The effect of delay, multiple actuations and spacer static charge on the *in vitro* delivery of budesonide from the Nebuhaler

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A multistage liquid impinger was used to determine the amount of budesonide available from the NebuhalerTM spacer device following alteration of spacer static charge, delay in sampling from the spacer, and multiple actuations of the metered dose inhaler into the spacer prior to sampling. The mean amount of budesonide (s.d.) recovered per 200 µg actuation in particles smaller than 5 µm increased from 30.5 µg (8.8) to 69.3 µg (17.9) with a low static spacer. A 20 s delay between actuation and inhalation reduced the amount recovered to 10.9 µg (3.2), but no reduction was seen when using a low static spacer after the same delay. Multiple actuations into the spacer before sampling also reduced the recovery to 24.8 µg (3.4) after two actuations, and 13.5 µg (7.6) after five actuations. When using a Nebuhaler with budesonide metered dose inhalers, more respirable drug will be obtained if the aerosol is inhaled immediately after actuation, and multiple actuations into the spacer device are avoided. Low static spacers may also improve drug delivery. Attention to the details of spacer use may reduce the incidence of therapeutic failure and the cost of inhaled medications.

Keywords budesonide corticosteroids drug administration-inhalation drug delivery devices asthma electrostatic charge

Introduction

Spacer devices are often used to improve inhalational drug delivery in bronchial asthma. Optimum spacer use improves asthma management, reducing side effects and the cost of wasted drugs from poor inhaler technique [1]. We have previously shown that the delivery of drugs from different spacers is greatly affected by the exact method of use [2, 3, 4]. In this paper we describe the effect of spacer static charge, multiple actuations and delay on the delivery of budesonide from the Nebuhaler spacer device.

Methods

A Multistage Liquid Impinger (MSLI) [5] was used to determine the size distribution of the budesonide aerosol under different conditions. This draws aerosol 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. After each experiment, the stages were washed with ethanol, and the amount of drug collected in each stage was assayed by high performance liquid chromatography. An isocratic system using an ethanol:water mobile phase, 5 cm ODS1 column and internal standard methodology was used. Detection was by u.v. spectrophotometry at a wavelength of 252 nm.

Spacer electrostatic charge was determined by measuring the field strength within the spacer with an electrostatic meter (EVM12, Static Safe Environments Ltd, Birmingham UK). Field strength was measured inside both ends of the spacer device at a fixed position under identical conditions immediately prior to each experiment, and is reported in arbitrary units of charge.

Six MDIs of budesonide (Pulmicort, 200 µg per actuation, Astra Pharmaceuticals, Kings Langley, UK) were used, and six new Nebuhalers (Astra Phar-

maceuticals, Kings Langley, UK). One Nebuhaler was treated by coating the inside with an antistatic lining (Static Safe Ltd, Birmingham, UK).

The first ten actuations from each MDI were fired to waste. For each experiment the MDI was shaken for 10 s and actuated into the spacer. This was then attached to the MSLI. In this way, a total of ten actuations were fired into the spacer to facilitate the drug assay.

To assess the effect of delay prior to sampling, the MDI was actuated and 1, 10 or 20 s allowed to elapse prior to attaching the spacer to the MSLI.

To assess the effect of multiple actuations into the spacer, the MDI was actuated into the spacer one, two or five times prior to attaching it to the MSLI.

Immediately after each experiment, the amount of budesonide delivered from a single actuation of the MDI was determined to ensure that the prescribed amount of drug was delivered under the test conditions.

Each experiment was repeated four times. Mean temperature during the experiments was 24°C (range 22–26) and the mean relative humidity was 59% (range 53–68). There was no significant difference in these parameters between the different experiments.

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 known particle size distribution. From this a log-probability plot was constructed [6], and the mass median aerodynamic diameter (MMAD), and the geometric standard deviation (GSD) were determined. Recovery of drug contained in particles smaller than 5 and 3 µm and the total dose recovered from the MSLI under the differ-

ent test conditions was compared using analysis of variance after log transformation. Analysis was undertaken using Minitab statistical software (Clecom Ltd, Birmingham, UK).

Results

Particles smaller than 5 µm are thought to enter the respiratory tract (the respirable range). We report on the amount of drug recovered (mean and s.d.) in particles smaller than 5 and 3 µm, the MMAD and GSD for the different experiments (Table 1).

Use of the antistatic spacer significantly increased respirable drug ($P < 0.001$) from a mean of 30.5 µg (s.d. 8.8) to 69.3 µg (17.9) (Figure 1) and total drug delivery ($P < 0.001$) from 47.5 µg (9.5) to 110.9 µg (8.9).

Drug recovery decreased with increasing residence time ($P = 0.019$). After 20 s the mean amount of respirable budesonide fell to 22.9 µg. This effect was not seen with the antistatic spacer (Figure 1).

Multiple actuations also decreased respirable drug recovery per actuation ($P = 0.045$) from 30.5 µg (8.8) with one actuation to 24.8 µg (3.5) with two actuations and 13.5 µg (7.6) with five actuations (Figure 1).

The coefficient of variation of the budesonide assay was 6%, and the mean total recovery of budesonide was 171 µg per 200 µg actuation. Mean field strength in the Nebuhalers was 2867 arbitrary units, range 250–7900. By comparison, field strength in the antistatic spacer was less than 100.

Table 1 The effect of different methods of use of the Nebuhaler on the delivery of budesonide.

Method of delivery	Mean amount of budesonide recovered (µg) per 200 µg actuation (s.d.)				
	Dose to patient	In particles < 5 µm	In particles < 3 µm	MMAD (µm)	GSD
<i>Effect of anti-static lining*</i>					
Standard Nebuhaler	47.5 (9.5)	30.5 (8.8)	15.4 (8.9)	4.0 (0.7)	1.8 (0.2)
Anti-static Nebuhaler	110.9 (8.9)	69.3 (17.9)	25.8 (9.9)	4.4 (0.7)	1.6 (0.04)
<i>Effect of delay†</i>					
No delay	47.5 (9.5)	30.5 (8.8)	15.4 (8.9)	4.0 (0.7)	1.8 (0.2)
10 s delay	30.6 (20.6)	22.9 (15.6)	10.7 (6.7)	3.5 (0.3)	1.7 (0.2)
20 s delay	14.2 (4.1)	10.9 (3.2)	5.9 (1.6)	3.3 (0.1)	1.7 (0.03)
Anti-static +20s delay	89.5 (13.7)	62.8 (17)	22 (11)	4.1 (0.5)	1.5 (0.1)
<i>Effect of multiple actuations††</i>					
1 actuation	47.5 (9.5)	30.5 (8.8)	15.4 (8.9)	4.0 (0.7)	1.8 (0.2)
2 actuations	38.9 (10.2)	24.8 (3.5)	9.4 (2.7)	4.1 (0.6)	1.6 (0.1)
5 actuations	18.7 (10.6)	13.5 (7.6)	6.8 (3.8)	3.6 (0.2)	1.7 (0.1)

* $P < 0.001$ Effect of the use of anti-static spacer on the recovery of drug in particles smaller than 5 µm.

† $P = 0.019$ Effect of increasing delay on the recovery of drug in particles smaller than 5 µm.

†† $P = 0.045$ Effect of multiple actuations on the recovery of drug in particles smaller than 5 µm.

Figure 1 The amount of budesonide (+ s.d.) contained in particles less than 5 µm (per 200 µg actuation) available for inhalation from the nebulizer spacer device under various experimental conditions.

Discussion

This study shows that the amount of budesonide available for inhalation from the Nebuhaler spacer device is decreased by high spacer static charge, by delay prior to inhalation and by multiple actuations of the metered dose inhaler into the spacer prior to inhalation. This is clearly important in the delivery of a drug where clinical response is related to the dose administered. Incorrect use of the Nebuhaler may lead to therapeutic failure. The present study confirms the work of ourselves and others into multiple dosing into spacer devices with beclomethasone dipropionate [4], sodium cromoglycate [3, 7, 8] and nedocromil sodium [2].

We have also shown that static charge affects sodium cromoglycate delivery from a Fisonair™ spacer [3]. Low static spacers may allow reduction of drug dosage and hence reduced drug costs with the same clinical effect. They may also allow a delay between actuation and inhalation, which is important when administering the drug to a non-cooperative

patient or child. Care should be taken however as the low static spacer also increased delivery of larger particles of budesonide, which may contribute to local and systemic side effects.

This laboratory study suggests that the optimum way to use the Nebuhaler spacer device is to inhale immediately after actuation of the metered dose inhaler and avoid multiple actuations into the spacer. Spacer static charge may also play an important part in reducing drug delivery from the Nebuhaler. We hope to confirm the importance of these results with clinical trials on patients with asthma.

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References

- 1 Keeley D. Large volume plastic spacers in asthma (editorial). *Br Med J* 1992; **305**: 598–599.
- 2 Barry PW, Robertson C, O'Callaghan C. Optimum use of a spacer device. *Arch Dis Child* 1993; **69**: 693–694.
- 3 O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in Drug delivery from spacer devices by use of an anti-static lining. *Thorax* 1993; **48**: 603–606.
- 4 O'Callaghan C, Cant M, Robertson C. Delivery of beclomethasone dipropionate from a spacer device: What dose is available for inhalation? *Thorax* 1994; **49**: 961–964.
- 5 Bell JH, Brown K, Glasby J. Variations in the delivery of isoprenaline from various pressurised inhalers. *J Pharm Pharmacol* 1973; **25** (Suppl): 32–36.
- 6 Hinds WC. *Aerosol Technology*. Wiley, New York, 1983.
- 7 Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. *Arch Dis Child* 1992; **67**: 580–585.
- 8 Clark AR, Rachelefsky G, Mason PL, Goldenhersh MJ, Hollingworth A. The use of reservoir devices for the simultaneous delivery of two metered dose aerosols. *J Allergy Clin Immunol* 1990; **85**: 75–79.

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