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The bronchodilator response from increasing doses of terbutaline inhaled from a multi-dose powder inhaler (Turbuhaler®)

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The bronchodilator response from increasing doses of terbutaline inhaled from a multi-dose powder inhaler (Turbuhaler®). G. Persson, J.E. Wirén.
ABSTRACT: Twelve adult asthmatics inhaled single doses of 0.5, 2.0 or 4.0 mg of terbutaline, respectively, *via* Turbuhaler, on three separate days. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and pulse rate were measured 15, 30, 45 and 60 min after inhalation from the inhaler and then hourly up to 8 h. The results showed that a more rapid onset of action, a greater maximal response and a longer duration of action can be achieved by exceeding the standard dose of terbutaline of 0.5 mg. The incidence of adverse effects was very low even at the highest dose, 4 mg. This study emphasizes the need for individual dosing of inhaled bronchodilators.
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Terbutaline is a selective $ß_2$-adrenoceptor agonist which is used as a bronchodilator. Recent dose response studies with inhaled terbutaline have shown that maximal bronchodilation is not achieved with the widely used dose of terbutaline of 0.5 mg [1, 2]. From a safety point of view it has been shown that a single dose of inhaled terbutaline sulphate of 4 mg does not cause any significant adverse effects [3].

The aim of this study was to compare the bronchodilator response in terms of magnitude and duration, achieved by three different single doses of terbutaline sulphate, inhaled from Turbuhaler [4].

Patients and methods

Thirteen patients were included in this double-blind, double-dummy, randomized study carried out on three separate occasions, at least 7 days apart. Twelve patients between 20 and 46 yrs of age (median 36.5 yrs) completed the study. All 12 patients fulfilled the following inclusion criteria: 1) age>18 yrs; 2) chronic stable asthma; 3) baseline forced expiratory volume in one second (FEV_1) <70% of predicted value; 4) improvement in FEV_1 >15% 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 or calcium channel blocker therapy; 5) insulin-dependent diabetes; 6) baseline variation of FEV_1 >15% between the three study days.One patient was withdrawn from the study because of baseline variation in FEV_1 exceeding 15% between the study days.

Theophylline, oral/inhaled beta-stimulants and anticholinergics were withdrawn 48, 12/8 and 48 h, respectively, prior to the study. Steroids and antihistamines were continued.

Bricanyl Turbuhaler delivering a metered dose of 0.5 mg of pure terbutaline sulphate, and corresponding placebo inhaler, were used in the study. Randomization was carried out using a computer programme. In randomized order, the bronchodilator response from three different doses of inhaled terbutaline sulphate was studied. The studied doses were 0.5, 2.0 and 4.0 mg.

On each study day the patients performed a total of eight inhalations at 30 s intervals according to the following scheme:

Treatment	Inhaler 1 (1 inhal.)	Inhaler 2 (3 inhal.)	Inhaler 3 (4 inhal.)
0.5 mg	active	placebo	placebo
2.0 mg	active	active	placebo
4.0 mg	active	active	active

Pulse rate, followed by FEV_1 and forced vital capacity (FVC) (best of 3), was measured before inhalation and then 15, 30, 45 and 60 min and then hourly until 8 h after treatment. The measurements were stopped before 8 h after treatment if both FEV_1 and FVC had returned to baseline values plus 5%. A Vitalograph® dry-bellows spirometer was used to measure FEV_1 and FVC. Pulse rate was measured by palpation of the radial artery.

Immediately before the lung function measurements the patients were asked for subjective adverse effects (tremor, headache, palpitations and other adverse effects)

according to the following score system: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Editing of data was performed before breaking the study code. For measured variables, comparisons of change *versus* baseline were made using a parametric analysis of variance (ANOVA) model. Scored and counted variables were analysed by non-parametric methods based on ranks. Area under curve (AUC) was calculated using the trapezoidal rule.

The study was approved by the local Ethics Committee and was performed according to the Declaration of Helsinki. The informed verbal consent of the patients was obtained.

Results

FEV_1

There were statistically significant differences between 0.5 and 2.0 mg of terbutaline up to 1 h after inhalation and statistically significant differences between 0.5 and 4.0 mg throughout all of the measurements (fig. 1 and table 1). No statistically significant differences were found between 2.0 and 4.0 mg of terbutaline. For the FEV_1 measurements at 8 h, two patients were not back to baseline values after 0.5 mg of terbutaline, five were not back to baseline values after 2.0 mg, and four were not back to baseline values after 4.0 mg.

FVC

The increase in FVC was relatively small, being maximally 8% after 0.5 mg of terbutaline, 14% after 2.0 mg, and 13% after 4.0 mg. No statistically significant differences were found between the three treatments.

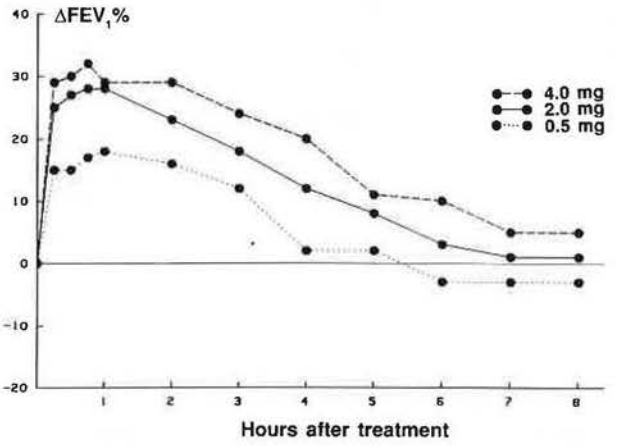

Fig. 1. – FEV_1 differences from baseline (%) after inhalation of 0.5, 2.0 and 4.0 mg of terbutaline sulphate. FEV_1: forced expiratory volume in one second.

Pulse rate, adverse effects

The AUC for pulse rate was 76.5 after inhalation of 0.5 mg of terbutaline, 77.9 after 2.0 mg, and 86.0 after 4.0 mg.

The corresponding AUCs for tremor were 0, 0.02, and 0.20, respectively, and for palpitations 0.01, 0, and 0.13. As regards pulse rate, tremor and palpitations, the 4.0 mg AUCs were significantly different both when compared with the 0.5 mg AUCs ($p<0.05$) and the 2.0 mg AUCs ($p<0.05$). The differences between 0.5 and 2.0 mg were not significant.

The AUC for restlessness was 0, 0 and 0.03 after 0.5, 2.0 and 4.0 mg, respectively. The corresponding AUC values for headache were 0.05, 0.30 and 0.23, respectively. There were no statistically significant differences between the treatments as regards restlessness and headache.

Table 1. – FEV_1 before and after inhalation of terbutaline sulphate

	0.5 mg	2.0 mg	4.0 mg	Comparison between treatments		
Time	mean (SEM) *l*	mean (SEM) *l*	mean (SEM) *l*	0.5–2.0 mg	0.5–4.0 mg	2.0–4.0 mg
0 (baseline)	2.18 (0.16)	2.18 (0.17)	2.21 (0.15)	NS	NS	NS
15 min	2.51 (0.15)	2.73 (0.15)	2.84 (0.14)	*	**	NS
30 min	2.51 (0.15)	2.77 (0.14)	2.88 (0.15)	*	***	NS
45 min	2.56 (0.17)	2.79 (0.15)	2.91 (0.13)	*	***	NS
1 h	2.57 (0.15)	2.78 (0.14)	2.85 (0.13)	*	**	NS
2 h	2.52 (0.16)	2.68 (0.18)	2.85 (0.13)	NS	*	NS
3 h	2.45 (0.17)	2.58 (0.19)	2.75 (0.13)	NS	**	NS
4 h	2.22 (0.19)	2.45 (0.20)	2.64 (0.16)	NS	**	NS
5 h	2.22 (0.19)	2.35 (0.19)	2.46 (0.17)	NS	*	NS
6 h	2.12 (0.19)	2.25 (0.20)	2.42 (0.16)	NS	**	NS
7 h	2.11 (0.19)	2.17 (0.19)	2.33 (0.16)	NS	*	NS
8 h	2.11 (0.19)	2.16 (0.20)	2.33 (0.17)	NS	*	NS

FEV_1: forced expiratory volume in one second; NS: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

Only one patient had comments on other adverse effects. This patient felt dizzy after both the 2.0 and 4.0 mg treatment.

Discussion

The present study of terbutaline inhaled *via* Turbuhaler showed that maximal bronchodilation is not always achieved by one dose. This is in agreement with the findings in a study where terbutaline was inhaled from a metered dose inhaler with a tube-spacer by patients with severe asthma [5]. Studies with salbutamol have also shown that maximal bronchodilatation is not always achieved by the recommended dose [6, 7].

It is of great importance to get a high degree of bronchodilation early after inhalation of a bronchodilating agent. In this study, a mean increase in FEV_1 of 15% was found 15 min after inhalation of 0.5 mg of terbutaline, whereas an increase in FEV_1 of 25% and 29% was found 15 min after inhalation of 2.0 and 4.0 mg of terbutaline, respectively. This difference might be of importance, especially to patients with moderately to severely impaired lung function and in acute situations. A higher dose of terbutaline than the recommended 0.5–1.5 mg might, therefore, be of value in such cases.

In this study, the peak FEV_1 value was also reached earlier with 2.0 and 4.0 mg of inhaled terbutaline as compared to 0.5 mg. However, the within dose differences between the FEV_1 values after 15, 30, 45 and 60 min were so small that they are not likely to be of any clinical significance.

If an FEV_1 value, that is at least 10% above the baseline value, is taken as an indication of remaining bronchodilator action of the inhaled agent, the bronchodilation lasted on average 3 h after inhalation of 0.5 mg of terbutaline, 4 h after 2.0 mg, and 6 h after 4.0 mg. Thus, the duration of action of inhaled terbutaline powder can be prolonged by increasing the dose. The same results have been found with salbutamol [7]. However, because of interindividual differences the duration of action can not be predicted from this study but must be evaluated clinically in the individual patient.

Skeletal muscle tremor, tachycardia and palpitations are well-known extrapulmonary effects of $ß_2$-agonist therapy [8]. Such effects can be minimized by use of the inhaled route which delivers the drug predominantly to the airways. The incidence of adverse effects in this study was very low. Tremor was non-existent with the lowest dose of terbutaline and increased to only 0.2 on a 3 grade scale with the 4.0 mg dose. Pulse rate increased by ten beats per min from the lowest to the highest dose. This increase is likely to be acceptable to most patients in most situations.

In conclusion, this study of terbutaline inhaled *via* Turbuhaler showed that a more rapid onset of action, a greater maximal bronchodilation, and a longer duration of action can be achieved by exceeding the recommended dose. The incidence of adverse effects was still very low with the highest dose in this study, 4.0 mg. This study, thus, emphasizes the need for individual dosing of inhaled bronchodilators.

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Réponse bronchodilatatrice à des doses croissantes de terbutaline en provenance d'un Turbuhaler (inhalateur multi-dose de poudre). G. Persson, J.E. Wirén.
RÉSUMÉ: Douze asthmatique adultes ont inhalé des doses uniques de 0.5 mg, 2.0 mg et 4.0 mg de terbutaline, respectivement, par l'intermédiaire d'un Turbuhaler à trois jours séparés. Le ventilation expiratoire maximal seconde (VEMS), la capacité vitale forcée et le pouls, ont été mesurés 15, 30, 45 et 60 minutes après l'inhalation du Turbuhaler, et ensuite toutes les heures jusqu'à 8 h. Les résultats ont montré un début d'action rapide, une réponse maximale plus élevée et une action plus durable, lorsque l'on dépasse la dose standard de 0.5 mg de terbutaline. L'incidence des effets collatéraux reste très faible, même à la dose la plus élevée de 4 mg. Cette étude fait ressortir la nécessité d'un dosage individuel des bronchodilatateurs administrés par inhalation.
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