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The bronchodilator response from inhaled terbutaline is influenced by the mass of small particles: a study on a dry powder inhaler (Turbuhaler®)

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The bronchodilator response from inhaled terbutaline is influenced by the mass of small particles: a study on a dry powder inhaler (Turbuhaler®). G. Persson, J.E. Wirén.

ABSTRACT: This study was carried out to investigate if particles <~5 μm are optimal when delivered from a dry powder inhaler. It was performed as a cumulative dose response study of twelve asthmatic adults. Three different versions of a dry powder inhaler, Bricanyl® Turbuhaler®, were studied. Each inhaler delivered 0.5 mg of pure terbutaline sulphate with each dose. Out of this 0.5 mg, they delivered 90 μg, 40 μg and 5 μg, respectively, of particles <~5 μm with each dose at an inspiratory flow rate of 28 $l \cdot min^{-1}$. Terbutaline 0.5 mg, 0.5 mg, 1.0 mg and 2.0 mg was inhaled with a 30 min interval between the doses. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured 5 and 20 min after each dose. The bronchodilator response was greater with the inhaler delivering 90 μg of small particles with each dose than with the inhaler delivering 5 μg, thus confirming the importance of small (<~5 μm) particles.

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Inhaled beta-agonists are well accepted in the treatment of asthma. Successful inhalation therapy probably depends on the drug being delivered to the lungs, *i.e.* deposition in the mouth and upper airways should be avoided. When deposition is plotted as a function of airway generation, particles in the 1–5 μm range in aerodynamic diameter show peak deposition in the small conducting airways and alveoli, whilst particles in the 5–10 μm range have a peak deposition in the large conducting airways [1–3]. With increasing particle size there is an increase in oropharyngeal deposition [4]. Particles <~5 μm in aerodynamic diameter have arbitrarily been defined as the "respirable range" for therapeutic aerosols [5], although even in this range of particle sizes some will be exhaled and some will be deposited in the oropharynx. The aerodynamic behaviour of inhaled particles might change when they reach the airways, *e.g.* due to absorption of water [6]. Therefore, it is important to study how changes in the mass of particles in the respirable range from an inhaler influence the clinical effect.

The aim of the present study was to compare the bronchodilation achieved with terbutaline sulphate from three versions of a dry powder inhaler, Turbuhaler® [7], delivering different masses of particles within the respirable range.

Material and methods

The study was of a single-blind crossover design carried out as a cumulative dose response study on three separate occasions at least 7 days apart. Twelve patients between 22 and 45 yrs (median 41 yrs) completed the study. One patient who was included had a baseline forced expiratory volume in one second (FEV_1) of 72% of predicted value. With this exception all patients fullfilled all of the following inclusion criteria: 1) age >18 yrs; 2) chronic stable asthma; 3) baseline FEV_1 <70% of predicted value; 4) improvement >15% in FEV_1 and reaching FEV_1 >60% of predicted value after 0.5 mg of inhaled terbutaline sulphate.

None of the patients had: 1) hypersensitivity to sympathomimetics; 2) significant cardiac disease; 3) hyperthyroidism not adequately controlled; 4) beta-blocker therapy; 5) insulin-dependent diabetes; 6) baseline variation of FEV_1 >15% between the three study days.

Theophylline, oral/inhaled beta-stimulants and anticholinergics were withdrawn 48, 12/8 and 48 h, respectively, prior to study start. Steroids and antihistamines were continued. Patient data are listed in table 1.

Bricanyl Turbuhaler delivering a metered dose of 0.5 mg pure terbutaline sulphate per dose, without any additives, was used in the study. Randomization was carried out using a computer programme. In randomized order, three different versions of the inhaler were studied, one giving 90 μg (inhaler A), one giving 40 μg (inhaler B) and one giving 5 μg (inhaler C) of particles <~5 μm with each dose at an inspiratory flow rate of 28 $l \cdot min^{-1}$. Inhaler A had a standard spiral insert in the mouthpiece. The channels in the mouthpiece insert were widened in inhaler B. The insert in the mouthpiece was absent in inhaler C. The estimations of the mass of particles <~5 μm were performed using an impactor, the Andersen Mark II sampler [8]. This device fractionates and

Table 1. – Patients' demographic data

Patient n	Sex	Age yrs	Height cm	Weight kg	Duration of asthma yrs	Ordinary asthma maintenance therapy
1	M	42	185	73	5	IB, TH
2	M	35	173	70	7	IB, OB, TH
3	M	44	174	70	5	IB
4	F	35	160	57	30	IB, OB, IS
5	F	45	163	63	24	IB, OB, IS
6	F	45	167	65	10	IB, OB
7	F	32	179	70	7	IB, OB, IS, TH
8	M	36	165	70	6	IB, OB, AH
9	F	41	166	92	17	IB, OB, TH
10	F	22	167	55	17	IB
11	M	44	185	88	40	IB, TH
12	F	41	170	60	9	IB, OB, IS, TH
Mean		39	171	69	15	
Range		(22–45)	(160–185)	(55–92)	(5–40)	

IB: inhaled β-stimulant; IS: inhaled corticosteroid; AH: antihistamine; TH: theophylline; OB: oral β-stimulant.

collects aerosol particulates by aerodynamic diameter through serial multistage impaction.

Each study day the patients inhaled 0.5 mg, 0.5 mg, 1.0 mg and 2.0 mg of terbutaline, 30 min apart, from one version of the Turbuhaler. The inhaler was attached to a hot wire spirometer (Monoghan 403). By means of a connected oscilloscope, the patients were checked to retain an inspiratory flow rate of about 28 $l \cdot min^{-1}$. This flow rate was chosen according to the performance of the impactor. FEV_1, forced vital capacity (FVC) and pulse rate were measured before treatment and then 5 and 20 min after each inhaled dose. FEV_1 and FVC were measured using a Vitalograph dry-bellows spirometer.

Editing of data was performed before opening of the treatment codes. Parametric ANOVA followed by pairwise comparisons (t-test) between the treatment was used in the analysis of FEV_1, FVC and pulse rate. The area under curve (AUC) values for FEV_1 and FVC were calculated using the trapezoidal method with normalized time span.

The study was approved by the local Ethical Committee. The patients were informed of the nature and purpose of the study verbally and in writing. The verbal consent of the patients was obtained.

Results

The FEV_1 dose response curves (mean values) are shown in figure 1. Treatment with all three inhalers already resulted in a significant increase in FEV_1 at the measurement 5 min after the first dose (inhaler A: $p<0.001$; B and C: $p<0.05$). There were significant differences ($p<0.05$) in FEV_1 between inhalers A and C after each inhaled dose.

The AUC value as regards FEV_1 of inhaler A (2.96) was significantly greater ($p<0.05$) than that of inhaler C (2.70). The FEV_1 AUC value of inhaler B was 2.87.

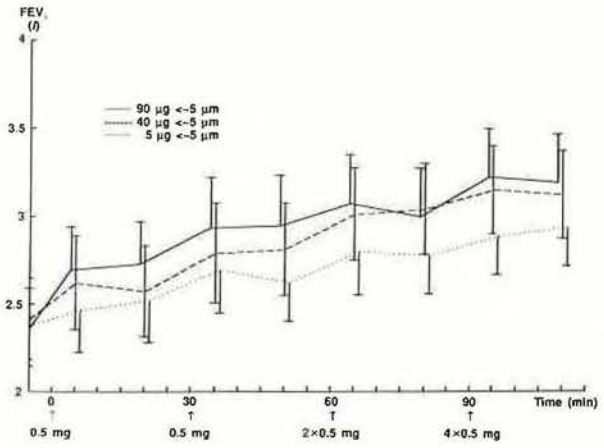

Fig. 1. – Forced expiratory volume in one second (FEV_1) dose response curves (mean±SEM) after administration of terbutaline sulphate from three versions of Turbuhaler delivering different masses of particles <~5 µm.

The FVC dose response curves (mean values) are shown in figure 2. Treatment with all three inhalers already resulted in a significant increase in FVC at the measurement 5 min after the first dose (inhaler A: $p<0.01$; B: $p<0.05$; C: $p<0.01$). There were significant differences ($p<0.05$) in FVC between inhalers A and C after the second and fourth inhaled doses.

No statistically significant differences between the inhalers in AUC values were found regarding FVC (inhaler A: 4.07; B: 3.99; C: 3.90).

No significant increase in pulse rate occurred with either treatment. The pulse rate ($beats \cdot min^{-1}$) before treatment

was 78±2 (mean±SEM) on all study days. Twenty minutes after the last inhalation from inhaler A the pulse rate was 79±3. The corresponding values after treatment with inhalers B and C were 77±2 and 78±2, respectively.

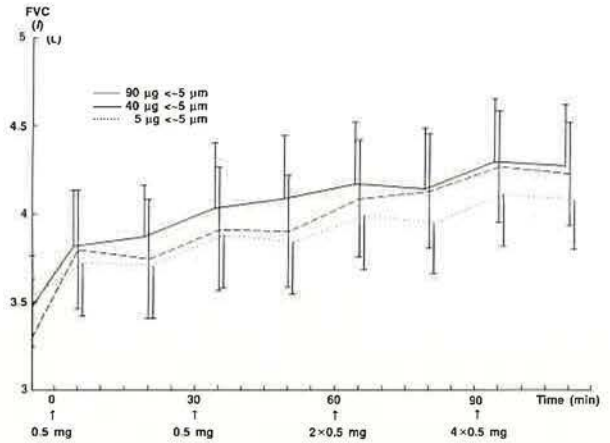

Fig. 2. – Forced vital capacity (FVC) dose response curves (mean±SEM) after administration of terbutaline sulphate from three versions of Turbuhaler delivering different masses of particles <~5 µm.

Discussion

In an earlier study of inhaled terbutaline it was shown that inhalation from a metered dose inhaler (MDI) delivering particles within the "respirable range" resulted in greater bronchodilation than inhalation from MDIs delivering particles above this size [9]. The same observation was made when using terbutaline in three different nebulizers, which created three different particle size distributions [10]. Our present results, obtained from three versions of a terbutaline dry powder inhaler, Bricanyl® Turbuhaler®, are in agreement with those of earlier studies on inhalation of terbutaline of different size distributions from MDIs and nebulizers. Five minutes after the first dose the increase in FEV_1 after treatment with the inhaler delivering only 5 µg of respirable particles was about a third of the increase obtained with the inhaler delivering 90 µg of respirable particles. The increase in FEV_1 with the inhaler delivering 40 µg of respirable particles was between the other two inhalers. Thus, it seems as important to achieve a large proportion of small particles when using a dry powder inhaler as when using an MDI or a nebulizer.

High interparticulate forces must be overcome to deaggregate the powder in dry powder inhalers to create an aerosol with small particles [3]. In the Turbuhaler this is achieved by a spiral insert in the mouthpiece [7]. This insert also increases the resistance whereby the inspiratory flow rate is decreased. This makes particles less likely to impact at the back of the throat. The insert in the mouthpiece was absent in inhaler C which delivered only 5 µg of small particles and had the lowest bronchodilator efficacy.

It is an interesting observation that statistically significant bronchodilation was already achieved 5 min after the first dose with all three versions of the inhaler, although the patients were instructed to keep an inspiratory flow rate as low as 28 $l \cdot min^{-1}$. This low inspiratory flow rate is normally only present in cases with severely impaired ventilatory capacity. Doubling the inspiratory flow rate through the Turbuhaler roughly doubles the amount of particles within the respirable range. Doubling the inspiratory flow rate has been shown to increase the bronchodilator response [11].

In conclusion, this study shows that the bronchodilator response from terbutaline, when inhaled from a dry powder inhaler, increases with an increasing mass of particles with an aerodynamic diameter <~5 µm with each dose.

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La réponse bronchodilatatrice à l'inhalation de terbutaline est influencée par la masse des petites particules. Une étude sur un inhalateur à poudre sèche (Turbuhaler®). G. Persson, J.E. Wirén.

RÉSUMÉ: L'objet de cette étude est d'investiguer si les particules inférieures à environ 5 µm sont optimales lorsqu'elles proviennent d'un inhalateur à poudre sèche. Il s'agit d'une étude dose-réponse cumulative chez 12 adultes asthmatiques, au moyen de trois versions différentes d'un inhalateur à poudre sèche, Bricanyl® Turbuhaler®. Chaque inhalateur fournit une dose de 0.5 mg de sulfate de terbutaline pure par dose. De cette

dose de 0.5 mg, des quantités respectives de 90 µg, 40 µg et 5 µg de particules inférieures ou égales à 5 µm sont produit avec chaque propulsion, à un débit inspiratoire de 28 $l \cdot min^{-1}$. L'on a administré des doses successives de 0.5 mg, 0.5 mg, 1.0 mg et 2.0 mg de terbutaline, avec un intervalle de 30 minutes entre chacune d'elles. Le VEMS et la capacité vitale forcée ont été mesurés 5 et 20 minutes après chaque dose. La réponse bronchodilatatrice s'avère plus grande au moyen de l'inhalateur fournissant 90 µg de particules <5 µm par dose, qu'avec l'inhalateur délivrant 5 µg, confirmant ainsi l'importance des particules inférieures ou égales à 5 µm.

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