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Delivery of HFA and CFC salbutamol from spacer devices used in infancy

Jean-Christophe Dubus [a,*], Rodney Rhem [b], Myrna Dolovich [b]

[a] *Department of Pediatrics, CHU Timone-Enfants, 13385 Marseille Cedex 5, France*

[b] *Department of Nuclear Medicine, Health Sciences Centre, Room 1V18, McMaster University, 1200 Main Street West, Hamilton, Ont., Canada L8N 3Z5*

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Abstract

The aim of the study was to compare the in vitro delivery of four salbutamol pressurized metered-dose inhalers (pMDIs) via the three spacer devices commonly used in European infants: Aerochamber-Infant®, Babyhaler®, and metallic NES-spacer®. Emitted dose (ED) and fine particle dose (FPD, particles < 5.8 μm) of each combination of spacer device and pMDI (chlorofluorocarbon-based Ventoline®, Eolène®, Spréor®, and hydrofluoroalkane-based Airomir®) were measured respectively using unit dose sampling tubes ($n = 30$ per combination) and an 8-stage cascade impactor ($n = 6$ per group). The results were compared by analysis of variance and the Student–Newman–Keuls method. ED of Airomir® was always greater than for Ventoline® ($P < 0.05$). FPD obtained with Ventoline® was the lowest, with Eolène® > Airomir® = Spréor® > Ventoline® ($P < 0.05$). Only Airomir® produced a similar FPD with all three spacer devices. Chlorofluorocarbon-salbutamol pMDIs are not generics when used with spacer devices. The three spacer devices may be used interchangeably with Airomir®.

Keywords: Chlorofluorocarbon; Hydrofluoroalkane; Inhaled therapy; Pressurized metered-dose inhaler; Salbutamol; Spacer devices

1. Introduction

Bronchial asthma is the most common chronic illness in childhood, and pressurized metered-dose inhalers (pMDIs) are the commonest drug delivery device for asthma medications (Warner and Naspitz, 1998; Dolovich, 1999). Spacer devices are used to enhance drug delivery by eliminating the need for the patient to coordinate inhalation and pMDI actuation, and by retaining the large, fast moving particles that would otherwise impact on the oropharynx (Hindle and Chrystyn, 1994; Dolovich, 1995). In children and many adults, the use of spacer devices improves drug delivery compared to the pMDI alone, and in acute severe asthma, salbutamol or terbutaline delivery by pMDI and spacer device is equally or more efficacious than via nebuliser (Lin and Hsieh, 1995; Parkin et al., 1995; Warner and Naspitz, 1998).

* Corresponding author. Tel.: +33-4-91386739; fax: +33-4-91386726.

E-mail address: jdubus@mail.ap-hm.fr (J.-C. Dubus).

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Recent changes, with important therapeutic consequences, have been undertaken with pMDIs and spacer devices. Firstly, in response to concerns about the ozone depleting potential of chlorofluorocarbon (CFC) propellants used in pMDIs, CFCs are being replaced with hydrofluororalkane (HFA) propellants and several pMDIs have been reformulated (Tansey, 1995; June, 1997; McDonald and Martin, 2000). Changes are in progress and, at this time in our country, HFA-salbutamol and HFA-fluticasone propionate pMDIs are available. Secondly, several studies have demonstrated that the behaviour of an aerosolized drug with a spacer device is specific to the drug (Ahrens et al., 1995; Barry and O'Callaghan, 1996, 1997; Lipworth and Clark, 1998a,b). In practice, the efficacy of a particular spacer device with one formulation cannot be assumed for another formulation, even for the same drug. Consequently, it may be inappropriate to use any drug with any spacer device just because the pMDI adapter fits.

In France, four salbutamol pMDIs are currently available: the innovator CFC-salbutamol (Ventoline®, Glaxo-Wellcome), two CFC-salbutamol generic formulations (Eolène®, Rhône-Poulenc-Rorer, and Spréor®, Inava-Pierre Fabre Médicaments) and a HFA 134a-salbutamol sulphate canister (Airomir®, 3M Pharmaceuticals). Efficiency of these inhaled products, particularly HFA 134a-salbutamol, admistered with spacer devices, was poorly assessed in children. To our knowledge, no previous study has compared these four formulations of salbutamol used with the three currently available in Europe small volume valved spacer devices used with the attachment of a facemask to treat the youngest patients, i.e. Aerochamber Infant® (Trudell Medical Int'l, Canada), Babyhaler® (Glaxo Wellcome, Swizerland) and the metallic NES-spacer® (also called Nebuchamber®, AstraZeneca, Sweden). The aim of this in vitro study was to provide drug delivery data to allow physicians to make informed choices when changing from one formulation or spacer device to another.

2. Material and methods

2.1. Emitted dose of salbutamol

The emitted dose of salbutamol (ED, in μg/100 μg salbutamol) was determined using a collection tube for individual doses of Airomir®, Eolène®, Spréor® and Ventoline® pMDIs and then with the pMDIs via Aerochamber Infant®, Babyhaler® and NES-spacer®. All pMDIs formulations are marketed to deliver 100 μg of salbutamol base per actuation. Because the Eolène® pMDI actuator did not fit the Babyhaler®, the pMDI cradle of the Babyhaler® was cut off to allow the actuator to fit into the spacer device. We did not used adapters for the other drug-spacer device combinations. The unit dose collection tube, adapted from the United States Pharmacopea recommendations, was equipped with a Gelman type A/E filter and operated by drawing the aerosol from the pMDI into the tube at a constant suction flow rate of 28.3 l/min (Lpm). Three new pMDIs and three sets of new spacer devices were used for each individual drug. Before use and between each experiment, the spacer devices were washed with lukewarm water and allowed to dry in ambient air. Immediately before each experiment the pMDI was vigourously shaken for 30 s and primed by firing one actuation to waste. This procedure was repeated twice for a total of three priming actuations following which the pMDI was shaken for 30 s and, with the 28.3 Lpm suction flow on, actuated directly into the collection tube or into the spacer device hermetically attached to the tube. The flow was stopped 10 s after the actuation. The pMDI was removed from the tube and stored on its side. This operation was repeated with a fresh sampling tube, collecting ten doses per pMDI and spacer device, for a total of 30 measurements per group. The order in which the pMDIs were tested was randomized.

A cap was then put on each collection tube instead of the pMDI actuator or the buccal tip of the spacer device. At the distal end, the filter was pushed into the tube and sealed with a second cap. Ten milliliters of solvent, consisting of

4 g of sodium hydroxide/l of distilled water, were introduced into each tube to soak the filter. The tubes, with the filters and the solution, were shaken on an agitator for 30 min. The 10 ml were then collected from each tube and filtered with a 0.2 μm filter (Nylon Acrodisc®, Gelman Sciences, Montreal, Quebec, Canada). The amount of drug collected was assayed by spectrophotometry (Hitachi Spectrophotometer, Model 100-60) at a wavelength of 243 nm. All measurements were performed under the following ambient conditions: mean temperature 23.9°C (range 23–26°C) and mean relative humidity 42.3% (range 21–63%).

2.2. Particle size distribution of salbutamol

This was measured using an 8-stage non-viable Anderson cascade impactor operated at 28.3 Lpm. The different parameters [fine particle fraction or FPF (percentage of particles < 5.8 μm), mass median aerodynamic diameter (MMAD, μm) and geometric standard deviation (GSD)] were determined from the cumulative mass distribution plot. Five puffs of salbutamol administered at 30-s intervals were collected for each sizing run. Following the sizings, the stage plates of the impactor were washed with solvent (sodium hydroxide: 5 ml for each stainless steel plate, 10 ml for end filter stage and throat inlet) and the amount of drug determined by spectrophotometry. The same protocol was observed for sizing with the spacer devices and the pMDIs described previously. Measurements for the pMDI alone or pMDI plus spacer device were performed twice and three sets of pMDIs and spacer devices were used for a total of six measurements per group. The fine particle dose (FPD = ED from the sampling tube experiments × FPF from the Anderson impactor, in μg/100 μg salbutamol) was calculated for each pMDI-spacer device combination ($n = 6$ per group).

2.3. Statistical analysis

The inter-variability of the ED measurements for each of the three sets of ten samples and the FPD measurements for each set of two samples was calculated before pooling the results. The results were expressed as mean (S.D.). Comparison between groups was made using the 2-tailed unpaired t-test and Mann–Whitney Rank Sum test where appropriate. Comparison among multiple groups was made using a one way analysis of variance (ANOVA) and the Student–Newman–Keuls test for pairwise multiple comparisons.

3. Results

There was no significant difference in data measurements between the three groups, and, therefore, the results were pooled.

3.1. pMDIs tested alone

All generic EDs were within 75–125% of label claim. Airomir® and Spréor® had a lower ED than Eolène® and Ventoline® ($P < 0.05$; Table 1). Airomir® delivered 63.5% of its particles with diameters < 5.8 μm, while Spréor® 54.8%, Ventoline® 41.6% and Eolène® only 38.1% ($P < 0.05$; Table 1). In this size range among the CFC-salbutamol generics, Spréor® had a greater FPD than Eolène® and Ventoline® ($P < 0.05$; Table 1). The MMADs and GSDs were similar for all the MDIs.

Table 1
Values expressed as mean (S.D.) of emitted dose (ED, μg/100 μg actuation), fine particle fraction (FPF,%) and fine particle dose (FPD, μg/100 μg actuation) of different salbutamol pMDIs

pMDI	Propellant	ED (μg) ($n = 30$)	FPF (%) ($n = 6$)	FPD (μg) ($n = 6$)
Airomir®	Hydrofluoroalkane 134a	85.3 (5.4)	63.5 (6.1)	54.1 (4.1)
Eolène®	Chlorofluorocarbon (generic)	100.0 (10.0)	38.1 (5.0)	38.1 (6.9)
Spréor®	Chlorofluorocarbon (generic)	89.4 (7.8)	54.8 (2.5)	48.9 (5.4)
Ventoline®	Chlorofluorocarbon (innovator)	96.9 (6.9)	41.6 (10.2)	40.3 (8.4)

Table 2
Values expressed as mean (S.D.) of emitted dose (ED, μg/100 μg actuation), fine particle dose (FPD, μg/100 μg actuation), mass median aerodynamic diameter (MMAD, μm) and geometric standard deviation (GSD) of different sabutamol pMDIs from small spacer devices

Method of delivery		ED (μg) ($n = 30$)	FPD (μg) ($n = 6$)	MMAD (μm) ($n = 6$)	GSD ($n = 6$)
Aerochamber-Infant®	Airomir®	69.9 (4.6)	68.3 (4.5)	2.78 (0.02)	1.47 (0.01)
	Eolène®	55.6 (6.6)	55.3 (6.7)	2.35 (0.05)	1.43 (0.02)
	Spréor®	70.9 (6.2)	69.6 (6.0)	2.36 (0.07)	1.58 (0.03)
	Ventoline®	53.7 (5.1)	52.4 (5.1)	2.69 (0.05)	1.46 (0.02)
Babyhaler®	Airomir®	68.5 (5.1)	67.5 (5.1)	2.68 (0.04)	1.39 (0.03)
	Eolène®	80.5 (4.8)	80.2 (4.8)	2.50 (0.13)	1.50 (0.01)
	Spréor®	75.4 (5.2)	74.9 (5.2)	2.32 (0.06)	1.56 (0.03)
	Ventoline®	65.0 (4.4)	64.4 (4.3)	2.68 (0.05)	1.49 (0.03)
NES-spacer®	Airomir®	80.2 (6.1)	73.2 (5.6)	2.77 (0.05)	1.47 (0.02)
	Eolène®	81.1 (6.4)	76.2 (6.5)	2.44 (0.09)	1.49 (0.04)
	Spréor®	81.4 (9.3)	74.8 (8.9)	2.37 (0.07)	1.61 (0.03)
	Ventoline®	73.0 (5.4)	66.4 (5.8)	2.70 (0.02)	1.47 (0.01)

3.2. pMDIs tested with spacer devices

Administered via spacer devices, the differences were more pronounced. The values of ED and FPD (μg/100 μg actuation), MMAD (μm) and GSD of salbutamol inhalers administered via the three small valved spacer devices are shown Table 2.

For all spacer devices, the ED of the HFA salbutamol, Airomir®, was greater than for the innovator Ventoline® ($P < 0.05$). Overall for all four pMDI types, EDs from the NES-spacer® were greatest than from the other two spacers ($P < 0.05$). EDs for the two French CFC generics and the CFC innovator pMDI, Ventoline®, were lower ($P < 0.05$) when delivered through the Aerochamber-Infant® than the Babyhaler® or NES-spacer®.

Because the measurement of ED represents the total dose, containing particles inhaled and deposited above and below the larynx, the FPD was calculated using the cascade impactor measurements. All pMDIs used without a spacer device had a lower FPD compared to pMDIs administered with the spacer devices ($P < 0.05$). At a constant sampling flow rate, similar FPDs were measured between Eolène® and Ventoline® with Aerochamber-Infant® and between Airomir® and Ventoline® with Babyhaler®. Further analysis showed that the CFC- and HFA-salbutamol generic and innovator pMDIs used with small spacer devices delivered a greater dose containing more particles < 5.8 μm than the innovator Ventoline® ($P < 0.05$). Airomir® and Spréor® were the drugs with the lowest variability in FPD within the three spacer devices (Fig. 1). Whatever the CFC-pMDI, the Babyhaler® and the NES-spacer® were comparable in FPD salbutamol delivery and greater than with the Aerochamber-Infant® ($P < 0.05$; Fig. 1). However, Airomir®, the HFA-pMDI, produced a similar FPD with all spacer devices ($P > 0.05$).

There was a tendency for the MMAD for Airomir® and Ventoline® through the three spacer devices to be greater than that for the two CFC generics, but this did not reach statistical significance. There was no difference in the GSDs for all drugs through the three spacer devices.

4. Discussion

The main findings of our study were that, in vitro, the tested CFC-salbutamol generic pMDIs (Eolène®, Spréor®) were not true generics and that HFA-salbutamol pMDI (Airomir®) may be delivered with equal efficacy from the three small valved spacer devices.

All tested CFC-salbutamol generic pMDIs had different EDs and greater (Spréor®) or equal (Eo-

lène®) FPDs compared to Ventoline® when the pMDIs were tested alone. Using the spacer devices, these differences were more pronounced and all CFC-pMDIs were found to deliver more salbutamol than Ventoline®. Salbutamol generics and innovator pMDIs should be theoretically identical. However, other features of generic pMDIs supplied from different manufacturers to the innovator is that the canister and the metering valve and actuator may be possibly leading to differences in drug output (Saarelainen and Sovijärvi, 1991; Derom and Pauwells, 1995). Similar particle size distribution to the innovator is required before licensing generic pMDIs (Chrystyn, 1994). However, similar ED or FPD do not necessary result in equivalence when pMDIs are delivered from spacer devices. Changes in the delivery system, giving rise to differences in aerosol plume geometry (form, speed or volume of the aerosolized cloud) between pMDIs, may effect a specific dynamic behaviour for each combination of drug and spacer device (Barry and O'Callaghan, 1997). The real clinical importance of this finding is unknown but the CFC generic formulations pMDIs should be tested and compared in carefully designed pharmacodynamic studies with and without spacer devices.

Airomir®, one HFA 134a-salbutamol pMDI replacement formulation for CFC-salbutamol pMDI, was particularly interesting to study. CFC-free pMDIs are not considered to be generics because the use of the HFA has highly modified the characteristics of the pMDIs. A redesign of both actuator and the metering valve by 3M Pharmaceuticals has produced a formulation of fine drug particles in suspension (June, 1997). However, it has been demonstrated that CFC- and HFA-salbutamol formulations have the same

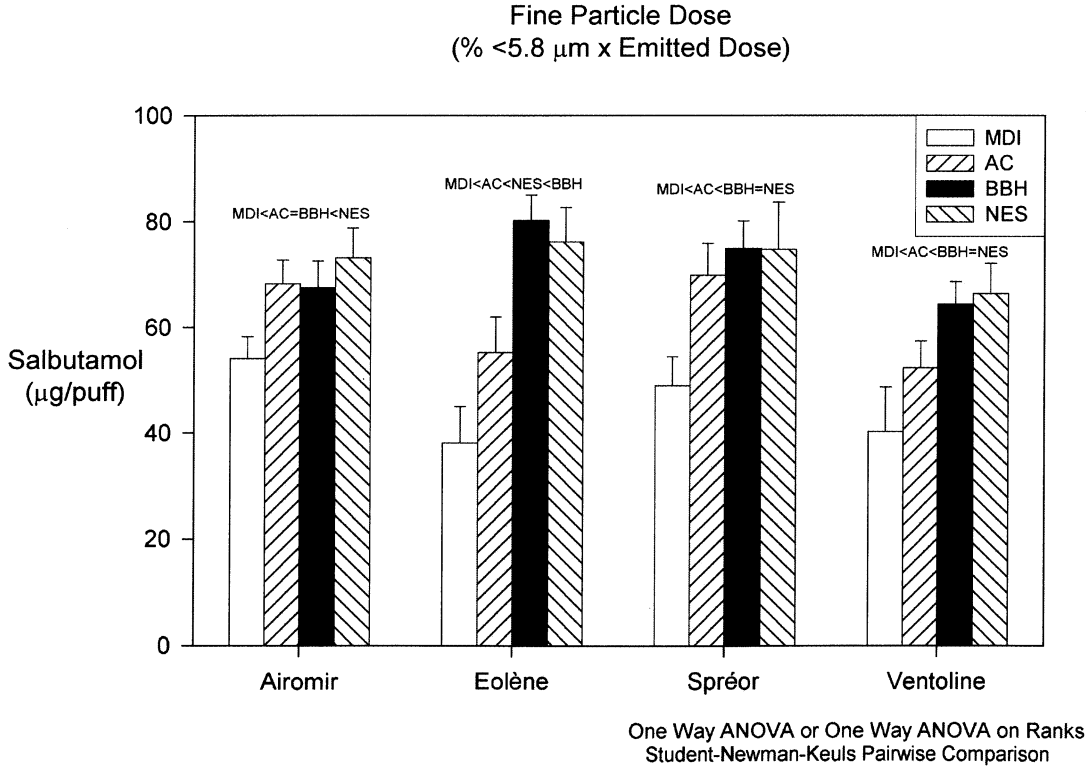

Fig. 1. Fine particle dose (particles < 5.8 μm, μg/100 μg actuation) from CFC-innovator (Ventoline®), CFC-generics (Eolène®, Spréor®) and HFA-salbutamol (Airomir®) pMDIs administered via small valved spacer devices (AC, Aerochamber-Infant®; BBH, Babyhaler®; NES, NES-Spacer®).

clinical effect when given to adults by pMDI and no spacer device, and the same lung deposition when given to adults by pMDI or pMDI with large volume spacer devices (Dockhorn et al., 1995; Bleecker, 1997; Lipworth and Clark, 1998a). Pharmacokinetic measurements have shown that the lung deposition of Airomir® was enhanced by using the Nebuhaler® or the Volumatic®, compared to the pMDI alone (Lipworth and Clark, 1998b). In healthy adults, a 2-fold increase in salbutamol plasma concentrations was noted when Airomir® was given via the metallic NES-spacer® compared to the same dose of salbutamol delivered from Turbuhaler® (Lipworth and Clark, 1997).

Pediatric studies with HFA 134a-salbutamol pMDI are less frequent. Only one parallel-group study compared, in 10–12-year-old mild to moderate asthmatic children, the effect of the delivery of two puffs of Airomir® or Ventolin® administered via a Volumatic® (Desager et al., 1996). A comparable increase in pulmonary function measured 10 min after the delivery in the two groups was shown. A recent pharmacokinetic study conducted in five children, aged 7–12 years, reported that a significantly higher lung dose of salbutamol was obtained when the HFA-salbutamol pMDI was delivered through a non-electrostatic Babyhaler® (coated with benzalkonium chloride) rather than through a new Babyhaler® (more electrostatic) or a new not static-reduced Aerochamber-Child® (Anhoj et al., 1999).

To our knowledge, three particle size distribution studies have characterized salbutamol delivery from a HFA-salbutamol pMDI used with various spacer devices (Barry and O'Callaghan 1997; Wildhaber et al., 1998; Finlay and Zuberbuhler, 1999). However, the comparison in the same study of the three small volume spacer devices commonly used for European infants was never done. Barry and O'Callaghan (1997) demonstrated, using a 4 stage multistage liquid impinger operating at a constant flow of 60 Lpm, that the HFA formulation delivered approximately 2-fold more salbutamol than the conventional formulation when used either with the Aerochamber-Child® or the Nebuhaler®. Our results confirm these last findings, i.e. a greater ED and FPD for Airomir® used with the small volume spacer devices than for the innovator, despite different and lower sampling flow rates and the use of the cascade impactor rather than the liquid impinger.

The two other in vitro studies used a simulated pediatric tidal breathing model. Using a 4-kg in vitro model of a pediatric ventilatory circuit (endotracheal tube 4.0 mm, tidal volume of 40 ml, 30 breaths/min, peak inspiratory pressure of 20 cm H_2O), the mean salbutamol deposition on the inspiratory system was $14.3 \pm 1.3\%$ when Airomir® was used with the Aerochamber-MV® and $7.2 \pm 2.1\%$ when used with the Nebuhaler® (Wildhaber et al., 1998). As for the last study, an apparatus allowing a simulated tidal breathing pattern to occur through each spacer device was used, while the inhaled aerosol was collected at a constant flow rate of 28.3 Lpm into an Anderson cascade impactor (Finlay and Zuberbuhler, 1999). Particle size measurements of the aerosol inhaled from the five spacer devices for young children in North America (Aerochamber®, E-Z spacer®, NES-spacer®, Optichamber®, Vent170spacer®) used with Airomir® indicated that amounts of inhaled fine particle (1.1–4.7 or 1.1–3.3 μm) were different between the spacer devices used. The NES-spacer® delivered a significantly higher amount of salbutamol than the other spacer devices, including the Aerochamber-Child® and the Aerochamber-Infant®. When comparing their present results for HFA-salbutamol pMDIs with similar data that they previously obtained with CFC-salbutamol pMDIs (Finlay and Zuberbuhler, 1998), they stated that amounts of salbutamol collected in the two fine particle doses did not differ from the CFC formulation for the Aerochamber®, but were significantly smaller with the HFA formulation than with the CFC formulation for the E-Z spacer® and the Optichamber®. In this study, we have demonstrated that the inhalable amount of salbutamol was nearly similar with the all three small volume spacer devices used with HFA-salbutamol pMDI. At first, these apparent discrepancies between the two studies may be due to methodological differences (constant flow of air with the pMDI actuated into the spacer device with the impactor airflow already

being drawn through it for mimicking clinical practice versus simulated breathing pattern). On the other hand, electrostatic charge of plastic spacer devices, which greatly affects the delivery of inhalable particles (Barry et al., 1993; Wildhaber et al., 1996a,b, 1997), has to be considered. Piérart et al. (1999) recently described a method to obtain a consistent reduction in spacer device static charge and an increased lung deposition of inhaled drug: plastic spacer devices should be soaked in a dilute solution of detergent and then allowed to drip-dry, without water-rinsing. Because our work was anterior to these recommendations, we washed our spacer devices only with lukewarm water which had been shown to result in similar lung bioavailability of salbutamol to spacer devices treated with an antistatic agent (Clark and Lipworth, 1996). Finlay and Zuberbuhler (1999) washed the plastic spacer devices with dish soap and water, then with distilled water, and finally with methanol. Finlay's mode of rinsing may affect the static charge of the spacer devices and our spacer devices may be less static than those of Finlay. This may explain why our results (Babyhaler® = NES-spacer® > Aerochamber®) were similar to those obtained in vitro with treated, not static, spacer devices (Wildhaber et al., 1996a).

In conclusion, this in vitro study compared the administration of four different salbutamol pMDIs via three small valved spacer devices currently used in young patients. Our work confirms the general principle that spacer devices act differently with different formulations of the same drug, with Babyhaler® and NES-spacer® showing comparable results in this study. The two CFC generics tested with the spacer devices gave greater results compared to the innovator CFC-salbutamol pMDI. Airomir®, which will serve as a replacement formulation for CFC-salbutamol pMDIs, appears to provide similar drug delivery from all three spacer devices. Clinical trials with these drugs and with the other future HFA-salbutamol pMDIs, administered without and with all the known spacer devices, should be performed to provide data for clinicians on which to base their choice of drug delivery system for treatment of their patients.

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