A comparative analysis of the particle size output of beclomethasone dipropionate, salmeterol xinafoate and fluticasone propionate metered dose inhalers used with the Babyhaler, Volumatic and Aerochamber spacer devices

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Aims To determine *in vitro* the effect of delay, inspiratory flow, and spacer washing on the drug output of metered dose inhalers (MDIs) used with different spacer devices.

Methods The amount of drug in particles $<5\ \mu\text{m}$ diameter from MDI + spacer, sampling after a delay of up to 20 s, was measured using a Multistage Liquid Impinger. Drug output was also measured at different flow rates, and after washing the Babyhaler in household detergent.

Results More fluticasone in small particles was recovered from the Babyhaler than the Volumatic or the Aerochamber spacers, and more beclomethasone and salmeterol was recovered from the Babyhaler and Volumatic spacers than from the Aerochamber. Washing the Babyhaler reduced the recovery of salmeterol, and did not alter the recovery of the other drugs tested.

Conclusions Spacer devices need to be fully evaluated for each drug prescribed for them.

Keywords: asthma, drug administration—inhalation, spacer devices

Introduction

Spacer devices are increasingly used to aid inhalation therapy. They reduce the need for co-ordination of metered dose inhaler (MDI) actuation and inhalation, and reduce extrathoracic deposition of medication [1]. Delay between MDI actuation and inhalation, and high spacer static charge reduce the output of some medications from some spacer devices [2–4]. To investigate this further, we undertook an *in vitro* study to determine the amount of beclomethasone dipropionate, salmeterol xinafoate and fluticasone propionate available for inhalation from three commonly used spacer devices under different conditions.

Methods

New MDIs of beclomethasone dipropionate (Becotide 50 μg /actuation, Allen & Hanburys, Uxbridge, UK), salmeterol xinafoate (Serevent 25 μg /actuation, Allen & Hanburys, Uxbridge, UK) and fluticasone propionate (Flixotide 50 μg /actuation and 125 μg /actuation, Allen & Hanburys, Uxbridge, UK) and new Babyhaler (Allen &

Hanburys, Uxbridge, UK), Volumatic (Allen & Hanburys, Uxbridge, UK) and Aerochamber (Trudell Medical, Ontario, Canada) spacer devices were obtained.

The four stage Multistage Liquid Impinger (MSLI) [5] was used to determine the particle size of aerosols from the spacers. The MSLI draws aerosol through a glass 'throat' and then a series of stages, each containing a glass impaction plate. Progressively smaller particles collect at each stage and a final filter. The cut off diameters of the four stages were 12 μm , 7 μm , 4.7 μm and 0.9 μm , respectively. After each experiment, the MSLI was washed with an appropriate solvent and the amount of drug collected determined by high performance liquid chromatography.

Flow through the MSLI was $60\ \text{l min}^{-1}$ for all experiments except those investigating the effect of reduced flow. The MDI was shaken for 10 s, then actuated into the spacer. After a delay of between one and 20 s, the MSLI was attached to the spacer for 30 s. This procedure was repeated 10 times in total (20 times in the case of experiments with salmeterol) to facilitate the drug assay.

The following experiments were undertaken:

To determine the effect of delay between MDI actuation and sampling, drug was aspirated from the spacers after a delay of 1, 5, 10 and 20 s from MDI

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actuation. Each spacer/drug combination was assessed at each time delay on four occasions.

To determine the effect of different inspiratory flows, the spacer devices were aspirated at flows of 20 and 60 l min⁻¹. For each flow, spacer and drug combination, the experiment was repeated on four occasions.

To determine the effect of washing the Babyhaler, drug output was measured from a Babyhaler before and after washing 10 times with warm soapy water, rinsing and drip drying. This washing technique was chosen to simulate normal, household washing. Eight Babyhalers were assessed with each drug in this way.

Statistical methods

Results are expressed in terms of the total amount of drug recovered from the MSLI, and that recovered from stages 4 and filter, representing particles smaller than 4.7 µm at a flow of 60 l min⁻¹. Analysis of differences between different spacers, flows and times was by analysis of variance (ANOVA). Drug half life within the spacer was determined by linear regression of the logarithm of drug recovery against time. Differences in recovery between different flows and between new and washed spacers were compared using unpaired *t*-tests. Probability values are given without correction for multiple comparisons and statistical significance is assumed at *P*=0.05.

Results

Drug output (Table 1)

The results show a higher recovery of small particles (<5 µm diameter) of fluticasone (50 µg) from the Babyhaler device than the Volumatic spacer or the Aerochamber (*P*<0.001). More small particle beclomethasone, fluticasone (125 µg) and salmeterol was recovered from the Babyhaler and Volumatic spacers than from the Aerochamber (*P*<0.001).

Delay

All the spacers tested have a lower recovery of drug after a delay between MDI actuation and sampling (Table 1) (*P*<0.0001). The drug half-life was ≈15 s for beclomethasone, 8–10 s for salmeterol and 8–9 s for fluticasone irrespective of the spacer studied.

Flow

Testing the spacers at low flow reduced the total recovery of salmeterol via the Babyhaler (*P*=0.003), but not the Volumatic or Aerochamber. The recovery of fluticasone 125 µg was reduced at low flow via the Volumatic spacer (*P*=0.008) but not from the other spacers. The recovery

of beclomethasone and fluticasone 50 µg was not affected by flow. In general, the variability of recovery was greater for the Babyhaler than the other spacers.

Washing the spacer

Washing the Babyhaler increased the recovery of small particles from the fluticasone 125 µg MDI (from a mean of 29.6 µg (new spacer) to 39.8 µg (washed spacer), *P*<0.01), did not alter the recovery of beclomethasone (from 19.3 µg to 17.1 µg, *P*=0.1) or fluticasone 50 µg (from 15.7 µg to 13.3 µg, *P*>0.05), and reduced the recovery of salmeterol (from 13.3 µg to 9.7 µg, *P*<0.0002).

Total recovery

The total recovery of drug from the adapters, spacers and all parts of the MSLI was determined. A mean of over 88% of the nominal dose was recovered from the experiments with beclomethasone, salmeterol and fluticasone 125 µg, but only 72.8% (95% CI 70.0%–75.5%) of the nominal dose from the experiments with fluticasone 50 µg. Repeat experiments with a different batch of fluticasone 50 µg MDIs confirmed this low total recovery. Total recovery was not significantly different between the various experiments with the same drug.

Discussion

This study has demonstrated a reduction in drug delivery *in vitro* from three commonly used spacer devices when there is delay between MDI actuation and inhalation. These findings are consistent with previous studies of other drugs [2–4, 6] and have been supported by recent pharmacokinetic studies in adult volunteers [7].

The length of time that the drug aerosol remains suspended in the spacer is dependent upon the drug analysed, the 'half-life' being significantly longer for beclomethasone than for fluticasone or salmeterol. There was no difference in half life for each drug between the different spacers. This suggests that different drugs interact differently with spacers. One difference may be in the level of static charge on different aerosols. Static charge accumulates on the walls of polycarbonate spacers, attracting charged drug particles. Highly charged spacers have been shown *in vitro* [4, 6] and *in vivo* [8] to reduce the output of some medications. This has led to recommendations to wash spacers with detergent [9] to reduce their charge and increase the half-life of medication within the spacer. This may be important when administering drugs to uncooperative patients or children with small tidal volumes who will take longer to clear the spacer. We found a variable effect of washing on the

Table 1 Drug output of beclomethasone, salmeterol and fluticasone (50 µg and 125 µg per actuation) from spacers when assessed with the MSLI. Figures are µg per actuation, **Mean** and (95% confidence intervals).

	<i>Beclomethasone</i> dose to patient (µg)	<i>Dose in</i> <i>particles</i> < 4.7 µm (µg)	<i>Salmeterol</i> dose to patient (µg)	<i>Dose in</i> <i>particles</i> < 4.7 µm (µg)	<i>Fluticasone</i> dose to patient (µg)	<i>(50 µg) dose</i> <i>in particles</i> < 4.7 µm (µg)	<i>Fluticasone</i> dose to patient (µg)	<i>(125 µg) dose</i> <i>in particles</i> < 4.7 µm (µg)
<i>Effect of delay</i>								
<i>Babyhaler</i>								
1s	23.8 (22.5–25.2)	19.3 (18.3–20.4)	13.8 (13.1–14.4)	13.3 (12.7–13.9)	16.7 (15.0–18.4)	15.7 (14.1–17.2)	31.8 (28.3–35.2)	29.6 (26.7–32.6)
5s	19.6 (19.0–20.2)	15.7 (15.0–16.5)	8.0 (5.9–10.2)	7.8 (5.7–10.0)	12.2 (10.9–13.5)	11.5 (10.3–12.7)	15.8 (12.6–19.1)	15.4 (12.3–18.5)
10s	13.8 (11.5–16.2)	11.1 (9.5–12.8)	7.3 (6.6–8.0)	7.2 (6.6–7.8)	7.0 (5.1–8.8)	6.7 (4.9–8.4)	9.6 (8.1–11.0)	9.3 (7.9–10.6)
20s	9.3 (8.9–9.6)	7.6 (7.5–7.7)	4.4 (4.2–4.5)	4.3 (4.2–4.5)	4.0 (3.1–5.0)	3.8 (2.9–4.7)	6.1 (4.3–7.9)	6.1 (4.3–7.8)
<i>Volumatic</i>								
1s	22.7 (19.4–26.1)	17.3 (15.5–19.1)	13.2 (12.7–13.8)	12.5 (11.9–13.1)	11.4 (10.2–12.5)	10.5 (9.4–11.6)	30.6 (26.8–34.4)	28.7 (25.1–32.2)
5s	18.2 (16.0–20.3)	13.5 (11.7–15.3)	8.2 (7.7–8.8)	8.0 (7.5–8.6)	7.2 (4.9–9.6)	6.9 (4.7–9.1)	15.2 (13.9–16.6)	14.9 (13.6–16.2)
10s	14.9 (13.9–16.0)	12.1 (11.0–13.2)	5.3 (4.3–6.2)	5.3 (4.3–6.2)	5.1 (3.6–6.5)	4.8 (3.4–6.3)	11.3 (7.7–14.8)	11.0 (7.7–14.2)
20s	10.8 (7.7–13.9)	8.0 (5.4–10.5)	3.9 (2.6–5.2)	3.8 (2.6–5.1)	3.3 (2.7–3.9)	3.2 (2.6–3.8)	4.4 (3.7–5.1)	4.4 (3.7–5.1)
<i>Aerochamber</i>								
1s	15.2 (12.0–18.5)	11.5 (9.4–13.6)	9.6 (8.2–11.0)	8.2 (7.3–9.1)	7.1 (4.9–9.3)	6.6 (4.5–8.8)	17.9 (15.4–20.5)	17.0 (14.7–19.3)
5s	10.7 (8.9–12.4)	8.4 (7.0–9.7)	4.0 (3.7–4.3)	3.8 (3.6–4.0)	4.7 (4.2–5.3)	4.2 (3.2–5.3)	8.4 (6.4–10.5)	8.1 (6.4–9.8)
10s	8.8 (7.9–9.7)	7.2 (6.5–8.0)	3.6 (2.9–4.2)	3.6 (2.9–4.2)	3.5 (2.3–4.7)	3.3 (2.4–4.1)	7.0 (5.5–8.6)	6.9 (5.4–8.4)
20s	4.5 (3.3–5.6)	3.3 (2.1–4.5)	2.1 (1.5–2.7)	2.1 (1.5–2.7)	1.9 (1.6–2.2)	1.9 (1.6–2.2)	5.4 (4.5–6.3)	5.3 (4.3–6.2)
<i>Effect of flow</i>								
<i>Babyhaler</i>								
20 l min ⁻¹	21.7 (19.8–23.5)	17.0 (15.8–18.1)*	11.1 (10.2–12.0)	10.5 (9.7–11.3)*	14.4 (11.9–17.0)	13.2 (10.9–15.6)*	29.1 (26.4–31.7)	27.5 (24.9–30.2)*
60 l min ⁻¹	23.8 (22.5–25.2)	19.3 (18.3–20.4)	13.8 (13.1–14.4)	13.3 (12.7–13.9)	16.7 (15.0–18.4)	15.7 (14.1–17.2)	31.8 (28.3–35.2)	29.6 (26.7–32.6)
<i>Volumatic</i>								
20 l min ⁻¹	23.5 (22.3–24.6)	17.4 (16.4–18.4)*	11.6 (10.0–13.3)	11.2 (9.6–12.8)*	9.8 (8.0–11.7)	9.2 (7.5–10.9)*	21.0 (18.0–23.9)	19.7 (17.0–22.4)*
60 l min ⁻¹	22.7 (19.4–26.1)	17.3 (15.5–19.1)	13.2 (12.7–13.8)	12.5 (11.9–13.1)	11.4 (10.2–12.5)	10.5 (9.4–11.6)	30.6 (26.8–34.4)	28.7 (25.1–32.2)
<i>Aerochamber</i>								
20 l min ⁻¹	13.0 (12.3–13.6)	10.3 (10.2–10.4)*	8.0 (7.2–8.8)	7.7 (6.9–8.4)*	7.0 (6.4–7.6)	6.6 (6.0–7.2)*	16.5 (15.2–17.7)	15.9 (14.8–17.1)*
60 l min ⁻¹	15.2 (12.0–18.5)	11.5 (9.4–13.6)	9.6 (8.2–11.0)	8.2 (7.3–9.1)	7.1 (4.9–9.3)	6.6 (4.5–8.8)	17.9 (15.4–20.5)	17.0 (14.7–19.3)

*At 20 l min⁻¹ flow, particles smaller than 8 µm aerodynamic diameter would collect on stages 4 and filter.

output of different drugs from the Babyhaler, which increased the recovery of fluticasone (125 µg strength), did not alter the recovery of small particles of beclomethasone or fluticasone (50 µg strength), and *reduced* the recovery of salmeterol. Spacers were washed by briefly immersing them in dilute household detergent and rinsing them with tap water. Charge is variably affected by some washing processes [10], and it may be that we did not reduce the charge on the spacer which we were unable to measure at the time of the study. Others have shown a small increase in the output of salbutamol from a Volumatic spacer only after soaking it in soapy water for 15 min [9] or longer [10], without subsequent rinsing. It is clear from this study and others [9, 10] that the fine detail of washing and handling the spacer affects the output of certain drugs. Further research is needed to provide definitive guidance to patients on the optimal washing regime for their spacer.

Testing the spacers at low flow did not affect the delivery of most drugs from most spacers tested. However, there should be some caution in inferring clinical effect from *in vitro* experiments of particle size, made under constant flow conditions, which may not reflect drug delivery when the device is used with 'real' breathing patterns [11]. However, other findings using the MSLI at 60 l min⁻¹ have been supported by pharmacokinetic studies *in vivo* [7], suggesting that the method does have some clinical relevance.

In summary, when administered through the spacer devices tested here, medications should be inhaled immediately after actuation. Washing the Babyhaler in the way described affects the output of different medications in a variable and unpredictable way. The spacers tested differed substantially in the amount of drug delivered from them. It is clear that spacer devices need to be fully evaluated for each drug prescribed for them.

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