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A new baby-spacer device for aerosolized bronchodilator administration in infants with bronchopulmonary disease*

R. Kraemer, P. Birrer, K. Modelska, C. Casaulta Aebischer, and M. H. Schöni

Paediatric Respiratory Research Group, Department of Paediatrics, University of Berne, Inselspital, CH-3010 Berne, Switzerland

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Abstract. The response of salbutamol (Ventolin, Glaxo), topically administered from a metered dose inhaler (MDI) through a new baby-spacer-device (Babyhaler, Glaxo) was studied in 14 infants (8 wheezy infants, 3 infants with cystic fibrosis and 3 infants after respiratory distress syndrome), age 2.9–18.8 months. Changes in thoracic gas volume (TGV) as an estimate of pulmonary hyperinflation and changes in airway conductance (Gaw) as an estimate of bronchial obstruction were assessed by whole-body plethysmography. After baseline measurements, 1 puff of 100 μg salbutamol was given repeatedly at 5 min intervals until 600 μg have been inhaled and TGV and Gaw were measured after each inhalation at 5, 10, 15, 20, 25 and 30 min. Significant improvement in lung function was achieved in 57.1% of infants after 400 μg and in 92.9% of infants after 600 μg salbutamol. The study shows usefulness of bronchodilator treatment in infants with bronchopulmonary disease by a system with a MDI and baby-spacer-device. However a special dose-time relationship must be respected.

Key words: Bronchodilators – Infants – Bronchopulmonary disease – Baby-spacer device – Babyhaler

Introduction

In most infants with bronchopulmonary disease the degree of pulmonary hyperinflation as well as the degree of bronchial obstruction improve after systemic administration of salbutamol [10, 11]. Although little is known concerning the amount of drug deposited in the respiratory tract of infants [24], preference, however, would be given to a topical administration of the drug by inhalation. This would have the advantages of smaller dosage [26], less side-effects [12, 13] and more rapid onset of drug action [22]. Inhalation treatment in infants by compressor generated aerosols are rather difficult because of co-operation for the requested inhalation time of 10–15 min with a mask closely fitted on the face. Therefore, alternative delivery systems are needed which allow rapid and effective administration of broncholdilators. In order to use drugs delivered by metered dose inhalers (MDI) through an auxiliary device, several technical specifications must be taken into account. This is essential for optimal aerosol deposition in the infant's lung and minimizing oropharyngeal deposition of the drug [7, 9]. Moreover, efficacy from optimal drug deposition in the bronchial tree must be studied with respect to the special physiopathological situation in the wheezing infant [21, 25].

Therefore, a new infant drug delivery system, the Babyhaler inhaler (Trade Mark of the Glaxo Group of Companies), has been designed, by which salbutamol can be administered from a MDI. The purpose of the present study was to demonstrate the dose-time course of bronchodilator response in wheezy infants, infants with cysti fibrosis (CF) and infants recovering from infant respiratory distress syndrome (iRDS). Changes in pulmonary hyperinflation and bronchial obstruction after drug administration were measured by plethysmography.

Subjects and methods

Patients

Fourteen infants with bronchopulmonary diseases aged between 2.9 and 18.8 months (mean 10.1 ± 5.4 months) were investigated. Eight infants had wheezy bronchitis, 3 CF with pulmonary symptoms, and 3 had iRDS due to hyaline membrane disease or pneumonia during the neonatal period. All iRDS subjects were premature infants, initially intubated and ventilated mechanically and investigated for this study 2–3 months after the acute phase of the disease. None of the patients had been previously treated with beta agonists. Informed consent was obtained from the parents and the study was approved by the local ethical committee.

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Offprint requests to: R. Kraemer

Abbreviations: CF = cystic fibrosis; Gaw = airway conductance; iRDS = infant respiratory distress syndrome; MDI = metered dose inhaler; SD-S = standard deviation score; TGV = thoracic gas volume

Fig. 1. The Babyhaler inhaler in its application to an infant

Lung function measurements

Thoracic gas volume (TGV) and Gaw (Gaw being the reciprocal value fo airway resistance) were measured by plethysmographic technique [1, 6] with an infant plethysmograph (Jaeger, Würzburg, FRG), as previoulsy described [11]. All measurements were performed 15–20 min after a feed and after the infants had been sedated with chloral hydrate (80–100 mg/kg). During the plethysmographic measurements pulse-oximeter monitoring of heart rate and oxygen saturation (Biox III, Omeda, Bolder, USA) was done.

Bronchodilator administration

After two plethysmographic baseline measurements cumulatively 1 puff (100 µg) salbutamol was given in 5 min intervals repeatedly administered from a MDI through a baby-spacer device until 6 puffs (600 µg) have been inhaled. Lung function measurements were repeated each 5 min after each dose to give six post-salbutamol measurements. All patients completed the test procedure within 30 min without waking up.

The Babyhaler inhaler device

In Fig. 1 the Babyhaler is shown in its application to an infant. For optimal functioning of such an inhalation system the following technical consideration may be made. According to the conditions by which infants and young children are able to inhale aerosol with normal tidal breathing the dimensions of the spacer were defined. Infants usually have a tidal volume of 5–8 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 = 35–70 ml; 10 kg = 70–140 ml). Therefore, the volume of the chamber intended to be substantially greater than the tidal inhalation volume of the infant or young child was chosen to be 350 ml, enabling the child to evacuate the chamber within ten breathing cycles. The distance between the chamber inlet and the chamber outlet is such that the mass percentage of aerosol particles with a diameter from 1.0 to 5.0 microns is at a maximum at the chamber out-let (for salbutamol (Ventolin)-MDI: 230 mm) [21]. The chamber has an inlet adapted to receive the MDI device. The outlet communicates with a face mask by two valves, the first of which (inlet valve) permits to inhale aerosolloden air from the chamber. Exhalation is performed through a second valve (outlet valve) which communicates with the atmosphere. In this design the inspiration line is completely separated from the exhalation line. Resistance to the flow of the valves is less than 0.02 kPa/l/s for a flow rate of > 5 ml/s. The positive end-expiratory pressure created by the exhalation valve is less than 0.05 kPa. The dead space within the valve arrangement is about 16 ml. An infant mask available in three different sizes covering the nose and mouth of the infant is attached to the chamber.

Data analyis

In order to show individual values of TGV and Gaw numerically free from sex, age, and height bias, lung function data were expressed as standard deviation scores (SD-S) by dividing the absolute residual by the residual standard deviation which was taken from the regression equation of a normal population [15, 16]. By such a computation age-independent values weighted for the degree of pulmonary hyperinflation (TGV) and the degree of bronchial obstruction (Gaw) were obtained. A change after drug inhalation of at least 2 SD of either TGV and/or Gaw was considered as a significant response. For each dose (100 µg to 600 µg in 100 µg steps) the ratio of responder/non-responder was calculated and statistically evaluated by the chi-square test. Differences between groups were evaluated by Fisher's *t*-test.

Results

Biometric data of the subjects are summarized in Table 1. Gestational age postconceptional age, and weight were lower in the iRDS group than in wheezy infants or those with CF; this difference was statistically significant only for gestational age ($P < 0.05$). Baseline values for TGV and Gaw in SD-S are given in Table 2. Seven of 14 patients (2/8 wheeze; the 3 CF; 2/3 RDS) had a pulmonary hyperinflation (SD-S TGV > 2). Twelve of 14 patients (the 8 wheeze; 2/3 CF; 2/3 RDS) showed bronchial obstruction (SD-S Gaw < 2). With respect to the mean of the SD-S, infants with CF had significant pulmonary hyperinflation (SD-S TGV = 6.8; $P < 0.05$).

Table 1. Biometric data of the subjects investigated

	Wheeze	CF	RDS
Number	8	3	3
Gestational age (weeks ± SD)	39.1 2.4	38.0 1.0	31.0* 2.6
Postconceptional age (weeks ± SD)	87.8 21.8	86.0 29.3	51.0 8.9
Age (months ± SD)	11.5 5.0	11.5 6.7	4.8 1.7
Body weight (kg ± SD)	8.7 0.9	7.4 2.3	5.0 2.7

* $P < 0.05$

Table 2. Baseline values of TGV and Gaw as mean of SD-S with range and repartition into the three functional groups (bronchial obstruction and/or pulmonary hyperinflation)

	Wheeze	CF	RDS	All
TGV (SD-S) (range)	1.0 ±7.1	6.8* ±3.4	4.9 ±5.4	3.1 ±6.3
Gaw (SD-S) (range)	−7.5 ±1.8	−4.9 ±3.7	−3.9 ±2.3	−5.9 ±2.9
Hyperinflation	0/2	1/2	1/2	2
Mixed type	2/5	2/5	1/5	5
Bronchial obstruction	6/7	0/7	1/7	7

Hyperinflation: SD-S TGV > 2; bronchial obstruction SD-S Gaw < 2; * $P < 0.05$

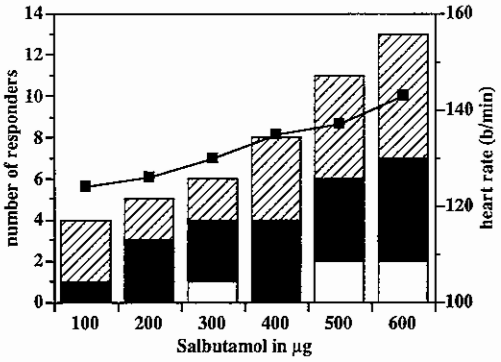

Fig. 2. Response to salbutamol (Ventolin) 6 times 100 µg administered by the Babyhaler inhaler within time of 30 min. Response is shown for each of the three functional groups (bronchial obstruction and/or pulmonary hyperinflation separately. *HR*, Changes in heart rate. —■— HR; ▨ obstructed ($n = 7$), ■ mixed ($n = 5$), □ hyperinflated ($n = 2$)

The response to salbutamol inhalations are given in Fig. 2. After 400 µg of salbutamol (Ventolin) (4 puffs after 20 min) 8 of 14 patients, mainly those with bronchial obstruction, responded favourably (changes in TGV and/or Gaw > 2 SD). After 600 µg salbutamol 13 of 14 patients were identified as responders. The remaining non-responding infant with CF presented with excess of bronchial secretion which had not been cleared during the study period (baby asleep).

Non serious side-effects following inhalation of salbutamol were noted. Pulse oximetry showed a mean of oxygen saturation of 89.7% + 4.0% which remained unchanged (88.9% + 3.6%). In some cases oxygen supply was requested in order to overcome the timely limited ventilation/perfusion disturbance [23]. Heart rate increased significantly from 124 + 14/min to 143 + 13/min (Fig. 2; $P < 0.01$).

Discussion

In recent years aerosol therapy in asthmatic children older than 4 years of age became more convenient and cost-effective by the extended use of pressurized metered dose inhalers in connection with large spacer auxiliary inhaler devices such as the Volumatic and Nebuhaler instead of nebulized drug solutions. Various spacer devices have also been applied in infants [3, 14, 18, 24, 28]. There is growing evidence that applications of beta-adrenoreceptor agonists are effective in infants younger than 18 months systemically given [10, 11] or by inhalation [3, 14, 18, 28]. Recently a 500 ml plastic bottle, shaped to fit an infant's face was shown to be effective for delivering relatively large doses of aerosol generated by metered-dose inhalers [14]. O'Callaghan et al. demonstrated usefulness of a 750 ml spacer device (Nebuhaler) as a rebreathing chamber attached to a Laerdal resuscitation face mask [18]. Yuksel et al. investigated ten wheezy preterm infants administering 500 µg terbutaline from an inhaler using a coffee cup as a spacer device for 2 weeks showing improvement of the symptom score by 65% during the active treatment compared to 32% during placebo treatment [28]. In these studies however, effectiveness of aerosol therapy in infants and young children with reversible airflow obstruction was only shown by improvement of clinical scores. To our knowledge no data are available demonstrating effectivenss of topical drug administration in infants with lung disease by objective lung function data.

This paper shows that in infants with bronchopulmonary disease an improvement in lung function can be documented after topical administration of beta agonists if changes in both, TGV and Gaw, are examined and the drug is inhaled from a MDI via a size-adapted, double-valved, low resistance and low dead-spaced auxiliary device, like the Babyhaler. However, in interpreting our results some technical aspects of the auxiliary device and some aspects of lung function testing in infants have to be discussed.

Technical aspects

Pressurized aerosols obtain their driving force from chlorofluorocarbon propellants at a pressure of approximately 400 kPa, and the aerosol cloud consequently emerges from the canister at a high speed [17]. Furthermore, the drug crystals are initially trapped within large propellant droplets whose mass diameter may exceed 30 µ. Large particles travelling at high velocities are very susceptible to deposition by inertial impaction on the oropharyngeal surface [8, 19, 20] allowing only a small quantity to enter the lung [4, 17]. If the aerosol is actuated into a spacer device, the propellant droplets should evaporate and be slowed down by air resistance so that a finer and more slowly moving aerosol could be inhaled [2].

Physiological aspects

As previously demonstrated [11], an important functional disorder found in infants with lung disease is pulmonary hyperinflation, a condition which can only be detected by measuring end-expiratory resting lung volume (helium dilution technique, plethysmography). Pulmonary hyperinflation may be or not be combined with obstruction of airways (mixed type). It has also been shown that a decrease in lung volume will itself narrow the airways, and airway resistance may not fall unless the diameter of the airway was changed substantially [11]. An interesting question concerning the action of inhaled bronchodilator drugs, in particular beta-2-agonists is whether they act topically or whether they have been absorbed into the circulation before causing smooth muscle relaxation. It is well known that airway resistance in healthy adults reflects mainly the dimension of the large, central airways [1]. Improvement in Gaw could therefore imply also in our babies a dilatation of these central airways. However, it was shown in a previous study [27] that bronchodilation was present before detectable plasma concentrations of the drug were observed. To prove the exact site of bronchodilator action in the bronchial tree of such subjects radionuclide map-

ping studies in order to demonstrate the exact localization of drug deposition are needed. In agreement with DeTroyer [5] we assume, that due to the very small dimensions of the infant's airways, aerosolized drugs are preferentially deposited in the large airways. Therefore, dilation of terminal lung units and by that improvement of their time constants must by a systemic drug effect. The parallel increase of heart rate seems to support this assumption. In addition, it is suggested that the percentage of aerosol reaching the central bronchial tree in babies is less than in older children or adults. This might explain why doses up to 600 µg salbutamol are needed to demonstrate efficacy.

Application of beta adrenoreceptor agonists inhaled from metered dose inhalers through the new designed baby-adapted auxiliary device produced improvement of lung function in 13 of 14 infants with bronchopulmonary disease, although a dose of up to 600 µg salbutamol was requested. In infants with disturbed gas exchange (especially CF infants), deterioration in oxygenation due to ventilation/perfusion disturbances may occur, requesting oxygen supply. In further studies recommendations for daily long-term treatment must be worked out.

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