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RAPID COMMUNICATION

A multicentre comparison of the efficacy of terbutaline Turbuhaler™ and salbutamol pressurized metered dose inhaler in hot, humid regions

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A multicentre comparison of the efficacy of terbutaline Turbuhaler™ and salbutamol pressurized metered dose inhaler in hot, humid regions. D.A. Lindsay, N.L. Russell, J.E. Thompson, T.H. Warnock, I.D. Shellshear, P.R. Buchanan. ©ERS Journals 1994.

ABSTRACT: Twenty seven adults and 20 children with previously diagnosed stable asthma, using a salbutamol pressurized metered dose inhaler (P-MDI) and living in Cairns, Townsville and Southport, Queensland, Australia participated in a randomized, open-label cross-over comparison of terbutaline administered *via* Turbuhaler™ and salbutamol administered *via* P-MDI. The aim of the study was to compare the clinical effectiveness and patient acceptance of the two treatments in hot, humid regions.

Terbutaline was administered *via* Turbuhaler and salbutamol *via* P-MDI on at least two occasions per day during each four week treatment period. Spirometry was performed at the start of the study, after the two week run-in and at the end of each treatment period. Patients used diary cards to record morning and evening peak expiratory flows, daily symptom scores and daily intake of β_2 agonist medication. At the end of the study, patients answered a treatment preference question.

Forty six patients completed the study. No statistically significant differences were observed between the two treatments in peak expiratory flow, change in morning peak expiratory flow pre- and post-beta-agonist, daily symptom scores, diurnal variability and spirometry. Forty four percent of patients preferred the terbutaline Turbuhaler and 39% preferred salbutamol P-MDI. Both agents were similarly tolerated.

Terbutaline delivered by Turbuhaler is as clinically effective as salbutamol delivered by P-MDI in patients with asthma living in hot, humid regions.

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Inhalation of β_2-agonist aerosol produced by a conventional pressurized metered dose inhaler (P-MDI) is an effective method of delivering the drug directly to the large surface area of the tracheobronchial tree and alveoli. However, despite adequate tuition, many patients are unable to use a pressurized inhaler efficiently. Failure to co-ordinate inhaler actuation with inspiration is the most important error, since patients must time their inhalation correctly in order to catch the rapidly moving bolus of aerosol [1–3]. Pressurized inhalers also contain chlorofluorocarbon propellants and lubricants, which may cause bronchoconstriction [4].

The Turbuhaler is a breath-actuated dry powder inhaler, which has been designed to overcome these problems. Bricanyl™ Turbuhaler has been subjected to extensive quality assurance testing and has proved to be robust with an approved shelf-life of 2 yrs. Terbutaline sulphate is not hygroscopic, but being water soluble it has to be protected against exposure to extreme moisture, which might affect the dosing characteristics. To prevent any hardening of the drug aggregates in humid conditions, Turbuhaler is fitted with a protective sleeve that screws on to the base, making the device watertight. Dessicant is stored in the base of Turbuhaler, which keeps the interior dry and ensures drying capacity for two year's storage, with opening and closing of the device. Variations in temperature and relative humidity over this time do not affect performance [5]. Although it has been shown that the bronchodilating effect of the Bricanyl Turbuhaler is not affected when used in humid climates with a mean monthly temperature range of -3.5°C to 15.7°C and relative humidities ranging 59–95% [6], it was considered that the device should be tested in the clinical setting in the extremes of both high temperature and high relative humidity, as experienced in northern Australia.

The aim of this study was to compare the clinical effectiveness and patient acceptance of terbutaline delivered *via* Turbuhaler and salbutamol *via* pressurized metered dose inhaler in hot, humid regions.

Patients and methods

Adults and children (≥7 yrs) with previously diagnosed asthma (American Thoracic Society criteria [7]) were recruited from three adult and two paediatric clinics. All patients had stable asthma, as defined by: no office visits for asthma exacerbation, no emergency room visits or hospitalizations due to asthma, or use of antibiotics for asthma or respiratory illness in the three weeks preceding entry into the study. Patients were judged as having asthma of at least moderate severity with a need to use salbutamol P-MDI as beta-agonist therapy on two or more occasions per day, in addition to their other asthma therapy. They were capable of measuring and recording peak flows and of charting symptoms and treatment. All patients/parents gave written informed consent. The study was approved by the Townsville General Hospital Ethics Committee for all five centres in Cairns, Townsville and Southport and conducted according to Good Clinical Research Practice [8].

Study design

A randomized, open-label, cross-over design was used, comparing terbutaline *via* Turbuhaler with salbutamol *via* P-MDI. The study was carried out over two sequential four week treatment periods after a two week run-in period, during which the patients continued their usual medication whilst measuring and charting peak expiratory flows and symptom scores and recording daily intake of β_2-agonist medication. The period chosen for the investigation was December 1991 to May 1992. During patient treatment days, at the three meteorological centres in Cairns, Townsville and Southport, the mean minimum and maximum temperatures were 22°C and 30°C, respectively, (range 14–39°C). The 9 a.m. mean relative humidity was 71% (range 41–98%), whilst the 3 p.m. mean relative humidity was 61% (range 25–98%). The maximum relative humidity was ≥70% for 95%, 68% and 46% of patient treatment days at Cairns, Southport and Townsville, respectively.

Previous studies have shown that terbutaline, 0.5 mg, given *via* a P-MDI is equipotent to salbutamol, 0.2 mg, given *via* a P-MDI [9, 10]. Inhalation of 0.5 mg terbutaline *via* Turbuhaler has been shown to be equipotent to 0.5 mg terbutaline *via* a P-MDI [11–14].

Terbutaline was administered at a dose of 1×0.5 mg inhalation each morning and evening and 0.5 mg (one inhalation) at other times, when required to relieve symptoms of asthma. Salbutamol was given at a dose of 2×0.1 mg puffs each morning and evening and 2×0.1 mg puffs as required at other times. Dosing of both drugs could be repeated every 4 h as necessary.

Patients were given verbal and written instructions on the correct use of both the salbutamol P-MDI and terbutaline Turbuhaler. Inhaler technique was checked at each clinic visit. Patients unable to perform the correct inhaler technique reliably with either inhaler were not included in the study.

No other β_2-agonist or nebulized therapy were allowed. Treatment with oral or other inhaled bronchodilators, including anticholinergics and theophylline, was allowed provided that their doses remained constant throughout the study. Other anti-inflammatory medications, such as inhaled and oral glucocorticosteroids were allowed provided that their doses remained constant throughout the study.

Morning and evening peak expiratory flow rates were measured (best of three) before and 15 min after administration of the β_2-agonist using a mini Wright peak flow meter. Patients were instructed, whenever possible, to withhold their β_2-agonist dose for at least 4 h prior to measuring the initial morning and evening peak expiratory flow (PEF). Symptoms of wheeze, cough, sleep disturbance and breathlessness on exertion were recorded each evening for the previous 24 h, according to the following scale (0=none, 1=mild, 2=moderate, 3=severe). All β_2-agonist medication taken over the preceding 24 h was also recorded.

Diurnal variability (DV) in PEF, was calculated for each patient, using the following formula:

$$\text{DV PEF \%} = \frac{\text{PEF best - PEF worst}}{\text{PEF best}}$$

Spirometric assessment of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) was made at each clinic visit at the beginning, end of the run-in and at the end of each treatment period. At the end of the study, patients were asked to state their preference for the devices used and to provide a reason for this preference.

Adverse events were recorded at each clinic visit during the study.

Statistical analysis

The calculation of sample size was based on a mean difference in % predicted normal PEF between the treatments of 7%, a standard deviation of 15% and power of 80%. Under these conditions, 40 patients were required to complete the study. SAS statistical package, version 6.06 was used to perform the statistical analysis. The primary efficacy analysis was on all patients who received at least one dose of study drug (all-patients-treated approach) and who completed both treatment periods (n=45). A per-protocol analysis was also carried out for the primary efficacy variable. As there was no difference between the all-patients-treated and the per-protocol analyses, only the results of the all-patients-treated analysis are included in this paper. The values at the end of each treatment period were compared using paired t-tests. In the analysis of diary card data, (PEF, differences between morning PEF pre-and post-β_2-agonist (ΔPEF), symptoms and β_2-agonist dose), the mean values for the last 14 days of each period were used. For the primary efficacy variable, morning PEF pre-β_2-agonist (expressed as % predicted) [15, 16], a test for possible carry-over effects was also carried out, which included the factors of sequence, treatment and patient. The preference data were analysed using a Chi-squared test of association.

Results

Twenty seven adults (15 females and 12 males) aged 51±11 (mean±SD) yrs (height 166±8 cm and weight 72±13 kg) and 19 children (6 girls and 13 boys) aged 11±2 yrs (height 146±15 cm and weight 39±13 kg) randomly assigned to the two treatment groups, completed the study. All patients had previously diagnosed asthma, with a need to use β_2-agonist therapy on at least two occasions per day, and had demonstrated at least 15% reversibility in FEV_1 or PEF in response to bronchodilator prior to commencement of the study. All but three patients were treated with concomitant asthma therapy during the study (table 1). Sixteen patients violated the protocol by altering their prescribed concomitant therapy during the study, thereby excluding them from the per-protocol analysis. The majority of these patients required additional oral or inhaled steroids for treatment of asthma exacerbations.

One child failed to attend clinic visits after completing five weeks of study treatment, for reasons unrelated to the study and was withdrawn. Three children were hospitalized for exacerbations of asthma, two during the salbutamol treatment period and one during the terbutaline period. However, all three patients completed treatment in the study. All four children were excluded from the per-protocol analysis.

No carry-over effect was detected for the primary efficacy variable. Comparison of diary card data for PEF, ΔPEF, symptom scores and diurnal variability after the two treatment periods showed no statistically significant differences between terbutaline Turbuhaler and salbutamol P-MDI (table 2). For cough symptoms, there appeared to be a trend in favour of terbutaline, as the result approached statistical significance (p=0.06). A formal comparison of mean PEF at the end of the run-in, to the mean at the end of each treatment period, was not performed. However, there did not appear to be any change in lung function during the study as mean morning PEF values pre-β_2-agonist (expressed as % predicted) were 78.8, 78.5 and 79.1 for the run-in, terbutaline and salbutamol periods, respectively. The mean difference between terbutaline and salbutamol was -0.6, (95% confidence interval (CI) -2.6 to 1.5; p=0.6). The standard deviation of the difference was 7%, which resulted in this study having a power of 80% to detect a mean difference of 3%. Nonparametric tests were also performed; these gave the same p-value. Mean differences between morning PEF pre- and post-β_2-agonist (ΔPEF), were 11.6, 10.5 and 11.3. for the run-in, terbutaline and salbutamol periods, respectively, indicating that there was no difference in the bronchodilator effect of both treatments. The mean difference between terbutaline and salbutamol was -0.8, (95% CI -2.4 to 0.7; p=0.28). There were no statistically significant differences between the treatments for clinic visit spirometry (table 2). The mean (±SD) number of doses of beta-agonist taken over 24 h were 3.2 (±1.6) inhalations of terbutaline (1.6 mg) and 5.8 (±2.3) inhalations of salbutamol (0.58 mg).

Table 1. – Concomitant asthma medication during each treatment period (n=46)

Medication	Patients using terbutaline Turbuhaler		Patients using salbutamol P-MDI	
	n	%	n	%
Inhaled steroids	44	96	43	93
Oral steroids	5	11	6	13
Theophylline	9	20	8	17
Sodium cromoglycate	7	15	7	15
Anticholinergics	5	11	4	8

P-MDI: pressurized metered dose inhaler.

Table 2. – Peak expiratory flow (PEF), change in peak expiratory flow (ΔPEF), diurnal variability, symptom scores and clinic visit spirometry for the two treatments (n=45)

	Run-in	Terbutaline Turbuhaler™	Salbutamol P-MDI	Mean difference terbutaline and salbutamol (95% CI)	p-value
PEF % pred*					
PEF morning pre-β_2-agonist	79±3	79±3	79±3	-0.6 (-2.6, 1.5)	0.6
PEF morning post-β_2-agonist	90±3	89±3	90±3	-1.4 (-3.3, 0.5)	0.1
ΔPEF % pred*	12±1	11±2	11±1	-0.8 (-2.4, 0.7)	0.3
Diurnal variability %	18±1	17±1	18±1	-0.9 (-2.5, 0.7)	0.2
Symptom scores					
Sleep disturbance	0.4±0.1	0.3±0.1	0.3±0.1	-0.04 (-0.2, 0.1)	0.5
Cough	0.5±0.1	0.5±0.1	0.6±0.1	-0.12 (-0.2, 0.0)	0.06
Wheeze	0.5±0.1	0.4±0.1	0.5±0.1	-0.05 (-0.2, 0.1)	0.4
Breathlessness on exertion	0.6±0.1	0.6±0.1	0.6±0.1	-0.03 (-0.1, 0.1)	0.9
Total symptom score	2.0±0.3	1.8±0.3	2.0±0.3	-0.2 (-0.6, 0.2)	0.3
Spirometry % pred*					
FEV_1		71±4	72±4	-1.4 (-4.2, 1.5)	0.3
FVC		84±3	85±3	-1.2 (-3.7, 1.3)	0.3

Data are presented as mean±SEM values over the last 14 days of each treatment period. *: expressed as percentage predicted [15, 16]. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; P-MDI: pressurized metered dose inhaler; CI: confidence interval.

The preference questionnaire was completed by 46 patients. Twenty patients (44%) preferred the terbutaline Turbuhaler, 18 (39%) preferred the salbutamol P-MDI and 8 patients (17%) recorded no preference. There was no association detected between treatment preference and any of the factors of age, sex or treatment sequence.

No differences were detected in the occurrence of adverse events between the two treatments. Thirty percent of patients reported adverse events during the two week run-in period. During the study periods, 51% of patients reported adverse events when taking terbutaline Turbuhaler, whilst 54% of patients reported adverse events when taking salbutamol P-MDI. Aggravated asthma and upper respiratory tract infection were the most commonly reported adverse events.

Discussion

This study demonstrated that terbutaline inhaled *via* Turbuhaler produced effective bronchodilation when used in hot, humid regions. Terbutaline *via* Turbuhaler provided as much control of peak flow and symptoms as salbutamol P-MDI in asthmatic patients of at least moderate severity. Temperatures and relative humidity readings reached extremely high levels during the study period.

Despite the fact that all study patients were effectively using salbutamol P-MDI before the study, 44% of them preferred terbutaline Turbuhaler at the conclusion of the relatively brief study period. Most of the adult patients had used salbutamol P-MDI for a number of years before the study. It is therefore perhaps surprising that so many accepted the new terbutaline Turbuhaler so readily. However, a considerable proportion (39%) of the patient group were not influenced by the introduction of the terbutaline Turbuhaler and showed preference for their prestudy delivery system.

In summary, we conclude that prescribers of beta-agonist bronchodilators can be confident of the efficacy and acceptability of terbutaline Turbuhaler in hot, humid regions.

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