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Terbutaline *via* pressurised metered dose inhaled (P-MDI) and Turbuhaler® in highly reactive asthmatic patients

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Terbutaline via *pressurised metered dose inhaled (P-MDI) and Turbuhaler in highly reactive asthmatic patients. L. Jackson, E. Ståhl, S.T. Holgate. ©ERS Journals Ltd 1994.*
ABSTRACT: There is some concern over the environmental consequences of chlorofluorocarbons (CFCs) used in pressurized metered-dose inhalers (p-MDIs). Turbuhaler® was designed to deliver a drug as a dry powder without administering additives directly to the airways. The aim of this study was to evaluate the comparative irritant and bronchodilating effects of the same dose of terbutaline delivered by a p-MDI and *via* Turbuhaler®.

Ten symptomatic, asthmatic patients, with highly reactive airways (provocative concentration of methacholine producing a 20% fall in forced expiratory volume in one second (PC_{20}) <0.2 mg·ml^{-1}), inhaled, on separate days, 0.25 mg terbutaline *via* p-MDI or Turbuhaler®. Changes in airway calibre were followed as specific airways conductance (sGaw). On a third day, patients inhaled from a placebo p-MDI containing all constituents except terbutaline. The study was conducted in a single-blind fashion and in random order. There were no significant differences in baseline sGaw on any of the study days.

Inhalation of terbutaline from the p-MDI produced a transient percentage fall in sGaw at 1 min, reaching a mean maximum ± SD of 17±8% at 10 s and then returning to baseline value after 20 s, followed by a progressive increase in sGaw to a maximum of 39±45% above baseline at 45 min. In contrast, inhalation of terbutaline *via* Turbuhaler® caused no significant bronchoconstriction (fall in sGaw, 3±16%) at 10 s and achieved a greater increase in sGaw, reaching 63±51% at 45 min, although just failing to reach statistical significance compared to terbutaline p-MDI inhalation. The placebo p-MDI caused a 16±15% fall in sGaw at 10 s, with values not returning to baseline until after one minute

The present study showed that in highly reactive patients, inhalation of terbutaline *via* Turbuhaler® is an alternative to p-MDI, to avoid paradoxical bronchoconstriction.
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The most effective bronchodilator agents known for treatment of asthma are the β_2-agonists, when administered by inhalation. Broadly speaking, there are three drug formulations allowing topical delivery of these drugs, aqueous solutions given by nebulizers, suspensions in pressurized metered-dose inhalers (p-MDIs), and dry powder inhalers. The p-MDI and dry powder formulations are the most practical for regular low dose use.

The use of p-MDI is a convenient and effective way of administering bronchodilators, but the method suffers from the disadvantage of requiring patient co-ordination to optimize bronchodilator responses [1]. In addition, p-MDIs contain chlorofluorocarbon (CFC) propellants (usually CFC-11, -12 and -114) and surfactants, including oleic acid, sorbitan trioleate and soy lecithin. Whilst these agents have all been subjected to extensive toxicological studies and are regarded as safe, asthmatic patients do, in fact, experience some side-effects, ranging from cough [2] to paradoxical bronchoconstriction which, on occasions, may be severe [3, 4]. Even with one of the latest long-acting β_2-agonists, salmeterol administered *via* p-MDI, paradoxical bronchoconstriction has been reported in susceptible patients [5] and, as with excipients present in inhaled anticholinergic drugs [6], this may interfere with the clinical efficacy of the drug.

Dry powder inhalers provide an alternative formulation for delivering drugs to the airways. For both bronchodilator and nonbronchodilator drugs, the active agent is mixed with an excipient, usually lactose, to facilitate dispersion of the particles. The Turbuhaler® dry powder device allows a multi-dose delivery of a drug, such as terbutaline and budesonide, in the absence of added carriers [7].

The present study was designed to evaluate the effects of terbutaline on airway calibre in highly reactive asthmatics, when the same dose was administered *via* p-MDI and Turbuhaler®. Airway calibre, measured as specific airway conductance (sGaw) were followed

continuously, so that the effects of the two formulations could be observed during the immediate period postinhalation when paradoxical bronchoconstriction may occur. The study design was placebo-controlled and single-blind.

Patients

The study was of a single-blind, randomized, crossover design and carried out on three separate days with an interval of at least 2 days between study days. The study was approved by the Ethics Committee of the University of Southampton, UK. Ten asthmatic patients (3 males and 7 females) with highly reactive airways were selected. Their airway condition was defined as a provocative concentration of methacholine producing a 20% fall in forced expiratory volume in one second (PC_{20}) ≤ 0.2 mg·ml^{-1} and a diurnal variation of peak expiratory flow of >15%. All 10 patients used short-acting inhaled β_2-agonists on a regular basis, and nine of them also required inhaled regular corticosteroids for symptom control (table 1). The mean age of the patients was 42 yrs (range 19–66 yrs) and their mean duration of asthma was 33 yrs (range 15–50 yrs). Regular anti-asthma medication was withdrawn prior to each study period: inhaled β_2-agonists 6 h, oral β_2-agonists 8 h, oral controlled release β_2-agonists 12 h, and oral theophylline and anticholinergics 48 h. Concomitant prophylactic treatment with inhaled corticosteroids and sodium cromoglycate was allowed to continue throughout the study period.

Methods

Measurement of airway calibre

Specific airway conductance (sGaw) was measured on each occasion using a constant volume whole body plethysmograph (Fenyves and Gut, Basel, Switzerland) on line to a microcomputer that computed airways resistance (Raw) and thoracic gas volume (TGV) use, from which values of sGaw were derived. This equipment also enabled pulmonary function measurements to be made at 10 s intervals using 10 breaths to acquire mean values. After obtaining steady baseline levels of sGaw, patients inhaled 0.25 mg terbutaline *via* p-MDI or Turbuhaler®, or placebo from a p-MDI. The placebo p-MDI used in the study, contained the same propellants as the active drug. Specific airways conductance was measured at 10 s intervals for the first 2 min and, thereafter, at regular intervals up to 45 min postinhalation.

Statistical analysis

Changes in airway calibre were expressed as Δ-sGaw to take account of the inverse relationship between Raw and TGV. Values of sGaw postinhalation were expressed as percentages of the mean baseline values. The postinhalation bronchoconstriction was quantified as the fall in sGaw at 10 s and the area under the curve of sGaw *versus* time (AUC) between 0–1 min. The bronchodilator response was expressed as the increase at 45 min postinhalation and the AUC between 1 and 45 min. Comparisons between treatments were performed on AUC values and maximum percentage fall within one minute, using fixed effects analysis of variance (ANOVA) models on ranked values, with the factors patient, treatment and visit. Ranked values were used in order to avoid dependence on distributional assumptions. In all statistical tests, two-tailed alternatives were considered and the significance level was 5%.

Results

The geometric mean PC_{20} for the group was 0.11 (range 0.04–0.20) mg·ml^{-1}. The baseline mean values

Table 1. – Demographic data

Patient No.	Sex	Age yrs	Height cm	Weight kg	Duration of asthma yrs	PC_{20} methacholine mg·ml^{-1}	Concomitant medication
1	F	66	157	60.0	46	0.08	IB
2	F	39	159	57.5	35	0.07	IB, IS
3	F	30	154	55.5	25	0.09	IB, IS
4	F	43	168	69.8	41	0.16	IB, IS
6	F	19	165	60.0	18	0.04	IB, IS, OB, C
7	M	60	182	99.5	20	0.14	IB, IS
8	M	19	177	81.5	15	0.20	IB, IS
9	F	52	159	80.0	50	0.13	IB, IS
10	M	40	171	69.5	36	0.6	IB, IS
11	F	48	174	65.0	40	0.17	IB, IS, T
Mean		42	167	69.8	33	0.11	
SD		16	9	13.7	12.3	0.05	
Min		19–66	154–182	55.5–99.5	15–50	0.04–0.20	

Patient No. 5 was never treated. PC_{20}: provocative concentration of methacholine producing a 20% fall in forced expiratory vol-

of sGaw on the terbutaline p-MDI, Turbuhaler® and placebo p-MDI days were 0.82, 0.80, and 0.81 $kPa \cdot l \cdot s^{-1}$ respectively, which were not significantly different. Inhalation from all three inhalers caused a detectable fall in sGaw that was apparent within the first 10 s and diminished thereafter (fig. 1). When compared to the preinhalation baseline, terbutaline inhaled *via* the p-MDI produced at 10 s postinhalation a 17±8% (mean± SD) fall in sGaw, compared to 3±16% after the terbutaline Turbuhaler® and 16±15% after the placebo p-MDI.

The mean maximum percentage decrease within one minute was 2±8% after terbutaline p-MDI, 6±16% after terbutaline Turbuhaler®, and 25±15% after placebo p-MDI. There was a statistically significant difference in maximum percentage fall in sGaw within one minute between the three treatments (p=0.038), with the major difference between Turbuhaler® and placebo p-MDI (p=0.015). The time course of the constrictor response also differed between the three treatments, showing the greatest deviation for the placebo p-MDI and least with Turbuhaler®. When quantified as the $AUC_{0-1\ min}$, there was a statistically significant difference in mean values between the treatments (p=0.017), with the source of differences being found between the two active treatment and placebo p-MDIs (for terbutaline Turbuhaler® *vs* placebo p-MDI p=0.007, and terbutaline p-MDI *vs* placebo p-MDI p=0.027), but not between the two active treatments.

The two active terbutaline, but not the placebo inhalations, had a marked effect in increasing sGaw. After terbutaline *via* p-MDI, the mean increase in sGaw was not apparent until 30 s postinhalation, beyond which values progressively increased to a mean maximum of 39±45% above baseline at 45 min. Terbutaline *via* Turbuhaler® produced an almost immediate bronchodilating response to reach a mean maximum 63±51% increase at 45 min. By contrast, the placebo p-MDI inhalation produced no significant change in sGaw between 1 and 45 min. When the three treatments were compared, there was a statistically significant difference in the mean values of AUC (p=0.0001), with a source of difference being found between the two active treatments and placebo (p=0.10).

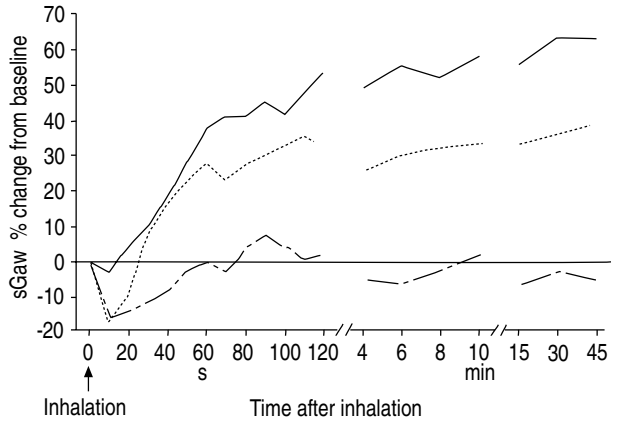

Fig. 1. – Mean percentage change in specific airway conductance (sGaw) from baseline in 10 hyperreactive asthmatic patients following inhalation of terbutaline *via* Turbuhaler®. (—) and pressurizes metered dose inhaler (P-MDI) (----) compared to the response to placebo by P-MDI (—·—). Each value represents the mean of 10 observations.

Discussion

Using a sensitive measure of airway calibre, sGaw, we have confirmed that a "short-acting" β_2-agonist, terbutaline, when administered by inhalation from a p-MDI to hyperreactive asthmatic patients, caused a transient bronchoconstriction before the onset of measurable bronchodilation. A similar degree of bronchoconstriction was observed when the excipients in the p-MDI were administered in the absence of terbutaline, suggesting that the paradoxical response was caused by the additives rather than the active drug. This is further supported by showing that terbutaline, when administered as pure drug through Turbuhaler® in the absence of any additives, had no significant bronchoconstrictor effect, and although just failing to reach statistical significance, seemed to cause a greater degree of bronchodilation when compared to the p-MDI formulation.

Paradoxical bronchoconstriction, when it happens following administration of an inhaled drug formulation in patients with asthma, occurs immediately after inhalation. We chose whole body plethysmography as the optimum method to follow changes in airway calibre for two reasons. Firstly, using the on line computerized analytical system, linked to the plethysmograph, we could obtain measurements at 10 s intervals for the immediate period following inhalation. Secondly, in selecting patients with a high level of bronchial hyperresponsiveness, repeated deep inspiration, followed by forced expiration used for spirometry, may in itself produce bronchoconstriction.

Both the terbutaline and placebo p-MDI formulations caused a similar transient fall in sGaw that reached a maximum within the first 10 s of inhalation. The exact mechanisms of this paradoxical constrictor response are not known for certain, but the response is probably related to the inhalation of nondrug additives, since it was minor when terbutaline (in pure drug form) was administered in the same dose *via* Turbuhaler®. In a study involving orciprenaline, as the active drug administered by the p-MDI, YARBROUGH *et al.* [8] concluded that the propellants, which accounted for the transient bronchospastic response observed, caused a fall in FEV_1 of 10% or more from baseline in 6.9% of the asthmatic subjects in the study. The bronchoconstriction after inhalation had a duration between 3–5 min. However, some patients experienced bronchospasms up to 30 min after. The authors suggested that the bronchoconstricting activity of the inactive agents may overwhelm the bronchodilating properties of the active ones. In addition, a case report indicates that paradoxical bronchoconstriction occurred after nebulized albuterol, but not with terbutaline. This means that paradoxical bronchoconstriction to β_2-agonists is not inevitably a class-effect, but can be related to exposure to a specific β_2-agonist and not to others [9]. In a detailed appraisal of the problem, ENGEL *et al.* [10] concluded that a rapid cooling of the upper airways produced with CFCs, plus the irritant effect

of the nondrug components, were producing the paradoxical constrictor response.

Although the mean maximum fall in sGaw was similar following inhalation of terbutaline and placebo *via* p-MDI after placebo, the effect lasted longer and was not followed by bronchodilation. Thus, it is likely that the onset of bronchodilation, resulting from the terbutaline, competed with any constrictor response by functional antagonism to prematurely terminate the postinhalation constrictor response. In support of this conclusion is the recent observation of quite marked bronchoconstriction that may occur in moderately severe asthmatics when they inhale salmeterol *via* the p-MDI [5]. Salmeterol is a long acting β_2-agonist with a slower onset of action than the short-acting drugs, salbutamol and terbutaline, thereby giving a larger window for paradoxical bronchoconstriction to occur before being overtaken by β_2-receptor functional antagonism. Interestingly, in this study, salmeterol, administered in the same dose *via* a dry powder inhaler, did not cause bronchoconstriction despite the presence of a large amount of nondrug carriers in the Diskhaler dry powder formulation. The short duration of bronchoconstriction in the present study could be explained by the fact that forced expiratory tests were avoided. Three to five minutes duration was mentioned as short in the study by YARBROUGH *et al*. [8], but when compared, in our study the duration of bronchoconstriction was even shorter being approximately 1 min duration. In the present study, sGaw was chosen to avoid possible artefacts of forced expiration.

Other side-effects reported when using p-MDIs are cough and wheezing. In a study by SHIM and WILLIAMS [11], inhalation of beclomethasone p-MDI gave a decline in forced expiratory volume in one second (FEV_1) which was attenuated when pre-treatment with a β_2-agonist was given. In another study, also by SHIM and WILLIAMS [12], beclomethasone p-MDI was compared with triamcinolone p-MDI This study showed that cough and wheezing occurred after inhalation of beclomethasone p-MDI but that this was not the case after triamcinolone p-MDI. It was suggested that oleic acid was the most likely source of irritation in the tracheobronchial tree, causing cough and bronchoconstriction either by reflex or direct effect.

Of particular interest is the almost total absence of any postinhalation bronchoconstriction observed with terbutaline *via* Turbuhaler®. Moreover, the rate of onset and the maximum increase in sGaw was greater with this formulation than with the same dose administered *via* the p-MDI, although it failed to reach statistical significance, possibly because of the limited number of patients. Thus, it would appear that the administration of pure drug *via* Turbuhaler® has distinct advantages over the p-MDI formulation, both in terms of adverse events and possibly efficacy.

With the phasing-out of CFCs by 1995, to meet the International Ruling relating to the Environment, alternative forms of volatile propellant are being sought. However, it is most unlikely that these propellants will complete their toxicological and safety evaluation within this time-frame and, thus greater reliance will have to be placed on dry powder drug delivery systems. During the intervening period of p-MDIs, containing non-CFCs, it would be timely to carefully assess whether nonirritant additives could replace those currently in use. In the case of ipratropium bromide administered by an aqueous aerosol, concern expressed about the irritant properties of ethylene diamine tetra-acetic acid (EDTA) and benzalkonium chloride, has led to the removal of these nondry components, and, as a consequence, improved clinical efficacy [3].

In conclusion, the present study showed that in highly reactive patients, inhalation of terbutaline *via* Turbuhaler® is an alternative to p-MDI when considering avoidance of paradoxical bronchoconstriction.

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