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The effect of spacers on the delivery of metered dose aerosols of nedocromil sodium and disodium cromoglycate

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Abstract

The effect of the spacers (Fisonair®, Breath-A-Tech®, Volumatic® and Nebuhaler®) on the in vitro aerosol characteristics of two propellant-driven metered dose inhalers (MDIs), Tilade® (nedocromil sodium) and Intal® (disodium cromoglycate), was studied. The measurement was carried out on a Marple–Miller impactor operating at 30 l/min. Five actuations were collected for the drug assay. The results showed that Tilade® (label claim 2 mg active per actuation) and Intal® (label claim 5 mg active per actuation) generated aerosols with a fine particle mass (FPM, i.e. mass of particles 5 μm in the aerosol) of 0.34 mg (S.D. 0.01, $n = 4$) and 0.02 mg (S.D. 0.01, $n = 4$) per actuation, respectively. For both inhalers, large volume spacers increased (Fisonair® > Nebuhaler® > Volumatic®) while small volume spacer (Breath-A-Tech®) decreased the FPM. The FPM (per actuation) for Tilade® with Fisonair®, Nebuhaler®, Volumatic® and Breath-A-Tech® was 0.52 (0.03), 0.45 (0.03), 0.41 (0.04) and 0.09 (0.04) mg, respectively, while for Intal® the corresponding values were 0.41 (0.02), 0.32 (0.04), 0.28 (0.03) and 0.08 (0.01) mg. Thus, the fine particle mass can be either increased or decreased, depending on the spacer selected. In addition, all spacers significantly reduced the coarse particle (≥ 10 μm) mass, with Fisonair®, Breath-A-Tech®, Nebuhaler® and Volumatic® producing only 7.6, 0.4, 5.2 and 2.6%, respectively of that from Tilade® alone and 15.6, 0.7, 5.4 and 4.1%, respectively of that from Intal® alone. The general trends for Tilade® and Intal® were similar but not quantitatively identical. The proper choice of spacers is therefore important for the optimal delivery of Tilade® and Intal®.

Keywords: Nedocromil sodium; Disodium cromoglycate; Spacers; Aerosols; Metered dose inhalers

1. Introduction

Propellant-driven metered dose inhalers (MDIs) are the most popular aerosol device used for pulmonary drug delivery (Clark, 1995). However, because of the impaction loss of the high momentum aerosol particles in the oropharynx, coupled with the coordination problems between MDI actuation and aerosol inhalation by patients, only a small fraction of the emitted dose penetrates into the lung (Newman, 1993; Clark, 1995). The problem has been alleviated by using spacers attached to the MDI to allow time for inhalation and for the momentum of the particles to decay.

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The performance of spacers depends on a number of physical factors. Electrostatic charges on the spacer plastic surface, prolonged residence time of the aerosol inside the spacer and multiple actuations of the MDI into the spacer are known to reduce the amount of drug available for inhalation (Wildhaber et al., 1996; O'Callaghan, 1997; Kenyon et al., 1998). The size of the spacer is also important for pediatric patients who are unable to empty the volume in one single breath (Finlay, 1998). To date, a number of spacer studies have been carried out on bronchodilators (e.g salbutamol, (Barry and O'Callaghan, 1994; Wildhaber et al., 1996)) and glucocorticosteroids (e.g., beclomethasone, (O'Callaghan, 1997); budesonide (Kenyon et al., 1998)). However, very little work has been done on the prophylactic drugs except disodium cromoglycate (Holzner and Muller, 1994; Barry and O'Callaghan, 1996). Although the general effect of spacer devices on the characteristics of MDI aerosols has existed in the literature, the outcome for a particular MDI and spacer in combination cannot be quantitatively predicted a priori. The aim of this study was to evaluate the effect of various spacers on the in vitro aerosol characteristics of the Tilade® (nedocromil sodium) MDI. Tilade® is used for prophylaxis of asthma but gives an unpleasant taste if the drug particles are deposited in the oropharynx (Hogate, 1986; Ruffin et al., 1987; Konig, 1995). For comparison, measurements were also performed on Intal® (disodium cromoglycate) which has a similar drug profile as nedocromil sodium.

2. Materials and methods

2.1. Materials

Tilade® (2 mg nedocromil sodium (NS) per actuation, Fisons, Loughborough, UK), Intal® Forte (5 mg disodium cromoglycate (DSCG) per actuation, Fisons, Loughborough, UK) and spacers: Fisonair® (volume 800 ml, Fisons), Breath-A-Tech® (200 ml, Scott Dibben), Volumatic® (700 ml, Allen and Hanburys) and Nebuhaler® (750 ml, Astra) were used in this study.

2.2. Aerosol characterisation

A five-stage Marple–Miller Impactor (plus filter, MSP, MN) with a stainless steel 90° entry port (USP, 1995) was used to characterize the aerosols. The flow rate through the impactor was adjusted to 30 l/min using a rotameter and verified by a mass flowmeter (Model 822S, Sierra Instruments, CA). The cut-off diameter of each stage from the first to the filter is 10, 5, 2.5, 1.25, 0.625 and >0 μm, respectively. Aerosol characteristics of the MDI or MDI-spacer combination was measured in quadruplicate at ambient conditions (21 ± 1°C, 45 ± 5% relative humidity) using a new MDI and/ or spacer in each experiment.

2.2.1. MDI alone

The MDI was shaken for 10 s with the first five actuations fired to waste. The weight of the canister was recorded just before the start of experiment. The MDI was then shaken for another 10 s and actuated into the impactor running at 30 l/min. This procedure was repeated 4 times (i.e. total of five actuations) during each experiment with one-minute intervals in between. During actuation, the canister was pressed down for 2 s before it was released. The MDI was held at the entry port for 5 s after each actuation. Custom-designed rubber adaptors were molded from the mouthpieces of each MDI to aid the alignment and sealing of the MDI to the entry port. At the end of the five actuations, the pump was turned off. The canister was re-weighed to ensure the delivery of the required metered dose. The MDI mouthpiece and various stages of the impactor including the throat were each rinsed with an appropriate amount of carbon tetrachloride (AR grade, BDH Chemicals, Poole, England) onto a Millipore filtration unit (0.22 μm Type GV filter, Millipore, MA), to remove the residual surfactant present in the sample. The drug collected on the filter was quantitatively dissolved in deionized water for UV analysis. The rinsing step with carbon tetrachloride did not interfere with drug recovery and is in fact important since the surfactant, being hydrophobic in nature, was found to hinder complete dissolution of the active ingredient.

2.2.2. MDI with spacers

The above procedure was followed until the pump was turned on and the flow rate was adjusted to 30 l/min. Thereafter, the procedure was modified according to the spacer of interest. The purpose was, within practical feasibility of the experimental setup, to simulate the patient's use as recommended in the manufacturer's instructions for each spacer.

Fisonair® While the impactor was still running, the spacer was attached to the entry port with the aid of a custom-designed rubber adaptor molded from the mouthpiece of the spacer. The MDI was then actuated into the spacer. The procedure was adopted in order to eliminate the variation in the residence time of the aerosol cloud inside the spacer.

Breath-A-Tech® The MDI was actuated into the spacer, followed by the removal of the cap for the mouthpiece. With the aid of a rubber adaptor molded from the mouthpiece of the spacer, the spacer was attached to the entry port of the running impactor.

Volumatic® and Nebuhaler® The MDI, with a Tilade®/Intal® mouthpiece adaptor (RPR Pharmaceuticals, Australia) attached in place to aid fitting into the spacer, was actuated into the spacer which, in the case of Nebuhaler®, was slightly tilted up to ensure the one-way valve was closed. The spacer, with a rubber socket attached to its mouthpiece, was subsequently attached to the entry port of the impactor. The Tilade®/Intal® mouthpiece adaptor was essential because of the difference in shape between the MDI mouthpiece and the spacer entry port. After sampling, the spacer was completely dismantled and washed according to the manufacturer's instructions.

2.2.3. Assay methods

Nedocromil sodium (NS) and disodium cromoglycate (DSCG) were analyzed by UV spectrometry (Hitachi U-2000, Tokyo, Japan) at wavelengths of 253 and 326.5 nm, respectively. A standard curve was prepared using standard solutions of NS or DSCG dissolved in deionized water. The standard curve for NS was linear at concentrations between 0.002 and 0.014 mg/ml (absorbance, 71.90* concentration (mg/ml) + 0.0029, R^2, 0.9999, $n = 5$). The standard curve for DSCG was linear at concentrations between 0.005 and 0.05 mg/ml (absorbance, 14.96* concentration (mg/ml) + 0.0067, R^2, 0.9998, $n = 6$).

2.2.4. Data analysis

2.2.4.1. Fine Particle Mass (FPM). The fine particle mass (FPM) per actuation is defined as the mass of aerosol particles that are ≤ 5 μm in size (which coincide with the effective cut-off diameters of stage 3 and below in the impactor). Numerically, the FPM is the sum of the drug mass collected from stages 3, 4, 5 and filter of the impactor.

2.2.4.2. Fine particle fraction. The fine particle fraction (FPF) is defined as the fraction of the mass of aerosol particles that are ≤ 5 μm in size. Numerically, the FPF is the FPM divided by the emitted dose (which is the accumulated mass on all the stages of the impactor including the entry port) and multiplied by 100.

2.2.4.3. Coarse particle mass. This is defined as the sum of the drug mass per actuation collected on the entry port and stage 1. This accounts for particles that are ≥ 10 μm.

2.3. Statistical analysis

The data were evaluated by one-way analysis of variance (ANOVA). Significant differences between spacers were further analyzed using unpaired t tests and P values of < 0.05 were considered to be significant.

3. Results

Tilade®(Table 1)

A significant difference was observed between the fine particle mass (FPM) delivered from the MDI alone and the spacers ($P < 0.0001$, ANOVA). Tilade® (label claim 2 mg per actuation) alone generated aerosols with a FPM of 0.34 mg (S.D., 0.01, $n = 4$) per actuation, equivalent to an average fine particle fraction of 20.8 wt%. The

spacers, Fisonair®, Nebuhaler® and Volumatic® significantly enhanced the FPM by 52.3, 32.0 and 19.8%, respectively, while Breath-A-Tech® reduced it by 75.0%. Significant differences in FPM were found between the large volume spacers Fisonair® and Volumatic® ($P = 0.004$) as well as between Fisonair® and Nebuhaler® ($P = 0.017$).

The coarse particle mass (CPM) was found to be significantly reduced by all spacers as compared with the MDI alone ($P < 0.0001$, ANOVA), with the Fisonair®, Breath-A-Tech®, Nebuhaler® and Volumatic® producing only 7.6, 0.4, 5.2 and 2.6%, respectively, of that from the Tilade® MDI alone. A significant difference was found between the Breath-A-Tech® and all the other spacers ($P = 0.0003–0.007$).

Intal®(Table 2)

A significant difference was found between the FPM delivered from the MDI alone and the spacers ($P < 0.0001$, ANOVA). Intal® (label claim 5 mg per actuation) alone generated aerosols with a fine particle mass of about 0.02 mg (S.D. 0.01, $n = 4$) per actuation, equivalent to an average FPF of 5.5 wt.%. The spacers, Fisonair®, Nebuhaler® and Volumatic® significantly enhanced the FPM by 87.3, 44.6 and 28.2%, respectively, while Breath-A-Tech® reduced it by 65.4%. Significant differences were found between the FPM delivered from the large volume spacers Fisonair® and Volumatic® ($P = 0.0006$), as well as Fisonair® and Nebuhaler® ($P = 0.006$). Furthermore, all the spacers significantly reduced the coarse particle mass, with Fisonair®, Breath-A-Tech®, Nebuhaler® and Volumatic® producing only 15.6, 0.7, 5.4 and 4.1%, respectively, of that from the MDI alone. A significant difference was observed between the Breath-A-Tech® and all the other spacers ($P = 0.02–0.00001$).

Table 1
Effect of spacers on the delivery of Tilade® aerosols[a]

Experiments ($n = 4$)	Tilade® only (S.D.)	Fisonair® (S.D.)	Breath-A-Tech® (S.D.)	Volumatic® (S.D.)	Nebuhaler® (S.D.)
Emitted dose (mg)	1.66 (0.03)	0.89 (0.05)	0.11 (0.06)	0.61 (0.07)	0.76 (0.06)
Fine particle mass (mg)	0.34 (0.01)	0.52 (0.03)	0.09 (0.04)	0.41[b] (0.04)	0.45[c] (0.03)
Fine particle fraction (%)	20.8 (0.9)	59.1 (3.4)	78.6 (4.9)	68.2 (2.9)	59.7 (1.7)
Coarse particle mass (mg)	1.13 (0.04)	0.09[d] (0.02)	0.01 (0.00)	0.03[e] (0.00)	0.06[f] (0.01)

[a] The difference between the emitted doses, with and without spacers, is due to deposition in the spacer (same for Table 2).
[b] Significantly different from the Fisonair® ($P = 0.004$).
[c] Significantly different from the Fisonair® ($P = 0.017$).
[d] Significantly different from the Breath-A-Tech® ($P = 0.007$).
[e] Significantly different from the Breath-A-Tech® ($P = 0.001$).
[f] Significantly different from the Breath-A-Tech® ($P = 0.0003$).

Table 2
Effect of spacers on the delivery of Intal® aerosols

Experiments ($n = 4$)	Intal® only (S.D.)	Fisonair® (S.D.)	Breath-A-Tech® (S.D.)	Volumatic® (S.D.)	Nebuhaler® (S.D.)
Emitted dose (mg)	4.02 (0.10)	1.46 (0.08)	0.14 (0.03)	0.68 (0.06)	0.92 (0.21)
Fine particle mass (mg)	0.02 (0.01)	0.41 (0.02)	0.08 (0.01)	0.28[a] (0.03)	0.32[b] (0.04)
Fine particle fraction (%)	5.5 (0.1)	28.2 (1.0)	54.8 (1.7)	41.2 (2.4)	34.3 (3.5)
Coarse particle mass (mg)	3.48 (0.12)	0.54[c] (0.05)	0.02 (0.00)	0.14[d] (0.00)	0.19[e] (0.08)

[a] Significantly different from the Fisonair® ($P = 0.0006$).
[b] Significantly different from the Fisonair® ($P = 0.006$).
[c] Significantly different from the Breath-A-Tech® ($P = 0.0002$).
[d] Significantly different from the Breath-A-Tech® ($P = 0.0001$).
[e] Significantly different from the Breath-A-Tech® ($P = 0.02$).

4. Discussion

Various studies have demonstrated a large variation in the proportion of respirable particles of the same drug available from different spacers (O'Callaghan, 1997). To date, the effect of only one particular spacer device has been reported for the widely prescribed prophylactic agent nedocromil sodium for asthma (Barry et al., 1993), although a body of literature exists for another prophylactic, disodium cromoglycate. Our results demonstrated significant differences in the FPM not only between the large and small volume spacers, but also among the large volume spacers. Further, the qualitative trend for Tilade® and Intal® was similar but the results were not quantitatively identical. Thus, the efficacy of a particular spacer with a specific drug is not necessarily be directly applicable to another drug.

In our study, large volume (750–800 ml) spacers increased the amount of fine particles in the aerosol (Fisonair® > Nebuhaler® > Volumatic®) while Breath-A-Tech®, which has a smaller volume (200 ml) has an opposite effect. This agrees with the results of Barry and O'Callaghan (1996) who also found that small volume spacers delivered lower amounts of small particles than large volume spacers, but Breath-A-Tech® was not included in their study and its effect on aerosols delivery is not available in the literature.

As Tilade® gives a bad taste when deposited in the mouth (Konig, 1995), the reduction in the amount of coarse particles (Breath-A-Tech® > Volumatic® > Nebuhaler® > Fisonair®) is an advantage. The higher emitted dose and coarse particle mass obtained from the Fisonair® than the other large volume spacers could be explained by the differences in the valve design of spacers (Holzner and Muller, 1994). The flexible rubber membrane at the mouthpiece of the Fisonair® may cause less impaction loss of the aerosol than with the rigid plastic valves in the Volumatic® and Nebuhaler®. Since the flow path and the valve of the Breath-A-Tech® is similar to those of the Fisonair®, it is likely that the volume of the device accounts for the enhanced deposition inside the small volume spacer. The emitted doses obtained from the Breath-A-Tech® were 5–8 times lower than those from the larger volume spacers.

In conclusion, all of the spacers tested were highly effective in reducing the amount of coarse particles in the aerosols. Large volume spacers increased the amount of fine particles in the aerosols while a smaller volume spacer had the opposite effect. The general trend for Tilade® and Intal® was similar but not quantitatively identical. The present data have provided quantitative information for the proper choice of spacers for the optimal delivery of Tilade® and Intal®.

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References

Barry, P., O'Callaghan, C., 1994. Multiple actuations of salbutamol MDI into a spacer device reduce the amount of drug recovered in the respirable range. Eur. Resp. J. 7, 1707–1709.

Barry, P., O'Callaghan, C., 1996. Inhalational drug delivery from seven different spacer devices. Thorax 51, 835–840.

Barry, P., Robertson, C.F., O'Callaghan, C., 1993. Optimum use of a spacer device. Arch. Dis. Childhood 69, 693–694.

Clark, A.R., 1995. Medical aerosol inhalers: past, present and future. Aerosol Sci. Tech. 22, 374–391.

Finlay, W.H., 1998. Inertial sizing of aerosol inhaled during pediatric tidal breathing from an MDI with attached holding chamber. Int. J. Pharm. 168, 147–152.

Hogate, S.T., 1986. Clinical evaluation of nedocromil sodium in asthma. Eur. J. Resp. Dis. 69 (Suppl 147), 149–159.

Holzner, P.M., Muller, B.W., 1994. An in vitro evaluation of various spacer devices for metered-dose inhalers using the Twin Impinger. Int. J. Pharm. 106, 69–75.

Kenyon, C.J., Thorsson, L., Borgstrom, L., Newman, S.J., 1998. The effects of static charge in spacer devices on glucocorticosteroid aerosol deposition in asthmatic patients. Eur. Resp. J. 11, 606–610.

Konig, P., 1995. Clinical overview of nedocromil sodium. Alerg. Proc. 16, 73–76.

Newman, S.P., 1993. Therapeutic aerosol deposition in man. In: Moren, F., Dolovich, M.B., Newhouse, M.T., Newman, S.P. (Eds.), Aerosols in Medicine, Principles, Diagnosis and Therapy. Elsevier, Amsterdam, pp. 375–391.

O'Callaghan, C., 1997. In vitro performance of plastic spacer devices. J. Aerosol Med. 10, S31–S35.

Ruffin, R.E., Alpers, J.H., Pain, M.C.F., et al., 1987. The efficacy of nedocromil sodium (Tilade®) in asthma Aust NZ. J. Med. 17, 557–561.

United State Pharmacopeia, XXIII, 1995. General chapter on aerosols [601], USP Convention Inc., Rockville, MD, pp. 1763–1765.

Wildhaber, J.H., Devadason, S.G., Eber, E., et al., 1996. Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. Thorax 51, 985–988.