Equivalent therapeutic ratio of salbutamol given by Turbuhaler® and Diskus®

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Some inhalers have been claimed to give better deposition, resulting in higher efficacy. In a previous study we did not find any evidence of different potency of salbutamol given either via pMDI or Turbuhaler®. The aim of the present study was to compare the efficacy and safety of salbutamol given via Diskus® or Turbuhaler. Twenty-five asthmatics with step-wise reversible airflow obstruction (total reversibility of at least 15%) were included in a randomized, double-dummy, placebo-controlled cross-over study. On each study day, the patients were given placebo repeatedly, or cumulative doses of 200, 400, 800, 1600 and 3200 μg salbutamol given via either device (double-blind, placebo-controlled). Salbutamol caused a dose-related increase in FEV1 when given by Diskus or Turbuhaler. The improvement in FEV1 was similar regardless of whether salbutamol was given via Diskus or Turbuhaler, at equivalent microgram doses. After a total cumulative dose of 3200 μg, mean FEV1 for Diskus was 2.46 l (change from baseline of 20.5%), for Turbuhaler 2.50 l (change from baseline 24.6%) and for placebo 2.11 l (3% change from baseline). After correcting for different baseline differences, the percentage difference between Diskus and Turbuhaler was -1.8% (P=0.2). Systemic effects (potassium and heart rate) did not differ between Diskus or Turbuhaler. We conclude that the efficacy of salbutamol given at equivalent microgram doses, as well as side-effects, are comparable when the drug is given via Diskus or Turbuhaler. The present data shows that salbutamol given by these devices have similar therapeutic ratios.

Key words: asthma; Salbutamol; inhalers; Turbuhaler®; Diskus®; lung.
when salbutamol is delivered via Diskus or Diskhaler. No data have been presented, comparing directly the safety and efficacy of salbutamol given via the Diskus or Turbuhaler.

The aim of the present study was to evaluate whether any differences in the topical or systemic effects of salbutamol are evident when the drug is given as the same cumulative doses via Diskus or Turbuhaler.

**Patients and methods**

The study was performed in accordance with the principles stated in the Declaration of Helsinki, and was approved by the Ethics Committee of Göteborg and the Swedish Drug Agency (Uppsala, Sweden). Furthermore, Good Clinical Trial Practice principles were applied, and the study was monitored by the sponsor (Glaxo Wellcome).

**PATIENTS**

Twenty-five adult patients (13 women), non-smokers, all with reversible airflow obstruction, were included. The mean age was 54 years (31–71), mean height 171 cm, and mean weight 72 kg. All patients were using inhaled glucocorticoids regularly, and short-acting $\beta_2$-agonists p.r.n. (as needed). The patients were permitted to use inhaled corticosteroids (up to 1000 $\mu$g b.d.), sodium cromoglicate, nedocromil sodium and antihistamines, provided that the dose was constant for 4 weeks prior to visit 1 and remained constant during the trial.

Regarding $\beta_2$-agonists, they were not allowed to take long-acting $\beta_2$-agonists for 12 h and short-acting for 6 h prior to each clinic visit.

**STUDY DESIGN**

The study was designed as a randomized, double-blind, double-dummy, cross-over study to measure the topical and systemic effects in cumulative doses of salbutamol delivered by the Turbuhaler compared with the Diskus inhaler. Topical effects were assessed by measurement of FEV$_1$ and the systemic effects by serum potassium, heart rate, systolic and diastolic blood pressure. The same equipment (Vitalograph Compact, Vitalograph, Birmingham, U. K.) was used at all four clinic visits. The device was calibrated every morning. The highest of three technically acceptable measurements of FEV$_1$ was recorded in the Case Report Form.

At the pre-study visit, eligibility was assessed, which was followed 36 h–10 days later by three study visits (spaced 36 h–10 days apart). Finally, a post-study check was performed to complete the study.

At the pre-study screen, patients received 200 $\mu$g salbutamol (given by pMDI, Ventoline) followed 30 min later by 1600 $\mu$g salbutamol. The improvement seen should be at least 10% 15 min after 200 $\mu$g salbutamol, followed by another at least 50% increase of the effect observed after the lower dose.

The patients were not allowed to take an inhaled short-acting $\beta_2$-agonist 6 h, long-acting $\beta_2$-agonist 12 h, or an oral/sustained-release $\beta_2$-agonist 24 h prior to pre-study day, or on the three study days. Theophyllin, oral corticosteroids or leucotriene synthesis blockers/receptor antagonists were not permitted during the conduct of the study or for the 4 weeks prior to visit 1.

On the three study days, each patient were given the following treatments in a randomized order: (a) salbutamol via Turbuhaler and placebo via Diskus or (b) salbutamol via Diskus and placebo via Turbuhaler or (c) placebo via Turbuhaler and Diskus.

Salbutamol was given in cumulative doses at approximately 30-min intervals (time = 0, 30, 60, 90 and 120 min). The doses were 200, 200, 400, 800 and 1600 $\mu$g, resulting in cumulative doses of 200, 400, 800, 1600 and 3200 $\mu$g. The nominal dose per actuation was 100 $\mu$g from the Turbuhaler and 200 $\mu$g from the Diskus ($2+2+4+8+16=32$ inhalations via the Diskus and twice as many via the Turbuhaler per day). During the placebo day, exactly the same protocol was followed.

Blood samples for potassium was taken prior to the cumulative design regimen (baseline). After that, blood samples for potassium, blood pressure and FEV$_1$ measurements were taken 20–25 min after each cumulative dose. Heart rate was measured by taking pulse at the level of arteria radialis.

**STATISTICAL METHODS**

Pre-study power calculation gave an estimate that 24 patients would give 80% power to show equivalence of the treatments. Retrospective analysis show that the equivalence region (95% confidence intervals) for any time point is always within 0.12 l for FEV$_1$. The data obtained 20 min after each cumulative dose was averaged. The baseline value obtained prior to dosing was used as the value for a zero cumulative dose. Each of the variables (FEV$_1$, heart rate and plasma potassium) were summarized in three ways:

- the mean values obtained after cumulative dose;
- area under the response time curve;
- the slope from linear regression of the response against cumulative dose of each treatment (logged data).

Comparison of mean values at nominal time points or after specified cumulative doses was performed by analysis of covariance using SAS proc GLM. The model included terms for patient, visit (i.e. period), baseline (pre-dosing) level, as well as treatment group. Estimates of the difference between treatments, Diskus vs. turbuhaler, Diskus vs. placebo, Turbuhaler vs. placebo were calculated together with 95% confidence intervals.

Comparison of mean area under the response-time curve (AUC) and the mean slope of regression of response on (log-) cumulative dose (slope) for each individual patient were carried out using the same procedure as above, though with a change of response variable (AUC or SLOPE) as appropriate.
Results

Twenty-five patients were included in the study and all patients completed the study. Salbutamol given either by Turbuhaler or Diskus caused significant and dose-related improvement in FEV\(_1\) (Fig. 1). Mean FEV\(_1\) 20 min after the end of dosing (cumulative dose of 3200 \(\mu\)g), was 2.50 l with Turbuhaler, 2.46 l with Diskus and 2.11 l with placebo. These values correspond to a percentage change from baseline of 24.6%, 20.5% and 3.2% with Turbuhaler, Diskus and placebo respectively. After correction for baseline (pre-dosing) differences, the percentage difference between Diskus and Turbuhaler was -1.8% (\(P=0.2\)). Comparing Diskus vs. placebo, the difference was 16.3% (\(P<0.001\)) and when comparing Turbuhaler vs. placebo, the difference was 18.5% (\(P<0.001\)). The 95% confidence intervals were -4.7 to +1.8% for the comparison between Diskus and Turbuhaler. Looking at all time points throughout the observation period, the maximal 95% confidence intervals between treatments are ±5.5%, which equates to a maximal treatment difference of ±0.12 l.

The average AUC difference over the interval (\(t=0-t=140\) baseline to 3200 \(\mu\)g) between salbutamol Turbuhaler and Diskus was calculated, and equalled to -0.02 l (CI: -0.09–0.05 l). Comparison of average regression slopes over the dosing interval showed similar results (data not shown). With salbutamol Turbuhaler, FEV\(_1\) increased by 0.07 l for each doubling dose, with salbutamol Diskus this increase was 0.06 l, and on placebo 0.02 l. The difference between active treatments corrected for baseline differences was 0.009 l per doubling dose.

There was no tendency for difference in the induced changes in S-potassium (Fig. 2), in heart rate (Fig. 3) or diastolic blood pressure, and after total cumulative dosing, these variable were all within the defined region for equivalence comparing the two active treatments (95% confidence intervals for the true difference).

Discussion

In their effect on FEV\(_1\), this study clearly demonstrates the equivalence of delivery of salbutamol in a doubling dose schedule via either Turbuhaler or Diskus. In addition, it demonstrates that both treatments show a marked benefit
compared to placebo. Likewise, effects on systemic parameters, heart rate and plasma potassium, are similar with either device.

The Turbuhaler has been suggested to improve lung deposition of inhaled drugs vs. several other inhalers (1,8), but no direct comparison of Turbuhaler versus Diskus has been reported. This difference in lung deposition has been suggested to improve the efficacy of terbutaline and budesonide given by the Turbuhaler vs. their corresponding pMDI (1,4,5). Some studies have also argued that salbutamol Turbuhaler is more efficacious than salbutamol pMDI (6,10–12). However, one weakness of these studies is that the drugs were not compared on equal µg doses. Also, in the study by Lofdahl (6), the observed differences in FEV1 between the lowest and highest dose of salbutamol was quite small, amounting to a mean of 0.15 l suggesting a quite shallow dose–response curve in the studied patients. In a more recent study, we have been unable to detect any significant differences in the improvement in FEV1 between the lowest and highest dose of salbutamol in the studied patients. This is likely important, since the Turbuhaler has been suggested to give more peripheral deposition, which hypothetically could result in more prominent side-effects, because of more systemic absorption from peripheral airways and lung tissue. Thus, the improved peripheral deposition of bronchodilators given by the Turbuhaler does not seem to lead to improved clinical efficacy, and does not affect the therapeutic ratio.

The dose response effect between the lowest and highest dose of salbutamol was quite high in the present study, amounting to 0.29 l, showing that a dose-related effect of salbutamol was present in the studied patients. This is likely to be due to our selection of patients, i.e. needing to show a dose-related bronchodilation at inclusion. Many bronchodilator studies are unable to show dose-related effects of cumulative doses of drugs. We therefore suggest that including patients with step-wise improvement in FEV1, within the doses studied in a randomized stage of the study, increases the possibility of producing data with dose-related effects.

We conclude that no or very small differences in potency and efficacy between salbutamol Turbuhaler and salbutamol Diskus are present in asthmatic patients. More importantly, the differences in therapeutic ratio of these treatments are minimal, or non-existent.

References