In Vitro Delivery of Budesonide From 30 Jet Nebulizer/Compressor Combinations Using Infant and Child Breathing Patterns

Elna B Berg and Robert J Picard IMBA

BACKGROUND: An aerosol of budesonide inhalation suspension is delivered when used with various jet-nebulizer/compressor combinations. The constant introduction of new nebulizer/compressor combinations raises the question of whether the performance of these match the performance of existing devices. The aim of this study was to determine in vitro the inhaled mass and aerosol characteristics of budesonide inhalation suspension from a selection of jet-nebulizer/compressor combinations presently marketed in the United States, Europe, and Japan. METHODS: The in vitro characterization was performed using standardized and published methods. Each nebulizer was charged with 1 vial (2 mL) of budesonide inhalation suspension 0.25 mg/mL (0.5 mg budesonide) and run until end of aerosol formation. Droplet size and distribution was determined using a cooled impactor at air flow of 15 L/min. The inhaled mass of budesonide (ie, mass on the inhalation filter) was collected using a breathing simulator that mimicked the breathing patterns of an infant and a child. The aerosol was collected on filters placed between the nebulizer mouthpiece and the breathing simulator. Budesonide was quantified via standard high-performance liquid chromatography. RESULTS: The mass median aerodynamic diameter of the aerosol measured with the cooled impactor ranged between 4.8 μm and 9.9 μm, and the geometric standard deviation ranged between 1.7 μm and 2.1 μm. The inhaled mass of budesonide expressed as a percentage of the nebulizer charge ranged from 1% to 9% (infant) and from 4% to 20% (child). CONCLUSIONS: The in vitro budesonide mass collected on the inhalation filter and delivery characteristics differed considerably between the 30 nebulizer/compressor combinations. The present in vitro characterization of jet nebulizers can be used as a guidance for selection of jet-nebulizer/compressor combinations for delivery of the budesonide nebulization suspension in the home-care setting. Further investigations of new nebulizer/compressor combinations are warranted. *Key words: budesonide inhalation suspension, nebulizer, in vitro.* [Respir Care 2009;54(12):1671–1678. © 2009 Daedalus Enterprises]

Introduction

Aerosolization is widely used to deliver drug to the respiratory system for the management of respiratory diseases such as asthma, in both adults and children.[1,2] The advantages of aerosol therapy for the management of respiratory disease lies in the direct delivery of active drug to the target organ, thereby allowing for lower doses to be used and limiting systemic exposure, with fewer or less severe systemic adverse effects.[1] Aerosol drug delivery to infants and young children presents additional clinical challenges in that they often lack the coordination and/or the ability to cooperate actively in order to achieve optimal delivery using pressurized metered-dose or powder inhalers. For these patients, nebulization offers a more effective and acceptable delivery system, as it allows for inhalation during tidal breathing.

Currently available jet nebulizers for home use deliver only a fraction of the nebulizer charge (the amount of drug that is loaded into the unit) to the patient. As such, it is important to understand that differences in drug delivery exist between nebulizers, so that physicians will be aware

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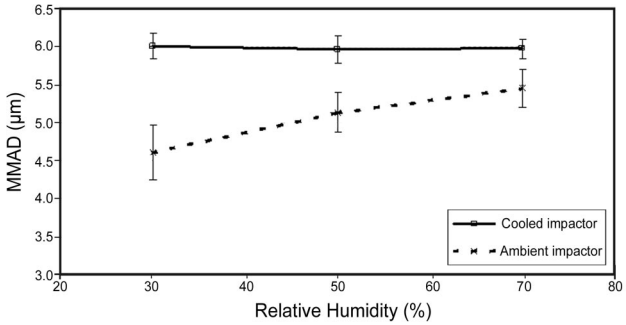

Fig. 1. Mass median aerodynamic diameter (MMAD) as function of relative humidity, of budesonide inhalation suspension nebulized with a jet nebulizer.

that adjustments to dose or nebulization time may be needed when changing nebulizer systems. A variety of mechanical and formulation-specific factors have been shown to affect the proportion of the nebulizer charge that can become inhalable, and thus the amount of active drug actually delivered to the airway. These include the physicochemical properties of the formulation, which can affect the efficiency of aerosol formation and droplet size distribution. The properties of the nebulization unit are also important, as these can affect the efficiency of aerosol formation, droplet size distribution, and delivery losses due to deposition of aerosol on the inner surfaces of the unit.[1,3-5]

Budesonide inhalation suspension (Pulmicort Respules, AstraZeneca, Lund, Sweden) is an aqueous suspension of budesonide widely used for the treatment of asthma.[6-10] The budesonide inhalation suspension is delivered to the patient using various jet-nebulizer/compressor combinations.[9,10]

We report the results of an in vitro evaluation of the droplet size distribution and the inhaled mass of budesonide captured on inhalation filters, using a simulated tidal breathing model. Thirty different jet-nebulizer/compressor combinations commonly used in Europe, the United States, and Japan were included in the in vitro evaluation.

Table 1. Droplet Size Distribution

Reference	Nebulizer	Compressor	Mass Median Aerodynamic Diameter (mean ± SD µm)	Geometric Standard Deviation (mean ± SD µm)
1	AeroEclipse II	PortaNeb	5.7 ± 0.1	1.8 ± 0.0
2	Assister KN-180	Assister KN-180	7.8 ± 0.2	1.9 ± 0.0
3	Genki	Genki	7.3 ± 1.3	1.8 ± 0.1
4	Hudson	DeVilbiss Pulmo-Aide Compact 3655	6.1 ± 0.1	1.7 ± 0.0
5	Medel Clenny	Medel Clenny	7.0 ± 0.3	1.9 ± 0.1
6	Medel SkyNeb	Medel SkyNeb	6.8 ± 0.4	1.9 ± 0.0
7	Mefar 2000	Voyage	7.7 ± 0.5	1.8 ± 0.0
8	Mefar 2000	Promenade-Car	7.5 ± 2.2	1.7 ± 0.0
9	Mefar 2000	Euro Sol	7.8 ± 0.7	1.8 ± 0.1
10	Micromist	Pulmo-Aide 5650N	6.5 ± 0.4	1.8 ± 0.1
11	Millicon S	Millicon S	7.4 ± 0.0	1.8 ± 0.0
12	Nesco Jet AZ-11	Nesco Jet AZ-11	7.7 ± 0.5	1.9 ± 0.0
13	Nissho	Nissho	9.9 ± 2.3	2.1 ± 0.1
14	Omron NE-C13	Omron NE-C13	6.8 ± 0.1	1.8 ± 0.0
15	Omron NE-C16	Omron NE-C16	6.9 ± 0.2	1.8 ± 0.0
16	Omron NE-C28	Omron NE-C28	5.5 ± 0.2	1.7 ± 0.1
17	Omron NE-C30	Omron NE-C30	5.9 ± 0.1	1.7 ± 0.0
18	Pari LC Plus	Pari Boy	6.2 ± 0.3	1.8 ± 0.0
19	Pari LC Plus	Uni Light	7.2 ± 0.2	1.8 ± 0.0
20	Pari LC Plus Junior	Pari Boy	7.6 ± 0.3	1.8 ± 0.0
21	Pari LC Sprint	Pari Boy SX	5.8 ± 0.4	1.8 ± 0.0
22	Pari LC Sprint	Pari Boy Mobile S	6.1 ± 0.2	1.9 ± 0.0
23	Pari LC Sprint	Pari Turbo Boy S	6.6 ± 0.1	1.8 ± 0.0
24	Pari LC Sprint Baby	Pari Turbo Boy S	4.8 ± 0.1	1.7 ± 0.0
25	Pari LC Sprint Junior	Pari Turbo Boy S	5.9 ± 0.2	1.8 ± 0.0
26	Pari LC Star	Pari Master	4.8 ± 0.2	1.8 ± 0.0
27	Pari LL	Pari Boy	5.8 ± 0.4	1.8 ± 0.0
28	Sidestream	Vigor Mist	5.3 ± 0.2	1.7 ± 0.0
29	Sidestream Plus	MiniElite	7.7 ± 0.2	1.8 ± 0.0
30	Ventstream	PortaNeb	5.0 ± 0.1	1.7 ± 0.0

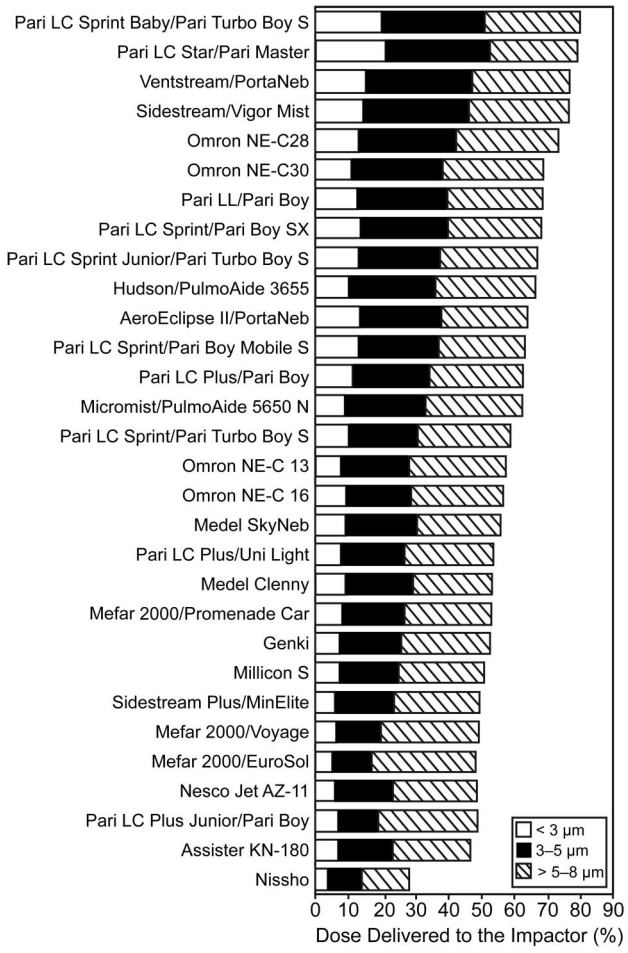

Fig. 2. Droplet size distribution of budesonide inhalation suspension up to 8 μm diameter (mean of 3 tested units), expressed as a percentage of budesonide mass delivered to the impactor.

Methods

Of all the 30 jet-nebulizer/compressor combinations tested, 3 were purchased from commercial sources rather than being obtained directly from the manufacturing companies, and were set up according to the manufacturers' package inserts. For evaluation of both the droplet size and the inhaled mass (filter dose), 3 nebulizer units of each brand were tested, to obtain mean values. In vitro characterization was performed using standardized methods.[3,4,11-13]

Droplet Size Distribution

The droplet size distribution within the aerosol cloud generated by each nebulizer was determined using a cooled (5°C) impactor (Next Generation Pharmaceutical Impactor, MSP, Shoreview, Minnesota) at an air flow of 15 L/min,[14] using a previously developed protocol.[11,13] The method measures the droplet size distribution of droplets containing budesonide. The impactor was refrigerated prior to use, to overcome the potential problem of water evaporation from the emitted aerosol,[11,15] allowing determination of the droplet sizes as they are when they leave the mouthpiece. On removal from refrigeration, the impactor was connected to the vacuum source, the flow rate (15 L/min) was set, and the nebulizer was connected. Nebulization was continued for 3–5 min, depending on the nebulizer being tested.

Budesonide that had been deposited in the United States Pharmacopoeia throat and in the collecting cups of the impactor was quantified using a standard high-performance liquid chromatography method.[11]

The mass median aerodynamic diameter (MMAD) and geometric standard deviation were calculated according to the United States Pharmacopoeia.[16] In the published work[11,13] the testing has been made on solutions for nebulization. The results presented in this paper also included ambient temperature and cooled impactor at different relative humidities (room condition) performed on budesonide inhalation suspension.

Inhaled Mass of Budesonide

A breathing simulator (Compass, Pari, Starnberg, Germany) was used to mimic 2 standardized sinusoidal breathing patterns: one for infants (< 1 year old, tidal volume 50 mL, respiratory rate 30 breaths/min, duty cycle 0.33), and one for children (approximately 4 years old, tidal volume 155 mL, respiratory rate 25 breaths/min, duty cycle 0.5).[17,18] The inhaled mass of budesonide was captured on inhalation filters placed between the nebulizer mouthpiece and the breathing simulator. The inhalation filters (Filter Pads, Pari, Starnberg, Germany) were changed at 3-min intervals until no further visible aerosol was generated. The amount of budesonide on the filters was quantified using a standard high-performance liquid chromatography method. Each nebulizer was charged with one ampoule (2 mL) of budesonide inhalation suspension 0.25 mg/mL (0.5 mg in total). The cumulative inhaled mass of budesonide was calculated by summing the results for the first 3 min of nebulization with the results of subsequent 3-min intervals up to 18 min. The cumulative mass of budesonide is presented as a percentage of the nebulizer charge.

Results

Droplet Size Distribution

The MMADs for the jet nebulizer tested with budesonide inhalation suspension with ambient and cooled impactor are presented in Figure 1. The MMAD and geo-

Table 2. Percentage of Budesonide Nebulizer Charge Collected on the Inhalation Filter

Reference	Nebulizer	Compressor	Nebulization Time (min)*	Percentage of Nebulizer Charge Collected on the Inhalation Filter		Infant/Child Ratio
				Infant	Child	
1	AeroEclipse II	PortaNeb	18	NT	20 ± 3.3	NA
2	Assister KN-180	Assister KN-180	9	5 ± 0.1	11 ± 2.2	0.51
3	Genki	Genki	6	4 ± 0.3	11 ± 0.7	0.35
4	Hudson	DeVilbiss Pulmo-Aide Compact 3655	6	3 ± 0.4	5 ± 0.8	0.50
5	Medel Clenny	Medel Clenny	12	8 ± 1.8	18 ± 1.3	0.43
6	Medel SkyNeb	Medel SkyNeb	12	8 ± 1.0	16 ± 1.5	0.46
7	Mefar 2000	Voyage	9	6 ± 0.7	12 ± 0.6	0.52
8	Mefar 2000	Promenade-Car	9	5 ± 1.0	10 ± 0.6	0.51
9	Mefar 2000	Euro Sol	12	5 ± 0.5	9 ± 1.5	0.47
10	Micromist	Pulmo-Aide 5650N	9	3 ± 0.5	11 ± 2.1	0.29
11	Millicon S	Millicon S	12	7 ± 0.3	15 ± 1.4	0.47
12	Nesco Jet AZ-11	Nesco Jet AZ-11	9	4 ± 1.0	10 ± 1.7	0.43
13	Nissho	Nissho	12	9 ± 2.2	15 ± 2.2	0.62
14	Omron NE-C13	Omron NE-C13	9	4 ± 0.6	10 ± 2.4	0.43
15	Omron NE-C16	Omron NE-C16	9	7 ± 0.5	10 ± 0.7	0.70
16	Omron NE-C28	Omron NE-C28	9	3 ± 0.4	8 ± 0.8	0.39
17	Omron NE-C30	Omron NE-C30	9	3 ± 0.2	9 ± 0.3	0.36
18	Pari LC Plus	Pari Boy	9	9 ± 0.9	20 ± 1.0	0.48
19	Pari LC Plus	Uni Light	9	7 ± 0.7	14 ± 0.2	0.45
20	Pari LC Plus Junior	Pari Boy	9	9 ± 0.2	18 ± 0.2	0.46
21	Pari LC Sprint	Pari Boy SX	6	4 ± 1.1	12 ± 1.4	0.39
22	Pari LC Sprint	Pari Boy Mobile S	9	6 ± 2.0	14 ± 0.5	0.45
23	Pari LC Sprint	Pari Turbo Boy S	9 (child) 12 (infant)	NT	14 ± 0.6	NA
24	Pari LC Sprint Baby	Pari Turbo Boy S	9 (child) 12 (infant)	4 ± 0.1	9 ± 1.5	0.37
25	Pari LC Sprint Junior	Pari Turbo Boy S	9 (child) 12 (infant)	6 ± 0.3	13 ± 1.4	0.37
26	Pari LC Star	Pari Master	9	4 ± 0.5	11 ± 0.7	0.37
27	Pari LL	Pari Boy	9	5 ± 0.3	15 ± 0.8	0.36
28	Sidestream	Vigor Mist	6	1 ± 0.1	4 ± 0.2	0.29
29	Sidestream Plus	MiniElite	9	5 ± 0.7	17 ± 0.5	0.24
30	Ventstream	PortaNeb	9	NT	8 ± 0.2	NA

* Time until drug-release stopped; for example, 9 min means that drug-release stopped between 6 min and 9 min.
NT = not tested
NA = not applicable

metric standard deviation for each nebulizer tested are shown in Table 1. The MMAD of the tested nebulizers ranged from 4.8 μm to 9.9 μm, and the geometric standard deviations ranged from 1.7 μm to 2.1 μm. The droplet size distribution data (sizes: < 3 μm, 3–5 μm, and > 5–8 μm) showed a considerable variation in the size of the droplets (Fig. 2).

Inhaled Mass of Budesonide

The cumulative inhaled mass of budesonide, expressed as a percentage of the nebulizer charge, from each nebulization unit, with both breathing patterns, is presented in Table 2. With the infant breathing pattern the inhaled mass of budesonide ranged from 1% to 9% of the nebulizer charge, whereas with the child breathing pattern the inhaled mass of budesonide ranged from 4% to 20% of the nebulizer charge (see Table 2, Fig. 3).

For all of the nebulizer/compressor combinations tested, the inhaled mass of budesonide with the infant breathing pattern was approximately 40% of that seen with the matching child's breathing pattern (see Table 2). However, the cumulative inhaled mass of budesonide collected in the first 5 min of nebulization (via

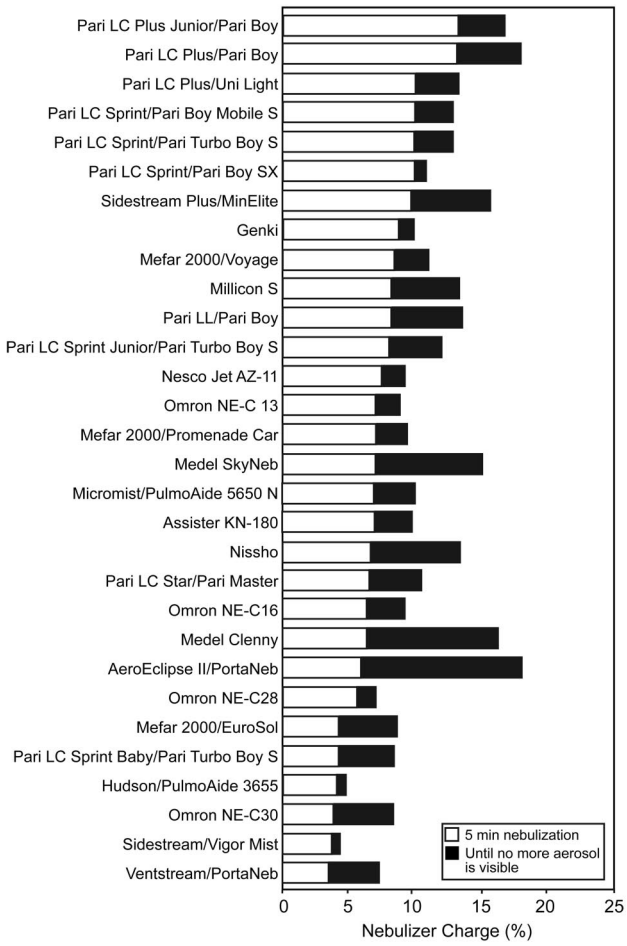

Fig. 3. Cumulative budesonide mass collected on inhalation filter (percentage of nebulizer charge) of budesonide inhalation suspension during child breathing pattern for 5 min of nebulization, and until no more visible aerosol is formed.

interpolation of data between 3 min and 6 min) varied considerably between the different nebulizers, for both the infant and child breathing patterns (Fig. 3 displays data for the child breathing pattern; data for infant breathing pattern is not presented as a figure). Similarly, the cumulative inhaled mass of budesonide collected until no more visible aerosol was formed also varied considerably for both infant and child breathing patterns (see Fig. 3).

The differences between the various nebulizer/compressor combinations were further highlighted when the cumulative inhaled mass was determined every 3 min of nebulization (Figs. 4 and 5).

Discussion

The results showed considerable variability in both droplet size and inhaled mass of budesonide for the 30 nebulizer/compressor combinations evaluated. The MMAD values ranged from 4.8 μm to 9.9 μm, and the inhaled mass ranged from 1% to 9% (infant breathing) and 4% to 20% (child breathing), depending on nebulizer/compressor combination. The inhaled mass of budesonide was higher with all the nebulizer/compressor combinations when running the child breathing pattern. The present results confirmed previous observations that different nebulizer/compressor combinations generate aerosols with different aerosol characteristics, inhaled masses, and delivery rates of budesonide.[5,19,20]

The range of the MMAD values (4.8–9.9 μm) in the present study was rather different from the range of MMAD values (3.8–5.5 μm) in a previous large characterization of 27 nebulizer/compressor combinations with nebulized budesonide.[9] The effect of evaporation on the aerosol droplet size during nebulization into the impactor has been shown to be a problem, and cooling of the impactor before the characterization of the aerosol has been shown to minimize this problem.[11,13] The use of an ambient impactor has been shown to result in a decrease in the droplet size of nebulized albuterol, in comparison with the use of an impactor during cooled conditions.[11,13] The results achieved with the cooled impactor for nebulized albuterol correlated well with those achieved with laser diffraction, a technique void of evaporative losses.[11] Due to the lack of evaporation, the aerosol characterized with a cooled impactor should match the state of the aerosol at the nebulizer mouthpiece when it is inhaled by the patient. This evaluation of nebulized budesonide with an ambient and a cooled impactor showed similar results to the previous study of nebulized albuterol (ie, a decrease in the droplet size of nebulized budesonide when using an ambient impactor [see Fig. 1]).

Solutions and suspensions for nebulization behave differently during nebulization. In a solution all aerosol droplets are uniform in regard to the amount of drug per droplet, whereas in a suspension the aerosol droplets contain a mixture of particles and drug in solution. The mean particle size of the budesonide powder suspended in the aqueous formulation is approximately 2 μm. The aerosol droplets will carry budesonide particles smaller than the size of the droplet, and small droplets mainly contain the dissolved budesonide (20 μg/mL). Due to the differences in formulation there will be a shift in the MMAD results between a solution and a suspension for a given nebulizer.[3] The magnitude of the shift will depend on the size of the suspended particles and the nebulizer droplet size. Consequently, big suspended particles in the suspension, in combination with a nebulizer that generate small droplets, will give the greatest difference, in comparison with a solution.

The evaporation effect on the droplets is judged to be the same regardless, whether the formulation is a solution or a suspension.

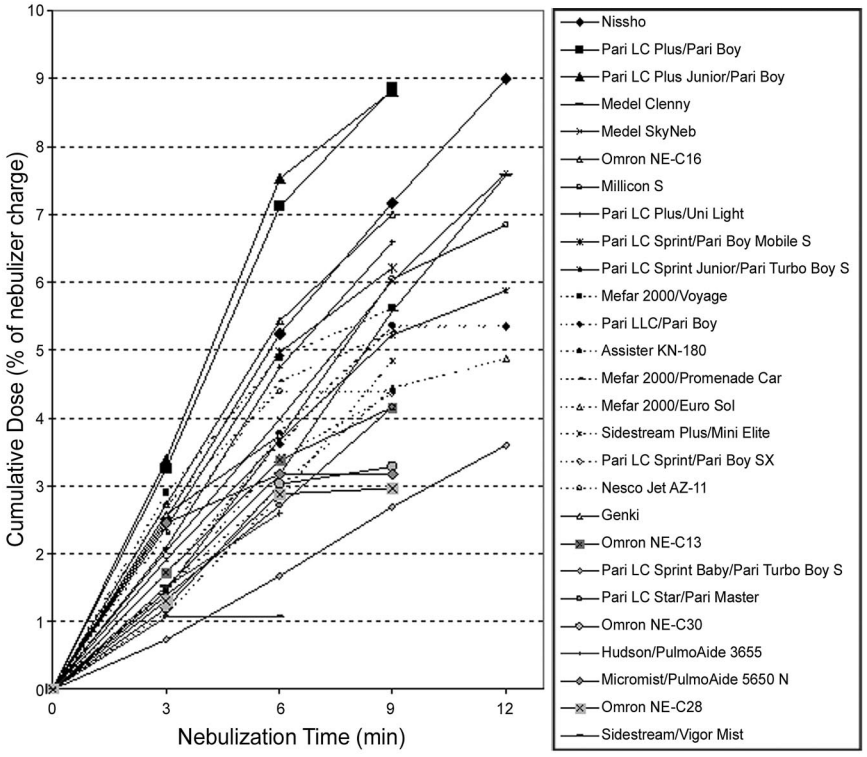

Fig. 4. Budesonide mass collected on inhalation filter (percentage of nebulizer charge) of budesonide inhalation suspension over 3-min intervals during infant breathing patterns for up to 12 min of nebulization. The slope of each curve represents the rate of budesonide delivery.

The simulated pediatric breathing pattern used in the Smaldone et al study (tidal volume 200 mL, respiratory rate 25 breaths/min, duty cycle 0.5) was relatively similar to the child breathing pattern used in the present study. The aerosol characteristics were, however, determined using an ambient low-flow Marple Personal Cascade Impactor SE 296.[9] The differences in MMAD could, therefore, mainly be attributed to the different techniques used for aerosol characterization, but also to the fact that different nebulizer/compressor combinations were tested in the 2 studies. Only the Hudson and Pari LC Plus nebulizers were tested in both studies, but with different compressors. The MMAD value was 3.8 μm (Hudson) and ranged from 5.0 μm to 5.2 μm for the Pari LC Plus nebulizer/compressor combinations in the Smaldone et al[9] study, whereas in the present study the MMAD values were 6.1 μm (Hudson/Hudson) and ranged from 6.2 μm to 7.6 μm with the Pari LC Plus/Pari Master nebulizer/compressor combinations. The differences in MMAD values for these 2 nebulizer brands between the studies and the trend to decreased MMAD values when using the ambient impactor are consistent with previous results on nebulized albuterol and budesonide.

The range of the inhaled mass of budesonide in the present study (4–20%) when using the child breathing pattern was, however, similar to that found by Smaldone et al (2–18%) in the previous study.[9] The similarity could be attributed to the similar simulated breathing patterns used, but is still surprising, as different nebulizer/compressor combinations were tested in the 2 studies. The inhaled masses for the 2 nebulizer brands tested using the child breathing pattern in both studies were 14% (Hudson) and ranged from approximately 16% to 18% with the Pari LC Plus nebulizer/compressor combinations in the Smaldone et al study,[9] and were 5% (Hudson) and ranged from 14% to 20% with the Pari LC Plus nebulizer/compressor combinations in the present study. The similarities in the Pari LC Plus nebulizer results between the 2 studies indicate that the in vitro method used for the evaluation of the inhaled mass was valid.

The large variability in nebulizer/compressor output rate in the present study was responsible for the variability of the inhaled mass. For most nebulizers a plateau phase followed the early steep output rate (see Figs. 4 and 5). From Figures 4 and 5 it can be seen that aerosol output (cumulative inhaled mass vs time) is a linear function until the nebulizer starts to sputter, at which time the plateau occurs; after the plateau is reached, the total inhaled mass does not increase substantially, even if the nebulizer is run for longer. This indicates that defining a specific nebulization time for a specific nebulizer/compressor combination is difficult. It was, however, obvious that the breath-

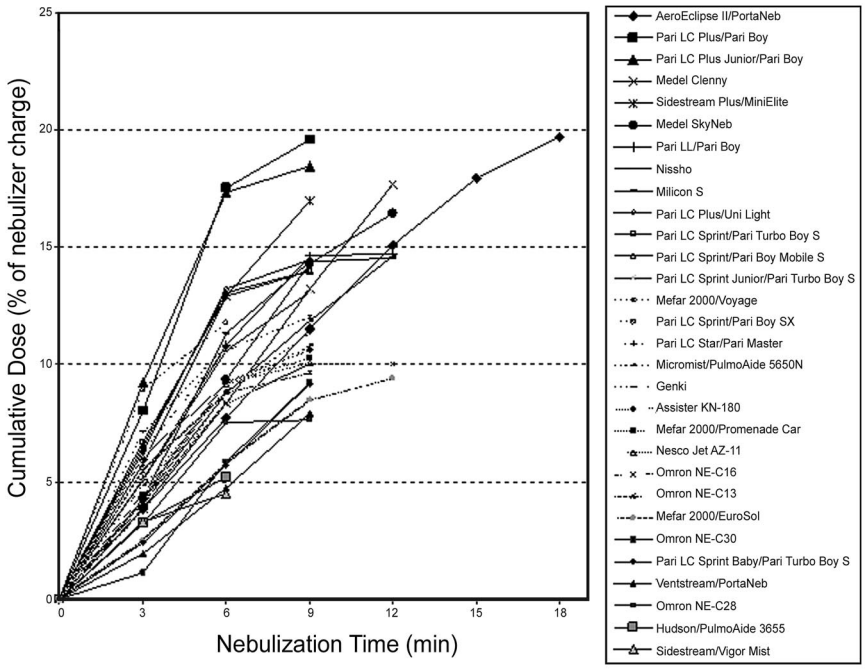

Fig. 5. Budesonide mass collected on inhalation filter (percentage of nebulizer charge) of budesonide inhalation suspension over 3-min intervals during child breathing patterns for up to 18 min of nebulization. The slope of each curve represents the rate of budesonide delivery.

activated AeroEclipse II nebulizer stood apart from the rest of the nebulizers, with a relatively steep output rate for 15–18 min. Breath activation of a nebulizer minimizes the waste of drug, but in this study did not really set AeroEclipse II apart from the Pari LC Plus, Pari LC Plus Junior, Medel Clenny, Medel SkyNeb, and Sidestream Plus nebulizers in terms of inhaled mass.

Is the large variability shown in the in vitro determined inhaled mass of nebulized budesonide of clinical importance? This can be discussed based on results from ex vivo filter dose studies, and on the results from clinical studies in patients with asthma with different jet nebulizers used to deliver budesonide. The results of 2 large ex vivo filter studies, which included over 200 young children and adolescents, have shown larger variability of the inhaled mass of nebulized budesonide with one nebulizer brand than that shown in the present in vitro study with 30 nebulizer brands.[21,22] The inhaled masses of nebulized budesonide for the children (ages 6 months to 7.9 years) ranged from 1.9% to 40.6%, and for the children and adolescents (ages 5.1 years to 15.7 years) ranged from 2.9% to 33.9% of the nebulizer charge. Thus, differences in breathing patterns while using one nebulizer brand create a larger variability in the inhaled mass than differences created by switching from a low-performing to a high-performing nebulizer.

Would it, however, be important to try to avoid using some of the nebulizer brands with very low inhaled masses? In the published clinical studies of nebulized budesonide in children with asthma showing good clinical efficacy of the treatment, a number of different jet nebulizers have been used, including Aiolos, DeVilbiss 646, Hudson Updraft Neb-U-Mist, Pari Inhaler Boy, Pari LC Plus, and Ventstream.[23-26] The inhaled masses of budesonide were for these nebulizers: Aiolos approximately 13.5%,[9] DeVilbiss 646 approximately 9.5%,[9] Hudson Updraft Neb-U-Mist approximately 14%,[9] Pari LC Plus 14–20%,[9] and Ventstream 8%. As these nebulizers have been shown to be clinically effective in delivering nebulized budesonide to children with asthma, it could be inferred—with caution—that any nebulizer which in vitro had an inhaled mass of budesonide within the range defined by these nebulizers (ie, 8–20%) would deliver a clinically effective dose of nebulized budesonide.

Further investigations of new nebulizer/compressor combinations are warranted.

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