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

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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. ©ERS Journals Ltd 1993.

ABSTRACT: Bambuterol is the first long-acting oral β_2-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 (FEV_1) ≥50% predicted).

After treatment with bambuterol, mean morning and evening PEF (SD) were 347 (122) and 365 (121) $l \cdot min^{-1}$, respectively and 346 (121) and 365 (122) $l \cdot min^{-1}$, respectively, after treatment with terbutaline. FEV_1 (SD) was 2.21 (0.91) l 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.
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Oral β_2-agonists are indicated when asthma symptoms, often nocturnal symptoms, are not controlled by high doses of anti-inflammatory drugs and standard doses of inhaled β_2-agonists [1]. To improve control of nocturnal symptoms and patient compliance, the use of long-acting β_2-agonists which have few adverse effects is warranted.

The most widely-used oral β_2-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 past decade.

Bambuterol is the first once daily β_2-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 (FEV_1) of ≥15% from baseline 15 min after inhaling 0.5 mg of terbutaline sulphate, and to have a baseline FEV_1 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 β_2-agonists (not later than 7 h prior to PEF and FEV_1 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 β_2-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 FEV_1 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 β_2-agonists within 14 h, inhaled β_2-agonists within 7 h, or oral β_2-agonists or anticholinergics within 8 h. FEV_1 was measured on the same spirometer at every clinic visit. If baseline FEV_1 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 leucocyte 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 ($l \cdot min^{-1}$; mini-Wright peak flow meter®) before medication, β_2-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). $Beta_2$-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 $l \cdot min^{-1}$, the intrapatient standard deviation was 50 $l \cdot min^{-1}$, 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 FEV_1 22% (range 15–58%), and mean FEV_1 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 FEV_1 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) $l \cdot min^{-1}$, respectively, during the run-in period, and 340 (±126) and 359 (±123) $l \cdot min^{-1}$, 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 β_2-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, FEV_1 number of puffs of β_2-agonists and asthma symptoms (score 0–3).

		Bambuterol		Terbutaline	
		Mean (SD)	Range	Mean (SD)	Range
PEF morning $l \cdot min^{-1}$	APT	347 (122)	97–656	346 (121)	120–664
	PP	345 (125)	97–656	344 (123)	120–664
PEF evening $l \cdot min^{-1}$	APT	365 (121)	135–642	365 (122)	136–660
	PP	364 (124)	135–642	362 (124)	136–660
FEV_1 l		2.21 (0.91)	0.72–4.70	2.27 (0.93)	0.60–4.80
β_2-agonist use puffs·day^{-1}		5.62 (4.43)	0.00–24.00	5.50 (4.39)	0.00–24.00
β_2-agonist use puffs·night^{-1}		1.40 (2.53)	0.00–15.27	1.38 (2.61)	0.00–13.64
Daytime symptoms score		0.67 (0.63)	0.00–2.20	0.71 (0.64)	0.00–2.25
Night-time symptoms score		0.44 (0.55)	0.00–2.09	0.42 (0.56)	0.00–2.00

PEF: peak expiratory flow; FEV_1: 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.

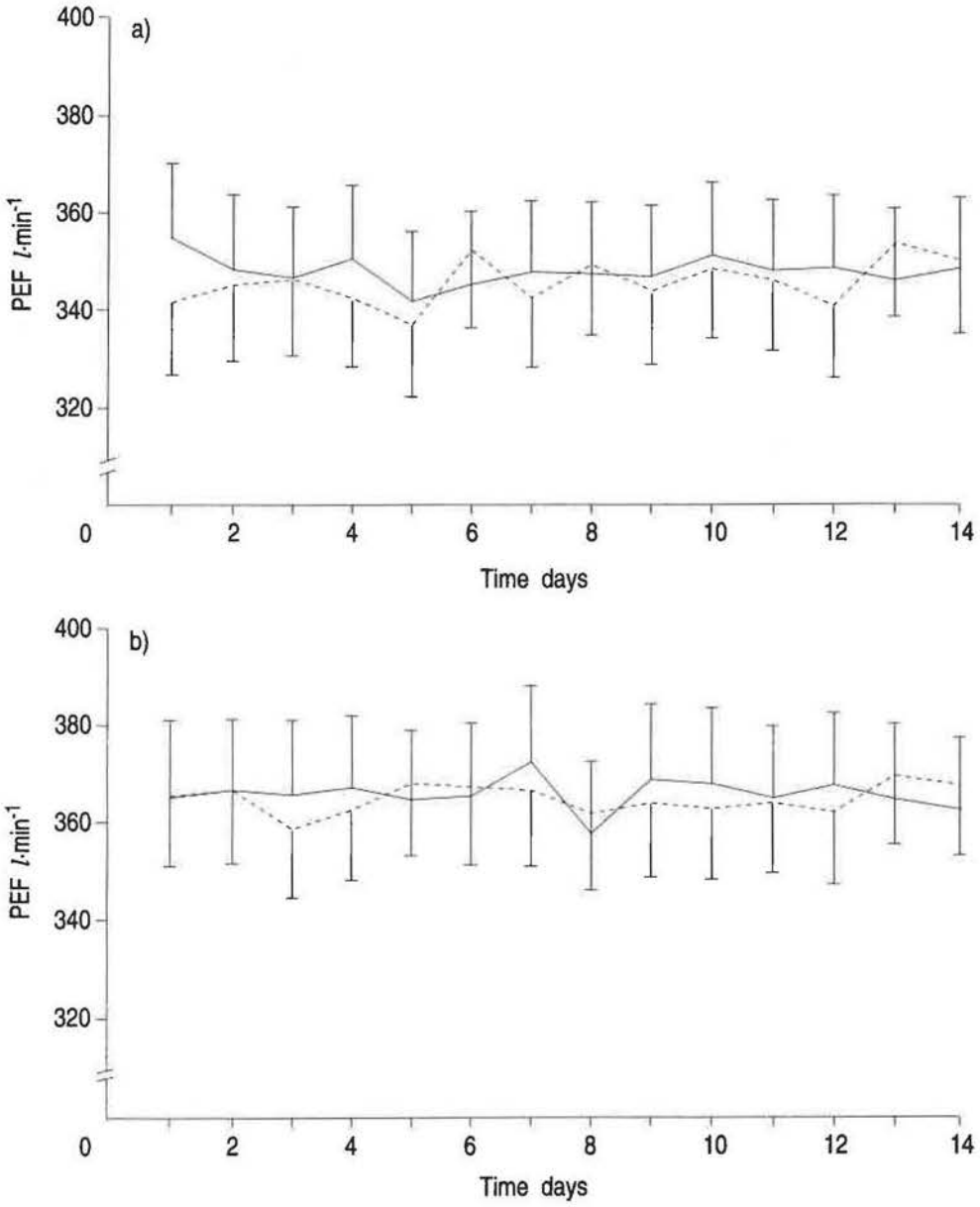

Fig. 1. – Day-to-day variations in a) morning and b) evening peak expiratory flow (PEF) during the two active treatment periods, for all patients treated. Data are presented as mean±SD. ——: bambuterol; – – –: terbutaline.

For all-patients-treated mean morning PEF (SD) was 347 (122) $l \cdot min^{-1}$ with bambuterol and 346 (121) $l \cdot min^{-1}$ with terbutaline. Evening PEF was 365 (121–122) $l \cdot min^{-1}$ 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 FEV_1 (SD) 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 β_2-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.

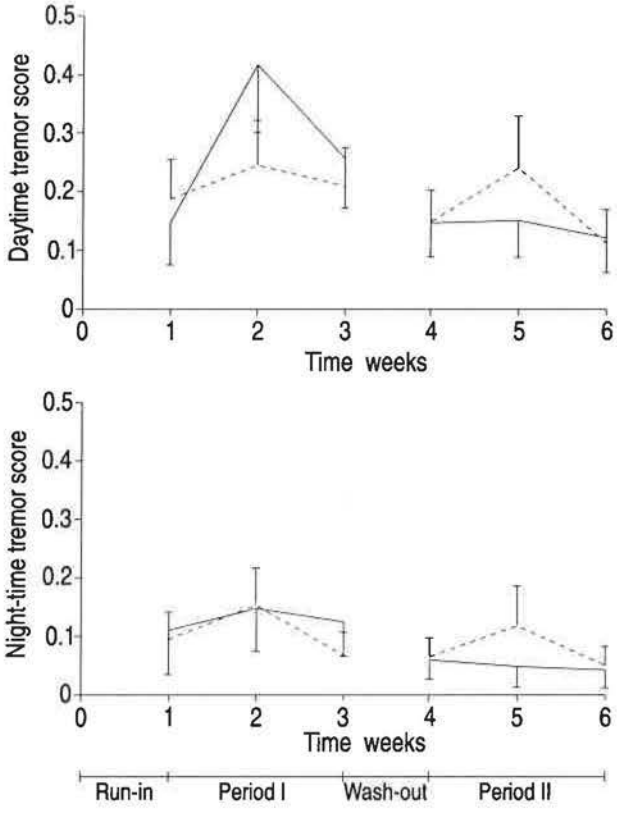

Fig. 2. – Weekly mean score of tremor, for all patients treated. Data are presented as mean±SD. a) daytime and b) night-time. For description of protocol see methods. Treatment order: ——: terbutaline-bambuterol; – – –: bambuterol-terbutaline.

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 $l \cdot min^{-1}$ was assumed in the calculations. The standard deviation, however, turned out to be about 25 $l \cdot min^{-1}$, which improved the statistical power considerably. Apart from statistical considerations, it is apparent from the similarities in morning and evening PEF and FEV_1 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 β_2-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 β_2-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

1. British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. – Guidelines for management of asthma in adults: I. Chronic persistent asthma. *Br Med J* 1990; 301: 651–653.
2. Olsson OAT, Svensson LÅ. – New terbutaline ester prodrugs with long effect duration. *Pharm Res* 1984; 1: 19–23.
3. Sandström T, Åsander L, Clemmensen IH, *et al.* – Bambuterol: clinical effects of different doses of a long-acting bronchodilator prodrug. *Respiration* 1988; 53: 31–36.
4. Nyberg L. – Pharmacokinetic properties of bambuterol in solution and tablet: basis for once daily dosage in asthma. *Acta Pharmacol Toxicol* 1986; 59 (Suppl. 5): 229s.
5. Fleetham J, Grossman R, Knight A, *et al.* – Bambuterol reduces the diurnal variation of peak expiratory flow rates in asthmatic patients. *Eur Respir J* 1991; 4 (Suppl. 14): 480s.
6. Smolensky MH, D'Alonzo GE. – Administration-time dependency of the kinetics and effect of once daily 20 mg dosing of bambuterol (B) *versus* placebo in asthma patients. *Eur Respir J* 1991; 4 (Suppl. 14): 555s.
7. Persson G, Pahlm O. – Efficacy and safety of bambuterol once daily in comparison with terbutaline *t.i.d. Clin Exp Allergy* 1990; 20 (Suppl. 1): 35s.
8. Van den Berg W, Alanko K, Sahlström K, *et al.* – Bambuterol once every evening in combination with terbutaline *t.i.d.* in asthmatic patients. *Clin Exp Allergy* 1990; 20 (Suppl. 1): 35s.
9. Knight A, Aoki F, Grossman R, Alexander M. – Bambuterol: a long-acting beta$_2$-agonist. A dose finding study in elderly COPD patients. *Eur Respir J* 1990; 3(10): 321S.
10. Danish Society of Lung Medicine. – Spirometry recommendation 1986. Copenhagen, Denmark.
11. Conover WJ, Iman RL. – Rank transformation as a bridge between parametric and nonparametric statistics. *Am Statist* 1981; 35(3): 124–129.
12. Petrie GR, Chookang J, Clark RA. – Bambuterol: efficacy in nocturnal asthma. *Am Rev Respir Dis* 1991; 143: A652.