Pediatric Pulmonology 29:120–126 (2000)

Diagnostic and Therapeutic Methods

Evaluation of Pulsed and Breath-Synchronized Nebulization of Budesonide as a Means of Reducing Nebulizer Wastage of Drug

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Summary. The aim of this open, randomized, crossover study was to compare the inhaled mass of budesonide suspension delivered by nebulization, using constant output, breath-synchronized, or pulsed jet nebulization techniques. The inhaled mass was defined as the amount of drug deposited on a filter between the inspiratory port of the nebulizer and the face mask or mouthpiece used by the subjects. The breath-synchronized nebulization delivered aerosol during the whole inspiration, whereas the pulsed nebulization was adjusted to deliver aerosol for up to 1 sec from the start of inspiration. Budesonide suspensions, 2 mL of 0.5 mg mL^{-1}, or 2 mL of 0.25 mg mL^{-1}, in single-dose respules, were used (AstraZeneca R&D Lund, Lund, Sweden). Eleven children (7 boys, age range 2.5–5.8 years) with either a clinical suspicion or a confirmed diagnosis of asthma and 11 healthy adolescents and adults (6 male, age range 13–52 years) were enrolled.

With constant output nebulization, the median inhaled mass of budesonide was about 17.6% (range 9.6–21.2%) of the nominal dose (i.e., dose of drug in the respule per label claim) in adolescents and adults, and 18.1% in children (15.7–21.4%). With pulsed nebulization the median inhaled mass increased to 23.4% (22.0–28.1%) in children and to 32.8% (24.8–38.0%) in adolescents and adults ($P < 0.001$). With breath-synchronized nebulization median inhaled mass increased to 30.1% (21.7–28.1%) in children, but was unchanged (30.8%, 27.0–38.0%) in adolescents and adults. The mode of nebulization (i.e., constant or breath-synchronized) had a statistically significant effect on the inhaled mass in children and adolscents or adults ($P < 0.001$). There was a statistically significant difference in inhaled mass between the breath-synchronized and pulsed nebulization in children only ($P < 0.05$).

The results support the use of breath-synchronized but not pulsed nebulization with conventional nebulizers. The results of pulsed nebulization in children warrants further clinical studies.
Pediatr Pulmonol. 2000; 29:120–126.

Key words: asthma; nebulization; breath-synchronization; budesonide; children; adults; pulsed jet nebulization; randomized controlled clinical trial.

INTRODUCTION

Conventional and breath-enhanced jet nebulizers for home care are designed to operate continuously. Nebulizers are usually charged with large doses of drugs or mixtures of drugs, and it is often assumed that the whole nebulizer charge is inhaled by the patient. The amount of nebulized drug inhaled by the patient (i.e., inhaled mass of drug) is, however, usually less than 25% of the nebulizer charge as it is mainly limited by the nebulizer's total drug output[1] and the patient's breathing pattern.[2] The total drug output is dependent upon nebulizer design, the compressor used, and the volume of nebulizer charge, but it is usually less than 50% of the nebulizer charge.

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Grant sponsor: AstraZeneca, Lund, Sweden.

There are no conflicts of interest.

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Received 11 March 1999; Accepted 29 September 1999.

With a duty cycle (duration of inspiration as a fraction of the total breath, t_i/t_{tot}) of 0.4–0.5, the inhaled mass would not exceed 20–25% of the nebulizer charge of drug.[1] Thus, approximately 25% of the nebulizer charge of drug is inhaled, 25% is lost to room air during the patient's expiration, and 50% remains in the nebulizer as a residual volume.[3] The nebulizer wastage of drug could thus be reduced if the nebulizer did not aerosolize drug during the patient's expiration, and the inhaled mass of drug could consequently be doubled with a t_i/t_{tot} of 0.4–0.5.

New breath-enhanced jet nebulizers have been developed to increase the inhaled mass of drug, and the new nebulizers have been shown in vitro to increase the inhaled mass compared with conventional jet nebulizers.[4,5] They cannot, however, eliminate the aerosol production during the patient's expiration and therefore only marginally reduce the waste of drug.[4] Breath-synchronized nebulization has, however, been shown both in vivo and in vitro to effectively reduce drug wastage during the expiratory phase.[2,4,6] Breath-synchronized drug nebulization has been widely used clinically only in bronchial provocation tests. During bronchoprovocation challenges, the aerosol is typically pulsed for 0.6 sec early during the patient's inspiration.[7] With the short nebulizer activation, the second half of the patient's inspiration is free of aerosol and the following expiration should contain only minute amounts of drug. The timing of the pulses early or late in the inspiration has been shown to have no significant effect on deposition of radioaerosol or on bronchodilatation with salbutamol in asthmatics.[8] Due to the cost of these devices the nebulizer systems used for bronchial provocation tests have not become widely used for nebulization of anti-asthma drugs and hence there is a lack of clinical data on pulsed or breath-synchronized nebulization of anti-asthma drugs.

The introduction of less expensive nonelectronic breath-synchronized jet nebulizers (AeroEclipse®, Trudell Medical International, London, Ontario, Canada and Smartstream®, Medic-Aid, Bognor Regis, UK)[9,10] and a new adaptive electronic dosimetric jet nebulizer (HaloLite®, Medic-Aid)[11,12] have, however, changed the situation. AeroEclipse® and Smartstream® are designed to deliver drug during the whole inspiration, whereas HaloLite® delivers drug during the first ~50% of each inspiration. This has raised the question regarding the optimal length of the pulse of aerosol, i.e., breath-synchronized to the whole inspiration or pulsed during a fraction of inspiration. None of these new nebulizers is, however, suitable for studies of different pulse lengths, as their designs do not allow for adjustments of the pulse. More traditional nebulizer designs such as the Spira Elektro 4® equipment (Respiratory Care Center, Hämeenlinna, Finland) do, however, allow adjustements of the pulse length from 0.1 to 3.0 sec.

The aim of this study was to investigate the Spira Elektro 4® equipment in healthy adults and asthmatic children, to assess the impact of pulsed and breath-synchronized nebulization on the inhaled mass of nebulized budesonide, and to compare the Spira Elektro 4® nebulizer with conventional constant output jet nebulization.

Abbreviations

BPM	Breaths per minute
HPLC	High-pressure liquid chromotography
MMD	Mass median diameter
ns	Not significant
t_i/t_{tot}	Duty cycle
V_I	Inspired minute volume
V_T	Tidal volume

MATERIALS AND METHODS

Study Design

The study was designed as a randomised, crossover, single-center trial and was performed over 2 days at the clinic with healthy adolescent and adult subjects and children. The healthy adolescent and adult subjects were included to provide a test group for the equipment setup and a comparator group to the children. The inclusion criteria for the children was either a clinical suspicion of asthma or a confirmed diagnosis of asthma. The jet nebulizer included in the Spira Elektro 4® system (Spira M1, Respiratory Care Center) was of a conventional T-piece design. The Spira® M1 nebulizer was used in three different modes: 1) constant output nebulization (Fig. 1a), 2) breath-synchronized nebulization with drug pulse up to 1 sec long delivered from the start of each inspiration (Fig. 1b), and 3) with drug nebulization during the whole inspiration up to 3 sec (Fig. 1b). An inspiratory-flow-activated synchronizer was connected between the jet nebulizer and the compressor for breath-synchronization (Fig. 1b). The tubing between the nebulizer and the synchronizer was 1 meter long. The sensitivity of the synchronizer was adjusted to match the inspiratory flows of either adults or children. The synchronizer was set to pulse compressed air through the jet nebulizer for up to 1 sec from the start of the inspiration, or through the whole inspiration up to the synchronizer's maximum pulse time of 3 sec. The maximal pulse length of 1 sec was selected based on an assumption of a median breathing frequency of 17–18 breaths per min (BPM) and a t_i/t_{tot} of 0.4 in children.[13] This would have given a t_i of ≈1.4 sec and the short pulse would consequently have been approximately 2/3 of the t_i. A reduction of the waste of aerosol during expiration would thus have been possible. Tight-sealing face masks (RMT-Set 2, Astra Meditec, Gothenburg, Sweden) were used for children and standard Spira® mouthpieces (Respiratory Care Center)

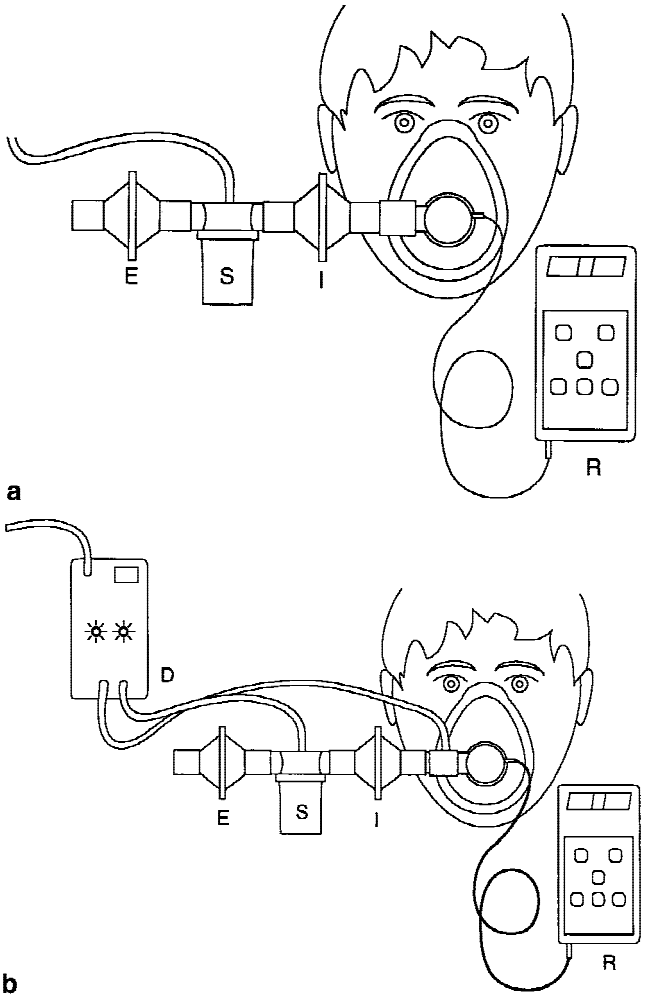

Fig. 1. Nebulizer setups. a: Inhalation port of the Spira® jet nebulizer (S) was connected in series with an inspiratory filter (I), a rotameter (R), and a face mask or mouthpiece. An expiratory filter (E) was connected to the exhalation port of the nebulizer. b: The synchronizer (D) with flow sensor was connected between the compressor and the nebulizer.

and noseclips (Vitalograph Ltd., Buckingham, UK) were used for adolescents and adults. The nebulizers were charged with 2 mL of budesonide suspension; a dose of 0.5 mg was placed into the nebulizer cup for the adults, and 1.0 mg was placed into the cup for the children to ensure sufficient amounts of budesonide on the filters (i.e., 2 mL of 0.5 mg mL^{-1}, and 2 mL of 0.25 mg mL^{-1}, 2 mL suspension, AstraZeneca R & D Lund, Lund, Sweden).

The total output of budesonide was determined by the sum of drug on both filters (Fig. 1a,b), whereas the total output of suspension was determined gravimetrically. The weight of the nebulizer cup including the amount of drug added to the nebulizer was measured before and during nebulization. During constant nebulization on the bench, the Spira® jet nebulizer reached the sputtering phase when approximately 0.6 mL liquid (i.e., 0.6 g) remained in the nebulizer cup. The output was linear up to the sputtering phase. In the present study, nebulization was therefore stopped when 75% of the nebulizer charge had been nebulized. This meant that out of a charge of 2 mL budesonide suspension, 1.5 mL (i.e., 1.5 g) had left the nebulizer. The change in the weight of the nebulizer was tested at regular intervals throughout nebulization to ensure a total output of 1.5 mL.

The jet nebulizers were connected to the Spira® compressor (Respiratory Care Center), which created a flow of 7.5 L min^{-1} through the nebulizers at pressures of 2.3 bar (constant output) and 2.7 bar (pulsed and breath-synchronized). The increase in pressure was required by the added resistance introduced by the synchronizer (Fig. 1b). The room temperature was ≈20°C. The inhaled mass was defined as the amount of budesonide deposited on an inspiratory filter (Marquest MQ-303 viral filters, Marquest Medical Products, Inc., Englewood, CO) located between the face mask or mouthpiece and the nebulizer's inspiratory port. The amounts of drug aerosolized during expiration were deposited on an expiratory filter (Fig. 1a,b). In vitro tests have shown that the Marquest filter can catch approximately 99.8% of the amount of budesonide sucked through the filter.[14] The inspiratory filter added an equipment dead space of approximately 30 mL to the nebulizer setup. Budesonide was eluted from the filters with a water/ethanol solution. The concentration and mass of budesonide were determined by high-pressure liquid chromotography (HPLC) at the Analytical Chemistry Department, AstraZeneca R & D.

The patients' inspiration through the nebulizers was recorded throughout nebulization with a Magtrac II general purpose respiratory flow sensor (Ferraris Medical Ltd., London, UK), which updated the recorded tidal volumes (V_T), BPM, and inspired minute volumes (V_I) every 20 sec. The aerosol droplet size was characterized with a Malvern Mastersizer® model MS1000 (Malvern Instruments Ltd., Malvern, UK). Three conventional constant output Spira® jet nebulizers were run continuously three times each with budesonide and three times each with isotonic saline. The mass median diameter (MMD) of the droplets was 3.7 μ m (range, 3.5–4.1 μm, SD 0.2) with budesonide and 3.6 μm (range, 2.7–4.2 μm, SD 0.6) with saline.

Subjects

Eleven healthy adolescent and adult subjects (6 males), and 11 children (7 boys) with either a clinical suspicion of asthma or a confirmed diagnosis of asthma, were included. The mean age of the healthy subjects was 37 years (range, 13–52 years), mean height 168 cm (155–178 cm), and mean weight 62 kg (40–75 kg). The mean age of the children was 4 years (range, 2.5–5.8 years), mean height 104 cm (84–115 cm), and mean weight 18

TABLE 1—Inhaled Mass of Budesonide, Exhaled Amount, Total Output, and Nebulization Time, Given as Group Median Values With Ranges

	Constant output	Pulsed	Breath-synchronized	Constant output	Pulsed	Breath-synchronized
Variable	Children			Adolescents and adults		
Inhaled mass (median and range, in % of nominal dose)	18.1 (15.7–21.4)	23.4 (22.0–28.1)	30.1 (21.7–35.3)	17.6 (9.6–21.2)	32.8 (24.8–38.0)	30.8 (27.0–38.0)
Expiratory filter (median and range, in % of nominal dose)	23.1 (19.7–28.4)	1.7 (0.6–3.4)	12.8 (6.1–18.6)	23.2 (17.6–27.8)	7.0 (4.6–11.0)	11.0 (8.0–14.0)
Total drug output (median and range, in % of nominal dose)	43.7 (35.4–48.4)	25.9 (23.0–31.5)	41.4 (34.9–45.6)	41.4 (27.6–45.4)	39.8 (30.0–47.0)	41.0 (37.8–47.6)
Gravimetric output (median and range, in milliliters)	1.50 (1.47–1.53)	1.50 (1.47–1.52)	1.50 (1.47–1.56)	1.54 (1.37–1.58)	1.55 (1.41–1.57)	1.54 (1.42–1.57)
Time from start to end of nebulization (median and range, in minutes and seconds)	3.50 (3.05–4.55)	10.50 (7.15–19.10)	8.20 (7.05–11.40)	4.00 (3.30–4.30)	9.00 (9.00–10.30)	8.00 (6.30–9.30)
V_T (mean of individual medians and range, in liters)	0.34 (0.26–0.62)	0.38 (0.27–0.52)	0.34 (0.22–0.55)	0.60 (0.37–0.92)	0.62 (0.40–0.93)	0.75 (0.60–1.02)
BPM (mean of individual medians and range, as number of breaths per minute	30.7 (19–52)	31.2 (19–49)	27.6 (13–42)	15.5 (10–23)	17.0 (14–24)	18.9 (13–25)
V_I (mean of individual medians and range, in liters)	9.5 (6.7–13.8)	10.8 (5.9–14.5)	8.9 (5.3–12.4)	9.0 (7.0–10.9)	10.3 (8.4–12.5)	13.0 (9.9–17.3)

kg (13.5–22.5 kg). The children were all used to inhalation from jet nebulizers. 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 Department of Allergic Diseases, Helsinki University Central Hospital, Helsinki, Finland.

Statistics

The two groups (children and adults) were compared within each nebulizer system by the nonparametric Wilcoxon rank-sum test. The same test was used for pairwise comparisons between the three nebulizer systems for each group (children and adults).

RESULTS

Breathing Pattern

The medians and ranges of V_T, BPM, and V_I are listed in Table 1. The results indicate that each group (children; adults and adolescents) inhaled within approximately the same range of V_T, BPM, and V_I during all three forms of nebulization. No correlations were found between the V_T, BPM or V_I, and the inhaled mass of budesonide. Children had a smaller V_T, but about the same V_I as the older subjects.

The t_i/t_{tot} has been shown to be reflected in the proportion of drug deposited on the inspiratory and expiratory filters when using the Spira® M1 nebulizer.[4] The filter data from the constant output nebulization indicated that the mean t_i/t_{tot} was 0.41 (range, 0.38–0.52) in children and 0.43 (0.35–0.47) in adults.

Total Drug Output

With constant output nebulization, the median total output of budesonide (i.e., sum of drug on inspiratory and expiratory filters) expressed in percent of the nominal dose was 43.7% for children and 41.4% for adults and adolescents (not significant (ns), Table 1). With nebulization synchronized to the whole inspiration, the median total output was 41.4% for children and 41.0% for adults and adolescents (ns, Table 1); with pulsed nebulization it was 25.9% for children and 39.8% for adolescents and adults ($P < 0.001$, Table 1). The total drug output with pulsed nebulization differed statistically significantly from the other modes of nebulization in children ($P < 0.001$).

Inhaled Mass of Drug

With constant output nebulization, the median inhaled mass of budesonide expressed in percent of the nominal dose was 18.1% for children and 17.6% for adolescents and adults (Fig. 2a,b, Tables 1, 2). The difference was not statistically significant. With pulsed nebulization, the median inhaled mass increased to 23.4% for children and to 32.8% for adolescents and adults ($P < 0.001$). With nebulization synchronized to the whole inspiration, the median inhaled mass increased further, to 30.1% for children but was unchanged (30.8%) for adolescents and adults. In adolescents and adults, the nebulizer system (i.e., constant output vs. breath-synchronized) had a statistically significant effect on the inhaled mass ($P < 0.001$, Fig. 2b), whereas there was no statistically significant difference between the breath-synchronized and pulsed modes of nebulization. In children, the nebulizer system (i.e., constant output vs. breath-synchronized) had a statistically significant effect on the inhaled mass ($P < 0.001$, Fig. 2a), and there was a statistically significant difference between the breath-synchronized and pulsed modes of nebulization ($P < 0.05$, Fig. 2a).

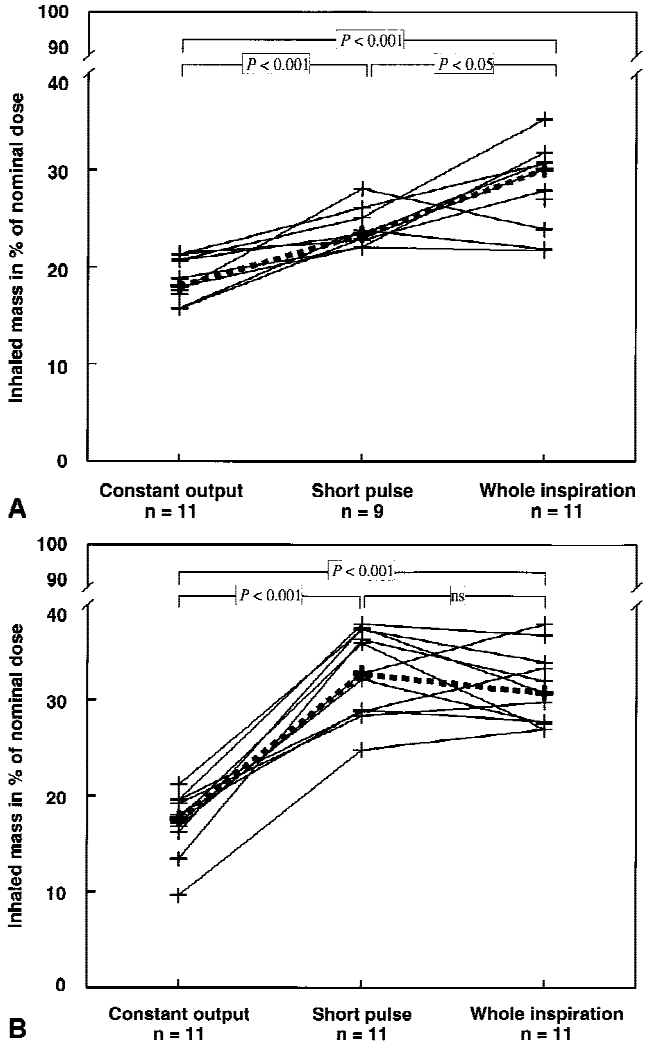

Fig. 2. A: Children: the individual inhaled mass of budesonide with the median values plotted for the three nebulization modes. The mode of nebulization had a statistically signficant effect on the inhaled mass ($P < 0.001$); there was a statistically significant difference between the breath-synchronized nebulization modes ($P < 0.05$). B: Adolescents and adults: the individual inhaled mass of budesonide with the median values plotted for the three nebulization modes. The mode of nebulization had a statistically signficant effect on the inhaled mass ($P < 0.001$); there was no statistically significant difference between the breath-synchronized nebulization modes.

DISCUSSION

We compared three different modes of nebulization in terms of the inhaled mass of nebulized budesonide, which was defined as the amount of drug deposited on a filter positioned between the nebulizer and the subject. The filter technique has previously been used in vitro[1,4,6] and in vivo[2] for the determination of the inhaled mass of nebulized budesonide. This technique has been shown in children to accurately reflect the amount of budesonide inhaled without a filter between the nebulizer and the patient.[15] The filter technique is therefore a useful tool in the development of inhalation devices. The filter technique provides, however, only a crude estimate of the amount of drug that might be deposited in the lungs. Lung deposition depends on differences in nebulization techniques and on choice of mouthpiece or face mask. In the present study, the MMD of the nebulized droplets was only measured during constant output nebulization and pulsed nebulization might have changed the droplet size. Lung deposition also depends on nasal or oral inhalation with face mask vs. oral inhalation with mouthpiece.[16]

With constant output nebulization the median inhaled mass of budesonide was ≈18% of the nominal dose in adolescents and adults, and in children. This is in rather good agreement with published in vivo[2] and in vitro[4] results. The median inhaled mass was close to what could be expected from theoretical calculations[2] based on a t_i/t_{tot} of ≈0.42, the Spira® jet nebulizer's in vitro budesonide output rate of 1.8 μg sec^{-1} (for 0.5 mg mL^{-1}),[2] and the mean nebulization time of ≈4 min, i.e., 0.42 × 1.8 μg sec^{-1} × 240 sec = 180 μg or ≈18% of the nominal dose. The variability in the amount of drug deposited on the filters was probably a combined effect of variations in t_i/t_{tot}, nebulizer output rate, and nebulization time.

With breath-synchronized and pulsed nebulization, the median inhaled mass of budesonide increased statistically significantly in adolescents and adults from 17.6% to 30.8% and 32.8%, respectively, at the expense of a prolonged nebulization time. In adults, the total output was similar for breath-synchronized and pulsed nebulization, i.e., 41.0% and 39.8%, indicating that the pulsed nebulization of budesonide was not affected by increased evaporation, although it increased the nebulization time from 8 to 9 min (Table 1). The inhaled mass was not equal to the total output, because the nebulizers wasted aerosol during expiration with breath-synchronized and pulsed nebulization. The waste of budesonide to the expiratory filters was probably related to a delay in the cutoff of the compressor flow. The time for the compressed air to reach 90% of the maximum pressure has recently been investigated with the Spira® equipment.[17] The results showed that the time to maximal compressed air pressure in the tubing between a breath-synchronized Spira jet nebulizer and the compressor was 157 msec, which was reduced to 8 msec by shortening the tubing and positioning the synchronizer closer to the nebulizer. The authors did not report the time for the pressure to decrease back to zero, but one can assume that the fall in pressure was similar to the increase. Consequently, the nebulizer and the filter housing were filled with aerosol at the end of each inspiration due to the slow decline in the pressure, and the aerosol cloud was then deposited onto the expiratory filter during each expiration.

In adolescents and adults the difference in the inhaled

TABLE 2—Individual Inhaled Mass of Budesonide in Percent of Nominal Dose

	Constant output	Pulsed	Breath-synchronized	Constant output	Pulsed	Breath-synchronized
Subjects	Children			Adolescents and adults		
1	15.8	23.8	21.9	9.6	24.8	27.0
2	21.3	26.1	30.7	16.2	37.6	30.8
3	17.6	28.1	23.9	13.4	36.4	32.0
4	18.9	22.0	21.7	21.2	37.4	34.0
5	20.7	23.4	30.8	19.2	28.4	29.8
6	20.8	25.1	35.3	17.6	36.0	27.0
7	18.0	22.1	31.8	17.2	32.2	27.6
8	15.7	23.0	30.1	16.8	32.8	38.0
9	21.4	22.8	27.9	19.6	28.8	33.4
10	18.1		31.8	18.0	29.0	27.8
11	17.2		27.0	19.6	38.0	36.8
Mean	18.7	24.0	28.5	17.1	32.9	31.3
SD	2.1	2.0	4.4	3.2	4.6	3.9
Median	18.1	23.4	30.1	17.6	32.8	30.8

mass between the breath-synchronized and pulsed nebulization did not reach statistical significance, although there was a small numerical difference in favor of the pulsed nebulization. With a median breathing frequency of 17–19 BPM and a t_i/t_{tot} of 0.4, the t_i would have been ≈1.3 sec long and the short 1-sec pulse ≈75% of the t_i. The pulsed nebulization should therefore in theory have eliminated the amount of budesonide on the expiratory filters. This was, however, not the case for any of the adolescents and adult subjects. The range of individual breathing frequencies was 13–25 BPM, and with a t_i/t_{tot} of 0.4, the t_i would have ranged from ≈1.0 sec to 1.8 sec. Assuming that not only the breathing frequencies but also the t_i/t_{tot} varied during the nebulization, a variability in t_i/t_{tot} from 0.3 to 0.4 would have given a t_i range from ≈0.7 sec to 1.8 sec. Consequently the short pulse of 1 sec was equal to the t_i, and the pulsed and the breath-synchronized nebulization was equally long for a number of the t_is. This, in combination with the delay in pressure to decrease back to zero, could explain the lack of a larger difference in inhaled mass between the breath-synchronized and pulsed nebulization in adolescents and adults.

In children, breath-synchronized nebulization increased statistically significantly the inhaled mass of budesonide from 18.1% to 30.1%, but it also prolonged nebulization time. The change was comparable to that seen in adolescents and adults. There was, however, a statistically significant difference in the median inhaled mass between the breath-synchronized (30.1%) and pulsed nebulization (23.4%) in contrast to the result in adolescents and adults. The reduction in the inhaled mass with pulsed nebulization was matched by a similar reduction in total budesonide output, but not by a reduction in gravimetric output. Thus the reduction in total budesonide output was a result of increased evaporation. The reduction was matched by an increase in nebulization time from 3.50 min to 10.50 min, whereas the breathing patterns remained similar. The entrainment of room air through the nebulizer (i.e., mean V_I minus compressed gas flow of 7.5 L min^{-1}) increased from 2 to 3.3 L min^{-1}. The total air entrainment (i.e., L min^{-1} times nebulization time) did consequently increase from 7 L to 34.7 L, which should have increased evaporation.

Our results highlight one of the limitations of the technique to set the pulse time in the conventional breath-synchronizers. The patient has to "standardize" the breathing pattern to the synchronizer's pulse of aerosol; otherwise, a pulse shorter than the inspiration is rather meaningless. If the patient's breathing pattern during home nebulization cannot be standardized as during bronchial provocation tests in a laboratory, the nebulization should only be synchronized to the whole inspiration with these kinds of devices. In order to fully utilize breath-synchronized nebulization, a conventional jet nebulizer like the Spira® M1 should be designed with valves guiding expiration past the interior of the nebulizer, and the flow sensor should be built into the nebulizer to minimize any delay from the flow sensor to the synchronizer and compressor.

The aim of this study was to investigate the impact of pulsed and breath-synchronized nebulization on the inhaled mass of nebulized budesonide. The results support the use of breath-synchronized, but not pulsed nebulization, with conventional nebulizers. The results of pulsed nebulization in children warrants further clinical studies.

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