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Jet Nebulizers versus Pressurized Metered Dose Inhalers with Valved Holding Chambers: Effects of the Facemask on Aerosol Delivery

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ABSTRACT

The delivery of an aerosolized drug to a child is a complex process requiring an interaction between parent, child, and inhalation device. Recent studies have shown that the facemask can be a key factor affecting aerosol delivery, particularly the influence of leaks between the facemask and the face. To further quantify these effects and design around them, we have developed a bench model consisting of a breathing simulator, an inhaled mass filter, and a "pediatric face." This paper reviews the development of this model and details important decisions made in its configuration, particularly inhaled mass filter location (e.g., between device and facemask, or in mouth) and mouth diameter (4 or 18 mm). With the final design, we used the model to measure the impact of the "blow-by" technique on nebulizer inhaled mass. In a separate series of experiments, we studied the effects of a "crying" pediatric breathing pattern on inhaled mass for both nebulizers and pressurized metered dose inhalers with valved holding chambers (pMDI VHCs). Results indicated that the location of the inhaled mass filter was a critical factor in assessing aerosol delivery through facemasks and that the "mouth diameter" was not an important variable. Failure to locate the filter in the mouth behind the face, especially for jet nebulizers, failed to accurately measure effects of the facemask and significantly overestimated aerosol delivery. Blow-by results indicated that a 1-cm gap between the facemask and the face was not critical when using a front-loaded facemask. Finally, even with optimal design, the combination of an aerosol generator and facemask with a crying breathing pattern reduced the inhaled mass to <1% of the label dose.

Key words: breathing pattern, facemask, inhaled mass, nebulizer, pediatric, pressurized metered dose inhaler, valved holding chamber

INTRODUCTION

THE AMOUNT OF AEROSOL delivered to a patient from jet nebulizers and pressurized metered dose inhalers with valved holding chambers (pMDI VHC) can be assessed non-invasively by a filter technique both *in vivo* and *in vitro*.[1,2] When the interface between the device and the patient is a mouthpiece, there is good agreement between *in vivo* and *in vitro* data particularly for adults.[3]

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The situation is more complex when adding a facemask to the device, as the facemask is a critical interface between the device and the patient, particularly in children.[4] For example, as children seem to dislike a facemask-face seal, a "blow-by" technique—the inhalation device with or without facemask is kept at some distance from the face of the child and the aerosol directed towards the nose and mouth—has often been adopted as an alternative technique. For this technique, the available *in vitro* and *in vivo* data indicate a reduction in inhaled mass of drug from jet nebulizers depending on the size of the gap between the facemask and the child's face.[5,6] Similarly, pMDI VHCs have been shown to be sensitive to a lack of seal between the facemask and the child's face.[7–11] However, the *in vivo* studies for both jet nebulizers and pMDI VHCs suffer from a critical flaw as the filter measuring inhaled mass is positioned between the device and the facemask. As opposed to using a filter in place of a mouthpiece, locating the filter between the device and the facemask adds dead space and fails to measure the influence of the facemask (e.g., any interaction between the facemask and the face) on aerosol delivery. In short, to accurately measure *in vitro* the inhaled mass of an aerosol delivery system with a facemask, the inhaled mass filter should be inside the patient's airway (e.g., inside the mouth). Therefore, short of formal scintigraphic or radiolabeled drug studies, the only possible way to assess the impact of a facemask as an interface between an aerosol device and a patient seems to be an *in vitro* model.

A bench model was therefore created in which the inhaled mass filter could be placed behind a "face" for the purpose of testing inhalation devices—jet nebulizers and pMDI VHCs—typically used with facemasks. The bench model was built around a breathing simulator with an inhaled mass filter in a filter holder in the mouth behind a face.[4] The inhalation device with the facemask interface was then attached to the face. With this configuration a number of factors responsible for drug delivery, including breathing pattern, aerosol device, facemask design, and facemask leaks (lack of facemask-face seal) could be tested. On the other hand, to isolate the contribution of the facemask leaks alone, a perfectly sealed configuration was needed. Attaining this goal has been difficult as facemasks and face models pressed together do not result in a perfect seal. In our studies, a "sealed configuration" has been created by replacing the face with a steel plate. This configuration tests aerosol device and breathing pattern and, as in classic drug output studies, the inhalation devices, connected to the plate with or without the facemask depending on seal, provide a measurement of the "maximal" inhaled mass of drug for this bench model. The results recently published on jet nebulizer and pMDI VHC facemask leaks using this bench model indicated that the bench model could be an important tool in the evaluation of the facemask-face interface.[4]

We have evaluated the bench model in terms of:

- The impact of position of inhaled mass filter either in front of or behind the face
- The impact of two different mouth diameters (4 or 18 mm) in the face replica

We have used the bench model to measure:

- The impact of the "blow-by" technique on nebulizer inhaled mass
- The impact of a "crying" pediatric breathing pattern on inhaled mass when using both nebulizers and pMDI VHCs with facemasks

METHODS

Bench model

The specific bench model consisted of a breathing simulator connected to an inhaled mass filter in a filter holder which was connected to the "mouth" behind the face.[4] In order to match different pediatric breathing patterns and different facemask sizes, two different breathing simulators were used and two different sizes of the "face" were created.

The two breathing simulators included in the bench model—the Mimic Breathing Emulator and the Micro Mimic Breathing Emulator (Respironics Respiratory Drug Delivery Ltd., West Sussex, UK)—were computer-controlled syringes.[12–14] The software—the Mimic Applications (Respironics Respiratory Drug Delivery Ltd.)—was included for the analysis of the breathing patterns in terms of tidal volumes (V_T), breaths per minute (BPM), duty cycles, inspiratory and expiratory flows and time spent on inhalation. A pneumotachograph with trans-

ducer—the Mimic Breathing Monitor (Respironics Respiratory Drug Delivery Ltd.)—has been extensively used for the recording of real-life breathing patterns.[15,16] It was also used for the calibration of the breathing simulators, and to monitor the performance of the breathing simulator.

The "face" created for the bench model (Fig. 1; PA Consulting Group, Cambridge Technology Centre, Melbourn, UK) was made in two different sizes to provide "typical" faces of 1- and 2-year-old children. The faces were made of plastic with a mouth diameter of 22 mm to accommodate the low dead space filter holder (Respironics Respiratory Drug Delivery Ltd.), with a resultant diameter of 18 mm with the filter holder inserted into the "mouth." The length of the mouth cavity was 42.5 mm, with a dead space of 15 mL. As it was obvious from the very first tests that a number of commercially available facemasks did not seal well against any of the two faces, a sealed configuration was created using a flat plate of stainless steel[4] (Fig. 1). The plate was made with a round hole with a plastic fitting in the middle of the plate as a substitute for a "mouth." The diameter of the mouth was 22 mm and with filter holder inserted into the "mouth" 18 mm. The length of the mouth cavity was 45 mm, with a dead space of 17 mL. The insertion of the low dead space filter holder into the "mouth" did not add dead space to the mouth cavity. Filter pads (diameter 67 mm, Filtrete Media; 3M Corp., St. Paul, Minn.) were used as inhaled mass filters in the low dead space filter holders.

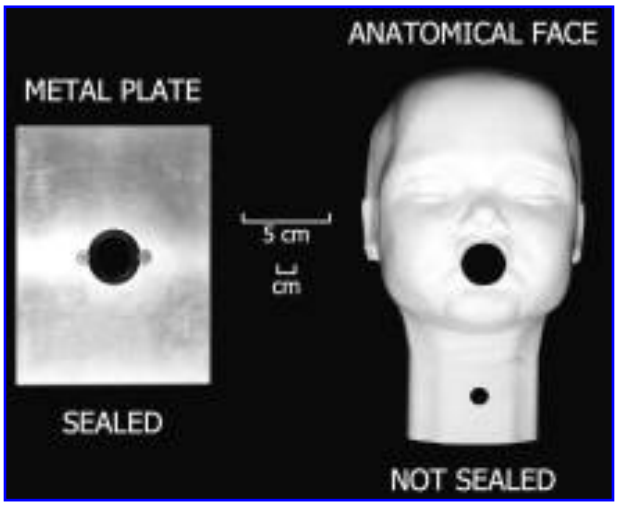

FIG. 1. A photo of the face replica and the plate used in the study.

Validation of the bench model: impact of filter position

The objective of the main validation of the bench model was to measure the impact of the position of the filter on the inhaled mass. In these tests, the low dead space filter holder was positioned either between the inhalation device and the facemask (Fig. 2A), which was then placed on the face (or plate), or in the mouth behind the face (or plate) with the device with facemask connected to the face (Fig. 2B).

The NebuChamber VHC (AstraZeneca R&D Lund, Lund, Sweden) with a Laerdal 2 facemask (Laerdal Medical Corporation, Wappingers Falls, NY), and the Pari LC Plus jet nebulizer (Pari Respiratory Equipment, Inc., Monterey, CA) with a Laerdal 2 facemask, and a Pari Master compressor (Pari Respiratory Equipment, Inc.) were used in these tests. The *in vitro* test setup consisted of the "face" models (anatomical face replica of a 2-year-old child and a flat plate, both with an 18-mm mouth diameter), filter holders, and a breathing simulator—the Micro Mimic Breathing Emulator—which was used to create a sinusoidal waveform with V_T 100 mL, 25 BPM, and a duty cycle of 0.5 (Fig. 2A,B). The breathing pattern was selected from recorded pediatric breathing patterns to age match the face replica.[15] The inhalation devices were connected to both face and plate with the Laerdal facemask attached. The study drugs included budesonide 200 μg/actuation chlorofluorocarbon pMDI (AstraZeneca R&D Lund) with the NebuChamber VHC, and budesonide inhalation suspension 0.125 mg/mL, 2 mL vial (AstraZeneca, Wilmington) with the Pari LC Plus jet nebulizer. Five devices of each brand were tested per filter position. With the jet nebulizer, both the compressor and the breathing simulator were started simultaneously and the nebulizer run to dryness during 6 min. With the pMDI VHC combination—after shaking the pMDI—the breathing simulator was started, a dose of drug actuated simultaneously, and the breathing was maintained for 10 sec.

Validation of the bench model: impact of mouth size

The objective of the second part of the validation was to test whether a small "mouth" size—

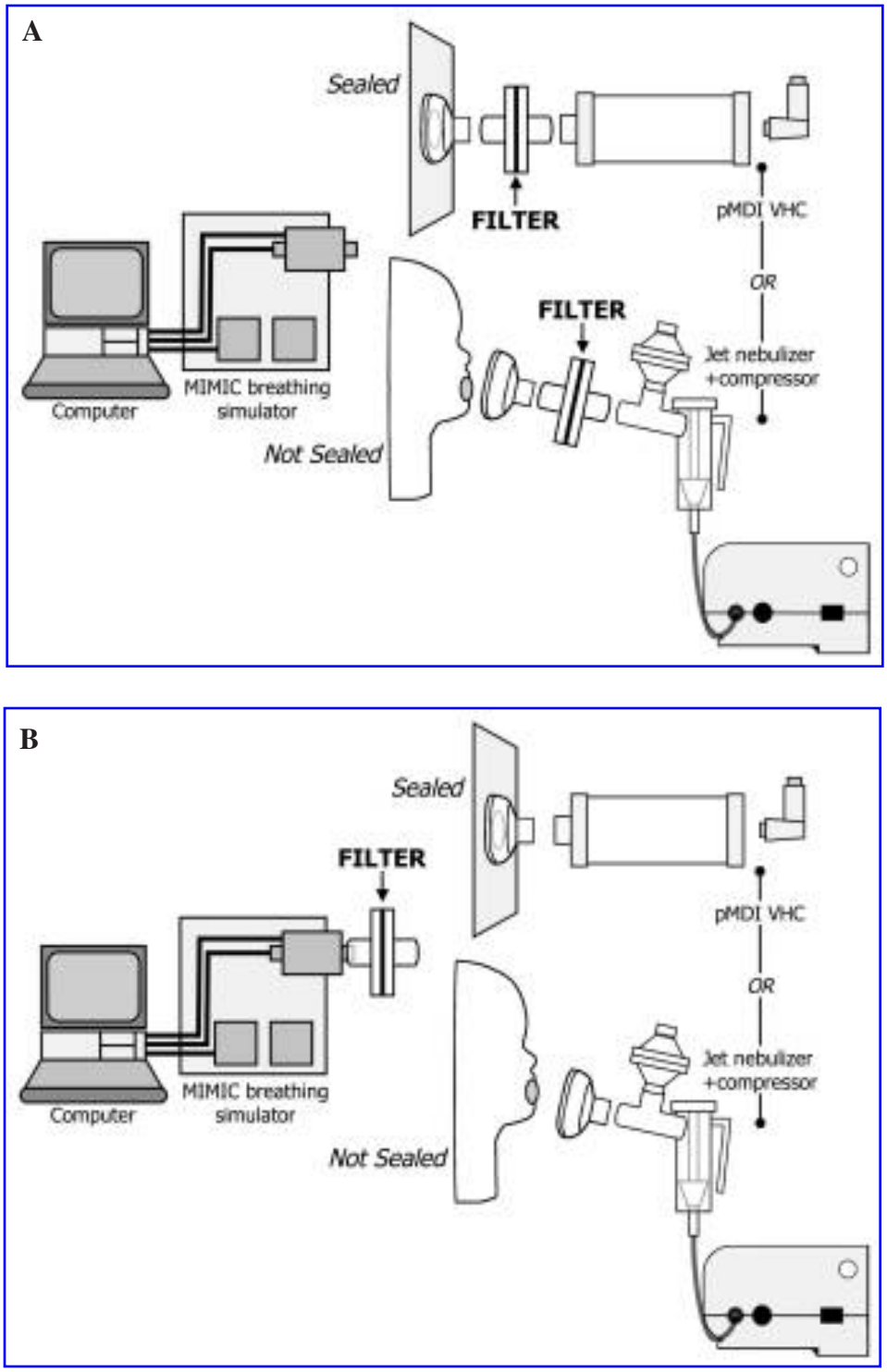

FIG. 2. (**A**) The bench model is shown with filter (arrow) positioned between device and facemask. (**B**) The bench model is shown with filter (arrow) positioned in the mouth behind face or plate.

small defined as a 4-mm-diameter mouth in the face replica—would result in a different inhaled mass compared to the previous test results as outlined above with a face replica with a mouth with a diameter of 18 mm. The low dead space filter holder was, as in the above outlined tests, positioned either between the device and the facemask or in the mouth behind the face (or plate) with the device with facemask connected to the face (Fig. 2A,B). The inhalation devices were con-

nected to both face and the plate with the Laerdal facemask attached.

The inhalation devices, facemasks, study setup, study drugs, breathing pattern, and analytical procedures were identical to those used in the main validation test as outlined above. Five devices of each brand were tested per filter position.

Impact of the blow-by nebulizer technique on the inhaled mass

The objective of these experiments was to measure the impact of the blow-by technique on the inhaled mass by using the bench model with the filter in the mouth behind the face, a Pari LC Plus jet nebulizer, and a Laerdal 2 facemask. The nebulizers were charged with 2 mL of normal saline mixed with 1–2 mCi of 99mTechnetium (^{99m}Tc), and run until dryness at 4.4 L/min using a Pari ProNeb Ultra compressor (Pari Respiratory Equipment, Inc.). The low dead space filter holders were connected in the mouth behind the face (2-year-old), between the breathing simulator and the face. The V_Ts, BPMs, and duty cycles of the two sinusoidal waveforms were as follows: V_T 50 mL, 25 BPM, and 0.4; and V_T 200 mL, 25 BPM, and 0.5. The test was run once per breathing pattern.

The facemask was first connected against the face, and then in 1-cm steps—at the same angle to the face—removed from the face to create gaps of 1, 2, 3, 4, and 5 cm between the edge of the facemask and the face. After nebulization to dryness, the filter holders were removed from behind the face and placed on a gamma camera, and the radioactivity was measured as counts/min converted to μCi by attenuation correction using known sources with similar geometry. The deposition on the inhaled mass filter was expressed as percent of the radioactivity of the 2-mL nebulizer charge.

Impact of a "crying" breathing pattern on the inhaled mass

Anecdotal and published evidence suggest that children dislike and often cry when the facemask is sealed onto the face.[8] We have, using the bench model with the filter in the mouth behind the face, quantified the impact of a "crying" breathing pattern on the inhaled mass of drug. The "crying "breathing pattern used was that of a 1-year-old child[15,16] (Fig. 3). The mean V_T of the whole pattern was 134 mL, with a duty cycle of 0.26. The BPM could not be reasonably defined. A Micro Mimic Breathing Emulator was used as a pediatric breathing simulator, and the face replica of a 1-year-old child was used in the bench model. The devices included in the tests were as follows:

- Hudson Up-draft II jet nebulizer with standard vented pediatric facemask and Pulmo-Aide compressor (Sunrise Medical Respiratory Products Division, Somerset, PA)
- Pari LC Plus jet nebulizer with Bubbles the Fish vented facemask (Pari Respiratory Equipment, Inc.) and Pari Master compressor
- AeroChamber Plus with small ComfortSeal facemask (Monaghan Medical Corporation, Plattsburgh, NY)
- OptiChamber with small sized facemask (Respironics Respiratory Drug Delivery, Cedar Grove, NJ)

Budesonide inhalation suspension 0.125 mg/mL (2-mL vial) was used with the jet nebulizers, and fluticasone propionate 220 μg/actuation chlorofluorocharbon pMDI (GlaxoSmithKline, Research Triangle Park, NC) with the VHCs. Five devices of each brand were tested. The VHCs used were not detergent coated.

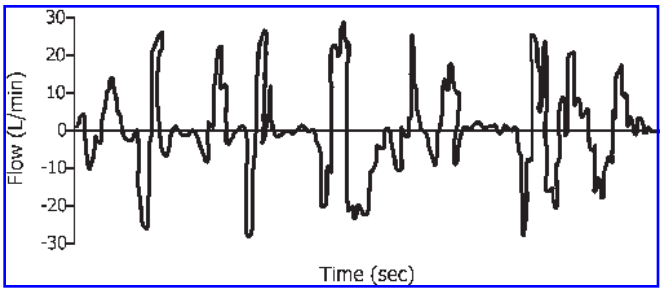

FIG. 3. The crying breathing pattern recorded from a 1-year-old child. The mean V_T of the whole pattern was 134 mL, with a duty cycle of 0.26. The BPM could not be reasonably defined.

Extraction and analysis of drug

Aerosolized budesonide and fluticasone propionate were extracted from filters and filter holders by washing with ethanol containing internal standard (fluocinolone acetonide). The concentration and mass of drug was determined by reverse-phase high-performance liquid chromatography at the Pulmonary/Critical Care Division Laboratory at SUNY at Stony Brook (Stony Brook, NY). The level of quantification was 1 μg for both drugs.

Statistical analysis

Data are reported as mean ± SD, and confidence limits for all experimental configurations apart from the blow-by tests are listed in Table 1. Comparisons were made between jet nebulizers

TABLE 1

Device	*Mouth size*[a]	*Facemask-face configuration*[b]	*Filter location*[c]	n	*Mean*[d] *(%)*	*SD*	*Confidence interval*
Impact of filter location and mouth size							
NebuChamber	18 mm	Plate	In front	5	31.7	1.4	30.0–33.5
			In mouth	5	21.3	2.2	18.6–24.0
		Face	In front	5	<1		
			In mouth	5	<1		
Pari LC Plus		Plate	In front	5	11.0	0.9	9.9–12.1
			In mouth	5	8.3	0.4	7.9–8.8
		Face	In front	5	23.2	2.5	20.1–26.3
			In mouth	5	9.6	0.4	9.1–10.1
NebuChamber	4 mm	Plate	In front	5	30.0	2.5	26.8–33.1
			In mouth	5	20.4	1.0	19.2–21.7
		Face	In front	5	<1		
			In mouth	5	<1		
Pari LC Plus		Plate	In front	5	11.5	0.7	10.6–12.4
			In mouth	5	8.6	0.4	8.1–9.2
		Face	In front	5	27.0	3.2	23.1–30.9
			In mouth	5	8.3	1.0	7.0–9.6
Impact of blow by							
Pari LC Plus	18 mm V_T 200 mL	No gap	In mouth	1	100		
		Gap 1 cm		1	102		
		Gap 2 cm		1	93		
		Gap 3 cm		1	74		
		Gap 4 cm		1	58		
		Gap 5 cm		1	46		
	18 mm V_T 50 mL	No gap		1	100		
		Gap 1 cm		1	105		
		Gap 2 cm		1	71		
		Gap 3 cm		1	55		
		Gap 4 cm		1	26		
		Gap 5 cm		1	29		
Impact of crying							
AeroChamber	18 mm	Plate	In mouth	5	<1		
		Face		5	<1		
OptiChamber		Plate		5	<1		
		Face		5	<1		
Pari LC Plus		Plate		5	4.6	1.2	3.1–6.0
		Face		5	<1		
Hudson Updraft II		Plate		5	1.3	0.5	0.6–2.2
		Face		5	<1		

[a]The mouth size was 18 mm in all tests apart from the "impact of mouth size" test, in which it was 4 mm.
[b]The facemask-face configuration is given either as "plate" to represent the data derived in the sealed configuration or as "face" to represent the data derived in the unsealed configuration.
[c]The filter location is given either as "in front" to represent the filter location between the device and the facemask or as "in mouth" to represent the filter location in the mouth behind the face.
[d]Mean numbers are given as percent of label dose and, for the blow-by tests, in percent of the "no gap" situation.

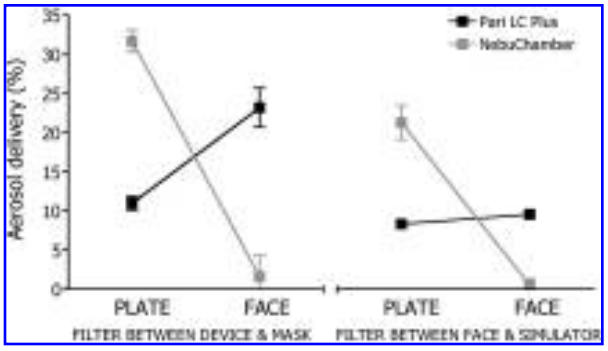

FIG. 4. The inhaled mass of budesonide is presented in percent of label dose for the jet nebulizer (Pari LC Plus) and for the pressurized metered dose inhaler with valved holding chamber (NebuChamber VHC). The inhaled mass filter was positioned either between the device and the facemask, or in the mouth behind the face or the plate.

and pMDI VHCs, and between sealed and face configurations by analysis of confidence limits. Inhaled mass data for all devices—apart from the blow-by test—are reported as percent of label dose. In the blow-by test, the data are reported as percentages of the no-gap baseline values.

RESULTS

Validation of the bench model: impact of filter position

The filter position—either between inhalation device and facemask, or in the mouth behind the face—had a major impact on the inhaled mass (Table 1, Fig. 4). In the sealed configuration (plate), the inhaled mass of budesonide for the NebuChamber VHC was 31.7 ± 1.4% with the filter between the device and the facemask, and 21.3 ± 2.2% with the filter in the mouth behind the face. In the face configuration, the inhaled mass was <1% for both filter positions.

For the Pari LC Plus jet nebulizer, the inhaled mass of budesonide was 11 ± 0.9% in the sealed configuration (plate) with the filter between the device and the facemask, and 8.3 ± 0.4% with the filter in the mouth behind the face (Table 1, Fig. 4). In the face configuration, the inhaled mass was 23.2 ± 2.5% and 9.6 ± 0.4%, respectively.

Validation of the bench model: impact of mouth size

The size of the mouth diameter—either 4 or 18 mm—had no impact on the inhaled mass (Table 1). In the sealed configuration (plate), the inhaled mass of budesonide for the NebuChamber VHC was 30 ± 2.5% (4 mm) versus 31.7 ± 1.4% (18 mm) with the filter between the device and the facemask, and 20.4 ± 1.0% (4 mm) versus 21.3 ± 2.2% (18 mm) with the filter in the mouth behind the face. In the face configuration, the inhaled mass for the NebuChamber VHC was <1% for the two mouth diameters and two filter positions.

For the Pari LC Plus jet nebulizer, the inhaled mass of budesonide (Table 1) was 11.5 ± 0.7% (4 mm) versus 11 ± 0.9% (18 mm) in the sealed configuration (plate) with the filter between the device and the facemask, and 8.6 ± 0.4% (4 mm) versus 8.3 ± 0.4% (18 mm) with the filter in the mouth behind the face. In the face configuration, the inhaled mass was 27 ± 3.2% (4 mm) versus 23.2 ± 2.5% (18 mm) with the filter between the device and the facemask, and 8.3 ± 1.0% (4 mm) versus 9.6 ± 0.4% (18 mm) with the filter in the mouth behind the face.

Impact of the blow-by nebulizer technique on the inhaled mass

Inhaled mass was unaffected or slightly increased by a 1-cm gap for both breathing patterns. However, with further increases in distance from the face, inhaled mass decreased to a minimum of 26% at 4 cm for the 50-mL tidal volume. When tidal volume was increased, the effect of the increasing gap was reduced by about half at each point (Table 1, Fig. 5)

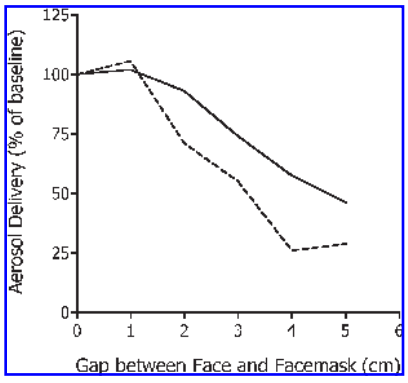

FIG. 5. The figure shows the impact of gaps between facemask and face on the amount of aerosol (99mTechnetium) delivered from a jet nebulizer when using the bench model with two breathing patterns: tidal volume 50 mL, 25 BPM, and duty cycle 0.4 (dotted line); and tidal volume 200 mL, 25 BPM, and duty cycle 0.5 (solid line).

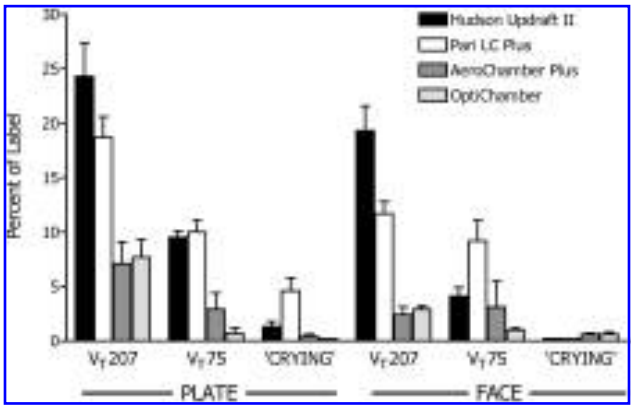

FIG. 6. The inhaled mass (nebulizers–budesonide; VHCs–fluticasone propionate) of drug is shown for different inhalation devices when used in a setup with a facemask-face seal (plate) and with a setup without the seal (face). The lack of seal, and the reduction of tidal volume reduced the inhaled mass. The "crying" breathing pattern reduced the inhaled to levels <1% of the label dose.

Impact of a "crying" breathing pattern on the inhaled mass

The impact of pediatric breathing patterns—V_Ts of 75 and 207 mL—on the inhaled mass from jet nebulizers and pMDI VHCs has been previously documented[4] with the bench model (Fig. 6). In that study, the pMDI VHCs were more sensitive to changes in breathing pattern than the jet nebulizers. In the present study, crying reduced the inhaled mass in the sealed configuration compared with the published data, and the differences between the nebulizers and the pMDI VHCs were significant. With lack of facemask-face seal (face configuration), crying reduced the inhaled mass for jet nebulizers from 1.3% to <1% (Hudson) and from 4.6% to <1% (Pari LC Plus). For the pMDI VHCs, the inhaled mass was unchanged at levels of <1%.

DISCUSSION

Leaks in the facemask–face interface (ranging from the blow-by technique to small minor leaks around the nose and chin) have been shown both *in vitro* and *in vivo* to have a major impact on the inhaled mass from pMDI VHCs and jet nebulizers.[4–7] Important differences in technique for the different studies may affect the interpretation of results. For example, any *in vitro* study using an inhaled mass filter without a face may not reveal major effects that limit drug delivery. These would be undetected because of lack of realistic leaks at the facemask-face interface (e.g., the high value of inhaled mass for the sealed Nebuchamber (Fig. 4). If a face is present, the influence of facemask volume, room air entrainment and filter dead space will not be detected unless the inhaled mass filter is in the mouth behind the face. Further, to differentiate factors at the facemask-face interface from all other factors, the experimental setup without interface leaks should be compared to the interface with leaks (e.g., sealed versus non-sealed). This approach has been followed for pMDI VHC by investigators using the SAINT model which has a face replica of a 9-month old infant and therefore cannot be used in the testing of facemasks for toddlers and young children.[9] More recent studies have looked directly at the facemask-face interface for both pMDI VHC and jet nebulizers.[4] Our group first tested a bench model in which the filter was positioned in the "mouth" behind the face—between a breathing simulator and the back of the face—creating a test setup that could begin to evaluate the facemask-face interface.[4] The present paper presents the results of a validation of this bench model, with additional data assessing the impact of the blow-by technique and crying on the inhaled mass.

The validation of the filter position in the bench model showed that the position of the filter had an impact on the inhaled mass of drug for both pMDI VHC and jet nebulizers, whereas the difference in the size of the mouth—4 or 18 mm—did not. We do not imply that the "mouth" in the face is anatomically correct, but simply that the difference in size of the "mouth" did not influence inhaled mass. Our results showed, however, that the position of the inhaled mass filter was of major importance. In the sealed configuration (plate) with the NebuChamber VHC the inhaled mass was higher when the filter was positioned between device and facemask (31.7%) and decreased (21.3%) with the filter in the mouth behind the face, between face and breathing simulator. As there were no leaks between the Laerdal facemask and plate, the decrease had to be related to the presence of the facemask, either a dead space effect or possible local airflow effects in the facemask.[17] In the face configuration with the NebuChamber VHC and the Laerdal facemask the inhaled mass dropped to levels below the limit of quantification. The most likely reason for this was the relatively high resistance in the

NebuChamber valve system, which makes it sensitive to lack of complete facemask-face seal.[8,9,11] In our experiments, facemask effects for the jet nebulizer were different from those of the pMDI VHC. In the sealed configuration using the Pari LC Plus jet nebulizer, the difference in inhaled mass was small with the filter between the device and the facemask, or with the filter in the mouth. In the presence of leaks at the facemask-face interface, inhaled mass actually increased as the continuous flow from the compressor kept the mask filled with aerosol.

In the evaluation of the blow-by technique with the bench model, the inhaled mass was clearly affected by the increasing distance between the face and the facemask. The changes were more significant for the breathing pattern with the smaller V_T. Interestingly, the inhaled mass increased slightly with a 1-cm gap, and then with a 2-cm gap dropped below 75% for the smaller V_T and was relatively unaffected for the larger V_T at ~90%. The difference between the two V_Ts remained and decreased to ~29–46% at 5 cm depending upon breathing pattern. These results are not in agreement with those published by Everard et al.[5] In their *in vitro* study, they used a V_T of 50 mL, and a plate as a "face," and the inhaled mass decreased from 100% to ~41% for a 1-cm gap, and to ~15% for a 2-cm gap. There is an important difference between the studies. In the present study, a front-loaded (nebulizer fitted to the back of the facemask) facemask was used with the Pari LC Plus jet nebulizer, whereas in the study by Everard et al. a bottom-loaded (nebulizer fitted to the bottom of the facemask) facemask was used with the Cirrus jet nebulizer. The position of the nebulizer fitting to the facemask has been shown to affect the inhaled mass such that front-loaded facemasks have a higher inhaled mass.[18] Thus, it is possible that the blow-by technique may be more effective if practiced with a jet nebulizer with a front-loaded facemask.

In spite of optimal use of jet nebulizer or pMDI VHC, our bench model indicates that crying has a major impact on inhaled mass essentially preventing significant delivery of aerosol to the patient. In the sealed configuration, the nebulizers were significantly more efficient than the pMDI VHCs in the delivery of aerosol. In the face configuration, there were no differences between nebulizers and pMDI VHCs, indicating that lack of facemask-face seal could almost eliminate aerosol delivery to crying children. These results are in agreement with the results of clinical studies showing diminished aerosol delivery when infants and children are distressed and/or crying.[8,19,20] Iles et al.[19] showed that infants who were distressed and/or crying when inhaling nebulized disodium cromoglycate through a facemask had significantly lower levels of the drug excreted in the urine, whereas Murakami et al.[20] showed decreased lung deposition in crying children. The present results indicated that crying during aerosol delivery brought the inhaled mass to <1%, almost eliminating any passage of aerosol into the mouth cavity.

The results presented highlight the fact that the facemask is a critical interface between the "patient" and the inhalation device, and that the performance of facemasks can be evaluated on the bench. The bench model is, therefore, a valuable tool in the development of new inhalation device/facemask designs. The impact of the lack of seal between facemask and face on the inhaled mass of drug demonstrated that any inhalation device with facemask should be developed as a unit. Our results indicate that regulatory guidelines and standards for devices should be applied to facemasks and inhalation device/facemask combinations.

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DISCUSSION

David Geller, M.D.: I want to ask about your comment that masks should probably have vented holes. We did some work a couple of years ago that looked at different nebulizers and the different facemasks that come with those nebulizers, and found that a larger dose of aerosol was delivered to the lung of the SAINT model with the AeroEclipse mask, which is not a vented mask but a tight-fitting, cushioned mask with a one-way valve for exhalation.

When we then took that mask and put it on a competitor's nebulizer device, we found a doubling of the lung dose delivered to the SAINT model. This shows that a mask can make a quite remarkable difference in aerosol delivery.

Kurt Nikander: I agree. Mask design can make quite a difference in aerosol delivery. But the devices you used with the masks weren't valved holding chambers.

Dr. Geller: No, they were nebulizers. The interesting thing, though, was that the two different masks—the Pari Bubbles and the Pari Baby, one with holes and the other without—performed equally, because I think there was a natural leak around the mask without holes.

Mr. Nikander: This is interesting considering our experience. When we used our *in vitro* model and tested a sealed Laerdal 2 face mask, which has no vents, with a nebulizer, we realized that aerosol was streaming either up toward the eyes or down toward the chin. Ideally, with a nebulizer-facemask combination that delivered more aerosol than a child could inhale, we would want to minimize the streaming of aerosol toward the eyes. This could, for example, be accomplished with facemask vents.

Hettie Janssens, M.D., Ph.D.: Kurt, you asked me a question about the comparison of your data and the data that we obtained with the facemask leaks. I think the difference is that you saw a bit larger dose being delivered from the holding chamber than we did, especially at a tidal volume

of 200 mL. But when you looked at a tidal volume of 75 mL, the dose was much lower. I think that means that, when you have a larger tidal volume, you can still extract aerosol from the holding chamber, even if there is a facemask leak, and I think that is an important difference.

Philip E. Silkoff, M.D.: As a general comment, I think there is a big gap in the approval of aerosol drugs and of the devices used to administer those drugs. We all know that spacers are often used off-label. I think we just assume that you can do what you like and that you'll get the same drug delivery no matter what, which is clearly not true. You may be underdosing or you may be overdosing. It reminds me of the old saying that "there is many a slip twixt cup and lip." I think that in some way we've got to move toward recognizing the wide off-label use of spacers and other devices, and study this more extensively and even get regulatory approval for certain devices.

Mr. Nikander: One of the important outcomes of the tests with our *in vitro* model was the large variability in the inhaled mass of drug, especially with the valved holding chambers. A question I'd address to all of you is whether it would be possible to design a valved holding chamber that could show the parents what kind of dosage of drug the valved holding chamber delivered with a particular face mask under different breathing patterns and user conditions. We designed in the past a "dosimetric spacer," which really was a valved holding chamber with an electronic dose control, but for various reasons we could not finalize it. In general, it would have been too expensive.

Dr. Silkoff: How would you do that?

Mr. Nikander: We designed a unit with which we could measure the inhaled volume of air through the valved holding chamber over time. With the data on the sedimentation time for the valved holding chamber, we could then work out the amount of drug inhaled from the chamber. We have published some of this. The question is, however, whether a device like this would be commercially feasible.

Mitchell A. Baran: I've been thinking about this for 25 years. To address your point, our view has always been that the aerosol device for a specific patient has to be selected by the physician. The physician is the one who titrates the medication according to the patient. The importance of that is stressed by the finding in clinical studies that even with an MDI alone, that somewhere from one-third to two-thirds of the patients show uncoordinated self-dosing. It means that each patient has to be treated individually. I think that's what's been lost in the shuffle.

The device has to have top performance and consistency, so that the physician is aware what its performance might be under all circumstances, but I don't think the device is at fault.

Dr. Silkoff: The danger is that it's easy to recognize undertreatment, but overtreatment is not so easy to recognize, and most patients are given higher dosing regimens than they really require.

Ann Graham: The way in which the FDA regulates nebulizers is complicated, but they are generally reviewed under section 510(k) of the Food Drug and Cosmetic Act. Dr. Silkoff is right in stating that many spacer devices are used off label, and also right in observing that many aerosol drug formulations have not changed over time to keep up with newer designs in nebulization. I'm thinking about the small piezoelectric-driven ultrasonic nebulizers, which may provide a much higher proportion or percentage of inhaled drug per breath than in the old jet nebulizers.

On the topic of masks, which is probably even more complex than that of nebulizers, most patient interface masks are regulated as Class I devices, which means that they're medical devices but that you don't have to make a 510(k) submission to market them in the United States. Because we cruise the Web just like everyone else does, we're aware of different masks, but we haven't reviewed any of the labeling for them and we don't know anything about their performance. I was talking about this earlier today with Mike Husband of the FDA, and the agency has been wrestling internally over the past couple of years with the way in which it reviews nebulizers. We know that one reason a device company would like a general 510(k) clearance is because it's easier to study a cleared device for a particular pharmaceutical product once its already on the market, and institutional review boards (IRBs) have fewer concerns with accepting stud-

ies involving such devices. That is one factor that's driving the 510(k) system for nebulizers.

But the point that has impressed me the most here, even given the lack of data available for holding chambers, is that the dose delivered to the patient is markedly determined by the patient-interface device. If you have a holding chamber with a specific mask, there probably isn't a clinician in the world who knows the actual dose that that system delivers to the patient. I'm probably overstating that a bit, but I base it on the data we've seen under controlled laboratory conditions in the studies reviewed here.

We are here today to engage in the conversation about understanding the role of patient interface devices in altering the delivered dose of a pharmaceutical product, the regulatory options available to pharmaceutical/ and/or device product developers. We hope that if you have questions about the performance data that would be required for a device, or other regulation-related issues, you'll come to us earlier rather than later in the regulatory process. The difficulty I see remaining, however, is that a nebulizer and a patient interface device may be marketed by different companies. The two devices don't need to be cleared for marketing as a system unless the clinical community and the academic research community believe that the safe performance of these devices is so critical that they do need to be marketed as a system. And all of that has both pros and cons.

The other thing I'd like to mention is that we're involved in writing a voluntary standard for nebulizers in the International Standards Organization (ISO). I would encourage all non-U.S.-based manufacturers to go to your national ISO member representative and become part of that process. United States members can participate through the American Society for Testing and Materials (ASTM) F29 Committee on Anesthesia and Respiratory Devices. If we try to develop a standard for nebulizers and we have only half the equation, our work is not going to be very fruitful. I'll conclude by pointing out that most nebulizers labeled as combination products have to undergo FDA review as a new drug application (NDA) and go through that process for their marketing approval.

Gene Scarberry: Having sat on ASTM committee meetings in setting standards for ventilators, I definitely concur that before you get to regulatory questions you want to know what's really going on with a device. Today, we're discussing new information that's changing radically. My experience in the sleep apnea market as well as with noninvasive ventilation is that the clinician wants to be able to adapt what they're comfortable with or what they've got experience with for each patient. If there are physiological differences in facial shapes, they want to use mask A or mask B as they see fit. It becomes a matter of personal selection. You need to leave that freedom to the clinician, and you can't do that if you lock aerosol delivery devices to patient interface devices.

Ms. Graham: I want to say something that I think ties in with an earlier comment, which is my belief that clinicians may not be aware of the variability, not only in the output of a device, but in the selection of a particular patient interface mask for use with it. In terms of patient safety, the primary intended use of a device consisting of a nebulizer with a mask is to give the patient the dose of an aerosolized drug that accords with the drug labeling. If you have data showing that you're not getting that dose with a particular nebulizer and particular mask, there is a disconnect. I guess that where we go from here, before we start regulating, is to setting standards, which I think are different and less daunting.

Jolyon Mitchell, Ph.D., FRSK (UK): I've got two things to say. First, in addition to the ISO work on a standard for nebulizers, another ISO group (Technical Committee [TC] 84) has been working for the past three or four years through Joint Working Group (JWG)5 toward developing an ISO standard for metered-dose inhalers (MDIs), including spacers and holding chambers, and dry powder inhalers (DPIs), and I would encourage each of you to get involved in that process. The standard for MDIs is already at the committee draft (CD) stage as ISO-CD-20072. A lot of comments have already come back through the various national standards bodies that are actively participating, and a second round of public review of the CD is scheduled for later this year. It's crucial that, wherever we can, we harmonize this standard with that planned for nebulizers that Ann Graham mentioned, to reflect what is needed in terms of their regulation and to help manufacturers design and develop suitable devices across the whole spectrum of inhalers and accessories.

Second, I wanted to ask whether, in the study with the facemasks, nebulizers, and holding chambers in 2-year-olds, in which you found leakage, you quantified the leakage with a pneumotachometer or other device so as to get an idea of the leakage rate in terms of the different tidal volumes with which you were working?

Mr. Nikander: We did not quantify the leakage during the test. We did, however, try to quantify the pressure required to seal the facemask against the faces that we used.

Dr. Mitchell: I think it's really crucial that when we refer to leakages, we quantify them, because otherwise we haven't a clue about what their numbers mean.

Mr. Nikander: I agree. And we need to further develop the faces so that we can test both the lack of a facemask seal and sealed facemasks.

Mr. Scarberry: To continue a previous comment, I would say that Kurt's presentation was wonderful, but was still based on a model examined in an artificial test environment. I'm new to this, and coming in from the fields of sleep apnea and ventilation, but it seems that the work with aerosols, masks, and ventilators is at the same place we were at 10 years ago in trying to decide what causes sleep apnea. Until it integrates more elaborate models for studying flow, and routine clinical testing to back up every stage of development, we're still some ways from establishing standards and other criteria.