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Factors affecting the efficiency of aerosol therapy with pressurised metered-dose inhalers through plastic spacers

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Summary

Aim: The main objective of this study was to compare the *in vitro* delivery of salbutamol from a chlorofluorocarbon(CFC)-propelled pressurised metered-dose inhaler (pMDI) versus a newly developed hydrofluoroalkane(HFA)-propelled pMDI through various spacers. In addition, we aimed to study the effect on bronchodilator response when using an optimal pMDI/spacer combination for aerosol delivery compared to a suboptimal combination.

Methods: Particle size distribution and output from salbutamol pMDIs containing either CFC propellants (Ventolin®) or HFA propellants (Airomir®) were measured using a multistage liquid impinger (MSLI) and compared to that through both detergent-coated (non-static) or untreated (static) large volume (Nebuhaler®, Volumatic®) and small volume (Aerochamber®) plastic spacers. Flow-volume curves (FEV_1) were obtained from twelve asthmatic children with known significant bronchodilator response (8 males), aged 13–17 years, randomly inhaling salbutamol from a CFC-pMDI through a static spacer (Nebuhaler®) and from an HFA-pMDI through a non-static spacer (Nebuhaler®).

Results: In vitro output of particles in the respirable range (<6.8 µm) from HFA-pMDIs was significantly higher than that from CFC-pMDIs using various spacers. Removal of electrostatic charge increased output from CFC- and HFA-pMDIs through all spacers by 17–82%. The mean (SD) bronchodilator response after inhalation of salbutamol from a CFC-pMDI through a static spacer was 7.1% (6.3%) compared to 17.5% (7.9%) after inhalation from an HFA-pMDI through a non-static spacer ($p = 0.002$).

Conclusions: Use of a newly developed HFA-propelled pMDI greatly improves drug delivery through spacers compared to a CFC-propelled pMDI. However, electrostatic charge in plastic spacers remains the key determinant limiting delivery of salbutamol from a pMDI through spacers, and can be reduced by soaking the spacer in a household detergent. Using an optimal pMDI/spacer combination leads to a significantly improved bronchodilator response.

Keywords: spacers; holding chambers; electrostatic charge; salbutamol; HFA; CFC; aerosol therapy

Introduction

Inhalation therapy plays a major role in the management of asthma [1]. The choice of an optimal inhalation device is essential in achieving effective, predictable and consistent dose delivery to the airways of asthma patients. Pressurised metered-dose inhalers (pMDIs) are the most widely used form of inhalation therapy for asthmatics. However, there are a number of problems associated with their use. After actuation, the aerosol cloud leaves the canister at very high speed, and thus leads to high aerosol deposition in the oropharynx when actuated directly into the mouth. To overcome these problems, holding chambers (spacers) are widely used [2]. The main function of a spacer device is to act as a chamber reservoir where the actuated aerosol cloud can be held prior to inhalation by the patient. The use of spacers is specifically recommended in children, in order to prevent difficulties in coordinating actuation and inhalation [3].

However, it has been shown that the actuated dose from a pMDI through a spacer reaching the lungs of children is still relatively low, suggesting that additional factors influence drug delivery. A radio-labelled deposition study in children has shown that only 5% at most of the total actuated dose from a pMDI through a plastic spacer actually reaches the lungs [4]. Several *in vitro* and *in vivo* studies have shown that various factors influence the dose delivered from a holding chamber and may be responsible for this poor efficiency [5–14]. These include chamber size, shape, resistance of the valve, dead volume, the use of multiple actuations, inhalation delay, and construction materials which affect the levels of electrostatic charge in the chamber. Electrostatic charge is inherent to all plastic devices, including plastic spacers, owing to their non-conducting properties. The charge varies in a random manner. The net effect of electrostatic charge is absorption of aerosol particles onto plastic surfaces of the spacers, leading to a significant reduction in the initial dose available for inhalation and hence the lung dose. The most widely marketed spacer devices are manufactured from plastic. Extensive *in vitro* and *in vivo* work has been carried out to determine the effect of static charge on drug delivery from pMDIs through plastic spacers, and it has been found that the output from these spacers can be increased by reducing static [5, 15].

Reducing electrostatic charge, and hence increasing the ratio between dose delivered to the patient and dose delivered to the spacer, not only increases drug delivery but also reduces variability in delivery [15]. This has major implications, especially for children, in whom drug delivery is already highly variable due to age-specific breathing patterns such as low tidal volumes and low inspiratory flows. It has been shown that drug delivery to children is much higher and less dependent on breathing patterns when using non-electrostatic spacers [12, 16].

Much of the work on the effect of detergent coating of spacers has been carried out using chlorofluorocarbon(CFC)-propelled pMDIs. Because of the harmful effect of CFC propellants on the ozone layer, these pMDIs are being phased out and replaced by pMDIs containing hydrofluoroalkane (HFA) propellants, which have different aerosol characteristics [17–22].

The main objective of this study was therefore to compare *in vitro* delivery of salbutamol from CFC-pMDIs versus the newly developed HFA-pMDIs through various spacers and under different conditions. In addition, based on our *in vitro* findings, the clinical impact of using an optimal pMDI/spacer combination on bronchodilator response was analysed.

Material and methods

In vitro

The particle size distribution and output from salbutamol pMDIs (nominal dose: 100 µg/actuation), containing either CFC propellants (Ventolin®, Glaxo Wellcome, UK) or HFA propellants (Airomir®, 3M Pharmaceuticals, UK) were measured and compared with those through both large volume (750 ml; Nebuhaler®, Astra-Zeneca, UK and Volumatic®, Glaxo-Wellcome, UK) and small volume (165 ml; Aerochamber®, Trudell, Canada) plastic spacers. The effect of electrostatic charge was tested by comparing new spacers carrying a static charge (3.3–6.7 $\mu C/m^2$) with spacers coated with detergent to remove static (0–1.2 $\mu C/m^2$). The impact of the valves on particle size distribution and output from non-static CFC-pMDIs was also analysed by removing the valves. To coat spacers with detergent, they were soaked for 20–30 minutes in a commercially available ionic detergent (Palmolive®, UK) and allowed to drip dry. Particle size distribution and total drug delivery was measured using a multistage liquid impinger (MSLI; Copley, Nottingham, UK) with an inhalation flow of 60 l/min. The pMDI was attached to the spacer and the spacer was inserted into the MSLI "throat". In each case, a complete seal was ensured by using an appropriate adaptor at the "throat". The pMDI was shaken vigorously for 30 seconds prior to actuation, and the first two actuations were wasted. In total, ten single actuations were introduced into the MSLI. The pMDI was shaken vigorously for five seconds between each actuation. The aerosol generated by the pMDI was drawn immediately through the MSLI with the entraining airflow. Droplets were deposited on the actuator, spacer, throat and stages 1 to 4. The location of particle deposition was determined by the aerodynamic size of the particle. The sizes of particles depositing on stages 1, 2, 3 and 4 were >13 µm, 6.8–13 µm, 3.1-6.8 µm and <3.1 µm.

The actuator, spacer, throat and stages of the MSLI were washed with approximately 40 ml of methanol. Five ml of 0.1M NaOH was added to each wash, and the volume was then made up to a total of 50 ml with methanol. The absorbance (246 nm) of each sample was measured in duplicate on a spectrophotometer. The concentration of salbutamol in the samples was obtained by using the absorbance of a solution containing a known concentration of salbutamol. The standard curve for salbutamol was linear ($r^2 = 1.00$) for concentrations between 0 and 27 µg/ml. Each experiment was repeated four times and the temperature, relative humidity and barometric pressure were recorded.

In vivo

Twelve asthmatic children (8 males) under regular inhaled steroid therapy, with known airflow obstruction (mean [SD] % predicted FEV_1: 68% [9%]) and known significant bronchodilator response, aged 13–17 years, were studied in a randomised, double-blind, placebo-controlled, crossover trial twice. The children inhaled on two visits (one week apart) once 200 µg salbutamol from a CFC-pMDI (Ventolin®, Glaxo-Wellcome, UK) through a new, static spacer (Nebuhaler®, Astra Zeneca, UK) and 200 µg salbutamol from an HFA-pMDI through a detergent coated, non-static spacer (Nebuhaler®, Astra Zeneca, UK). The Nebuhaler® was chosen for its superior *in vitro* performance in delivering salbutamol. Flow-volume curves were obtained before and five minutes after in-

halation, and FEV_1 measurements were compared. Subjects were eligible if they had bronchodilator responsive airflow limitation, defined as an improvement in FEV_1 from baseline of at least 10%. The study was approved by the Hospital Ethics Committee and informed consent was obtained from the parents.

Statistical analysis

In vitro

Results were calculated as mean (SD) % of the total dose. Statistical analysis (StatView 512+; Abacus Concepts Inc., Berkely, CA, USA) was carried out using analysis of variance (ANOVA) for unmatched data. Post-hoc analysis was performed using the Fisher protected least significant difference (Fisher PLSD), with a significance level of 95% ($p < 0.05$), unless otherwise stated.

In vivo

The mean and standard deviation (SD) are reported for baseline spirometry and following inhalation of the bronchodilator. Paired t-test was used to determine the differences between responses with each spacer. Significance was accepted at the 0.05 level.

Results

In vitro

Output of particles <6.8 µm (stage 3 and 4; respirable range) from HFA-pMDIs was significantly higher than from CFC-pMDIs, using either static spacers or non-static spacers ($p < 0.0001$) (table 1).

Removal of static increased output from both CFC- and HFA-pMDI through all spacers by 17–82% ($p < 0.0001$) (table 1). Drug delivery from CFC-pMDIs through all spacers with static was similar and not significantly different (table 1). However, drug delivery from HFA-pMDIs through the static Nebuhaler® was higher compared to the static Volumatic® and the static Aerochamber® ($p < 0.0001$). Among the non-static spacers, the Nebuhaler® delivered a significantly greater amount of particles smaller than 6.8 µm from CFC-pMDIs ($p = 0.0001$) and HFA-pMDIs ($p < 0.0001$) as compared to the Volumatic® and the Aerochamber®. There was no significant difference in delivery between the Volumatic® and the Aerochamber® (CFC-pMDI; $p = 0.07$; HFA-pMDI; $p = 0.1$).

With the valves removed, all spacers had a greater output than with the valve in place (table 1). There was a smaller though significant increase in output from the non-static Nebuhaler® ($p = 0.0008$) and Aerochamber® ($p = 0.002$) without the valves, as compared to the remarkable increase in output after removal of the valves from the Volumatic® ($p < 0.0001$). Output from both large volume spacers with removed valves was significantly higher than from the small volume spacer ($p < 0.0001$) (table 1).

In vivo

The mean (SD) FEV_1 before and after inhalation of salbutamol from a CFC-pMDI through a static spacer was 2.78 L (0.53) and 2.98 L (0.55) respectively, with a mean (SD) bronchodilator response of 7.1% (6.3%). The mean (SD) FEV_1 before and after inhalation of salbutamol from an HFA-pMDI through a non-static spacer was 2.67 L (0.42) and 3.13L (0.51) respectively, with a mean (SD) bronchodilator response of 17.5% (7.9%) (fig. 1).

Table 1

Influence of various factors, such as the propellant used, electrostatic charge on the surface and design of the spacer, on the mean percentage (SD) drug output* of salbutamol through large (Nebuhaler® and Volumatic®) and small (Aerochamber®) volume spacers.

			Nebuhaler®	Volumatic®	Aerochamber®
CFC-pMDIs	**Static**	actuator	5.1 (1.0)	7.1 (0.9)	6.6 (1.6)
		spacer	57.0 (1.3)	55.0 (2.1)	54.2 (2.7)
		throat	0.9 (0.4)	1.2 (0.5)	1.5 (0.7)
		stages 1 and 2	3.8 (0.8)	4.1 (1.0)	2.6 (0.9)
		stages 3 and 4	**33.2 (1.9)**	**32.6 (1.8)**	**35.1 (3.5)**
	Non-static	actuator	6.8 (1.8)	8.2 (1.8)	7.1 (1.6)
		spacer	23.6 (4.2)	38.4 (2.0)	41.5 (1.7)
		throat	1.1 (0.5)	0.9 (0.4)	1.0 (0.3)
		stages 1 and 2	8.2 (1.1)	8.1 (1.4)	7.9 (1.4)
		stages 3 and 4	**60.3 (2.9)**	**44.4 (2.5)**	**42.5 (2.0)**
	Valve removed	actuator	8.4 (1.3)	6.6 (1.4)	9.2 (1.6)
		spacer	17.9 (2.3)	21.1 (2.2)	37.5 (0.7)
		throat	0.7 (0.5)	1.4 (0.4)	0.9 (0.3)
		stages 1 and 2	8.2 (1.6)	7.2 (0.7)	7.5 (1.7)
		stages 3 and 4	**64.8 (2.2)**	**63.7 (4.2)**	**44.9 (0.6)**
HFA-pMDIs	**Static**	actuator	4.1 (1.2)	5.2 (1.2)	4.1 (0.6)
		spacer	36.1 (1.6)	44.1 (3.0)	42.0 (2.5)
		throat	0.2 (0.2)	1.4 (0.8)	1.2 (0.3)
		stages 1 and 2	1.0 (0.5)	2.1 (0.4)	2.7 (1.2)
		stages 3 and 4	**58.6 (2.3)**	**47.2 (2.6)**	**50 (2.8)**
	Non-static	actuator	4.1 (0.5)	5.2 (1.6)	4.0 (1.0)
		spacer	19.0 (2.6)	30.8 (3.7)	32.5 (1.5)
		throat	2.0 (1.0)	1.4 (1.1)	1.2 (1.3)
		stages 1 and 2	5.9 (1.2)	6.2 (1.6)	4.0 (2.2)
		stages 3 and 4	**69.0 (1.2)**	**56.4 (2.5)**	**58.3 (2.4)**

* Cutoffs of particles >13, 6.8 to 13, 3.1 to 6.8, and <3.1µm for stage 1, 2, 3, and 4 respectively. Stages 3 and 4 contain particles <6.8µm, which are in the respirable range.

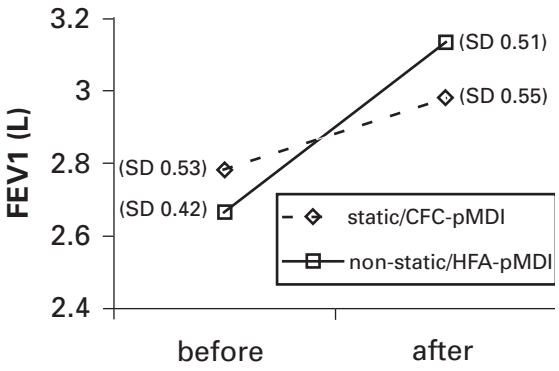

Figure 1

Flow-volume curves before and five minutes after inhalation of 200 μg salbutamol from a CFC-pMDI through a new, static spacer (Nebuhaler®) and from an HFA-pMDI through a detergent-coated, non-static spacer (Nebuhaler®).

Discussion

The results of this study indicate that the delivery of salbutamol from newly developed HFA-propelled pMDIs through spacers is significantly improved compared to CFC-propelled pMDIs. However, electrostatic charge on the surface remains the key determinant limiting delivery of salbutamol from either CFC- or HFA-pMDIs through both large and small volume plastic spacers. In addition, we have demonstrated a significant improvement in bronchodilator response when salbutamol was delivered from an HFA-pMDI through a non-static spacer, compared to a CFC-pMDI through a static spacer. These findings highlight the importance of using a non-static spacer for inhalation therapy with pMDIs, as well as the use of newly developed HFA-propelled pMDIs.

When CFC-pMDIs using various static spacers were compared, the output was uniformly low despite varying volume and design. This finding suggests that the buildup of sufficiently high levels of static in plastic spacers overrules the differences in output from CFC-pMDIs through spacers, owing to differing volume and design. However, when HFA-pMDIs using various static spacers were compared, the drug delivery through the static Nebuhaler® was higher compared to the static Volumatic® and the static Aerochamber®, indicating that the design of the spacer plays a role when using HFA-pMDIs. When static is reduced in different large and small volume spacers, there is still a difference in aerosol delivery and hence performance with both CFC- and HFA-pMDIs, due to differences in volume and design. Without static, the output from the Nebuhaler® was greater than from another large volume spacer, the Volumatic®, probably owing to resistance of the valve. This observation shows the importance of the valve in drug delivery from spacers and confirms the results of other studies [23]. When the valve from the Volumatic® was removed the output increased by 43%, indicating that this valve does indeed significantly impede drug delivery [23]. Only a small increase of 5.6–7.5% was observed when the Nebuhaler® or Aerochamber® valve was removed.

Electrostatic charge, volume and design of the spacer affect dose delivery differently depending on the pMDI used. Different pMDIs have different vapour pressures, and therefore different aerosol cloud velocities and volumes. Output of particles in the respirable range from CFC-pMDIs was significantly lower than from HFA-pMDIs, using either static or non-static spacers. In addition, static appears to have a much greater effect on the output from CFC-salbutamol pMDIs than from HFA-salbutamol pMDIs. These findings are due to differences in the way the aerosol cloud is emitted from the actuator. The aerosol cloud from an HFA-pMDI is emitted at a slower speed and occupies a smaller volume than the conventional CFC formulation, leading to a much lower impaction on the spacer surface. Several studies have shown these additional benefits of HFA-pMDIs as delivery is increased not only *in vitro* but also *in vivo* [24–26].

Conducting materials carry no electrostatic charge, so a metal spacer solves the problem of reduced drug delivery due to electrostatic charge [27]. A previous study has shown that a metal spacer is superior to plastic spacers, even if the electrostatic charge is reduced on the surface of a plastic spacer [27]. But in view of the present results and the issues of cost and availability, a simple plastic spacer may remain the device of choice worldwide. Washing in detergent does build up a conducting layer on the surface of the plastic, thus reducing static and hence the attraction of the aerosol particles to the spacer surface. Previous studies have already shown that reducing electrostatic charge on plastic spacers by coating them with an ionic detergent significantly improves *in vitro* and *in vivo* drug delivery [5, 15]. It has been shown that all commercial household detergents offer a simple, practical and cheap way of avoiding static. In contrast, priming a plastic spacer with multiple actuations has been shown not to be effective in reducing static [15]. The present study has demonstrated that the major improvement in delivery efficiency of inhalation devices brought about by a simple method for static reduction, such as detergent coating, has considerable impact on

bronchodilator response. In addition, this improvement is likely to have a notable economic impact. Improving delivery efficiency may also greatly increase efficacy and reduce treatment costs. However, important questions regarding the need to change current aerosol dosing practices have been raised in connection with previous deposition studies using spacers with static. Increased lung deposition by improved inhalation devices needs careful monitoring for potential systemic side effects, especially when using inhaled steroids. Framing of new guidelines will need to take these aspects into account.

In practice, plastic spacers should be soaked in a household detergent once a week, and subsequently drip dried. Alternatively, a metal spacer could be used. In addition, spacers should be used in conjunction with HFA-pMDIs.

In summary, this study offers new insights into the influence of the propellant used on the respirable range of drug output and its relation to spacer design. These findings highlight the importance of standardized inhalation methods for efficient and efficacious therapy. In addition, our results underline the difficulty of comparing drug deposition studies using different drugs, propellants, spacers and valve systems.

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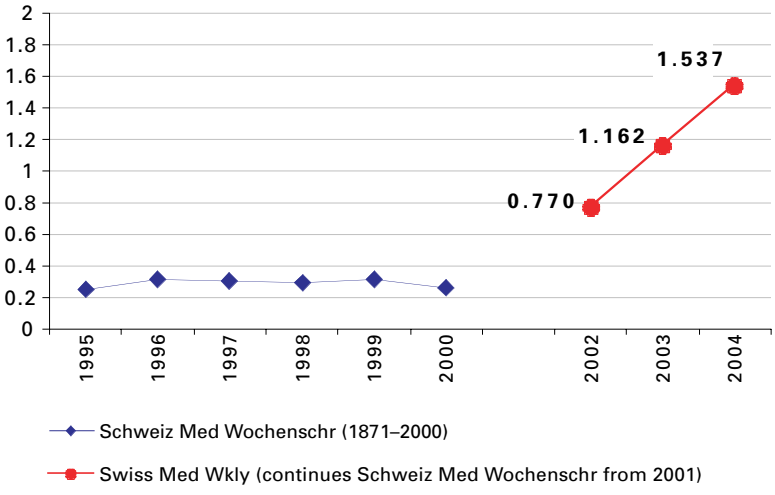

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