Dose-response protective effect of salbutamol on methacholine airway responsiveness using pressurized metered dose inhalers and Turbuhalers

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The purpose of this study was to estimate the relative dose potency of salbutamol Turbuhaler compared with salbutamol pressurized metered dose inhaler (pMDI) with respect to the protective effect against methacholine bronchoconstriction. Twenty-three asthmatic subjects with stable asthma participated in the study. Baseline forced expiratory volume in 1 s (FEV_1) was 70% or more of predicted, and baseline methacholine provocative concentration causing a 20% fall in FEV_1 (PC_{20}) was 4 mg/mL or less. The design was randomized, double-blind, double-dummy, crossover and placebo controlled and was conducted over seven study days. On each study day, the subjects inhaled 50 µg or 100 µg of salbutamol via Turbuhaler, 100 µg, 200 µg, 400 µg or 800 µg of salbutamol via pMDI, or placebo in randomized order. PC_{20} was determined 30 mins after inhalation. Increasing doses of salbutamol pMDI increased the PC_{20} in a dose-dependent fashion from 3.9 mg/mL after placebo to 13.3 mg/mL after pMDI 100 µg, 19.0 mg/mL after 200 µg, 32.6 mg/mL after 400 µg, and 35.1 mg/mL after 800 µg. The half-maximum response dose for pMDI (ED_{50}) was 104 µg. Salbutamol Turbuhaler 50 µg increased the PC_{20} to 10.0 mg/mL and 100 µg to 12.6 mg/mL. Salbutamol pMDI 200 µg provided significantly greater protection to methacholine than pMDI 100 µg or Turbuhaler 100 µg and significantly less protection than pMDI 400 µg ($P<0.05$). This study demonstrates that the relative protective dose potency of inhaled beta-agonists can be determined by comparing their effects on methacholine airway responsiveness. The estimated relative protective dose potency for salbutamol Turbuhaler in comparison with pMDI was 1.38 (95% CI 0.67 to 2.87) at 50 µg and was 0.96 (95% CI 0.56 to 1.64) at 100 µg.

Key Words: *Methacholine airway responsiveness, Pressurized metered dose inhaler, Salbutamol, Turbuhaler*

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Effet protecteur lié à la dose de salbutamol sur la réactivité des voies respiratoires à la méthacholine; par inhalateur à dose mesurée et par Turbuhaler

RÉSUMÉ : Le but de cette étude était d'évaluer la puissance comparative de la dose de salbutamol par Turbuhaler ou par inhalateur à dose mesurée pour ce qui est de l'effet protecteur contre la bronchoconstriction induite par la méthacholine. Vingt-trois sujets asthmatiques stables, ont participé à l'étude. Le volume expiratoire forcé au départ, par seconde (VEMS) était de 70 % ou plus de la valeur prévue et la concentration de méthacholine en test de provocation (CP) donnant au départ une baisse de 20 % du VEMS (CP_{20}) a été de 4 mg/mL ou moins. Il s'agissait d'un protocole randomisé à double insu, à double feinte avec permutation des groupes, contrôlé par placebo qui a duré sept jours. Chaque jour, les sujets ont inhalé 50 µg ou 100 µg de salbutamol par Turbuhaler, 100 µg, 200 µg, 400 µg ou 800 µg de salbutamol par inhalateur ou un placebo de façon randomisée. La CP_{20} a été déterminée 30 minutes après l'inhalation. L'augmentation des doses de salbutamol par inhalateur a haussé la CP_{20} de façon dose-dépendante de 3,9 mg/mL après le placebo, à 13,3 mg/mL après 100 µg, 19,0 mg/mL après 200 µg, 32,6 mg/mL après 400 µg et 35,1 mg/mL après 800 µg par inhalateur. La moitié de la réponse maximale liée à la dose pour l'inhalateur (DE_{50}) a été de 104 µg. Le salbutamol, 50 µg par Turbuhaler, a augmenté la CP_{20} à 10,0 mg/mL et 100 µg à 12,6 mg/mL. Le salbutamol 200 µg par inhalateur a conféré une protection significativement plus grande contre la méthacholine, comparativement à 100 µg par inhalateur ou Turbuhaler et une protection significativement moindre de 400 µg par inhalateur ($P < 0,05$). Cette étude confirme que le degré de protection lié à la dose des différents agonistes par inhalation peut être déterminée en comparant leurs effets sur la réactivité des voies respiratoires à la méthacholine. La puissance protectrice relative liée à la dose du salbutamol en Turbuhaler en comparaison avec l'inhalateur a été de 1,38 (IC 95 %, 0,67 à 2,87) avec 50 µg et a été de 0,96 (IC 95 %, 0,56 à 1,64 avec 100 µg).

Salbutamol is a selective beta-agonist that provides 4 to 6 h of bronchodilation upon inhalation. Until recently, this drug was administered mainly as aerosols from pressurized metered dose inhalers (pMDI). Many available pMDIs contain chlorofluorocarbons as propellants for aerosol generation (1). Problems exist with respect to coordination of actuation and inhalation, and, in some patients, the propellants can provoke acute transient bronchoconstriction (2). Turbuhaler (Astra Pharma Inc) is an inspiratory flow-driven, multidose, dry powder inhaler that provides the medication without the need for propellants. A randomized crossover comparison of five inhaler systems determined an overall preference for Turbuhaler with respect to ease of use (3).

Salbutamol inhaled via Turbuhaler and pMDI have been compared in recent studies. The same nominal dose of salbutamol given via Turbuhaler has been shown to be more potent than salbutamol via pMDI with respect to bronchodilator response and systemic effects (4,5). In addition, Turbuhaler gives a higher pulmonary deposition of terbutaline compared with pMDI (6) and significantly greater bronchodilation compared with terbutaline pMDI plus Nebuhaler (7).

The potency of beta-agonists can be expressed not only by their bronchodilator responses but also by their protective effect to bronchoconstrictor stimuli such as inhaled methacholine. Large doses of inhaled salbutamol pMDI have been demonstrated to shift the methacholine dose-response curve by four- to eightfold (8). However, by using different drug doses, it may be possible to construct a dose-response curve of airway responsiveness versus dose of salbutamol. In this way, the relative protective potency may be determined for salbutamol when delivered from different devices, such as salbutamol pMDI and salbutamol Turbuhaler. The relative protective potency concept assumes that the curves are parallel. The differences of one curve relative to the other may be represented by a constant, which is a measure of the relative protective potency. Developing a method of estimating relative protective potency is important for comparing single dose therapy of salbutamol Turbuhaler with salbutamol pMDI.

The purpose of this study was to construct a dose-response curve of salbutamol pMDI against methacholine airway responsiveness and estimate the relative protective potency of salbutamol Turbuhaler compared with salbutamol pMDI with respect to the protective effect against methacholine bronchoconstriction.

PATIENTS AND METHODS

Subjects: Twenty-three adults with asthma volunteered to participate in the study (Table 1). Each subject's asthma was stable, forced expiratory volume in 1 s (FEV_1) was 70% predicted or greater and methacholine provocation concentration to cause a fall in FEV_1 of 20% (PC_{20}) was 4 mg/mL or less. In addition, after salbutamol pMDI 200 µg was inhaled, PC_{20} had to increase at least fourfold. Four subjects were on regular treatment with inhaled steroid (mean 837 µg daily dose) and the dose had been stable for at least three months, and was kept constant throughout the study; no study subjects were on treatment with beta-receptor antagonists, prednisone, antihistamine or immunotherapy. Before each study day the following washout periods were applied: long-acting inhaled beta-agonists for 72 h; oral beta-agonists for 12 h; long-acting oral beta-agonists and methylxanthines for 48 h; anticholinergics for 12 h. No patient was taking regular short-acting beta-agonists at the time of the study. Oral and parenteral corticosteroids were not permitted for one month before visit 1. None of the subjects had symptoms of a respiratory tract infection or exposure to allergens to which they were sensitized for six weeks before or during the study, and none had exercised vigorously before any study visit. The study was approved by the Hospital Research Ethics Committee, written informed consent was obtained for each subject, and the performance of the study was in accord with the principles of the Declaration of Helsinki.

Study design: The study was of randomized, double-blind, double-dummy, crossover and placebo controlled design. There were two enrolment days (visits 1 and 2) and seven study days (visits 3 to 9). At visit 1, informed consent was obtained. At visit 2, criteria for entry into the study were

TABLE 1
Demographic data and baseline pulmonary function of patients participating in the comparison study

Characteristics	Mean	Range
Sex (male:female)	3:20	
Age (years)	28.3	19-50
Height (cm)	167	152-190
Weight (kg)	67.7	51-91
Duration of asthma (years)	13.4	1-37
FEV_1 (L)	3.13	2.35-4.04
FEV_1 % predicted	92.8	75.8-114.2
Slow vital capacity (L)	3.93	2.66-6.25

FEV_1 Forced expiratory volume in 1 s

TABLE 2
Individual PC_{20} comparisons for salbutamol Turbuhaler and metered dose inhaler

Comparison	Ratio (%)	95% CI
TBH 50 µg vs pMDI 100 µg	75.7	55.9-102.6
TBH 100 µg vs pMDI 100 µg	95	70.0-128.7
TBH 100 µg vs pMDI 200 µg	66.3	48.9-89.9
pMDI 100 µg vs pMDI 200 µg	69.8	51.6-94.6
pMDI 200 µg vs pMDI 400 µg	58	42.8-78.6
pMDI 400 µg vs pMDI 800 µg	91.9	67.8-124.6

PC_{20} Methacholine provocation concentration to cause a fall in FEV_1 of 20%; pMDI Pressured metered dose inhalers; TBH Turbuhaler

checked. The baseline methacholine PC_{20} was measured and, if it was 4 mg/mL or less and if no salbutamol was required to treat the methacholine bronchoconstriction, the protective effect of salbutamol pMDI 200 µg was examined. The latter was determined 115 mins after the last inhalation of methacholine, if the FEV_1 was greater than 90% of baseline. If the FEV_1 was not greater than 90% of baseline, FEV_1 was measured every 15 mins until this value was reached. Then salbutamol pMDI 200 µg was inhaled, and 10 mins later the methacholine inhalation test was repeated, beginning with a twofold dose below the baseline methacholine PC_{20}. If the postsalbutamol methacholine PC_{20} increased by more than fourfold, the subject was entered into the study.

At visits 3 to 9, the protective effect of the study drugs on the methacholine PC_{20} was examined, and between these visits, salbutamol 100 µg was allowed only when needed. At each visit, the subject had to be stable as indicated by symptoms, need for salbutamol and an FEV_1 that did not vary by more than 10% from visit 2. If FEV_1 was lower than this, the subject was re-examined on another day; if it was still abnormal, the subject was withdrawn. The washout period between treatments was two to seven days.

At each visit, the subjects inhaled, in randomized order, salbutamol 50 or 100 µg by Turbuhaler, or 100, 200, 400 or 800 µg by pMDI, or placebo. The active medication and placebo were administered in a double-dummy fashion to maintain blinding. The methacholine inhalation test was repeated 10 mins later, beginning with a twofold dilution below baseline on visit 2 so that the methacholine PC_{20} value would be determined about 30 mins after inhalation of the test medication. On each day, pulse rate, blood pressure and history of symptoms were recorded before and after the methacholine test.

Spirometric measurements and methacholine tests: The FEV_1 and slow vital capacity (SVC) were measured with a Vitalograph Compact Spirometer (Vitagraph Ltd, Buckingham, United Kingdom) according to American Thoracic Society guidelines (9). Methacholine inhalation tests were performed as described by Juniper et al (10) using a Wright Nebulizer (English Wright, Aerosol Medical Ltd, Colchester, United Kingdom) attached to a three-way Hans Rudolph Valve (Hans Rudolph Inc, Missouri), doubling concentrations of methacholine between 0.6 and 256 mg/mL and tidal breathing for 2 mins. The response was measured by change in FEV_1 recorded at 30 and 90 s, and then at 3 mins and every 2 mins thereafter until it stopped falling. The fall was recorded between the highest post-test drug, premethacholine value and the lowest postmethacholine value. The results were expressed as the methacholine PC_{20} obtained from linear interpolation of the last two methacholine doses below and above a 20% fall in FEV_1. A methacholine PC_{20} value was obtained from each subject at each visit, so no data censoring was necessary.

Statistical analysis: A dose-response curve for the pMDI doses was established by estimating a nonlinear regression of log methacholine PC_{20} versus dose of salbutamol pMDI. The standard dose-response curve was represented by the following equation:

$$\log PC_{20} = \log PC_{20}\ (\text{placebo}) + \text{Max}\ D^k/(K^k + D^k)$$

where D is the dose of salbutamol, Max is the maximal effect, K is the dose giving 50% of the maximal effect (ED_{50}) and k was the slope parameter. The same model was applied for Turbuhaler, and a different K value was obtained which was called *r*K. This model assumes that each Turbuhaler dose lies on an individual curve that is parallel to the pMDI dose-

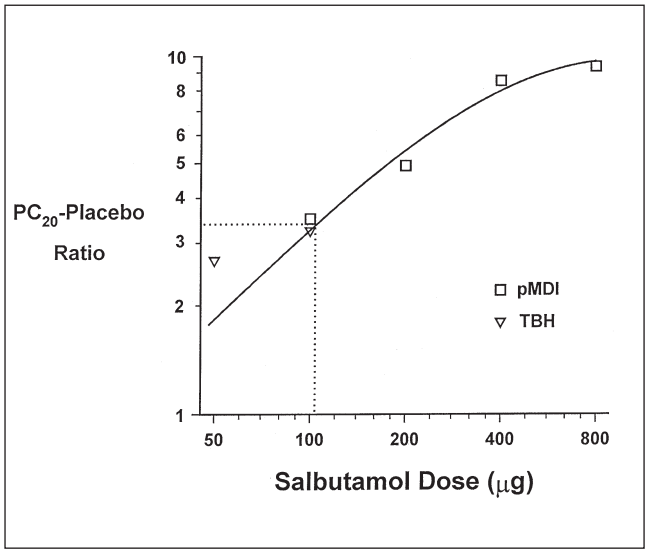

Figure 1) *Geometric mean methacholine provocative concentration causing a 20% fall in forced expiratory volume in 1 s (PC_{20}) ratio (adjusted relative to placebo) for salbutamol Turbuhaler (TBH) and pressurized metered dose inhaler (pMDI) following each salbutamol dose is shown on a logarithmic scale. Dose-response curve for salbutamol pressurized metered dose inhaler is shown by the solid line. The half-maximal response is represented by the dotted lines*

response curve. The relative dose potency was represented by the r value. Analysis of variance was used to obtain period-adjusted mean values and a correct variability. These data were then analyzed using nonlinear regression in order to estimate the r value and give confidence limits. For all analyses, a probability value of $P<0.05$ was considered significant. The adverse events were analyzed by means of descriptive statistics and qualitative analysis.

RESULTS

The mean baseline FEV_1 was 3.13 L, and the SVC was 3.93 L. The mean difference in baseline FEV_1 was 7.0% (range 3.0% to 13.2%) with a coefficient of variation (CV) of 2.7% (range 1.4% to 5.7%). The baseline PC_{20} was 1.8 mg/mL (range 0.4 to 3.8) and increased by 11.3-fold after two times 100 μg salbutamol pMDI to 17.0 mg/mL (range 4.6 to 56).

Increasing doses of salbutamol delivered by pMDI increased the methacholine PC_{20} in a dose-dependent fashion. The methacholine PC_{20} after placebo was 3.90 mg/mL (CV 128%). This increased to 13.3 mg/mL (CV 135%) after salbutamol 100 μg, to 19.0 mg/mL (CV 126%) after salbutamol 200 μg, to 32.6 mg/mL (CV 136%) after salbutamol 400 μg and to 35.1 mg/mL (CV 132%) after salbutamol 800 μg (Figure 1). The half-maximum response to pMDI (ED_{50}) was 104 μg (95% CI 63 to 171). Salbutamol delivered via Turbuhaler increased the methacholine PC_{20} to 10.0 mg/mL (CV 155%) after 50 μg and to 12.6 mg/mL (CV 124%) after the 100 μg dose. Salbutamol pMDI 200 μg provided significantly greater protection to methacholine than with either pMDI 100 μg or Turbuhaler 100 μg and was significantly different from pMDI 400 μg ($P<0.05$) (Table 2). There were no statistically significant differences when comparing Turbuhaler 100 μg with pMDI 100 μg, or Turbuhaler 50 μg with pMDI 100 μg. No further significant increase in PC_{20} was seen at 800 μg compared with 400 μg of salbutamol pMDI.

Nonlinear regression analysis revealed a relative dose potency of 1.38 (95% CI 0.67 to 2.87) for Turbuhaler 50 μg versus pMDI 50 μg, and 0.96 (95% CI 0.56 to 1.64) for Turbuhaler 100 μg versus pMDI 100 μg. This means that 50 μg from Turbuhaler on average would give the same protection against methacholine as 68.5 μg from pMDI (95% CI 33.6 to 105.9). Similarly, 100 μg from Turbuhaler on average would give the same protection as 96.9 μg from pMDI (95% CI 54.1 to 144.0).

Salbutamol was well tolerated at all doses. There were no significant adverse effects nor were there any significant changes in pulse rate or blood pressure.

DISCUSSION

This study has demonstrated the use of bronchoprotection against methacholine challenge as a method to determine relative protective potencies of different salbutamol formulations. The study suggests that the relative dose potency for salbutamol Turbuhaler was 1.36 at the 50 μg dose compared with pMDI and 0.96 at the 100 μg dose compared with pMDI.

A dose-response curve of methacholine PC_{20} versus doses of salbutamol was obtained for salbutamol pMDI. The ED_{50} response occurred at 104 μg which was close to the lowest dose of 100 μg. Methacholine PC_{20} increased significantly at doses of 100 μg, 200 and 400 μg, but did not change further with 800 μg. The demonstration of ED_{50} close to the lowest dose delivered by pMDI was unexpected and indicates that a major portion of the dose-response curve is located at 100 μg and below. Therefore, future studies could incorporate the use of lower doses of salbutamol pMDI (eg, 50 μg) to measure this part of the curve more accurately.

Studies have shown that Turbuhaler is effective in delivering a higher proportion of the nominal dose to the lungs compared with pMDI (11,12). In the present study, the relative dose protective potency of 0.96 for Turbuhaler 100 μg was not significantly different from that of salbutamol pMDI. Thus, Turbuhaler 100 μg would produce the same amount of bronchoprotection against inhaled methacholine as the pMDI. One explanation for this similarity could be a 'ceiling effect' where both devices produce the maximal possible bronchoprotection and, therefore, do not allow differences to be demonstrated between these devices. This is clearly not the case because a dose of 100 μg is close to the ED_{50}. This result does demonstrate the advantage of constructing dose-response curves, as was done in this study, because comparison of single doses from the two devices could not have eliminated this possibility.

Mildly asthmatic subjects (baseline methacholine PC_{20} of 1.8 mg/mL) with normal baseline pulmonary function were selected for this study. Dose-response curves may differ for asthmatics with moderate or severe asthma, or heightened

airway responsiveness. In these patients, pretreatment with salbutamol may produce additional bronchodilation that may interfere with the bronchoconstricting effects of methacholine. It is also possible that methacholine exerts its effect at locations different from the site of action of salbutamol when given by either Turbuhaler or pMDI or that there are differences in lung distribution pattern between Turbuhaler and pMDI. Several factors, such as inhalation pattern, airway calibre and degree of obstruction, have been shown to influence the site of deposition in the lung (13,14).

Because methacholine exerts its effects on the central airways, which are the main sites of the cholinergic receptors (15), the bronchodilating effects of a medication may not be representative of the protection it provides against a cholinergic bronchoconstrictor mediator, such as methacholine. This caveat also applies when comparing the results of the present study with those achieved using other provocation agents acting through other mechanisms.

CONCLUSIONS

This study has demonstrated that the relative dose protective potency of salbutamol given via Turbuhaler and via pMDI may be determined by comparing its effects on methacholine airway responsiveness. The relation between dose-protective potency obtained using other provocation agents, as well as the relation between protective and brochodilating potency, needs to be further investigated.

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