Therapeutic equivalence between bambuterol, 10 mg once daily, and terbutaline controlled release, 5 mg twice daily, in mild to moderate asthma

A.M. Fugleholm*, T.B. Ibsen**, L. Laxmyr*, U.G. Svendsen*

ABSTRACT: Bambuterol is the first long-acting oral β₂-agonist with a 24 h effective duration. In order to investigate the possibility of replacing established treatment modalities with bambuterol once daily, we wanted to compare the bronchodilating and tremorogenic effects of bambuterol, 10 mg once daily, and terbutaline, 5 mg controlled-release (CR) tablets twice daily.

The study was of a double-blind, double-dummy, randomized, cross-over design and involved two, two week treatment periods, separated by a one week wash-out period. Peak expiratory flow (PEF) recorded in patients' diaries was the primary efficacy variable. Seventy adult, asthmatic out-patients with mild to moderate asthma were included (forced expiratory volume in one second (FEV₁) ≥50% predicted).

After treatment with bambuterol, mean morning and evening PEF (m) were 347 (122) and 365 (121) l/min¹, respectively and 346 (121) and 365 (122) l/min¹, respectively, after treatment with terbutaline. FEV₁ (m) was 2.21 (0.91) and 2.27 (0.93) l after bambuterol and terbutaline treatments, respectively. Tremor scores tended to be lower during treatment with bambuterol, although not significantly so. Tremor scores were low, in general.

In conclusion, no difference in the bronchodilating effect was demonstrated between bambuterol, 10 mg once daily, and controlled release terbutaline, 5 mg twice daily. A tendency towards less tremor was seen with bambuterol.

Eur Respir J., 1993, 6, 1474-1478.

Oral β₂-agonists are indicated when asthma symptoms, often nocturnal symptoms, are not controlled by high doses of anti-inflammatory drugs and standard doses of inhaled β₂-agonists [1]. To improve control of nocturnal symptoms and patient compliance, the use of long-acting β₂-agonists which have few adverse effects is warranted.

The most widely-used oral β₂-agonist in Denmark is controlled-release (CR) terbutaline, of which the bronchodilatory properties and low frequency of side-effects have been well established in clinical practice during the last decade.

Bambuterol is the first once daily β₂-agonist. It is absorbed slowly after oral administration and is metabolized via oxidative and hydrolytic pathways to the pharmacologically active metabolite terbutaline [2]. Human pharmacokinetic and clinical studies have shown that bambuterol provides a safe and reliable generation of terbutaline, which results in a smooth curve of plasma concentration versus time [3, 4]. In this way, bambuterol provides good bronchodilation over 24 h, at the same level of efficacy as other oral bronchodilators, and with reduced systemic sympathomimetic adverse effects, such as tremor [5-9]. No comparison has been made, however, between commercially recommended doses of bambuterol and the widely-used (CR) formulation of terbutaline (Bricanyl®).

In order to evaluate the extent to which bambuterol can be substituted for terbutaline CR tablets, we have compared the lowest recommended doses, i.e. bambuterol, 10 mg once daily, with terbutaline CR, 5 mg twice daily, with regard to bronchodilating effects, primarily diary recordings of peak expiratory flow (PEF), side-effects, expressed as daily tremor scores, and possible changes in clinical chemistry and haematology variables.

Patients and material

For inclusion, patients were required to have a clinical diagnosis of asthma, to be more than 18 yrs of age, to demonstrate an increase in forced expiratory volume in one second (FEV₁) of ≥15% from baseline 15 min after inhaling 0.5 mg of terbutaline sulphate, and to have a baseline FEV₁ of ≥50% of predicted normal value [10]. Patients with known severe cardiovascular, renal or liver
disease, with current respiratory infection, or with known seasonal allergy present during the study period were excluded. Pregnant or lactating women and women of childbearing potential, who were not using contraceptives, were also excluded. The study was approved by the local Ethics Committee in Copenhagen County. All patients gave written informed consent.

Concomitant medication permitted during the study included inhaled β₂-agonists (not later than 7 h prior to PEF and FEV₁ measurements), disodium cromoglycate (if taken at a constant dose 2 weeks prior to and throughout the study), and inhaled or oral steroids (if taken at a constant dose one month prior to and throughout the study). Oral, nebulized and parenteral β₂-agonists other than the study medication, theophylline, anticholinergics and betablockers were not allowed during the study.

**Methods**

The study was randomized, double-blind, double-dummy and of a cross-over design. It consisted of a 7 day run-in period, followed by two 14 day treatment periods, which were separated by a 7 day wash-out period. During the treatment periods, patients received either bambuterol (Astra Draco AB) 10 mg tablets, once daily at 7 p.m., or terbutaline (Astra Draco AB) 5 mg CR, tablets twice daily at 7 a.m. and 7 p.m. Bambuterol placebo tablets were given at 7 p.m. during terbutaline treatment, and terbutaline placebo tablets were given at 7 a.m. and 7 p.m. during bambuterol treatment. Placebo tablets were also administered during run-in and wash-out periods. Compliance in medication intake should have been at least 90%, and was checked by counting remaining tablets after each period. The study involved five clinic visits; one at the start of the study and one at the end of each period. Visits were to be performed at the same time of the day.

At the first visit, a reversibility test was performed by measuring FEV₁ on a Vitalograph Compact, before and 15 min after inhaling terbutaline sulphate (powder) 0.5 mg. Before the test, patients were not to use theophylline or sustained release β₂-agonists within 14 h, inhaled β₂-agonists within 7 h, or oral β₂-agonists or anticholinergics within 8 h. FEV₁ was measured on the same spirometer at every clinic visit. If baseline FEV₁ after the run-in and wash-out periods differed by more than 20%, the patient was excluded. Other visit assessments included clinical chemistry and haematology (blood haemoglobin and leukocyte levels; serum creatinine, bilirubin, alkaline phosphatase and aspartate amino transferase (ASAT); urine albumin and glucose levels) measured before the study and after each treatment period, treatment preference regarding asthma control requested at the final visit, and incidence of tremor.

The following diary recordings were made by patients every morning and evening: PEF (l·min⁻¹; mini-Wright peak flow meter®) before medication, β₂-agonist use, asthma symptoms (wheeze, breathlessness, cough) on a scale from 0 to 3 (0=none, 3=inability to carry out activities or to sleep), adverse effects (tremor) using the same scale, and sleep disturbances due to asthma on a scale from 0 to 3 (0=none, 3=awake most of the night). β₂-agonist use, asthma symptoms, and adverse effects (tremor specified) were scored separately for day and night; night being defined as the time from lights out until final awakening.

**Statistical analysis**

Analysis of variance was used to analyse data. Scored and counted efficacy variables were analysed, using corresponding nonparametric methods based on rank transformations [11]. Tests for carry-over effects were performed, and found to be nonsignificant. Patient preference was analysed using a binomial test. Signed rank tests were used when analysing changes in clinical chemistry and haematology variables. Peak expiratory flow (the primary efficacy variable) was analysed, using both per-protocol data (66 patients) and all-patients-treated data (70 patients). For other efficacy and safety variables, only all-patients-treated data were used. The sample size was calculated, assuming that a clinically relevant difference in PEF between treatments was 18 l·min⁻¹, the intrapatient standard deviation was 50 l·min⁻¹, the power would be at least 80%, and the level of two-sided significance would be 5%.

**Results**

**Lung Function**

Between September 1989 and July 1990, a total of 70 patients (35 males and 35 females) were included in this study. Mean age was 54 yrs (range 21–76 yrs), mean duration of asthma 14 yrs (range 1–67 yrs), mean reversibility in FEV₁ 22% (range 15–58%), and mean FEV₁ at the first clinic visit 2.04 l (range 0.85–3.90 l), which was 66% of predicted normal value (range 41–104%) [10]. The patient with an FEV₁ of 41% of predicted normal value was excluded from the per-protocol analysis of PEF. Mean morning and evening PEF for all patients were 328 (±118) and 351 (±118) l·min⁻¹, respectively, during the run-in period, and 340 (±126) and 359 (±123) l·min⁻¹, respectively, during the wash-out period.

The difference between study medication given to the patients and returned medication corresponded to an average compliance of 100% of the intended intake in all study periods. In addition to the study medication, 97% of the patients used an inhaled β₂-agonist as needed, 91% used an inhaled steroid on a regular basis, and 4% used an oral steroid at a constant dose throughout the study.

Five patients withdrew from the study: two after the terbutaline period (adverse effects/personal reason), two after the bambuterol period (adverse effects/lack of efficacy), and one during wash-out (asthma deterioration necessitating admittance to the hospital).

Descriptive statistics of the efficacy variables during the two treatment periods are presented in table 1. The all-patients-treated and per-protocol analyses of the primary efficacy variable (PEF) produced similar results.
Table 1. - Descriptive statistics of PEF, FEV₁, number of puffs of β₂-agonists and asthma symptoms (score 0–3).

<table>
<thead>
<tr>
<th></th>
<th>Bambutero₂</th>
<th>Terbutaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Range</td>
</tr>
<tr>
<td>PEF morning l·min⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APT</td>
<td>347 (122)</td>
<td>97–656</td>
</tr>
<tr>
<td>PP</td>
<td>345 (125)</td>
<td>97–656</td>
</tr>
<tr>
<td>PEF evening l·min⁻¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APT</td>
<td>365 (121)</td>
<td>135–642</td>
</tr>
<tr>
<td>PP</td>
<td>364 (124)</td>
<td>135–642</td>
</tr>
<tr>
<td>FEV₁ l</td>
<td>2.21 (0.91)</td>
<td>0.72–4.70</td>
</tr>
<tr>
<td>β₂-agonist use puffs-day⁻¹</td>
<td>5.62 (4.43)</td>
<td>0.00–24.00</td>
</tr>
<tr>
<td>β₂-agonist use puffs-night⁻¹</td>
<td>1.40 (2.53)</td>
<td>0.00–15.27</td>
</tr>
<tr>
<td>Daytime symptoms score</td>
<td>0.67 (0.63)</td>
<td>0.00–2.20</td>
</tr>
<tr>
<td>Night-time symptoms score</td>
<td>0.44 (0.55)</td>
<td>0.00–2.09</td>
</tr>
</tbody>
</table>

PEF: peak expiratory flow; FEV₁: forced expiratory volume in one second; APT: all-patients-treated; PP: per-protocol. For efficacy variables, other than PEF, only all-patients-treated data were used.

Fig. 1. - Day-to-day variations in a) morning and b) evening peak expiratory flow (PEF) during the two active treatment periods, for all patients treated. Data are presented as mean±so. —— bambutero₂; —— terbutaline.
For all-patients-treated mean morning PEF (so) was 347 (122) l·min⁻¹ with bambuterol and 346 (121) l·min⁻¹ with terbutaline. Evening PEF was 365 (121–122) l·min⁻¹ with both bambuterol and terbutaline. Day-to-day variations in morning and evening PEF during the two active treatment periods are shown in figure 1. Mean FEV₁ (so) after bambuterol was 2.21 (0.91) l and after terbutaline 2.27 (0.93) l. The differences were not statistically significant.

No clinically or statistically significant treatment differences were detected for asthma symptoms day or night (table 1), or for sleep disturbances due to asthma. Mean scores for sleep disturbances due to asthma were 0.32 (range 0–2.09) with bambuterol and 0.29 (range 0–2.27) with terbutaline. There was no clinically relevant difference in the use of β₂-agonists between treatments (table 1). The statistically significant difference in nighttime use (p=0.04), refers to a difference of about two puffs per 100 nights, which may be considered to be of no clinical relevance.

There was no difference in patient preference regarding asthma control between treatments. Twenty three patients preferred bambuterol, 25 patients preferred terbutaline, and 17 patients had no preference.

Side-effects

Mean scores for daytime tremor were 0.18 with bambuterol (range 0–1.62) and 0.26 with terbutaline (range 0–2.14). The corresponding mean scores for night-time tremor were 0.07 (range 0–1.07) and 0.11 (range 0–1.67). There was a tendency for tremor scores to be higher with terbutaline than with bambuterol during the first week of treatment. The scores reduced somewhat during the second week with both treatments. None of the differences were statistically significant. Weekly mean scores for tremor day and night are shown in figure 2.

Other adverse effects were mild in intensity and reported with the same frequency in the two treatment groups. The most frequently reported adverse effect was headache, reported by four patients during each of the two treatments. Changes in the clinical chemistry and haematology variables during the two treatments were not statistically significant. None of the mean or individual changes were of clinical relevance.

Discussion

Bambuterol is a new oral treatment modality presently being introduced, which has the advantages of once daily dosing and improved control of asthma symptoms during the night [12]. The bronchodilatory properties of bambuterol have been demonstrated previously in placebo-controlled studies [5, 6, 9]. The design of the present study was chosen to demonstrate equality or superiority to an established treatment, rather than the absolute effect of each treatment. This was achieved by having a large sample size in a study of cross-over design. An intrapatient standard deviation of 50 l·min⁻¹ was assumed in the calculations. The standard deviation, however, turned out to be about 25 l·min⁻¹, which improved the statistical power considerably. Apart from statistical considerations, it is apparent from the similarities in morning and evening PEF and FEV₁ mean values and standard deviations that there is no difference between the bronchodilating effects of bambuterol, 10 mg once daily, and terbutaline CR, 5 mg twice daily. Also, the use of inhaled β₂-agonists was similar. No differences in asthma symptom scores could be detected, but scores were very low in general and, thus, firm conclusions are not possible other than that patients considered themselves well-treated.

Bambuterol, 10 mg once daily, has been compared to terbutaline, 5 mg plain tablets three times daily, and the two treatments were found to be clinically comparable in their bronchodilating effects, whereas tremor, in general, was milder and less frequent with bambuterol [8].

In the present study, this pattern was repeated. However, the majority of patients scored 0 as tremor score in both treatments. Consequently, differences between treatments were difficult to detect. Nevertheless, there were some indications that mean score of tremor was somewhat lower with bambuterol. None of the patients reported severe tremor during the bambuterol period as opposed to the terbutaline period. There were also indications that initial tremor during daytime was more intense with terbutaline than with bambuterol. Development of tolerance to β₂-agonist-induced tremor is known, and might
explain why some patients rated tremor lower in the second week of treatment.

In conclusion, terbutaline CR, 5 mg twice daily, can be substituted by bambuterol, 10 mg once daily, as no difference has been demonstrated in bronchodilatory action of the two drugs in patients with moderate to severe asthma using concomitant steroid therapy. Furthermore, a tendency towards a lower tremor score with bambuterol, especially initial tremor, was detected.

References