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Impact of Constant and Breath-Synchronized Nebulization on Inhaled Mass of Nebulized Budesonide in Infants and Children

Kurt Nikander, BA,[1]* and H. Bisgaard, MD, PhD[2]

Summary. The aim of the present study was to compare the output of a breath-synchronized jet nebulizer to a conventional constant output nebulizer over a fixed period of time in terms of inhaled mass of budesonide, i.e., the amount of budesonide deposited on a filter interposed between the nebulizer and the face mask. One hundred and sixty-five asthmatic children (103 boys) were enrolled in this open, randomized, crossover trial. Their age ranged from 6 months to 7.9 years, height from 69 to 132 cm, and weight from 8.2 to 31.3 kg. Their duration of asthma ranged from less than 1 to 7 years. Budesonide suspension, 0.5 mg mL^{-1}, 2 mL, was used.

With 5 min of constant output nebulization, the mean inhaled mass of budesonide in percent of the nominal dose was 11.4% in the youngest children and 14.9% in the 7-year-old children. Expressed in percent of the total output of budesonide, i.e., the amount that left the nebulizer as an aerosol, the inhaled mass ranged from 34.6–48.6%. Thus, 51.4–65.4% of the total output was deposited on the expiratory filter. With 5 min of breath-synchronized nebulization, the mean inhaled mass ranged from 10.5–14.9% of the nominal dose. For the youngest patients less than 3–4 years of age, it was approximately 80–90% of the total output. For the older patients the inhaled mass was approximately 95% of the total output, i.e., only small amounts of budesonide were deposited on the expiratory filter. For both modes of nebulization the between-subject variation in inhaled mass was large: up to 6-fold in the young children, and 3–4-fold in the older ones.

The results of the present study showed that the inhaled mass of budesonide was significantly age-dependent with both modes of nebulization, i.e., the inhaled mass was less in younger children. Breath-synchronized nebulization resulted in reduced waste of drug during expiration. **Pediatr Pulmonol. 1999; 28:187–193.**

Key words: breath-synchronized jet nebulizer; constant output jet nebulizer; budesonide; inhaled mass; filters; infants; children; asthma.

INTRODUCTION

The use of nebulizers has generally been advocated for patients who experience difficulties in the use of pressurized metered dose inhalers, dry powder inhalers, or spacers with face masks. Target groups for nebulizer treatment have been especially infants and young children.[1] Conventional constant output jet nebulizers, in which the drug is aerosolized irrespective of whether the patient inhales or exhales, have traditionally been the most commonly used.[2] During nebulization, the inhaled mass of drug (i.e., the amount of drug inhaled by the patient) is mainly a product of the nebulizer's drug output rate and the patient's duty cycle.[3] The duty cycle is the ratio between inspiration and the sum of inspiration and expiration, and for 12-month-old children is typically 0.42.[4] When a conventional constant output jet nebulizer is used in clinical practice, the drug output is usually less than 50% of the nebulizer charge of drug, and with a duty cycle of 0.42, the inhaled mass could not exceed 20–25% of the nebulizer charge of drug.[5] Thus, approximately 75–80% of the nebulizer charge of drug would either remain in the nebulizer as a residual volume or contaminate room air. The inhaled mass of drug can be measured by having the aerosol deposit on a filter at the nebulizer's inhalation port.[6,7] The filter technique for measurement of inhaled mass of drug has become a tool in the devel-

[1]AstraZeneca R&D, Lund, Sweden, and Department of Clinical Physiology, Malmö General Hospital, Malmö, Sweden.

[2]Department of Pediatrics, Pulmonary Service, Rigshospitalet, National University Hospital, Copenhagen, Denmark.

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*Correspondence to: Kurt Nikander, B.A., AstraZeneca R&D, S-221 87 Lund, Sweden. E-mail: kurt.nikander@draco.se.astra.com

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opment of and in the in vitro or in vivo assessment of inhalation devices.[3]

In order to increase the efficiency of a nebulizer's ability to deliver aerosolized drug to the patient, drug aerosolization has in some nebulizer systems been synchronized with inhalation. This has been achieved by the use of either manually operated valves or breath-activated mechanical or electronic valves. The synchronization of drug delivery with inspiration has been shown in two in vitro studies to increase the inhaled mass of budesonide compared to drug delivery during constant nebulization.[8,9] In these studies, the drug saved during the expiratory phase was available during the inspiratory phase, at the cost of a substantially prolonged nebulization time.[8,9]

The aim of the present study was to investigate in asthmatic children whether a breath-synchronized jet nebulizer offers any advantage in terms of inhaled mass compared to a conventional constant output jet nebulizer when a fixed nebulization time of 5 min was used. Budesonide suspension for nebulization was used as a marker.

MATERIALS AND METHODS

Study Design

The study was designed as a randomized, crossover single-center trial consisting of a 1-day clinic visit. At the clinic each patient inhaled from two conventional jet nebulizers (Spira® Modul 1 [Spira M1] Respiratory Care Center, Hämeenlinna, Finland) with face masks (Astra Tech, Gothenburg, Sweden): one in constant output mode (CO-mode), and the other in breath-synchronized mode (BS-mode) (Fig. 1). The nebulizers were connected to the medical air outlet in the wall, charged with 1 mg of budesonide (0.5 mg mL^{-1}, 2 mL suspension, AstraZeneca, Lund, Sweden) and run for 5 min at a flow of 7.5 L min^{-1} through the nebulizers at a room temperature of ~20°C. A new Spira M1 nebulizer was used for each test. Breath-synchronization was achieved through an inspiratory flow-activated electronic synchronizer (Spira Elektro 4, Respiratory Care Center) (D in Fig. 1). The synchronizer received the flow signal through the sensor tube connected between the face mask and the two-way valve (Astra Tech, V in Fig. 1). The synchronizer was connected to the medical air wall outlet, and the nebulizer received compressed air triggered by the synchronizer. The synchronizer was set to pulse compressed air through the nebulizer during the whole inspiration for up to 3 sec. The inhaled mass of budesonide was defined as the amount of drug deposited on an inspiratory filter (Marquest MQ-303 viral filters, Marquest Medical Products, Inc., Englewood, CO) located between the face mask and the nebulizer's inspiratory port. The amounts of budesonide aerosolized during expiration were deposited on an expiratory filter. In vitro tests have shown that the Marquest filter can catch approxi-

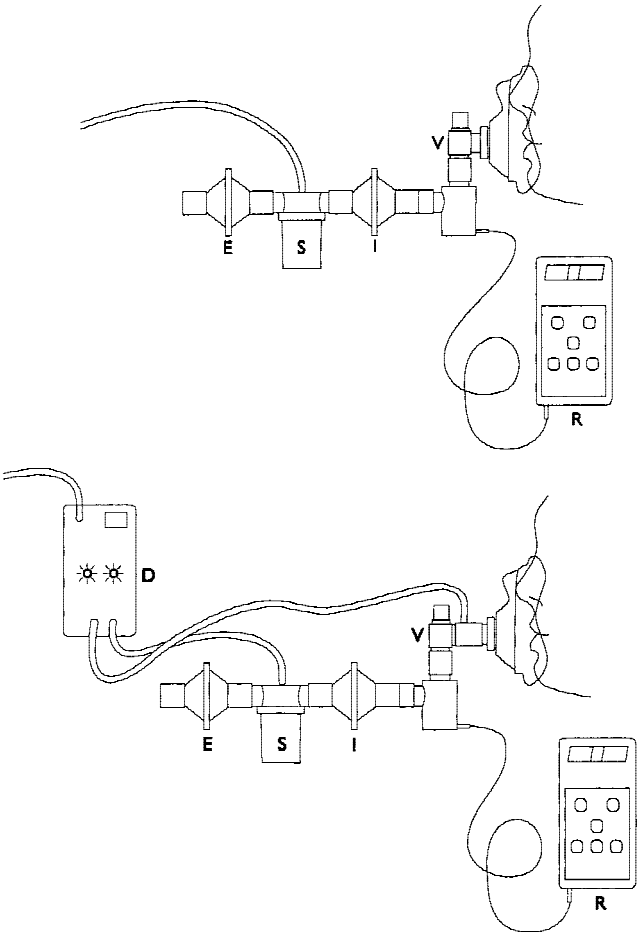

Fig. 1. For nebulization in CO-mode, the inhalation port of the Spira M1 nebulizer (S) was connected in series with a Marquest filter (I), a Magtrac (R) respiratory flow sensor with rotameter, a two-way valve (V), and a face mask. A Marquest filter (E) was connected to the exhalation port of the nebulizer. For nebulization in BS-mode, a Spira Elektro 4 synchronizer (D) with flow sensor was added. The flow sensor was positioned between the two-way valve and the face mask.

Abbreviations

BS-mode	Nebulization in a breath-synchronized mode
CO-mode	Nebulization in a constant output mode
f	Breathing frequency
HPLC	Reversed-phase high-performance liquid chromatography
Min	Minimum
Max	Maximum
N	Total number of patients
SD	Standard deviation
V_I	Inspiratory minute volume
V_T	Tidal volume

mately 99.8% of the amount of budesonide sucked through the filter.[10] The addition of the inspiratory filter to the nebulizer introduced an equipment dead space equal to half of the filter hosing's volume during the first breath only. For subsequent breaths, the additional equipment dead space was reduced as the patient's exhalation was directed via a two-way valve. After nebulization, the filter's entrance and exit were sealed, and the filters were stored in black plastic bags protected from light. The amount of budesonide on the filters was extracted by washing with ethanol. The concentration and mass of budesonide were determined by high-pressure liquid chromatography (HPLC) at AstraZeneca R&D Lund (Lund, Sweden).

The nebulizers were standardized in terms of solution output rate (i.e., output per unit time) by the manufacturer. The Spira M1 nebulizer's in vitro budesonide output rate was approximately 1.8 $\mu g\ sec^{-1}$ with a nebulizer charge of 1 mg budesonide (0.5 mg mL^{-1}, 2 mL), and it was linear until the sputtering phase was reached after approximately 5 min of nebulization time. The nebulizer's droplet size was measured when running the nebulizer in CO-mode. The mean mass median diameter was 3.8 μm in nine measurements, with a range of 3.4–4.3 μm (Malvern Mastersizer model MS1000, Malvern Instruments Ltd., Malvern, UK). Four nebulizer-filter setups (Fig. 1) were tested in vitro for passive budesonide deposition on the inspiratory filters. The aim was to evaluate whether any budesonide would contaminate the inspiratory filter during the patient's expiration through the two-way valve. The nebulizer-filter setups were charged with 1 mg budesonide (0.5 mg mL^{-1}, 2 mL) and run on the bench without any inspiratory flow through the nebulizer in CO-mode for 5 min each.

Patients

One hundred and sixty-five children (103 boys) with recurrent asthmatic symptoms were consecutively included. The inclusion of patients was aimed to provide an even number of patients in eight age classes from 0 (<1 year) to 7 (> 7 < 8). The outcome of the stratification was (age classes given in parentheses): 12 patients in (0), 25 in (1), 21 in (2), 15 in (3), 26 in (4), 26 in (5), 23 in (6), and 17 in (7). The patients' ages ranged from 6 months to 7.9 years, heights from 69 to 132 cm, weights from 8.2 to 31.3 kg, and asthma duration from <1 to 7 years. Before inclusion, the children were tested for cooperation, which was based on their willingness to inhale from a nebulizer with a tight-sealing face mask. The childrens' tidal volume (V_T), breathing frequency (f), and inspiratory minute volume (V_I) were recorded during the first minute of nebulization with a Magtrac II (R in Fig. 1) general-purpose respiratory flow sensor (Ferraris Medical Ltd., London, UK), which updated the recorded values every 20 sec. The study was performed in accordance with the principles stated in the Declaration of Helsinki and was approved by the local ethics committee of the Gentofte Hospital, Copenhagen, Denmark.

Statistical Methods

Regression lines of individual inhaled mass of budesonide (in percent of nominal dose) on age of the patients were fitted to data using a least squares method. *P*-values given in the text come from testing whether the slope was zero. The 95% prediction intervals were constructed in a nonparametric way by choosing lines parallel to the regression line, excluding 2.5% of the extreme data on either side of the regression lines.

RESULTS

Missing Data

For one 25-month-old child, data on inhaled mass were missing when nebulizing in the CO-mode, and for one 11-month-old child data were missing on inhaled mass using both modes of nebulization.

Passive Deposition on Filters

The mean (range) passive deposition of budesonide on the inspiratory filters was 0.5% (0.5–0.6%) of the nominal dose of 1 mg, whereas 31.7% (31.3–34.5%) was deposited on the expiratory filters. These results indicate that the measurements of inhaled mass reflected relatively accurately the amount of budesonide deposited onto the filter during inspiration.

Inhaled Mass

There was no statistically significant difference between the inhaled masses generated by the two modes of nebulization (Fig. 2a,b). The mean inhaled mass for each age class indicated age dependency for both modes of nebulization (Table 1). The plot of the individual inhaled mass of budesonide in percent of the nominal dose against the age of the patients showed statistically significant relationships between inhaled mass and age for both modes of nebulization ($P < 0.01$, Fig. 2a,b). For nebulization in CO-mode (Fig. 2a), the estimated regression line was $Y = 10.8 + 0.052X$, and for nebulization in BS-mode (Fig. 2b), $Y = 10.2 + 0.063X$. The correlation coefficients were 0.27 with confidence intervals 0.12 and 0.41 (CO-mode), and 0.33 with confidence intervals 0.18 and 0.46 (BS-mode).

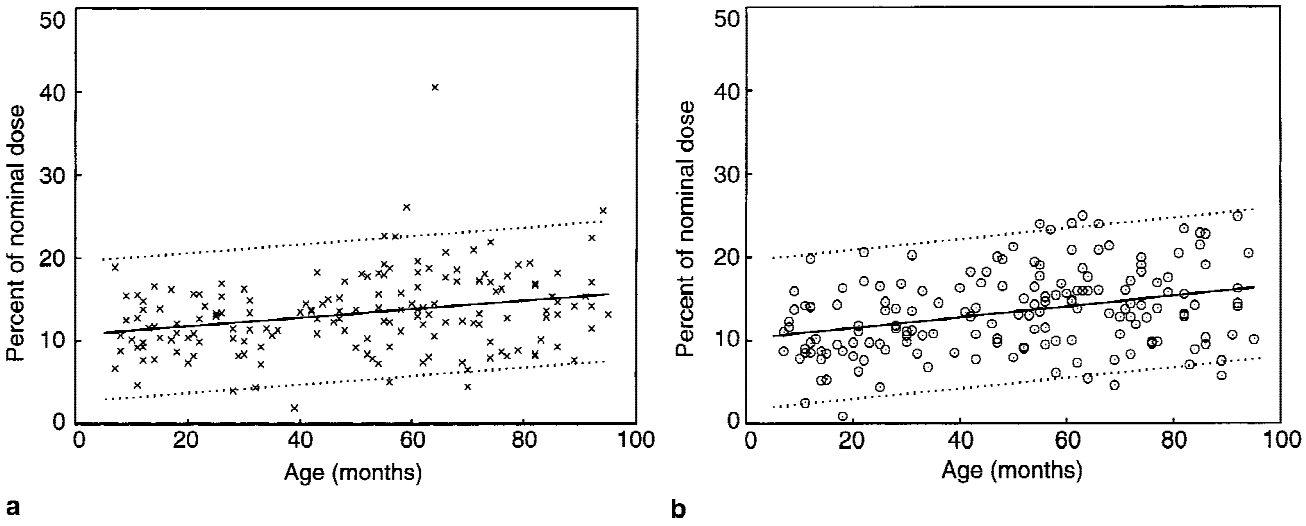

Fig. 2. The inhaled mass of budesonide plotted as percent of the nominal dose against the age of the patients with estimated regression lines and 95% prediction intervals. For nebulization in CO-mode (a) the estimated regression line was Y = 10.8 + 0.052X, and for BS-mode (b), Y = 10.2 + 0.063X.

TABLE 1—Inhaled Mass of Budesonide by Age Class for Both Modes of Nebulization

Age class	CO-mode					BS-mode				
	N	Mean[1]	SD	Min[1]	Max[1]	N	Mean[1]	SD	Min[1]	Max[1]
0	11	11.4	4.2	4.7	18.9	11	10.5	3.7	2.5	15.9
1	25	11.6	2.8	7.4	16.6	25	10.5	4.6	0.9	20.6
2	20	11.2	3.6	4.0	16.9	21	11.9	3.6	4.4	20.2
3	15	12.9	3.5	1.9	18.3	15	13.5	3.8	7.7	20.0
4	26	14.5	5.3	5.1	26.2	26	14.7	4.7	6.1	23.9
5	26	14.8	6.9	4.5	40.6	26	15.2	5.5	4.6	24.9
6	23	14.0	4.4	8.0	21.9	23	14.5	4.2	7.0	23.3
7	17	14.9	4.3	7.7	25.7	17	14.9	6.0	5.7	24.8

[1]The mean (min, max) inhaled mass is given as percent of the nominal dose. Min, Minimum; Max, maximum.

Total Output

The mean total output of budesonide (i.e., sum of budesonide on both filters) for each age class is displayed in Table 2. When nebulizing in BS-mode, the mean total output of budesonide was, as expected, quite close to the mean inhaled mass, i.e., only small amounts of drug were deposited on the expiratory filter. The individual total output of budesonide was therefore statistically significantly age-related ($P < 0.01$) for nebulization in BS-mode, whereas for nebulization in CO-mode it was not ($P = 0.06$).

Inhaled Mass in Percent of Total Output

The inhaled mass of budesonide in percent of the total output of budesonide, plotted against the age of the patient, reflects how effectively the nebulizer system was used by the patients. When using the nebulizer in CO-mode, the mean inhaled mass of budesonide in percent of the total ouput was 34.6% (SD 7.6, range 22.1–48.0) in the children below 1 year of age, and 48.6% (7.4, 36.8–62.3) in the 7-year-old children (Fig. 3). Thus, 51.4–65.4% of the total output was deposited on the expiratory filter. The correlation coefficient was 0.48, with confidence intervals 0.36 and 0.59. Nebulization in BS-mode showed (Fig. 3), on the contrary, that for patients less than 3–4 years of age, the mean amount of budesonide deposited on the inspiratory filter ranged from approximately 80–90% of the total output, whereas for the older patients the mean inhaled mass was approximately 95% of the total output. The small amounts of budesonide deposited on the expiratory filter explain why, during nebulization in BS-mode, both the inhaled mass and the total output of budesonide were of approximately the same magnitude and were therefore both age-related.

Tidal and Minute Volumes

Using the nebulizer in BS-mode, the mean V_T ranged between 0.21–0.29 L, and the mean V_I ranged between 5.67–6.93 L. The corresponding values measured during

TABLE 2—Total Output of Budesonide by Age Class for Both Modes of Nebulization

Age class	CO-mode					BS-mode				
	N	Mean[1]	SD	Min[1]	Max[1]	N	Mean[1]	SD	Min[1]	Max[1]
0	11	33.2	6.4	21.3	39.4	11	13.1	3.8	6.1	17.4
1	25	31.8	5.3	20.3	42.7	25	13.0	4.1	5.8	21.7
2	20	30.8	6.1	19.2	39.2	21	13.2	3.8	5.2	21.4
3	15	30.0	4.5	20.0	38.3	15	14.5	3.9	8.2	21.1
4	26	29.7	7.7	13.7	40.8	26	15.7	4.9	6.6	25.7
5	26	29.8	7.3	11.9	41.9	26	16.6	6.0	5.0	26.3
6	23	27.9	6.7	13.1	36.6	23	15.5	4.4	7.6	24.4
7	17	30.8	7.2	18.9	43.8	17	15.8	6.3	6.2	26.3

[1]The mean (min, max) total output is given as percent of the nominal dose. Min, minimum; Max, maximum.

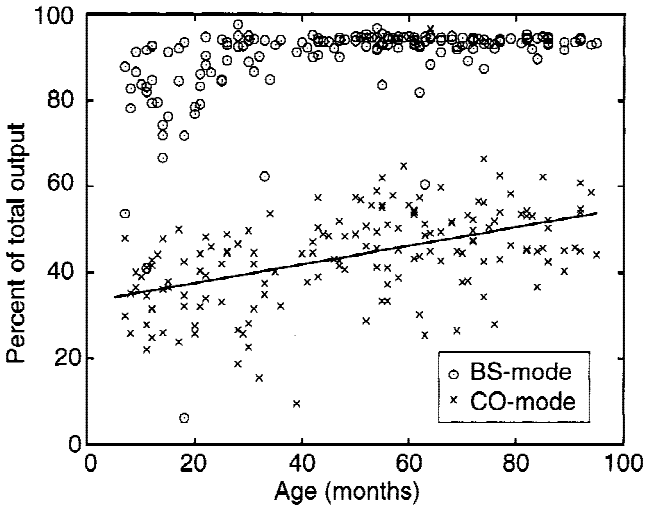

Fig. 3. The inhaled mass of budesonide in percent of the total output of budesonide plotted against the age of the patients for both modes of nebulization.

nebulization in CO-mode were 0.19–0.33 L for V_T and 4.80–6.71 L for V_I. The mean (range) breathing frequency during nebulization in BS-mode ranged between 24–28 (11–53) per min, and during nebulization in CO-mode between 21–27 (8–46) per min.

DISCUSSION

The inhaled mass of budesonide has been determined with the filter method both in vitro[8,9] and in vivo in children using nebulizers,[10] pressurized metered dose inhalers with spacers,[11] and dry powder inhalers.[12] The filter method reflects the total amount of drug inhaled including the amount that might be exhaled without a filter, thus resulting in slight overestimates of the inhaled mass of drug in a treatment situation. Filter studies of the inhaled mass of drug provide a crude estimate of the amount of drug that might be deposited in the lungs. Lung deposition of the nebulized aerosol has recently been shown to be largely influenced by the patients respiratory physiology, i.e., as the patient grows the upper airway deposition decreases.[13] The inhaled mass of drug determined with the filter method is not influenced by the patient's respiratory physiology to the same degree as the lung deposition of a drug. The major difference is that the size of the filter housing does not limit the deposition of the droplets on the filter. Results obtained with the filter method in infants and children would therefore not reflect lung delivery in absolute terms.

The droplet size generated was determined only during nebulization in CO-mode. Nerbrink and Ekelius recently showed that the rise time of the pulse to reach the maximal pressure with a Spira Elektro 4 was 157 msec at 2 bar of pressure,[14] i.e., the pressure was initially submaximal. The nebulizer's droplet size has been shown to be dependent on the driving pressure.[15] One might therefore assume that with short inspiratory times, the nebulizer's droplet size might be larger during nebulization in BS-mode than in CO-mode. With longer inspiratory times, the impact of the initially submaximal pressure on the droplet size would probably be negligible.

Conventional jet nebulizers for home care are generally designed to operate continuously, and drug output rate follows a roughly linear pattern over time until the nebulizer runs dry.[5] The inhaled mass is therefore primarily a function of the patient's breathing pattern and the nebulizer's drug output characteristics, provided the patient is able to use the mouthpiece or face mask efficiently. The main physiological determinants of the patient's breathing pattern are the duty cycle,[8] the inspiratory flow,[15] and the tidal volume.[16] The duty cycle is the major determinant in cases in which the patient's inspiratory flow exceeds the compressor's air flow, creating air entrainment.[16] In these cases the inhaled mass is the product of the patient's duty cycle, the drug output rate, and the total nebulization time.[3,17] The inhaled mass is, however, tidal volume-dependent when the patient's inspiratory flow is less than the compressor's air flow.[17] In this case the inhaled mass is the product of the patient's tidal volume, the drug output rate, and the total nebulization time. Thus, with a fixed rate of drug output and a set nebulization time, the patient's breathing pattern will

in either case determine the inhaled mass of drug. Any shift in the patient's breathing pattern would therefore either increase or decrease the inhaled mass of drug when conventional jet nebulizers are used.

The mean inhaled mass of budesonide expressed in percent of the nominal dose for both modes of nebulization ranged from 11% to 15%, showing a statistically significant age dependency. The mean inhaled mass was less than expected from theoretical calculations based on a duty cycle of 0.42,[4] the Spira nebulizer's budesonide in vitro output rate of 1.8 $\mu g\ sec^{-1}$, and the fixed nebulization time of 5 min, i.e., $0.42 \times 1.8\ \mu g\ sec^{-1} \times 300\ sec = 226.8\ \mu g$ (i.e., 23% of the nominal dose).[3] A number of patients, predominantly found in the older age classes, achieved inhaled masses around or over 20%. The reasons for the age dependency of the inhaled mass could therefore probably be attributed to age-dependent differences in adaptation to the test setup (i.e., seal of face mask against face) and age-dependent differences in the children's breathing pattern, i.e., V_I,[16] inspiratory flows,[17] and duty cycles.[18] However, the last two variables in the breathing pattern could not be recorded due to lack of suitable equipment.

Age or size dependency of nebulized drugs have been discussed in two published studies. Lödrup Carlsen et al. used in a filter study a constant output System 22 jet nebulizer-spacer combination (Medic-Aid Limited, Bogner Regis, UK) to deliver nebulized budesonide to six children aged 4–30 months.[10] The inhaled mass of nebulized budesonide increased with age from 9% to 19% of the nominal dose, but the study did not reach statistical significance due to the small number of subjects. In the filter study by Wildhaber et al., salbutamol was nebulized during 5 min to 20 wheezy infants aged 4–12 months with a constant output Pari-Baby® jet nebulizer (Pari, Starnberg, Germany).[19] The results indicated that the inhaled mass of salbutamol increased statistically significantly with body weight.

The inhaled mass of budesonide expressed in percent of the total output of budesonide demonstrated a clear difference between the two modes of nebulization. During nebulization in BS-mode, the inhaled mass of budesonide was approximately 95% of the total output in children older than 3–4 years. This indicated that these children's inspiratory flows surpassed the flow of compressed air through the nebulizer, i.e., air entrainment occurred.[16] The larger amounts of budesonide lost to the expiratory filters in the younger children was most probably due to the fact that these children did not entrain air through the nebulizer and consequently left aerosolized budesonide in the nebulizer at the end of each inspiration. These results indicate that if the breath-synchronized nebulizer had been run to dryness, the older children would have inhaled approximately 95% of the total output, which was constant over the age classes, thereby reducing the age dependency of the inhaled mass. In the younger children, however, breath-synchronized nebulization to dryness would have had less impact on the age dependency due to the larger waste of drug. The main clinical benefit of breath-synchronized nebulization would therefore be a decrease in age dependency in children between 4–8 years of age for the inhaled mass of drug.

Increased cost-effectiveness could theoretically be achieved with a breath-synchronized jet nebulizer through either a reduction of the volume or through a reduction of the concentration of drug in the nebulizer charge. A limiting factor for any reduction of the volume of the nebulizer charge is the significant drop in output rate when the volume of drug in the nebulizer is reduced from 2 mL to 1 mL.[5] The remaining option would be to use a less concentrated drug preparation. If the concentration of 1 mg in 2 mL had been halved, the output rate would also have been halved, to approximately 0.9 $\mu g\ sec^{-1}$. In order to achieve an inhaled mass of 230 μg of budesonide (i.e., 23% of the nominal dose), a nebulization time of approximately 10 min would have been required, i.e., $0.42 \times 0.9\ \mu g\ sec^{-1} \times 600\ sec = 227\ \mu g$. Thus, an increased cost-effectivenesss with presently available breath-synchronized conventional jet nebulizers could be achieved through a reduction of the concentration of drug in the nebulizer charge. The nebulization time would, however, be prolonged.

The results of the present study showed that the inhaled mass of budesonide was significantly age-dependent when a conventional constant output jet nebulizer was used, i.e., the inhaled mass was less in younger children. Similar results were obtained with a breath-synchronized jet nebulizer run for the same nebulization time. Breath-synchronized nebulization resulted in reduced waste of drug during expiration.

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