200 µg per actuation (Pulmicort, Astra Pharmaceuticals, Kings Langley, UK) in conjunction with the following spacers: the Fisonair (Fisons), Nebuhaler (Astra Pharmaceuticals), Volumatic (Allen & Hanburys), Inspirease (Key Pharmaceuticals, Miami, Florida, USA), Child Aerochamber (Trudell Medical, London, Canada), Aerosol Cloud Enhancer (DHD Corp, Canestota, NY, USA), and the Dynahaler (Healthscan Products, Cedar Grove, NJ, USA). The combinations of drugs and spacers evaluated are given in table 1. These combinations were chosen as they have been advertised as being appropriate or have been seen in our clinical practice. The features of each device are given in table 2.

New MDIs of each drug 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 one actuation. The MDI was then shaken for 10 seconds and actuated into the spacer which was immediately attached to the MSLI. This procedure was repeated 10 times during each experiment to facilitate the drug assay.

Patients using the Aerosol Cloud Enhancer and the Dynahaler are instructed to commence inhalation before MDI actuation. These spacers and, for comparison, the Fisonair were also assessed by connecting the spacer to the MSLI before MDI actuation, mimicking an inspiratory flow through the spacer during actuation of the MDI. These experiments were undertaken with DSCG only.

Table 2 Characteristics of the different spacer devices

Name	Shape	Length (cm)	Volume (ml)	Expiratory valve	Comments
Nebuhaler	Pear	23	750	✓	
Fisonair	Diamond	19	800	✓	
Volumatic	Diamond	23	700	✓	
Inspirease	Cylindrical	11.3	650	✗	Inspiratory alarm/collapsible
Aerochamber	Cylindrical	11	145	✓	
Aerosol Cloud Enhancer	Pear	17.5	160	✓	Inspiratory alarm
Dynahaler	Cylindrical	12	60	✗	

Four different Fisonairs, Nebuhalers, Aerosol Cloud Enhancers, Dynahalers, and Volumatic spacers, three Aerochambers, and one Inspirease were used. Experiments were repeated four times with each spacer type. Spacers were all cleaned with water and allowed to dry in air on the laboratory bench before each experiment. The laboratory temperature and relative humidity were recorded for each experiment.

To ensure that the MDI was delivering the prescribed amount of drug under the test conditions it was weighed before and after each experiment. The MDI from each experiment was actuated once into a flask. This was then washed out with the appropriate solvent and the amount of drug released in that actuation determined by analysing the flask washings.

STATISTICAL METHODS

The size distribution of the aerosol cloud was determined from the amount of drug recovered from each stage, the MSLI having been previously calibrated with an aerosol of di-n-butyl phthalate, a non-volatile oil, of known particle size distribution. From this information a log-probability plot was constructed³ for each experiment. A line of best fit was derived from this and used to determine the characteristics of the aerosol – for example, the amount of drug contained in particles less than 5 µm or 3 µm diameter, the mass median aerodynamic diameter (MMAD – the aerodynamic size of a particle such that half of the drug is in larger and half in smaller particles), and the geometric standard deviation (GSD), a measure of the heterogeneity of the aerosol particle size. Mean drug recovery for different devices was compared using analysis of variance (ANOVA). Where a significant difference was detected by ANOVA, recovery between individual devices was compared using unpaired *t* tests and *p* values are given without correction for multiple comparisons.

Results

Particles smaller than 5 µm in diameter are thought to be of optimal size to deliver drug to the lower respiratory tract⁴ and, for simplicity, we refer to this as the “fine particle dose”. The amount of drug recovered in particles smaller than 5 µm and 3 µm in diameter, the MMAD, and GSD were recorded. These results, expressed as the mean and 95% confidence intervals for each group of experiments, are given in tables 3–6 and, as a percentage of the nominal dose from the MDI, in figs 1–4.

DISODIUM CROMOGLYCAT

There was a significant difference in the fine particle dose delivered from the different devices ($p < 0.00001$, ANOVA; table 3, fig 1). The Fisonair and Nebuhaler increased the fine particle dose by 18% and 24% of the MDI dose, respectively ($p < 0.01$ and $p = 0.13$, *t* test). The Inspirease delivered 90% of the MDI fine particle dose whereas the smaller spacers all reduced the fine particle dose to 36% of that from the MDI with the Aerochamber, 33% with the Aerosol Cloud Enhancer,

Table 3 Effect of the use of different spacer devices on the mean amount of sodium cromoglycate recovered (mg) per 5 mg actuation (95% confidence intervals)

Method of delivery	Dose to patient	In particles < 5 µm	In particles < 3 µm	MMAD (µm)	GSD
Direct from metered dose inhalers	4.14 (3.99 to 4.29)	0.42 (0.40 to 0.44)	0.18 (0.15 to 0.20)	13.8 (13.2 to 14.4)	2.0 (1.8 to 2.2)
Via Fisonair	1.34 (1.25 to 1.44)	0.50 (0.45 to 0.54)	0.24 (0.20 to 0.27)	6.1 (5.9 to 6.4)	2.1 (2.0 to 2.2)
Via Nebuhaler	1.2 (1.0 to 1.3)	0.52 (0.42 to 0.61)	0.25 (0.21 to 0.28)	4.9 (4.6 to 5.3)	2.0 (1.98 to 2.05)
Via Inspirease	0.83 (0.75 to 0.92)	0.38 (0.36 to 0.40)	0.2 (0.19 to 0.21)	5.5 (5.1 to 5.8)	2.3 (2.2 to 2.3)
Via Aerochamber	0.35 (0.22 to 0.48)	0.15 (0.09 to 0.20)	0.07 (0.05 to 0.10)	5.9 (5.6 to 6.2)	2.4 (2.2 to 2.6)
Via ACE spacer	0.46 (0.40 to 0.53)	0.14 (0.11 to 0.17)	0.07 (0.05 to 0.08)	10.1 (8.3 to 11.9)	3.1 (2.7 to 3.5)
Via Dynahaler	0.32 (0.21 to 0.42)	0.09 (0.06 to 0.12)	0.04 (0.03 to 0.06)	8.3 (7.7 to 8.8)	2.4 (2.3 to 2.4)

MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation; ACE = Aerosol Cloud Enhancer.

Table 4 Effect of the use of different spacer devices on the mean amount of sodium cromoglycate recovered (mg) per 5 mg actuation (95% confidence intervals), sampling during MDI actuation

Method of delivery	Dose to patient	In particles < 5 µm	In particles < 3 µm	MMAD (µm)	GSD
Via Fisonair	1.7 (1.50 to 1.89)	0.50 (0.40 to 0.61)	0.25 (0.17 to 0.33)	7.5 (6.8 to 8.2)	2.2 (2.1 to 2.3)
Via Aerosol Cloud Enhancer	2.55 (2.48 to 2.62)	0.31 (0.24 to 0.37)	0.14 (0.11 to 0.17)	16.55 (12.5 to 20.6)	2.7 (2.1 to 3.2)
Via Dynahaler	1.0 (0.73 to 1.27)	0.26 (0.24 to 0.28)	0.13 (0.12 to 0.14)	9.1 (7.4 to 10.7)	2.5 (2.4 to 2.7)

MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation.

Table 5 Effect of the use of different spacer devices on the mean amount of salbutamol recovered (µg) per 100 µg actuation (95% confidence intervals)

Method of delivery	Dose to patient	In particles < 5 µm	In particles < 3 µm	MMAD (µm)	GSD
Direct from metered dose inhalers	90.5 (81.4 to 99.6)	46.3 (36.3 to 56.3)	34.4 (27.5 to 41.3)	5.2 (3.9 to 6.5)	4.8 (3.2 to 6.4)
Via Volumatic	62.1 (56.0 to 68.2)	54.3 (48.3 to 60.1)	44.9 (39.0 to 50.8)	1.7 (1.6 to 1.9)	2.4 (2.3 to 2.5)
Via Inspirease	30.1 (25.2 to 34.9)	25.6 (21.5 to 29.7)	21.0 (17.6 to 24.4)	1.9 (1.7 to 2.0)	2.6 (2.5 to 2.6)
Via Aerochamber	23.4 (16.3 to 30.6)	20.0 (15.6 to 24.5)	16.2 (12.7 to 19.7)	2.0 (1.2 to 2.8)	1.9 (1.9 to 2.3)
Via Dynahaler	3.1 (1.9 to 4.2)	3.1 (1.9 to 4.2)	—	—	—

MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation.

Table 6 Effect of the use of different spacer devices on the mean amount of budesonide recovered (µg) per 200 µg actuation (95% confidence intervals)

Method of delivery	Dose to patient	In particles < 5 µm	In particles < 3 µm	MMAD (µm)	GSD
Direct from metered dose inhalers	136.5 (131.6 to 141.5)	33.0 (25.5 to 40.4)	15.1 (12.2 to 18.0)	10.2 (7.4 to 13.0)	2.6 (2.3 to 2.9)
Via Nebuhaler	47.5 (38.2 to 56.8)	30.5 (21.9 to 39.2)	15.4 (6.7 to 24.2)	4.0 (3.4 to 4.7)	1.8 (1.6 to 2.0)
Via Inspirease	61.3 (53.8 to 68.8)	33.4 (29.8 to 37.1)	14.2 (12.5 to 15.9)	4.7 (4.2 to 5.2)	1.8 (1.7 to 1.8)
Via Aerochamber	40.2 (30.2 to 50.4)	25.6 (19.5 to 31.7)	13.7 (11.0 to 16.4)	3.9 (3.6 to 4.2)	2.0 (1.8 to 2.2)

MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation.

and 21% with the Dynahaler. There was no difference between the fine particle dose delivered from either of the two larger volume spacers – the Nebuhaler and the Fisonair – or between the smaller volume spacers – the Aerochamber, Aerosol Cloud Enhancer, and the Dynahaler. All the spacers except the Aerosol Cloud Enhancer reduced the MMAD of the aerosol compared with the MDI used without a spacer. This effect was greatest for the larger volume spacers, and for the Nebuhaler compared with the Fisonair ($p < 0.01$).

Sampling during MDI actuation, to represent coordination of inhalation and MDI actuation into the spacer, increased recovery of DSCG from the Aerosol Cloud Enhancer (0.14 to 0.31 mg) and Dynahaler (0.09 to 0.26 mg) (tables 3 and 4, fig 2). However, these spacers delivered less drug in small particles than the MDI or Fisonair assessed under the same conditions ($p < 0.001$, ANOVA).

SALBUTAMOL

There was a significant difference in the fine particle dose delivered from the different devices (table 5, fig 3; $p < 0.00001$, ANOVA). The Volumatic increased the fine particle dose by 17% ($p = 0.05$), and the smaller spacers reduced the fine particle dose compared with the MDI alone to 55% with the Inspirease and 43% with the Aerochamber. So little drug was obtained from the Dynahaler that a particle size distribution was impossible to obtain. With this exception, the spacers all equally reduced the MMAD of the aerosol compared with the MDI used without a spacer.

BUDESONIDE

There was no statistically significant difference between the different spacers in the delivery of budesonide (table 6, fig 4). The Nebuhaler and the Aerochamber reduced the fine particle

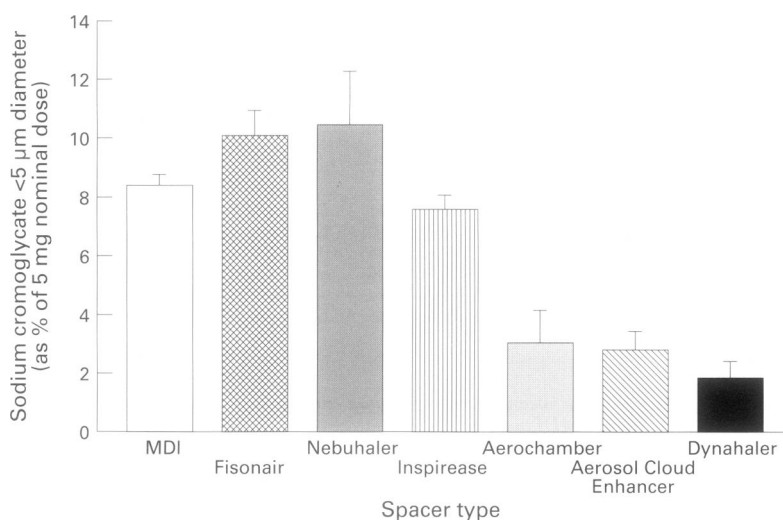


Figure 1 Amount of sodium cromoglycate (percentage of 5 mg dose) recovered in particles smaller than 5 µm aerodynamic diameter for seven different spacer devices. Vertical bars represent one standard deviation.

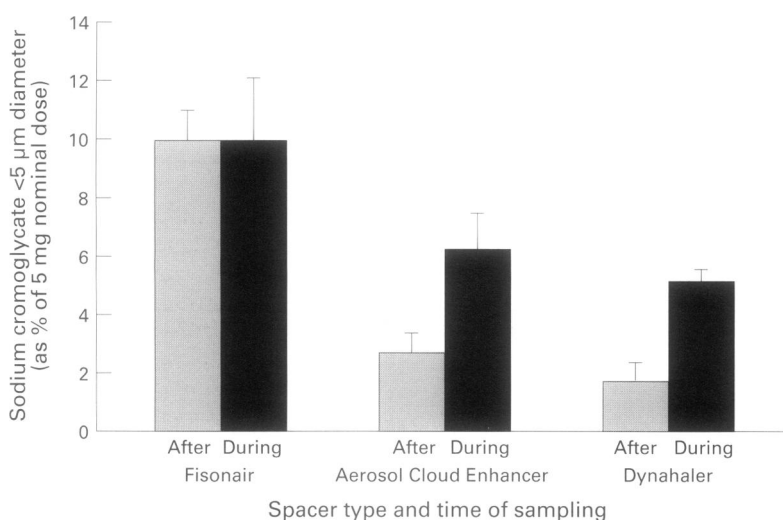


Figure 2 Amount of sodium cromoglycate (percentage of 5 mg dose) recovered in particles smaller than 5 µm aerodynamic diameter for three spacer devices sampled either one second after (shaded bars) or during (black bars) metered dose inhaler actuation.

dose to 92% and 78%, respectively, compared with the MDI whereas the Inspirease delivered the same amount of drug as the MDI. Reducing extrathoracic drug deposition is an important effect of spacer devices used with inhaled steroids and the three spacers all reduced the delivery of larger particles. Again the spacers all equally reduced the MMAD of the aerosol

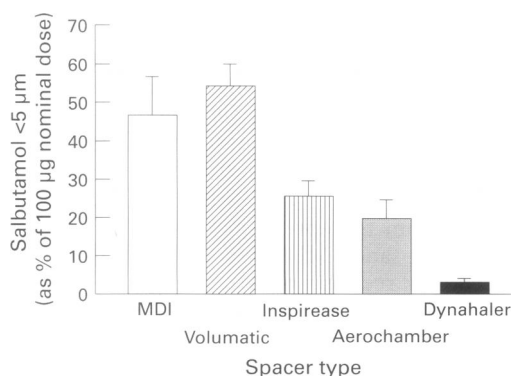


Figure 3 Amount of salbutamol (percentage of 100 µg dose) recovered in particles smaller than 5 µm aerodynamic diameter for five different spacer devices.

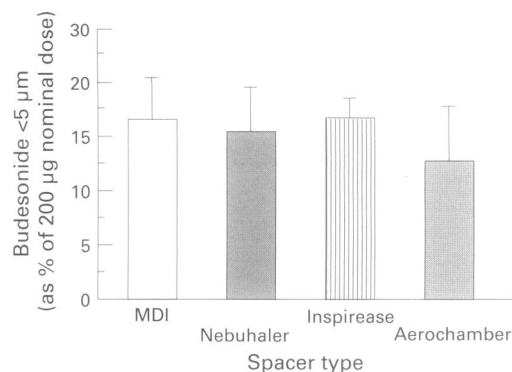


Figure 4 Amount of budesonide (percentage of 200 µg dose) recovered in particles smaller than 5 µm aerodynamic diameter for three different spacer devices.

compared with the MDI used without a spacer and the total drug delivery was a quarter of that from the MDI when a spacer was used ($p < 0.0005$, ANOVA).

The mean (SD) amount of drug recovered after a single actuation into a flask was 4.36 (0.28) mg for DSCG, 101 (13) µg for salbutamol, and 184 (9.5) µg for budesonide. Mean (SD) MDI weight loss per actuation was DSCG 138 (4.5) mg, salbutamol 86 (1.2) mg, budesonide 73 (2.6) mg. Coefficient of variation of the drug assay was 0.2% for DSCG, 2.1% for salbutamol, and 6% for budesonide.

During the experimental period the mean temperature was 23°C (range 21–25) and the mean relative humidity was 55% (range 51–63).

Discussion

This study demonstrates large variations in the amount of drug delivered from different spacer devices, and variations in the relative efficacy of a spacer to deliver different drugs. The Aerochamber, for instance, delivers only 36% of the fine particle dose of DSCG obtained when the MDI is used without a spacer, but 78% of the equivalent dose from the budesonide MDI. Both the Aerosol Cloud Enhancer and the Dynahaler delivered very small amounts of medication (less than 33% of the MDI fine particle dose). It is clear from these results that experiments with one spacer device or drug cannot be extrapolated to others.

Others have examined the effect of different size and shaped spacer devices on drug delivery in vitro, but have not investigated the particle size distribution of the spacer output, one of the main determinants of the site of drug deposition. Moren⁷ measured oral and spacer deposition of terbutaline using spacers of different length, diameter and shape and found that increasing the spacer length from 5 cm to 10 cm decreased oral deposition of drug but did not affect total drug recovery or, by inference, drug delivery to the patient. Maximum drug delivery was achieved using a pear shaped spacer of 25 cm length.

Kim *et al*⁶ compared the in vitro delivery of a variety of inhaled steroids and bronchodilators used with the Nebuhaler, Aerochamber, and Inspirease. They found that the large volume Nebuhaler substantially increased the aerosol delivery to the lung of their model (by up to

38% compared with the MDI), but that the smaller Aerochamber and Inspirease did not. They found increased delivery to their model lung when steroid suspensions were compared with bronchodilator solutions delivered through the smaller spacers, similar to our finding of less difference between spacers when used with the budesonide MDI.

Patient size and breathing pattern may also be important in the choice of spacer device. Particles settle in the spacer after only a few seconds⁷⁻⁸ and, from our results, the concentration of fine particles in small spacers is higher than in larger ones. This may be important in small children, for whom a few small breaths from concentrated aerosol in a small spacer may deliver more drug than would be obtained from a large spacer. This is supported by an in vitro study evaluating the total dose of DSCG aerosol obtained at different tidal volumes through spacer devices⁹ which showed that the Aerochamber delivered more drug than the Nebuhaler at tidal volumes below 50 ml, but that this was reversed at a tidal volume of 150 ml.

Other factors such as static charge,⁷ spacer shape, or valve design¹⁰ may be involved in determining drug delivery. These and other important factors in spacer design and use have not been investigated adequately.

In radiolabelled and clinical studies of adults and older children, large cone spacers are more effective than the MDI used alone¹¹⁻¹² whereas small volume spacers are only as effective as the optimally used MDI.¹³⁻¹⁴ Both the small and large volume spacers reduce oropharyngeal deposition and side effects of inhaled steroid therapy.¹⁵ There are few clinical data comparing different spacers in the delivery of inhaled steroids. Differences in clinical response to bronchodilators delivered via different spacer devices have been described in some studies,¹⁶⁻¹⁸ but not all,¹⁹⁻²⁰ perhaps because the dose of drug delivered tends to fall on the flat part of the dose response curve.²¹ The clinical relevance of small differences in bronchodilation with different spacers is not clear.

Although some spacers are physically suitable for many different brands of MDI and have been recommended for a range of inhalers,²² it may not be possible to use the results of an experiment with one particular MDI and spacer to predict the performance of the spacer with another drug. We have shown that differences in the delivery of budesonide from different spacers are not as great as those observed with DSCG and salbutamol. This may be due to a number of factors, such as decreased aerosol density with budesonide (one actuation of budesonide weighs 60–70 mg compared with 140 mg for DSCG), differences in aerosol cloud morphology, or interaction with the spacer walls due to static charge. The imminent phasing out of chlorofluorocarbon use in MDIs may change the aerosol cloud characteristics and necessitate a re-evaluation of MDIs and spacer devices.

Both the Dynahaler and Aerosol Cloud Enhancer gave very poor output of respirable drug. However, these spacers are designed for

adults who will be able to commence inhalation just before MDI actuation. Even when sampling is commenced before MDI actuation, mimicking the optimum clinical use, the spacers deliver small amounts of DSCG relative to a large volume spacer or the MDI alone. Up to 70% of adults are not able to coordinate the hand-breath manoeuvres of MDI use.²¹ Our study implies that the Dynahaler and Aerosol Cloud Enhancer may not be as useful for patients with poor inhaler technique.

All the spacers tested reduced the total amount of drug delivered from the spacer compared with the MDI alone and, in most cases, reduced the size of drug particles that were delivered, shown by the reduction in MMAD of the aerosol from the spacers. This is one advantage of spacer devices, as larger drug particles are retained in the device rather than being deposited in the oropharynx where they may contribute to drug related side effects.

The MSLI uses a series of inertial impactors to fractionate the aerosol cloud by particle aerodynamic size. It samples at a fixed flow rate of 60 l/min and is not intended to mimic respiration but to determine particle size, one of the main determinants of aerosol deposition. The issues of inspiratory flow, airway structure, and airway calibre are not addressed in this study in which we have determined the amount of drug below a certain size that is available for inhalation. The choice of 5 µm to define the "fine particle dose" is also arbitrary as the optimum particle size for an inhaled medication will depend on many factors such as inspiratory flow, upper airway geometry, and airway calibre. The MSLI may underestimate particle size due to desiccation of particles as they pass through the system, in contrast to the respiratory tract where hygroscopic drug particles would be expected to grow significantly in size.²³ This would affect all the spacers in the study, however, allowing devices to be ranked in terms of their drug output and valid comparisons between devices to be made.

We have shown that the in vitro delivery of drug in small particles varies greatly between different spacer devices and that the efficacy of a particular spacer with one drug cannot be assumed for another drug. The factors underlying this and the design of the optimum spacer are yet to be determined and confirmed in clinical trials, but our data suggest that it is inappropriate to use any drug with any device uncritically just because the MDI adapter fits.

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