A comparison of the clinical efficacy and patient acceptability of terbutaline Turbuhaler and salbutamol Rotahaler, in adult patients with asthma

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This open randomized, cross-over study compared the clinical efficacy and patient acceptability of the two bronchodilator delivery systems, terbutaline Turbuhaler® (0.5 mg t.i.d.) and salbutamol Rotahaler® (0.4 mg t.i.d.), each given for 3 weeks. Thirty-two adult asthmatics (21 males and 11 females with a mean age of 34 years) who demonstrated at least 15% reversibility in PEF or FEV₁ in response to terbutaline, were enrolled for study. The median reversibility in FEV₁ was 27.5% for the terbutaline-salbutamol group and 21% for the salbutamol-terbutaline group. Two patients discontinued during terbutaline treatment (one due to respiratory infection and one due to tachycardia, exhaustion and tremor) and five patients were lost to follow-up during salbutamol treatment, leaving data from 25 patients for an 'all patients treated' analysis.

Mean morning PEF was 426 l min⁻¹ during terbutaline and 410 l min⁻¹ during salbutamol (difference 16 l min⁻¹, 95% CI of difference 3–28 l min⁻¹, P=0.016), and mean evening PEF was 446 l min⁻¹ during terbutaline and 428 l min⁻¹ during salbutamol (difference 18 l min⁻¹, 95% CI 5–30 l min⁻¹, P=0.0076). No significant differences were detected in diary symptom scores or in use of additional study drug during the day or night, and no serious adverse events were reported. When asked to state their treatment preferences on the basis of effects, side-effects and overall, more patients preferred Turbuhaler in each case, although no statistically significant differences were detected.

In conclusion, terbutaline via Turbuhaler was significantly more effective than salbutamol via Rotahaler in controlling lung function (mean daily PEF) in adults with mild to moderate asthma, and it was the preferred treatment overall in 44% of patients, compared with 16% for Rotahaler (n.s.).

Introduction

Inhalation is the preferred method of administration for most drugs used in the treatment of airflow obstruction. However, many patients do not obtain maximum benefit from such therapy because they are unable to use their pressurized aerosols efficiently (1). The most common problems encountered involve the need to synchronize inhaler actuation with inspiration and it is for this reason that breath-actuated inhalers have been developed (2). Devices such as Rotahaler® require each dose of drug to be loaded in the form of a capsule containing drug and lactose carrier powder, whilst Turbuhaler® is a device which dispenses pure drug without additives, and is pre-loaded with 200 doses. In an acute cumulative dose-response study (3), 0.25 mg terbutaline by Turbuhaler was found to be equivalent to 0.2 mg salbutamol by Rotahaler. The purpose of this study was to compare the clinical efficacy (measured as daily PEF, morning and evening) and patient acceptability of the two devices for chronic use in asthma treatment when loaded with terbutaline 0.5 mg dose⁻¹ (Turbuhaler) or salbutamol 0.4 mg dose⁻¹ (Rotahaler).

Patients and Methods

Thirty-two adult patients with chronic asthma, who were taking regular β₂-agonist therapy, were recruited for study between September 1990 and March 1992. The inclusion criteria required a reversibility of at least 15% in FEV₁ or PEF after 3 × 0.5 mg doses of terbutaline via Turbuhaler, and the patients had to be sufficiently stable not to have experienced a marked exacerbation of their asthma during the month prior to the study. Patients who were hypersensitive to terbutaline or salbutamol, or who had significant concomitant disease of any system, were excluded from study, as were those with current respiratory infection. Patients who had
Table 1  Standardized checklists for evaluation of inhalation technique

<table>
<thead>
<tr>
<th>For Turbuhaler®</th>
<th>For Rotahaler®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficient technique</td>
<td>Efficient technique</td>
</tr>
<tr>
<td>Inhaler not loaded in upright (± 45°) position</td>
<td>Rotacap inserted incorrectly (e.g. not far enough in)</td>
</tr>
<tr>
<td>Rotation sequence incorrect – no dose loaded</td>
<td>Incorrect operation</td>
</tr>
<tr>
<td>Air inlet holes covered during inspiration</td>
<td>Capsule not separated by Rotahaler</td>
</tr>
<tr>
<td>Inspiration through nose rather than mouth</td>
<td>Inspiration through nose rather than mouth</td>
</tr>
<tr>
<td>Exhalation through Turbuhaler</td>
<td>Exhalation through inhaler</td>
</tr>
<tr>
<td>Breath not held after inspiration</td>
<td>Breath not held after inspiration</td>
</tr>
<tr>
<td>Other, specify</td>
<td>Other, specify</td>
</tr>
</tbody>
</table>

previously used Rotahaler (Turbuhaler was not available commercially at the time of study) were also excluded.

The study was designed as an open, randomized cross-over of two treatments: 0.5 mg terbutaline t.i.d. (via Turbuhaler) and 0.4 mg salbutamol t.i.d. (via Rotahaler), each given for a period of 3 weeks. Additional doses of trial medication were allowed as required, provided they were recorded in the diary cards.

Patients were asked to attend the clinic for assessment at entry and at the end of each treatment period. At the entry visit, demographic details and disease history were recorded and routine lung function tests were performed, which included measurement of FEV₁, FVC and PEF. The inhalation technique required for each delivery device was demonstrated in detail at the start of each treatment period and was then checked at the end of treatment using a standardized checklist (Table 1). Overall judgement of inhaler technique was then graded as ‘excellent’ if the patient followed all instructions exactly and inhaled correctly, ‘adequate’ if the patient made no major errors in the sequence of instructions, but did not follow the sequence of instructions exactly (these patients did inhale correctly), and ‘inadequate’ if the patient made a major error in the sequence of instructions, or had poor coordination or did not inhale correctly. Patients were supplied with diary cards and mini Wright peak flow meters (Clement Clarke International Ltd) to record morning PEF (immediately after rising) and evening PEF (at bedtime) prior to study medication, and preferably when β₂-agonists had not been used during the previous 2 h.

Patients were also asked to record their asthma symptoms at the same time on a scale where 0 = none, 1 = mild, 2 = moderate, 3 = severe. Extra study drug consumption during the day and night (between PEF measurements) was also recorded.

At the end of the study, patients were asked to state their treatment preference, if any, for one or other of the study treatments. Any adverse events experienced during the course of treatment were to be noted by patients in their diary cards and assessed jointly with the physician at the next clinic visit. If the event was severe or alarming, however, patients were requested to contact their doctor immediately.

Statistical Analyses

It was calculated that data from 32 evaluable patients would detect, with 90% power, a true mean difference in PEF between the treatments of 24.1 min⁻¹ using an estimated SD of 40.1 min⁻¹, where SD is the corresponding standard deviation of a within-patient difference between the two treatments. This was based on a two-sided, paired t-test at the 5% significance level. As data were evaluable for only 25 of the patients, the study power to detect this treatment difference was reduced to 80%.

For each patient, the mean values of PEF, asthma symptom scores and the number of extra inhalations of study drug were calculated for each 3-week treatment period. Two sample t-tests were used to compare terbutaline and salbutamol, according to Jones and Kenward (4). Each analysis was tested (with a significance level of 10%) for period effect and for the presence of carry-over. The patient’s treatment preference (for effect, side-effects and overall) was analysed using Prescott’s test (4), and the investigator’s assessment of patient technique using the two devices was compared using the Wilcoxon rank sum test (4).

Results

Patients

Thirty-two patients (21 males and 11 females) with a mean age of 34 years (range 14–58) and asthma history of 8.6 years (range 0.3–23) were enrolled
in the study. Their mean FEV\textsubscript{1}, FVC and PEF at entry were 2.74 \textsubscript{L}, 3.61 \textsubscript{L} and 408 \textsubscript{L} min\textsuperscript{-1}, respectively. Two patients, allocated to terbutaline-salbutamol, discontinued the study during terbutaline treatment; one due to tachycardia, exhaustion and tremor and one due to a respiratory infection. Five patients allocated to salbutamol-terbutaline were lost to follow-up during salbutamol treatment. An 'all patients treated' analysis was performed on data from the remaining 25 completed patients; 14 of whom received terbutaline-salbutamol and the remaining 11 received salbutamol-terbutaline. Mean baseline predicted FEV\textsubscript{1} was 70\% for the terbutaline-salbutamol group and 75\% for the salbutamol-terbutaline group.

Regular concurrent medication for asthma was taken by some of the patients: inhaled steroids were continued in six patients (five on terb-salb and one on salb-terb), disodium cromoglycate in 15 patients (eight on terb-salb and seven on salb-terb) and four patients took oral theophylline (three on terb-salb and one on salb-terb).

**DAILY LUNG FUNCTION AND SYMPTOMS**

Mean morning PEF (AM PEF) and evening PEF (PM PEF) calculated for each 3-week treatment period are presented in Table 2. Both morning and evening PEF were significantly higher during terbutaline treatment than during salbutamol treatment (\(P=0.016\) for AM PEF and \(P=0.008\) for PM PEF).

Mean symptom scores calculated from diary recordings over the same period were lower during terbutaline treatment than during salbutamol treatment, both during the daytime (0-4 vs. 0-55, n.s.) and during the night-time (0.52 vs. 0.65, n.s.). When intake of extra study medication was compared for the two treatment periods, there was no statistically significant difference. Nine patients required no rescue treatment during terbutaline treatment compared with eight patients during the salbutamol treatment.

**INHALER TECHNIQUE AND PATIENT PREFERENCE**

According to the investigator's assessment of patient inhaler technique, 19 patients demonstrated excellent (i.e. efficient) technique with Turbuhaler, compared with 15 patients who demonstrated excellent technique with Rotahaler (n.s.). The problems noted during the demonstration of each device by the patient are summarized in Table 3.

When patients were asked to state their preference for one or other of the devices on the basis of effect, 13 patients preferred Turbuhaler, eight preferred Rotahaler, and four said they were equal (n.s.). Comparing side-effects, 10 patients preferred Turbuhaler, one patient preferred Rotahaler, and 14 patients said they were equal (n.s.). When patients were asked to give an overall preference for one or other treatment, 11 stated a preference for terbutaline Turbuhaler, four preferred salbutamol Rotahaler, and 10 said they were equal (n.s.). Preference is summarized in Fig. 1.

**Discussion**

The purpose of this study was to compare both the efficacy and the patient acceptability of bronchodilator administered by Turbuhaler (terbutaline) and Rotahaler (salbutamol). It was also the intention to assess the patient preference for each device. This precluded the use of a double-blind study design where dummy inhalers are used simultaneously with each active treatment, as patients would not have known which device had given them symptomatic relief and their views concerning the ease of use of the devices might have been confounded by the inconvenience of having to use two devices on each

| Table 3 Problems noted during assessment by investigator of inhaler technique |
|-------------------------------|-------------------------------|
| Turbuhaler®                  | Rotahaler®                    |
| Inhaler not loaded in upright position (1) | Rotacap inserted incorrectly (6) |
| Breath not held after inspiration (4) | Breath not held after inspiration (5) |
| Rotation sequence incorrect (2) |                                |
occasion. These factors were considered to outweigh the inherent problems of the open design in this study. Hence, the study was performed as an open cross-over of the two treatments.

The diary lung function data showed that patients had significantly higher morning and evening PEF during Turbuhaler therapy than during Rotahaler therapy, regardless of the treatment order taken. Similar differences in AM PEF were noted by Anani et al. (5) in a study of more severe asthmatic adults who took each drug four times a day. Stallaert (6) compared the two devices in adults using the same dosing frequency as in the present study, with administration of each drug for 4 weeks. As in the Anani et al. study (5), significant differences were observed for AM PEF only.

If a device preference existed in the present study, it tended to be preference for Turbuhaler (44%) rather than Rotahaler (16%), although this difference did not reach statistical significance. In other studies (5–10), preference for Turbuhaler ranged from 50 to 79% and for Rotahaler from 9 to 33%. The physician's assessment of inhaler technique in this study found that 76% of the patients demonstrated 'excellent' technique for Turbuhaler compared with 60% for Rotahaler. These results are very similar to those found in a large audit of inhalers (11), where 78% of the patients obtained the highest score for technique using Turbuhaler compared with 50% using Rotahaler. In a randomized study comparing five inhaler systems which included Turbuhaler and Rotahaler (10), patients received a single instruction and demonstration of each device and were then assessed on their ability to use it correctly (defined as adequate preparation, coordination of actuation and breath-holding). The proportion of patients who used the device incorrectly, for one or more reasons, was 38% for Rotahaler compared with 0% for Turbuhaler. The ability of patients to use Turbuhaler so efficiently after only one demonstration provides convincing evidence that it is very simple to use, provided accurate instructions are given. The majority of the 'problems' observed in Turbuhaler patients during this study did not concern the device itself, but the breath-holding at the end of inhalation. When this study was designed, breath-holding after inhalation was believed to be an important feature of good inhalation technique. Consequently, it was used in the checklist for assessment of technique. It has since been demonstrated, however, that this manoeuvre does not influence the bronchodilating effect of terbutaline administered by Turbuhaler to adults (12). Thus, the 'breath-holding' problems noted with Turbuhaler in this study probably did not impede its efficacy, and this may explain why higher lung function was noted with Turbuhaler. Some of the patients in the present study complained that they could not feel the medication when they inhaled from Turbuhaler. This problem has also been described previously and it has been suggested by Crompton (13) that all patients for whom Turbuhaler is prescribed should be informed that they should not expect much taste or any sensation of drug entering their mouths. They are then less likely to perceive this feature of the medication as negative.

In conclusion, this study demonstrated that terbutaline via Turbuhaler was more effective than salbutamol via Rotahaler in controlling lung function in adult patients with mild to moderate asthma. Both inhalation devices were well-accepted, with 44% of patients preferring Turbuhaler, 16% preferring Rotahaler and 40% stating no preference for either device (n.s.).

References


7. de Graaff CS, van den Bergh JAHM, de Bree AF et al. A double blind clinical comparison of budesonide and beclomethasone dipropionate (BDP) given as dry powder formulations in asthma. *Eur Respir J* 1992; 5 (suppl. 15): 359S.


