Short-term Effect of Albuterol, Delivered via a New Auxiliary Device, in Wheezy Infants[1-4]

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SUMMARY In a double-blind, placebo-controlled study, the response of lung function to albuterol, topically administered by a metered-dose inhaler (MDI) through a baby-adapted auxiliary device, was evaluated in 36 wheezy infants (1.6 to 25.2 months of age; median 8.1 months). The auxiliary device contains an air chamber of 350 ml and two low-resistant valves separating the inspiratory from the expiratory line. After baseline lung function measurements by infant whole-body plethysmography, the patients were randomly assigned to inhale either three times two puffs albuterol (100 μg/puff) or three times two puffs placebo at 5-min intervals. Changes in the degree of pulmonary hyperinflation, estimated by thoracic gas volume (TGV) and/or in the degree of bronchial obstruction, estimated by thoracic gas volume (TGV) and/or in the degree of bronchial obstruction, estimated by airway conductance (Gaw), were measured at 5-min intervals for up to 30 min. TGV and Gaw were expressed as standard deviation scores (SDS) of values predicted, and patients improving TGV and/or Gaw more than 2 SD were considered responders. In comparison with placebo, a significant percentage improvement in TGV (by the mean 26 to 53%) and a significant percentage improvement in Gaw (by the mean 34 to 51%) could be found in the active treatment groups. The study documents the usefulness of a new auxiliary device for the administration of aerosolized bronchodilators to wheezy infants. AM REV RESPIR DIS 1991; 144:347-351

Introduction

It is widely accepted that wheezy bronchitis in infants represents a part of the spectrum of early asthma in childhood: it has been shown that infants who have more than one wheezing episode frequently develop the typical picture of asthma in later childhood (1-3). Although bronchodilator aerosols, whether administered by jet-type nebulization or by metered-dose inhaler (MDI), are common treatments for asthmatic patients, producing rapid and efficient relief of bronchospasm with low doses and avoiding adverse secondary effects, there are conflicting reports regarding the value of inhaled bronchodilators to treat wheezy infants (4-8). We have recently shown that in most infants with bronchopulmonary disease the degree of pulmonary hyperinflation as well as the degree of bronchial obstruction improved after oral administration of albuterol (9, 10). However, preference would be given to topical administration of the drug by inhalation either by nebulization or topically administered by spacer devices (15-17), which would have the advantages of smaller dosages (11), fewer side effects (12, 13), and more rapid onset of drug action (14). As inhalation from compressor-generated aerosols is difficult in infants with limited cooperation, alternative delivery systems are needed to facilitate the rapid and effective administration of bronchodilators from an MDI with an auxiliary device. However, the technical specifications for such a device are dependent on several physiopathologic characteristics of wheezing infants. Even for adults it has been shown that optimal aerosol generation is dependent on certain technical conditions of the device (18-21).

Therefore, a new infant drug delivery system, the Babyhaler™ inhaler (Glaxo Group of Companies), has been designed, by which medications can be administered from an MDI. The objective of this double-blind, placebo-controlled study was to evaluate the response of lung function to albuterol inhaled by the Babyhaler.

Methods

Patients

From 40 initially randomized patients (4 had to be excluded because of technical problems during performance of the second test) a total of 36 infants aged between 1.6 and 25.2 months (mean 9.3 ± 5.4 months; median 8.1 months) were investigated. The parents were referred to the pediatric clinic because of recurrent or persistent tachypnea, dyspnea, and expiratory wheezing. In most infants the onset of the illness was in the first 4 months of life. Although specific virology was not available, the infants were considered to have wheezing following initial viral bronchiolitis on clinical grounds. None of the infants suffered from any respiratory problems in the neonatal period, and appropriate investigations were undertaken to ensure that none had cystic fibrosis, gastroesophageal reflux, or cardiac disease. All infants had a history of a close relative (parent or sibling) with asthma or allergic rhinoconjunctivitis. They all failed to respond adequately to such treatment as anticough medication, antibiotics, and xanthines. None of the patients had been treated with β_2-agonists previously, and no patients receiving xanthines were included. Informed consent was obtained from the parents, and the study was approved by the local ethical committee.

Lung Function Measurements

Thoracic gas volume (TGV) and airway conductance (Gaw), the latter the reciprocal value of airway resistance (Raw) (22), were measured by an infant plethysmograph (Jaeger, Würzburg, Germany), a method that has previously been described (10). All measurements were done 15 to 20 min after a feed and after the infants had been sedated with chloral hydrate (80 to 100 mg/kg). During the plethysmographic measurements pulse-oximeter monitoring of heart rate and oxygen saturation (Biox® III; Ohmeda, Boulder, CO) was performed. The infant was placed in the supine position inside the whole-body infant plethysmograph. A mask, sealed around the nose and mouth to ensure an airtight fit, was carefully manipulated into place for the measurements. After the body-box was closed the infant breathed air from the box through a

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triple-valve system until thermal equilibrium was reached between the infant and the box. A differential pressure transducer was used to detect changes in box pressure (ΔP_b) relative to a compensating chamber of similar volume. The infant was then switched to the BTPS bag [body temperature, (water) pressure saturated] from which air at 36.5° C and 100% relative humidity was rebreathed. The phase relationship between flow (V'), measured by a baby-sized pneumotachograph (Jaeger), and P_b was checked by displaying both signals on an oscilloscope until a stable, almost closed pressure-flow loop was obtained. From the tracing of V' and P_b the uncorrected specific airway conductance (SGaw) was calculated (23). Changes in mouth pressure (ΔP_m) were obtained after the shutter was closed to occlude the airway while the infant made two to three respiratory efforts, breathing in most cases at a frequency between 30 and 40 breaths/min. TGV was measured from the angle β of the $\Delta P_b/\Delta P_m$ plot and corrected for instrument deadspace (30 ml). Gaw was calculated as reciprocal value of Raw from the angles of the $\Delta P_b/\Delta V'$ plot. The resistance of the pneumotachograph, 0.18 kPa/L/s, was subtracted from each calculated value of Raw.

Functional Groups

To evaluate drug response to the degree of pulmonary hyperinflation on the one hand and/or the degree of bronchial obstruction on the other hand, the infants were divided into functional groups. Infants having baseline TGV more than the mean (of predicted value) plus 2 SD (standard deviations) were considered hyperinflated. Infants with Gaw less than the mean (of predicted value) minus 2 SD were considered to have bronchial obstruction. A mixed functional group presented with increased TGV and decreased Gaw.

Bronchodilator Administration

After two plethysmographic baseline measurements (BLM), either three times two puffs (equal to three times 200 μg) albuterol or three times two puffs of a placebo preparation were administered in a randomized manner at 5-min intervals from an MDI through the new baby-adapted spacer device, so that at 15 min six puffs had been inhaled. Each puff was actuated separately, giving the child the opportunity to inhale the aerosol during 10 breathing cycles. By this procedure one group of infants (n = 20) received the active drug first, followed by placebo (Study Arm I) and the other group of infants (n = 16) received the placebo drug first, followed by the active drug (Study Arm II) (figure 1). In Study Arm I the efficacy of albuterol could be studied in its dose response in the first 15 min (A1) in addition to the time response in the second 15 min (P2). Lung function measurements were repeated every 5 min.

The Baby-Adapted Auxiliary Device

A centerline sectional longitudinal view of the Babyhaler is given in figure 2. The dimensions of the spacer were chosen according to certain criteria and according to the limit given by the conditions in which infants and young children are able to evacuate the aerosol from the spacer by normal tidal breathing. Infants usually have a tidal volume (VT) of 5 to 8 ml/kg body weight. During respiratory distress the range of tidal breathing of babies is from 7 to 14 ml/kg body weight (5 kg = 35 to 70 ml; 10 kg = 70 to 140 ml). The volume of the chamber should be substantially greater than the tidal inhalation volume of the infant or young child, and 350 ml was chosen, enabling the child to evacuate the chamber within 10 breathing cycles. The distance between the chamber inlet and the chamber outlet is such that the mass percentage of aerosol particles, having a diameter from 1.0 to 5.0 μm, was a maximum at the chamber outlet (for albuterol-MDI, 230 mm). Acryl tubes 44 mm in diameter were used as material for the chamber. The chamber inlet was adapted to receive the MDI devices. The outlet communicates with the face mask via a first valve that permits the infant or young child to inhale aerosol-carrying air from the chamber. Exhalation is performed via a second valve that communicates with the atmosphere. By this construction the inspiration line is completely separated from the exhalation line. The resistance of the inhalation valve is preferably not more than about 0.02 kPa/L/s for a flow rate of 75 ml/s. The positive end-expiratory pressure created by the exhalation valve is less than 0.05 kPa. The deadspace within the valve arrangement is 16 ml. The infant mask (available in three different sizes) covering the nose and mouth of the child is attached to the chamber.

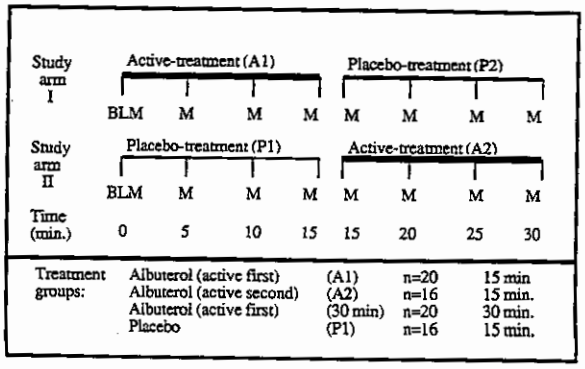

Fig. 1. Study protocol with two study arms (I and II) and four treatment groups (A1, A2, A1-P2, and P1). BLM = baseline measurements; M = 5-min measurements.

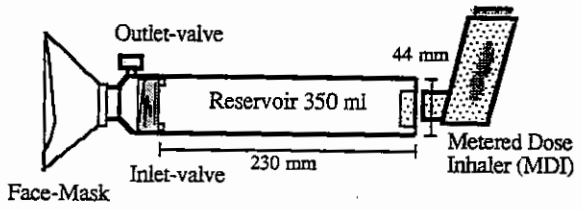

Fig. 2. Centerline sectional longitudinal view of the Babyhaler inhaler with its specification.

Data Analysis

To show individual values of TGV and Gaw numerically free from sex, age, and height bias, lung function data were expressed as SD scores (SDS) or as a Z score, defined as number of SD above or below the mean of distribution. The SDS can be obtained by dividing the absolute residual (difference between measured value and value predicted for each particular case) by the residual SD (24), which was taken from the regression equation of a normal population (25). This is a standard mathematical procedure that is always applied when weighted variables must be compared (growth studies), and its application to lung function data was presented recently (10). By such computation age-independent values, weighted for both the degree of pulmonary hyperinflation (TGV) and the degree of bronchial obstruction (Gaw), were obtained.

Because coupled variables (TGV and Gaw) can hardly be evaluated independently as single variables, changes in lung function were evaluated as SDS, in absolute terms, and as the mean of individual percentage changes. Infants showing an improvement of at least 2 SD in either TGV and/or Gaw after drug inhalation were considered responders. By such a computation volume responders can be distinguished from flow responders. For each dose step (200 to 600 μg in 200-μg ranges), therefore, the ratio of responders to nonresponders (response ratio) was calculated and statistically evaluated by a chi-square test. Differences between groups were evaluated by Fisher's *t* test.

Results

Biometric data (age, gestational age, postconceptional age, and body weight), heart rate, oxygen saturation, and VT of the subjects within the two Study Arms I and II are summarized in table 1. All these parameters were similar for the two study arms. Baseline values (BLM) for TGV and Gaw, given numerically free of sex, age, and height bias in SDS, in addition to absolute values in ml/kg BW and ml/s/cm H_2O/kg BW, are summarized in table 2. The age- and sex-corrected absolute mean values of functional abnormalities for both treatment arms showed that on the average bronchial obstruction was more pronounced (−6.4 SD and −6.3 SD) than pulmonary hyperinflation (−0.7 SD and 1.0 SD). However, by

TABLE 1

BIOMETRIC DATA OF THE PATIENTS WITHIN THE TWO STUDY ARMS I AND II

	Treatment I (Active 1st)	Treatment II (Placebo 1st)	Significance Probability (2-tailed)
Number	20	16	
Age			
months ± SD	9.2 ± 6.3	9.5 ± 4.3	0.46
median	8.6	7.5	
Gestational age			
wk ± SD	37.9 ± 2.8	38.3 ± 3.5	0.51
median	38	38	
Postconceptional age			
wk ± SD	77.3 ± 27.7	78.8 ± 19.1	0.50
median	76	70	
Body weight			
kg ± SD	8.3 ± 3.0	8.3 ± 2.6	0.97
median	8.5	9.0	
Heart rate			
beats/min ± SD	121 ± 8	123 ± 10	0.51
median	119	122	
Oxygen saturation (So_2)			
% ± SD	92.2 ± 3.2	90.3 ± 3.1	0.46
median	91	90	
Tidal volume (VT)			
ml ± SD	89 ± 45	91 ± 48	0.51
median	92	93	

TABLE 2

FUNCTIONAL DISORDERS WITH RESPECT TO PULMONARY HYPERINFLATION, BRONCHIAL OBSTRUCTION, OR BOTH AS FREQUENCY AND IN ABSOLUTE VALUES OF STANDARD DEVIATION SCORES (SDS) WITHIN THE TWO STUDY ARMS I AND II

	Treatment I (Active 1st)	Treatment II (Placebo 1st)
Number	20	16
TGV		
SDS	−0.7 ± 3.2	1.0 ± 4.0
ml/kg BW	35.9 ± 13.6	35.0 ± 10.7
Gaw		
SDS	−6.4 ± 2.4	−6.3 ± 3.3
ml/s/cm H_2O/kg BW	5.1 ± 1.8	4.8 ± 1.7
SGaw/s/cm H_2O	0.119 ± 0.051	0.110 ± 0.059
Repartition into functional groups		
Hyperinflation (SDS TGV > 2)	8/20	7/16
Obstruction (SDS Gaw < 2)	18/20	15/16
Including mixed type of both abnormalities	6/20	6/16

Definition of abbreviations: TGV = thoracic gas volume; Gaw = airway conductance; SGaw = specific airway conductance; SDS = standard deviation score; BW = body weight.

defining abnormal function outside the 2 SD range it can be shown that the number of infants within the functional groups (pulmonary hyperinflation, bronchial obstruction, or both) initially found in the two treatment arms was equally distributed. The repartition into functional groups showed 8 of 20 (active first) and 7 of 16 (placebo first), respectively, to be hyperinflated and 18 of 20 (active first) and 15 of 16 (placebo first), respectively, to be bronchially obstructed. There is an overlap of 6 infants in each treatment arm who showed both functional derangements. SGaw is given in absolute terms and was similar for both study arms.

Lung function data obtained after placebo (P1), active first (A1), active second (A2), and active first but evaluated after 30 min (A1 and P2) obtained within the two functional groups (hyperinflation or obstruction) are given in table 3. There was a significant decrease in TGV of at least 2.6 SD up to 4.2 SD, from 13.3 to 17.7%, respectively, in the actively treated groups with pulmonary hyperinflation, compared with 0.6 SD, and 2.9%, respectively, in the placebo group. Gaw increased significantly at least 2.5 SD up to 3.8 SD, from 34.1 to 50.6%, respectively, in the active treatment groups with bronchial obstruction in comparison with 0.5 SD and 9.5%, respectively, in the placebo group.

Estimation of the drug response, taking into account improvement in TGV (volume responders) as well as improvement in Gaw (flow responders) is shown in table 4. At 15 min 16 of 20 of actively treated first ($p < 0.001$) and 13 of 16 of actively treated second ($p < 0.01$) showed improvement in TGV and/or Gaw of more than 2 SD. When drug efficacy was examined at 30 min (A1-P2) all 20 infants showed a sufficient drug response ($p < 0.0001$).

In figure 3 the improvement in the response ratio (collecting both types of responders) over time is presented. It can be seen that in contrast to placebo the response ratio of the actively treated groups increased to a certain content in parallel with the heart rate (HR), achieving the best efficacy after 600 µg albuterol at 30 min. This drug response seems to be independent of the initial functional abnormality.

No serious side effects were observed following the inhalation of the β-agonist. Pulse oximetry showed a mean oxygen saturation of 89.3 ± 3.3%, which remained unchanged (90.5 ± 2.1%). Although HR remained unchanged in the placebo group (P1, 123 to 122 beats/min), it increased significantly in the groups treated with albuterol (A2, 123 to 142 beats/min; A1-P2, 129 to 149 beats/min), which suggests some systemic absorption of the drug.

Discussion

In the past, provision of aerosol therapy in asthmatic children older than 4 yr has been made more convenient and cost effective by the increased use of pressurized MDI in connection with large spaced auxiliary devices. After evidence that β-adrenoreceptor agonists are effective when systemically given in infants younger than 18 months (9, 10), improvement in clinical signs was also shown after topical administration by inhalation (15–17). Recently, a 500-ml plastic bottle, shaped to fit an infant's face, was effective for delivering relatively large doses of aerosol generated by metered-dose inhalers (15). O'Callaghan and colleagues demonstrated the efficacy of a 750-ml spacer device (Nebuhaler™; Draco Astra, Sweden) as a rebreathing chamber attached to a Laerdal size 2 resuscitation face mask (16). In these studies, however, the effec-

TABLE 3

LUNG FUNCTION AFTER INHALATION TREATMENT PRESENTED AS CHANGES IN SDS AND PERCENTAGE CHANGES WITHIN THE THREE FUNCTIONAL GROUPS*

	Placebo, 15 Min (P1)	Albuterol, 15 Min (A1)	Albuterol, 15 Min (A2)	Albuterol, 30 Min (A1 and P2)
Drug influence on pulmonary hyperinflation (TGV > mean ± 2 SD)				
Number	6 (all mixed)	8 (6 mixed type)	7 (6 mixed type)	8 (6 mixed type)
ΔTGV				
SDS	0.6 ± 1.3	−4.2 ± 2.4†	−2.6 ± 1.4‡	−4.0 ± 2.2†
ml/kg	1.1 ± 4.0	−8.2 ± 3.5‡	−7.0 ± 5.7	−8.8 ± 7.9‡
%	2.9 ± 8.7	−17.7 ± 6.0†	−13.3 ± 8.3	−15.0 ± 9.6‡
ΔSGaw, %	11.4 ± 13.7	35.1 ± 25.2	52.7 ± 70.6	25.7 ± 14.8
Drug influence on bronchial obstruction (Gaw < mean − 2 SD)				
Number	16 (6 mixed type)	18 (6 mixed type)	15 (6 mixed type)	18 (6 mixed type)
ΔGaw				
SDS	0.5 ± 1.2	2.5 ± 2.2†	2.8 ± 1.6§	3.8 ± 2.0§
L/s/H_2O/kg	0.4 ± 0.7	1.3 ± 1.3†	1.7 ± 0.9§	2.1 ± 1.5§
%	9.5 ± 15.7	34.1 ± 46.8‡	43.5 ± 27.8§	50.6 ± 40.3†
ΔSGaw, %	5.9 ± 17.2	19.6 ± 32.4	34.0 ± 31.1	25.4 ± 35.4

* Indicated values are statistically significant by *t* test.
† $p < 0.01$.
‡ $p < 0.05$.
§ $p < 0.001$.

TABLE 4

RESPONSE RATIO IN ABSOLUTE TERMS REACHED AFTER INHALATION TREATMENT*

	Placebo, 15 min (P1)	Albuterol, 15 min (A1)	Albuterol, 15 min (A2)	Albuterol, 30 min (A1 and P2)
Flow responder	1	8	7	11
Volume responder	1	8	6	9
Nonresponder	14	4	3	0
Chi-square		***	***	****

Definition of abbreviations: TGV = thoracic gas volume; Gaw = airway conductance; SGaw = specific airway conductance; SDS = standard deviation score; chi-square statistics: *** $p < 0.001$; **** $p < 0.0001$.
* Responder indicates improvement > 2 SD in TGV and/or Gaw. Indicated values are statistically significant by chi-square test.

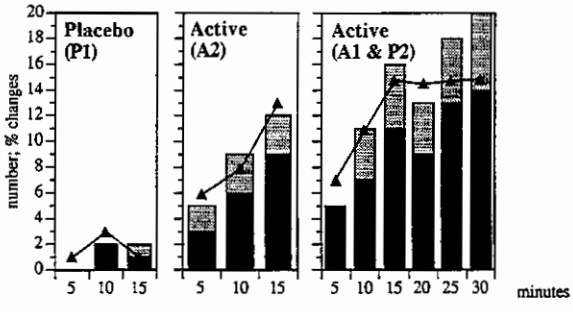

Fig. 3. Dose response and time course to albuterol assessed by the number of responders (improvement in lung function > 2 SD) and percentage increase in heart rate (HR) within the three treatment groups. Solid bars = flow responder; speckled bars = volume responder; triangles = HR% changes.

tiveness of aerosol therapy in children younger than 4 yr was assessed only by clinical scoring systems. Thus far, there is no study showing the effectiveness of such treatment by objective lung function data.

This study has shown that, in comparison with placebo, wheezy infants significantly improve lung function after the topical administration of β-agonists inhaled from an MDI through a baby-sized, double-valved, low-deadspace spacer device, the Babyhaler. However, changes in both TGV (as an estimate of pulmonary hyperinflation) and Gaw (as an estimate of airway function) must be examined. There is a close relationship between dose response to the lung function and dose response to heart rate (figure 3). Furthermore, the time-response relationship seems to be longer than previously found in older children (26, 27). There are several technical aspects related to the kind of evaluation by which infant's lung function data are evaluated, on the one hand, and the physical specification of an infant spacer device, on the other hand. Both seem to be determinants for the question of whether the drug response to adrenoreceptor agonists can be achieved and substantiated in infants.

Infant Lung Function Testing

Under the condition that flow is laminar, the resistance of an airway bears an inverse fourth-power relationship to its diameter (22). Although in wheezy infants this may not be the case everywhere in the bronchial tree, this exponential relationship serves to explain the mechanism that as an airway narrows, a progressively greater change in resistance is expected for a given change in smooth muscle length (and hence inspiratory lung volume). There is a linear relationship between lung volume and Gaw (22). Therefore, we anticipated in previous studies that the bronchodilator response to β_2-agonists must be measured in children and especially in infants by methods that evaluate changes in airway function in relation to changes in resting end-expiratory level (10, 26–28). The influence of changes in functional residual capacity on airway function was recently shown by Silverman's group, who demonstrated that indices of partial expiratory flow maneuvers may underestimate the actual changes in airflow when changes in end-expiratory level are not taken into account (29). This was demonstrated for histamine-induced bronchoconstriction in recurrently wheezy infants, but the converse effect after bronchodilator inhalation is based on the same mechanism.

Physical Conditions for an Infant's Spacer Device

Pressurized aerosols obtain their driving force from chlorofluorocarbon propellants at a pressure of approximately 400 kPa. Consequently, the aerosol emerges from the canister at a high speed (30). If the aerosol is actuated into a spacer device, the propellant droplets should evaporate and be slowed by air resistance so that a finer and more slowly moving aerosol can be inhaled (31). This mechanism depends largely on the size dimensions (length and volume) of the spacer. Choosing the MDI-specific appropriate length and volume, an aerosol with optimal particle size distribution can be generated (21) and inhalation can easily be performed within 1 min without sedimentation. Because of the separated two-valve system, rebreathing is avoided.

Mechanisms of Inhaled β-Agonist Action

An interesting question concerning the

action of inhaled bronchodilator drugs, in particular β_2-agonists, is whether the drug acts topically or whether it must be absorbed into the circulation before it causes smooth muscle relaxation. It is well known that values for airway resistance in healthy adults reflect mainly the dimensions of the large central airways (32). An improvement in Gaw could therefore imply dilation of these central airways in our patients. This effect, as suggested by previous studies with albuterol (26–28) in asthmatic children, may be in parallel with findings that bronchodilation could be observed before there were detectable plasma concentrations of the drug (33). We did not have the opportunity or facility to perform a radionuclide mapping study to demonstrate the exact location of drug deposition in the lungs of these infants. In agreement with De Troyer (34), however, we think that because of the very small dimensions of infant airways, aerosolized drugs are deposited predominantly in the large airways and therefore dilation of terminal lung units and improvement in their time constants must be a systemic effect of β_2-agonists. The parallel increase in heart rate appears to support this assumption. It is suggested that the percentage of aerosol reaching the central bronchial tree in adults is on the order of 20% and in children, about 10%. This percentage is markedly reduced when aerosols are administered to infants. This may explain the considerable differences in the time response of infants in comparison with older children (26–28).

Side Effects and Acceptance of the Device

None of the patients treated in this manner had adverse reactions. During the tests the Babyhaler was well tolerated, and parents reported that consecutive application of this device at home resulted in a significant improvement in signs of bronchial obstruction. Parents apply inhalations with this device while the infant is awake, and some indicated that the child sometimes cries during inhalation, which presumably favors inhalation. Nevertheless, in comparison with the use of jet nebulizers, we suspect that there is less stress when this procedure is used, probably because of its considerably shorter duration. Jet nebulization takes about 10 min, but the administration of bronchodilator with the MDI and Babyhaler system takes 1 min or less.

In conclusion, application of β-adrenoreceptor agonists inhaled from an MDI through a baby-adapted auxiliary device produces improvement in lung function in the majority of wheezing infants after 600 μg albuterol. Changes in resting end-expiratory level as well as concomitant changes in airway function must be considered. The drug response may be delayed until 30 min after administration. From the practical point of view we believe that an MDI with such an auxiliary device may be used more rapidly than a nebulizer, needing less time for delivering a precise dose and minimizing deposition in the upper respiratory tract. Furthermore, this aerosol delivery system is portable, does not require energy or compressed gas to operate, and parents or persons providing care for these wheezing infants can be easily instructed in its use. The doses to be administered daily are presumably higher than those recommended at present as a result of the low V_T-spacer volume ratio and the high frequent breathing, especially in infants in respiratory distress. However, the exact age-related dosage needs to be evaluated in a larger population of wheezy infants over a substantial range of time.

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