

# Levalbuterol Aerosol Delivery With a Nonelectrostatic Versus a Nonconducting Valved Holding Chamber

Dominic P Coppolo MBA RRT FAARC, Jolyon P Mitchell PhD CChem CSci, and Mark W Nagel

**BACKGROUND:** Hydrofluoroalkane-propelled levalbuterol (Xopenex) aerosol is a recently approved formulation for delivery via metered-dose inhaler for the treatment or prevention of bronchospasm in adults, adolescents, and children  $\geq 4$  years of age who have reversible obstructive airway disease. Valved holding chambers (VHCs) made from conventional polymers are susceptible to accumulation of electrostatic charge, which can be minimized by prewashing with ionic detergent, but it may be desirable to be able to use the product straight from the package, without pretreatment, especially during an exacerbation. **METHODS:** We studied the performance of the AeroChamber Plus and AeroChamber Max VHCs in delivering hydrofluoroalkane-propelled levalbuterol. Both VHCs were prewashed, rinsed, and drip-dried before testing. The AeroChamber Max is manufactured from charge-dissipative material and was therefore also evaluated without prewashing. Aerosol samples were collected at 28.3 L/min with an Andersen 8-stage cascade impactor, per the procedure specified in Chapter 601 of the United States Pharmacopeia. **RESULTS:** The mean  $\pm$  SD fine-particle mass (mass of aerosol particles  $< 4.7 \mu\text{m}$  aerodynamic diameter) values were  $33.5 \pm 1.4 \mu\text{g}$  and  $36.3 \pm 1.1 \mu\text{g}$  with the AeroChamber Max, without and with wash/rinse pretreatment, respectively, and  $28.5 \pm 2.4 \mu\text{g}$  with the prewashed AeroChamber Plus. **CONCLUSIONS:** We think the small differences we observed are unlikely to be of clinical importance, given the inter-patient variability seen with inhaled drug delivery. The performance of the AeroChamber Max was substantially comparable whether or not it was prewashed. *Key words:* pressurized metered-dose inhaler, holding chamber, pretreatment, electrostatic charge, hydrofluoroalkane levalbuterol. [Respir Care 2006;51(5):511–514. © 2006 Daedalus Enterprises]

## Introduction

Valved holding chambers (VHCs) are recommended, particularly for patients who have poor inhaler tech-

nique, to improve aerosol delivery from metered-dose inhalers, as well as to minimize systemic absorption of medication caused by deposition of coarser particles in the oropharynx.<sup>1,2</sup> However, the VHC's ability to efficiently deliver medication can be compromised, particularly by the presence of electrostatic charge on the inner walls of the chamber, acquired during manufacture and also introduced by the aerosol formed upon inhaler actuation.<sup>3</sup> Surface electrostatic charge can be mitigated to some extent by prewashing the VHC in detergent<sup>4</sup> or by manufacturing the VHC from anti-static materials,<sup>5</sup> as is the case for the stainless steel NebuChamber (AstraZeneca, Lund, Sweden) and the Vortex (Pari Respiratory Equipment, Midlothian, Virginia). However, recently, the use of charge-dissipative (non-electrostatic) material in the construction of a new VHC of the AeroChamber family (AeroChamber Max, Monaghan Medical, Plattsburgh, New York) has made it possible to achieve efficient aerosol delivery even when the device is used directly out of the packaging, without prewashing.<sup>6</sup> The in vitro performance of the Aero-

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Chamber Max was recently studied with a widely available hydrofluoroalkane (HFA) formulation of racemic albuterol.<sup>7</sup>

Levalbuterol, the R-enantiomer of racemic albuterol,<sup>8</sup> was recently approved as Xopenex (Sepracor, Marlborough, Massachusetts) for the United States market, for delivery via metered-dose inhaler for the treatment of reversible obstructive airway disease in adults, adolescents, and children  $\geq 4$  years old by  $\beta_2$  agonist. There is, as yet, no published data on the delivery of this medication via VHC. We studied in vitro delivery of levalbuterol via AeroChamber Max, tested both out-of-package (without prewashing) and after pretreatment in accordance with the manufacturer's instructions (wash in water containing detergent, rinse in clean water, and drip dry), and compared the results with equivalent data for a benchmark nonconducting VHC (AeroChamber Plus), prewashed per the manufacturer's instructions. Our motivation was twofold. First, we sought to determine whether the nonelectrostatic VHC is as effective without prewashing. Second, we compared its performance with that of the widely available nonconducting AeroChamber Plus, when prewashed in accordance with the manufacturer's instructions.

### Methods

We tested a group of 10 AeroChamber Max VHCs. First we tested the devices immediately after removing them from the packaging without pretreatment. Then we tested them again after washing (using mild ionic detergent [Sunlight, Unilever, Toronto, Ontario, Canada]), rinsing, and drip-drying per the manufacturer's instructions. We also tested a group of 10 AeroChamber Plus VHCs, prewashed in the same manner, immediately before evaluation. All measurements were undertaken in the temperature range 22–23°C and in the relative-humidity range 47–58%.

An Andersen 8-stage cascade impactor (Thermo Electron, Franklin, Massachusetts), equipped with a United States Pharmacopeia (USP) induction port, was operated at 28.3 L/min ( $\pm 5\%$ ), in accordance with the procedure described in USP Chapter 601.<sup>9</sup> Ten actuations of medication (45  $\mu\text{g}$  levalbuterol base equivalent per actuation emitted from the inhaler's mouthpiece) were delivered, at 30-s intervals, to the VHC, which was connected via a close-fitting adaptor to the entry of the induction port. Immediately before each actuation, the inhaler canister was shaken for 5 s. Flow through the impactor was continued for 30 s after the last actuation. After flow was discontinued, the VHC was removed from the apparatus and the particles that collected within the VHC, induction port, and on all stages of the impactor were recovered via elution in a known volume of pure methanol (100%). The mass of albuterol associated with each component was determined by high-performance liquid chromatography

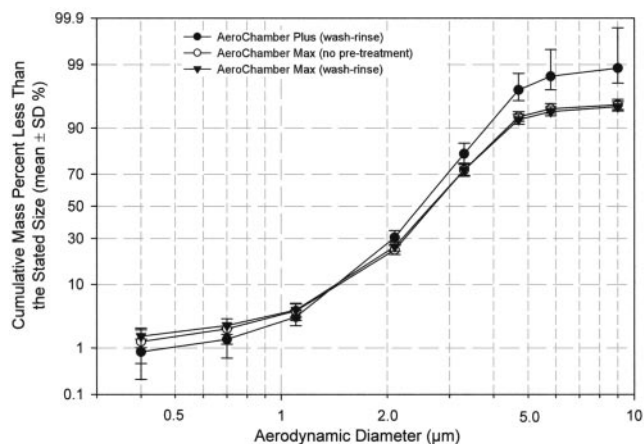


Fig. 1. Aerodynamic particle size analyses of aerosols emitted by the AeroChamber Plus and the AeroChamber Max. The error bars represent  $\pm 1$  standard deviation about the designated mean values. We tested 10 AeroChamber Plus devices and 10 AeroChamber Max devices.

ultraviolet spectrophotometry (Star System, Varian Associates, Walnut Creek, California) at a detection wavelength of 276 nm.

In addition to determining the cumulative mass-weighted size distribution of the particles emitted by each group of VHCs, we determined the fine-particle fraction (FPF, which is the percentage of aerosol particles  $< 4.7 \mu\text{m}$  aerodynamic diameter) and the fine-particle mass (FPM, which is the mass of the aerosol particles  $< 4.7 \mu\text{m}$ , calculated as total emitted mass  $\times$  FPF) of albuterol per actuation. The fine particles are the most likely to penetrate to bronchodilation receptors beyond the oropharynx.<sup>10</sup> FPM was based on the cumulative mass that collected on impactor stages 3 through 8 and the impactor's back-up filter.

Statistical calculations were made using statistical software (SigmaStat, SPSS Science, Chicago, Illinois). Differences were deemed significant when  $p < 0.05$ .

### Results

The mass-weighted aerodynamic-particle-size distributions emitted by these VHCs were qualitatively similar (Fig. 1), being unimodal and close to log-normal between the 5th and 90th percentiles. Prewashing of the AeroChamber Max had no effect on the size distribution (paired  $t$  test at each cascade-impactor-stage cut-point size,  $p \geq 0.13$ ), so the mass median aerodynamic diameter (estimated by interpolation) was in both cases close to  $2.6 \mu\text{m}$ , and the corresponding FPF values were  $92.2 \pm 1.2\%$  with prewashing, and  $92.9 \pm 1.1\%$  with no prewashing (Table 1).

The aerosol from the AeroChamber Plus VHCs contained slightly fewer particles  $> 2.1 \mu\text{m}$  aerodynamic diameter than did the aerosol from the prewashed Aero-

Table 1. Aerosol Particle-Size Distribution\*

Valved Holding Chamber Model†	Pre-treatment	MMAD ( $\mu\text{m}$ )	FPF (mean $\pm$ SD %)	TEM (mean $\pm$ SD $\mu\text{g}$ )	FPM (mean $\pm$ SD $\mu\text{g}$ )
AeroChamber Max	None	2.6	92.9 $\pm$ 1.1	39.1 $\pm$ 1.1	36.3 $\pm$ 1.1
	Wash, rinse, drip-dry	2.6	92.2 $\pm$ 1.2	36.3 $\pm$ 1.5	33.5 $\pm$ 1.4
AeroChamber Plus	Wash, rinse, drip-dry	2.5	97.2 $\pm$ 1.3	29.3 $\pm$ 2.5	28.5 $\pm$ 2.4

\*Levalbuterol aerosol (45  $\mu\text{g}$  levalbuterol per actuation)

†10 holding chambers per group

MMAD = mass median aerodynamic diameter. The MMAD values were obtained by estimation from the curves of cumulative mass percent, so no standard deviation values are reported.

FPF = fine-particle fraction (percentage of aerosol particles < 4.7  $\mu\text{m}$ )

TEM = total emitted mass

FPM = fine-particle mass (mass of particles in the fine-particle range [< 4.7  $\mu\text{m}$ ])

Chamber Max devices (via un-paired *t* test on a stage-by-stage basis,  $p \leq 0.001$  for stages 0 through 5), but the proportion of finer particles was comparable. The mass median aerodynamic diameter of the aerosol emitted from these VHCs was close to 2.5  $\mu\text{m}$ , with FPF of  $97.2 \pm 1.3\%$  (see Table 1). FPM was  $28.5 \pm 2.4 \mu\text{g}$ ,  $33.5 \pm 1.4 \mu\text{g}$ , and  $36.3 \pm 1.1 \mu\text{g}$  from the AeroChamber Plus (prewashed), AeroChamber Max (prewashed), and AeroChamber Max (no pretreatment), respectively (see Table 1). These differences were statistically significant (via 1-way analysis of variance,  $p < 0.001$ ).

### Discussion

Our investigation provides confirmatory data that the nonelectrostatic AeroChamber Max has comparable performance whether or not it is prewashed. It is well known that prewashing VHCs mitigates particle-loss from surface electrostatic charge.<sup>3-5</sup> However, Piérart et al,<sup>4</sup> in their comparison of various pretreatment techniques, observed that rinsing after washing is not as effective as washing and drip-drying without rinsing in detergent-free water. While it may therefore be appropriate to recommend the latter pretreatment, in the United States at least, this practice is not encouraged because of concerns about the possibility of contact dermatitis associated with components (in this case the mouthpiece of the VHC) that may contact the mucosa during administration of medication. Hence, manufacturer instructions for add-on devices specify the rinsing step. In the present study, if the performance of the untreated AeroChamber Max is taken as the benchmark condition, the fact that prewashing had an insignificant impact on performance is indicative that fine-particle delivery from these nonelectrostatic devices was close to optimum, irrespective of pretreatment. The assumption that medication delivery is maximized by the use of nonelectrostatic materials in the construction of the VHC is supported by the observations of Wildhaber et al.<sup>5</sup> They found that the mass of particles < 6.8  $\mu\text{m}$  with a racemic albuterol formulation delivered via the stainless steel Nebu-

Chamber significantly exceeded that of other, similar-sized, small-volume VHCs that had been pretreated with detergent.

The slightly finer particle-size distribution associated with the lower FPM values from the prewashed AeroChamber Plus might be anticipated as a result of increased retention of drug particles if the wash-rinse pretreatment was not fully effective at eliminating electrostatic charge. The precise relationship between electrostatic charge and particle size has not been studied with inhaler-produced aerosols, probably because of the wide variability in both magnitude and sign of electrostatic charge from one formulation to another,<sup>11</sup> as well as differences in the surface electrostatic charging properties of the wide variety of polymers used in inhalers and VHCs. However, the number of elementary charges that can be acquired mostly by field, but also partly by diffusion charging, increases as a strong function of particle size within the range of interest (0.4–10  $\mu\text{m}$  aerodynamic diameter).<sup>12</sup> This process may result in increased electrical mobility associated with larger particles, and therefore greater likelihood of electrostatic capture on the interior surfaces of the VHC.

The observation by Piérart et al<sup>4</sup> already mentioned, that wash/rinse pretreatment is less effective than washing without rinsing, is also pertinent, since their work was conducted with nonconducting devices in which electrostatic charge retention might be expected to be difficult to eliminate entirely when an electrically conducting layer of detergent was no longer present on the interior surfaces of the VHC. Although the FPM differences between the AeroChamber Plus and AeroChamber Max in the present study were statistically significant, they were comparable with differences seen in similar in vitro measurements with VHCs with HFA-based formulations.<sup>13</sup> Given the large inter-patient variability observed in records of breathing behavior of both children and adults with inhalers,<sup>14</sup> these differences are unlikely to be of clinical importance.

Our investigation was of necessity limited in scope, since its purpose was primarily to compare the performance of nonelectrostatic and nonconducting VHCs from

the same manufacturer, with this newly introduced formulation of albuterol. Furthermore, we avoided introducing other types of VHC, since Rau et al<sup>7</sup> have already compared the racemic albuterol FPM-delivery performance of several nonconducting VHCs with that of the AeroChamber Max, and they found that prewashing of the nonconducting VHCs they tested is necessary. Furthermore, they showed that with this formulation the performance of the AeroChamber Max was comparable, whether or not these nonelectrostatic devices were prewashed. The latter finding probably has more general applicability to other formulations, since Louca et al, who recently studied the delivery of HFA-fluticasone propionate to an infant face model, also reported comparable measures of total emitted mass from the AeroChamber Max with or without prewashing.<sup>15</sup>

### Conclusions

This laboratory investigation demonstrated that pretreatment of the nonelectrostatic AeroChamber Max, by washing in detergent, rinsing, and drip-drying in air in accordance with the manufacturer's instructions, has no impact on its performance with HFA levalbuterol. The nonconducting AeroChamber Plus delivers slightly less of this medication as fine particles if pretreated with the same protocol. These differences in VHC performance are unlikely to be of clinical importance. Further studies of this type are merited with other HFA-based formulations, to see if the findings are of a more general nature.

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