One month treatment with the once daily oral β_2-agonist bambuterol in asthmatic patients

G. Persson*, A. Baas**, A. Knight+, B. Larsen++, H. Olsson†

One month treatment with the once daily oral β_2-agonist bambuterol in asthmatic patients. G. Persson, A. Bass, A. Knight, B. Larsen, H. Olsson. ©ERS Journals Ltd 1995.

ABSTRACT: Bambuterol is a new long-acting oral bronchodilator for once daily use in patients with asthma. It is a prodrug of terbutaline, designed to be slowly metabolized to terbutaline. Results from comparative studies have shown that it has similar clinical efficacy to other oral bronchodilators, but less side-effects. The present study was aimed at verifying the 24 h effect duration of bambuterol, 10 and 20 mg in comparison with placebo during a one month treatment period.

The study was conducted as a double-blind, randomized, parallel group placebo-controlled, multicentre trial. It started with a one week run-in period with placebo, when oral bronchodilators were withdrawn. At the end of this reference period, the patients were randomized to one of three treatments: placebo, bambuterol 10 mg, or bambuterol 20 mg, once daily in the evening. The treatment period lasted for 4 weeks. Four hundred and eighty seven patients with a mean age of 45 yrs were included.

Mean baseline forced expiratory volume in one second (FEV_1) and FEV_1 % of predicted were 2.05 *l* and 62%, respectively. Administration of 10 mg bambuterol resulted in a significant 24 h effect duration, expressed as an increase in mean daily morning and evening peak expiratory flow (PEF) (+11 *l*·min^{-1}, adjusted means) throughout the study, as compared with placebo. Bambuterol, 20 mg, gave a significant 24 h effect duration in both FEV_1 and morning and evening PEF as compared with placebo. Furthermore, the adverse events observed during the study were relatively few and mild.

In conclusion, once daily oral bambuterol is a long-acting bronchodilator, leading to improvements in spirometry and in peak flows during regular treatment. Therefore, bambuterol should be considered as a suitable alternative for treatment of asthma.
Eur Respir J., 1995, 8, 34–39.

*Dept of Allergology, University Hospital of Lund, Lund, Sweden. **Hospital Rivierenland, Tiel, The Netherlands. +Sunnybrook Medical Centre, Toronto, Ontario, Canada. ++Dept of Respiratory Medicine, Aarhus University Hospital, Aarhus, Denmark. †Clinical Research and Development, Astra Draco AB, Lund, Sweden.

Correspondence: H. Olsson
Clinical Research and Development
Astra Draco AB
P.O. Box 34
S-221 00 Lund
Sweden

Bambuterol hydrochloride (Bambec®) is the first once daily oral β_2-agonist with a 24 h duration for the treatment of asthma. It is a prodrug of terbutaline, with a considerable presystemic and metabolic stability, designed to be slowly metabolized to terbutaline [1, 2]. It has similar clinical efficacy to other oral bronchodilators, but less side-effects, especially with regard to tremor [3–6]. The low occurrence of side-effects may be due to the smooth and sustained plasma levels of terbutaline generated at steady-state. Furthermore, bambuterol is intended for the maintenance managment of asthma to secure 24 h bronchodilation, as a complement to inhaled glucocorticosteroids for the control of airway inflammation and inhaled β_2-agonists for the rapid relief of acute asthma symptoms.

Bambuterol, given once every evening, has previously been tested in short-term placebo-controlled, cross-over studies at doses of 10 and 20 mg for one week treatment periods [7, 8]. Both doses given for 2 weeks have also been tested in a cross-over, comparative study with terbutaline 5 mg plain tablets *t.i.d.* [3]. The general conclusion of the studies mentioned above was that 10 mg tablets had a bronchodilating effect for 24 h when compared to placebo. Twenty milligrams bambuterol showed a better effect over a 24 h period and was, in general, more effective than 10 mg bambuterol.

The purpose of this study was to verify the 24 h effect duration of 10 and 20 mg bambuterol tablets, given once every evening for one month, as compared to placebo.

Material and methods

Patients

Four hundred and eighty seven patients (221 females and 266 males) with bronchial asthma were included in

Table 1. – Use of asthma medication prior to the study in the 3 groups

	Placebo %	10 mg B %	20 mg B %
Oral β_2-agonist	14	13	13
Theophylline	17	28	24
Inhaled β_2-agonist	96	95	98
Inhaled steroids	68	78	63
Sodium cromoglycate	5	5	3

B: bambuterol.

this parallel group study. Their mean age was 45±15 yrs (±SD) and the mean duration of their asthma was 14±12 yrs. Mean morning baseline forced expiratory volume in one second (FEV_1) was 2.05±0.64 l, mean FEV_1 % of predicted (% pred) 62±13%, and mean reversibility in FEV_1 with a β_2-agonist, 27±13%.

To be included in the study the patients had to show a reversibility in FEV_1 of ≥15% after one inhalation of terbutaline sulphate powder, 0.5 mg·inhalation^{-1} from Bricanyl® Turbuhaler®, and the basal FEV_1 value should have been between 40–80% of the predicted normal value. The patients were not allowed to use other oral β_2-agonists, nebulized β_2-agonists, theophyllines, oral steroids, anticholinergics or antihistamines during the study. Inhaled steroids and disodium cromoglycates were allowed, if the doses were kept constant for 4 and 2 weeks, respectively, prior to and throughout the study. Inhalation with short-acting β_2-agonists was allowed when needed, but should, if possible, be avoided within 7 h prior to the daily peak expiratory flow (PEF) measurements at home, and prior to the clinic visits. The use of asthma medication prior to the study is shown in table 1.

Study design

The study was of a double-blind, randomized, parallel group, placebo-controlled multicentre design. It started with a one week placebo reference period (run-in period). At the end of the reference period, the patients were randomized into one of three treatment groups: bambuterol hydrochloride 10 mg, bambuterol hydrochloride 20 mg, or placebo, with a duration of 4 weeks. The double-blind design was preserved by using a double-dummy technique. The tablets were to be taken once daily in the evening at 8 p.m. ±1 h.

The patients visited the clinic on five occasions during the study. At the first clinic visit, which was performed in the morning within the month prior to the start of the reference period, a reversibility test was performed. FEV_1 was measured with a Vitalograph®, before and 15 min after one inhalation of 0.5 mg terbutaline sulphate. Patient demographics and medical history were also obtained at the first visit. The clinic visits were made at: start of reference period (Visit 2); end of reference period (baseline, Visit 3); after one week of treatment (Visit 4); and after four weeks of treatment (Visit 5). Measurements were performed at 8 p.m. ±1 h without

taking the study drug, when FEV_1 was recorded before and 15 min after one inhalation of 0.5 mg terbutaline sulphate.

Adverse events, recorded by the patient in a diary, were discussed and noted in the case record forms at Visits 3–5.

Diary data were collected every morning and evening during the reference period and during the treatment periods. The following recordings were made:
1. PEF (l·min^{-1}), best of three attempts, was recorded with a mini-Wright peak flow meter® in the morning on awakening and in the evening at 8 p.m. ±1 h, before study drug intake.
2. PEF was also assessed at short intervals during two consecutive dose intervals (each 24 h) by a subgroup of 119 patients in Canada. PEF was measured at home before drug administration at 8 p.m., and then 1, 2, 4, 8, 12, 18 and 24 h later. The measurements were performed during the last two 24 h intervals, at the end of the reference period and at the end of the first week of treatment.
3. Use of inhaled β_2-agonists (number of inhalations and time).
4. Asthma symptoms during the day scored as follows: 0=no symptoms; 1=mild, symptoms easily tolerated; 2=moderate, discomfort/interference with daily life; 3=severe, inability to perform usual daily activities.
5. Asthma symptoms during the night scored as follows: 0=no symptoms, slept well all night; 1=mild, slightly disturbed sleep; 2=moderate, disturbed sleep; 3=severe, awake most of the night.
6. Adverse events (reported spontaneously) during day and night scored 0–3 according to the same system used for asthma symptoms.

Daytime was defined as the time from the morning PEF measurement until intake of study drug in the evening, and night from study drug intake in the evening until PEF measurements in the morning.

Statistical methods

The primary efficacy variable was change in FEV_1 from baseline (Visit 3) to 1 and 4 weeks treatment (Visits 4 and 5). Secondary efficacy variables were the diary data, *i.e.* PEF, asthma symptoms, and number of β_2-agonist inhalations, for which the analysis was based on the changes in means from reference to treatment period. FEV_1 and PEF were analysed with analysis of variance (ANOVA) followed by pairwise comparisons, and scored and counted variables were analysed with non-parametric methods, based on rank transformation.

Ethical considerations

The study was performed according to the Declaration of Helsinki. Before starting the study, approval was received by the National Boards of Health and Welfare in each country and by local Ethics Committees. Signed or witnessed verbal informed consent was also obtained from the patient before enrolment.

Table 2. – FEV_1 values at baseline and changes from baseline after 1 and 4 weeks treatment (24 h after dose), and comparisons between the treatments

Treatment Group	Patient n	Baseline[†] (Visit 3) FEV_1 l		Patient n	Δ 1 week treatment (Visit 4) FEV_1 l		Patient n	Δ 4 weeks treatment (Visit 5) FEV_1 l	
Placebo	162	2.25	(0.89)	159	0.00	(0.35)¬	159	-0.03	(0.53)¬
B 10 mg	165	2.14	(0.79)	163	+0.05	(0.35) ** ¬	163	+0.09	(0.49) **
B 20 mg	159	2.24	(0.69)	155	+0.12	(0.34)⌐ *	156	+0.12	(0.40) ⌐

Data are presented as mean, and SD in parenthesis. [†]: End of reference period; Pt: patient; FEV_1: forced expiratory volume in one second; B: bambuterol. *: $p < 0.05$; **: $p < 0.01$.

Results

Patients

Thirty two of the 487 patients included discontinued the study for the following reasons: 23 patients due to asthma deterioration - 6 (placebo), 8 (bambuterol 10 mg) and 9 (bambuterol 20 mg); 5 patients due to adverse events - 1 (bambuterol 10 mg) with tachycardia, and 4 (bambuterol 20 mg) with atrial fibrillation, weakness and vertigo (1), tremor (1), shaking and palpitations (1), and itching rash (1); and 4 patients due to personal reasons (placebo).

Spirometry

FEV_1. Mean baseline values (raw data) recorded at Visit 3 and changes from baseline to Visit 4 and 5, *i.e.* after 1 and 4 weeks treatment, respectively, are presented in table 2. The measurements were performed 24 h after dose intake, *i.e.* in the evening. When the different treatments were compared, it was found that after one week, bambuterol 20 mg differed significantly from placebo by 0.12 *l* (adjusted means, $p=0.009$), and from bambuterol 10 mg by 0.10 *l* (adjusted means, $p=0.02$).

There was no significant difference between bambuterol 10 mg and placebo. After 4 weeks treatment, bambuterol 20 mg differed significantly from placebo by 0.16 *l* (adjusted means, $p=0.01$), and there was a difference between bambuterol 10 mg and placebo (0.09 *l*).

Reversibility in FEV_1. The reversibility in FEV_1 was tested at Visits 3–5, in order to determine whether the response of a fixed dose of an inhaled β_2-agonist 0.5 mg terbutaline, changed after 1 and 4 weeks of treatment with bambuterol. As shown in figure 1, the response to inhaled terbutaline decreased with time during treatment with bambuterol. The reversibility was statistically significantly lower for both 10 and 20 mg bambuterol after 1 week treatment (Visit 4, $p=0.029$ and $p=0.032$, respectively), and after 4 weeks treatment (Visit 5, $p=0.004$ and $p=0.016$, respectively) as compared to the reversibility at the end of the reference period. This was not observed with placebo treatment.

PEF. Mean morning (10–12 h after dose) and evening PEF (=24 h after dose) for reference and treatment periods are presented in table 3. The mean morning PEF increase during 4 weeks of treatment from the reference period were significant with bambuterol 10 mg (+11 $l \cdot min^{-1}$, adjusted means, $p=0.01$) and 20 mg (+16
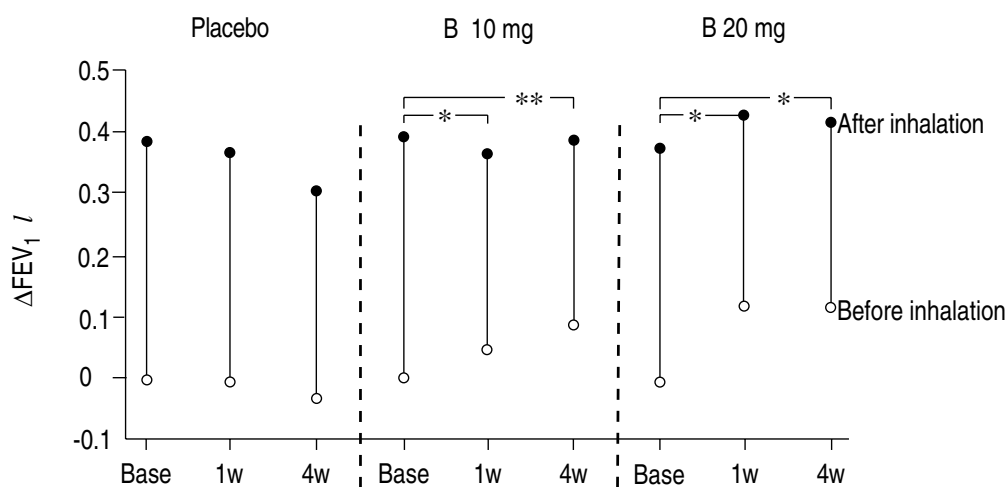

Fig. 1. – Changes in forced expiratory volume in one second (ΔFEV_1) pre ($\circ$) and post-inhalation (15 min) of 0.5 mg terbutaline sulphate ($\bullet$), recorded at baseline (end of reference period - Visit 3, Base) and after one (1w) and four (4w) weeks of treatment. B: bambuterol. *: $p < 0.05$; **: $p < 0.01$ for ΔFEV_1.

Table 3. – PEF mean values during the one week reference period, changes from reference period during 4 weeks treatment, and comparisons between the treatments

Treatment	Pt n	1 week reference period PEF $l \cdot min^{-1}$	Pt n	Δ 4 weeks treatment PEF $l \cdot min^{-1}$
Morning				
Placebo	162	367 (102)	162	+4 (35) ⎤ **
B 10 mg	165	352 (101)	165	+18 (33) ⎦ ***
B 20 mg	160	373 (96)	159	+24 (37) ⎦
Evening				
Placebo	162	405 (107)	162	-2 (32) ⎤ **
B 10 mg	165	389 (99)	165	+11 (28) ⎦ ***
B 20 mg	160	407 (96)	157	+17 (36) ⎦

Data are presented as mean, and SD in parenthesis. Pt: patient; PEF: peak expiratory flow; B: bambuterol. **: p<0.01: ***: p<0.001.

$l \cdot min^{-1}$ adjusted means p=0.0003) as compared with the changes observed with placebo. In the evening, the increase from the reference period, as compared with placebo, was also significant, with bambuterol 10 mg (+11 $l \cdot min^{-1}$, adjusted means p=0.01) and bambuterol 20 mg (+17 $l \cdot min^{-1}$ adjusted means p=0.0001). Changes in weekly means in PEF from the reference period are shown in figure 2. The weekly means of morning and evening PEF seemed to increase gradually with time during treatment with 10 mg and 20 mg bambuterol, whilst with placebo there was a tendency to lower PEF values after 2 weeks of treatment.

Impact of baseline PEF. The patients were stratified according to their baseline PEF during the reference period, into three groups: 30–60%; 60–80%; and >80% of predicted normal values. As shown in figure 3a, changes in mean morning PEF, measured during 4 weeks treatment from the reference period, were highest in the group with the lowest baseline PEF. The response in mean evening PEF followed the same pattern (fig. 3b).

PEF measured during 24 h intervals. The PEF values measured by a subgroup of 119 patients from clinics in Canada are presented in figure 4. The improvements in PEF were dose-related, and the treatment effect reached a maximum during the night or early morning. The onset of the effect was more rapid and the peak effect sustained for a longer period of time for bambuterol 20 mg than for 10 mg. Furthermore, the mean PEF (area under curve (AUC) /24 h) increased from reference period to treatment period by 10 $l \cdot min^{-1}$ for bambuterol 10 mg, and 28 $l \cdot min^{-1}$ for 20 bambuterol mg, and decreased by 6 $l \cdot min^{-1}$ for placebo. The difference was significant for bambuterol 20 mg as compared to placebo (p=0.01).

Use of inhaled β_2-agonists and asthma symptoms. The mean number of puffs, ranging 2.78–3.23 during the day and 1.53–1.80 during the night in the three different treatment groups, were small and not statistically different. Similar results were obtained with regard to asthma scores, ranging 0.55–0.64 during the day and 0.43–0.53 during the night.
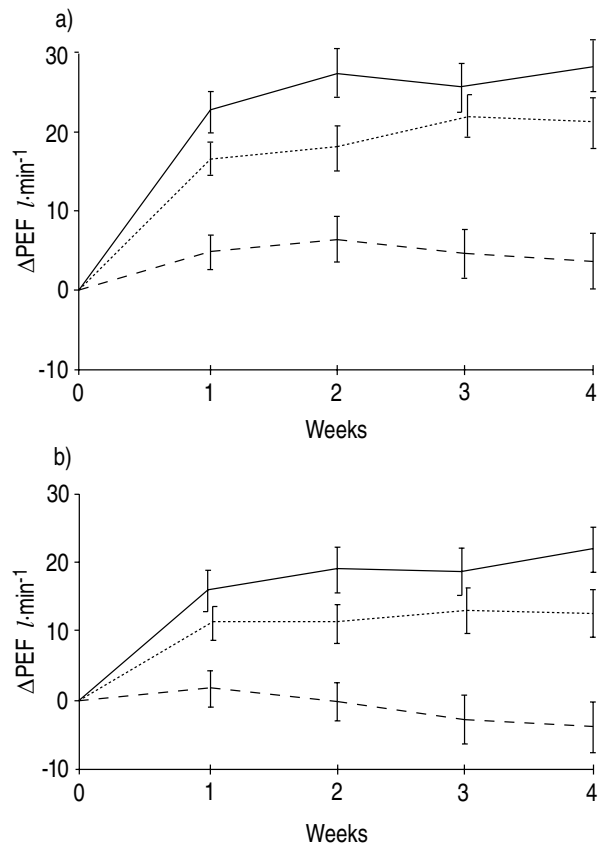

Fig. 2. – Change in: a) morning; and b) evening peak expiratory flow (ΔPEF), weekly means and SD, during treatment from the reference period with placebo (– – –); bambuterol 10 mg (··········); and bambuterol 20 mg (———).
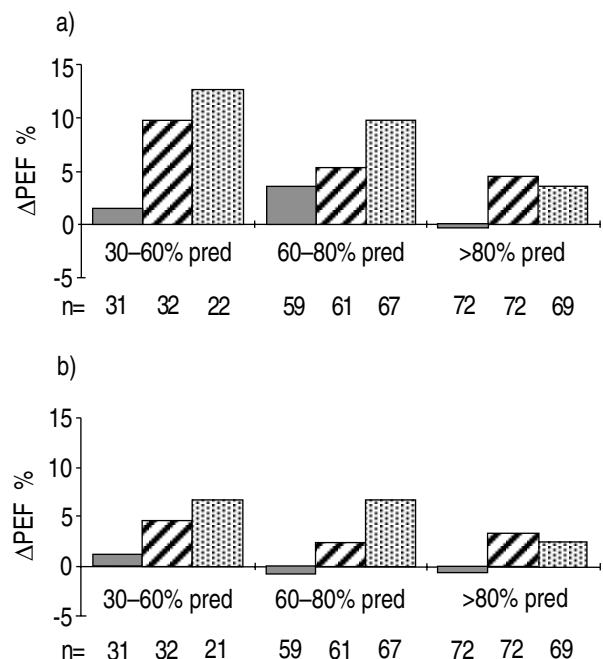

Fig. 3. – Changes in: a) mean morning peak expiratory flow (ΔPEF); and b) mean evening peak expiratory flow, measured during four weeks treatment from the reference period, in patients subgrouped with respect to baseline % of predicted normal PEF. ▨ : placebo; ▨ : bambuterol 10 mg; ▨ : bambuterol 20 mg.
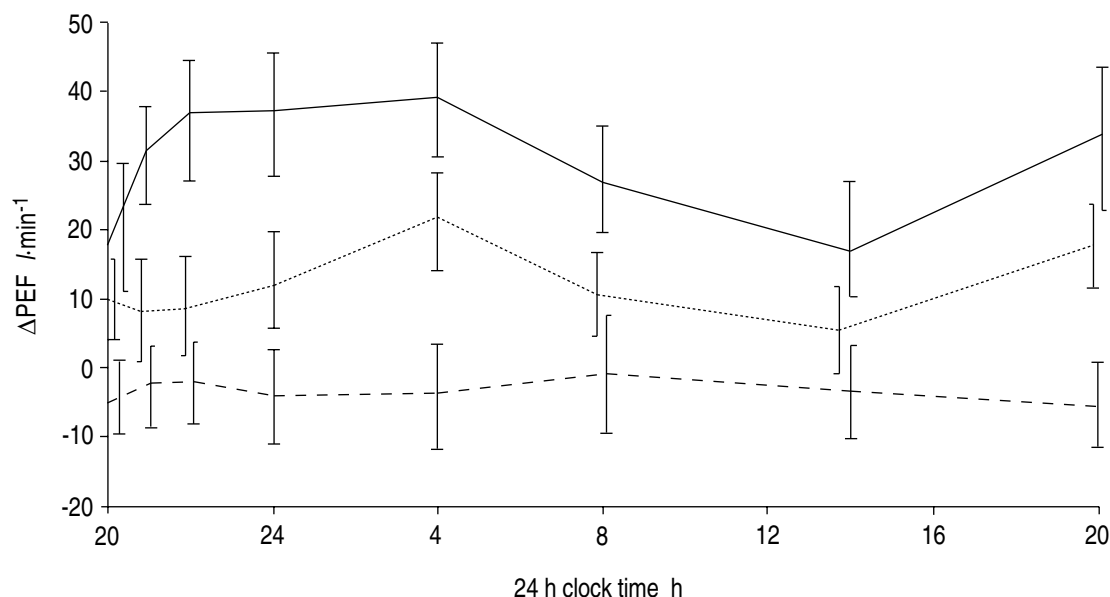
Fig. 4. – Change in peak expiratory flow *vs* time measured during the last 24 h at the end of the reference period, and the first week of treatment shown as treatment minus reference period and SEM for placebo (n=46) (− − −), bambuterol 10 mg (n=38) (⋯⋯⋯), and bambuterol 20 mg (n=35) (——).

Adverse events

The frequency of adverse events was relatively low and the intensities mainly mild or moderate. The most common events were headache and tremor. The percentage of headache was 28 and 26% during treatment with 20 and 10 mg bambuterol, respectively, and 27% during treatment with placebo. Tremor was reported by 23, 7 and 4% of the patients during treatment with 20 and 10 mg bambuterol and placebo, respectively.

Discussion

The present study was designed primarily to verify the 24 h effect duration of bambuterol 10 and 20 mg in comparison with placebo during a one month treatment period. In the study, we have chosen to place patients not "in optimal control", *i.e.* when bronchodilators are omitted, in order to be able to notice differences in the treatment groups.

Treatment with 10 mg bambuterol did not show a statistically significant difference *versus* placebo as measured by FEV_1, 24 h after administration. However, the 24 h effect duration of 20 mg bambuterol was confirmed by the improvements demonstrated in FEV_1 after 1 and 4 weeks treatment, as compared with placebo. The daily PEF recordings, on the other hand, presented a 24 h effect duration with both 10 and 20 mg bambuterol, as compared with placebo. Furthermore, a tendency to dose response in the bronchodilating effect was shown. The discrepancy between the outcome of FEV_1 and PEF assessments may raise the question of whether the mean PEF, based on daily measurements throughout the study, better reflects the changes in the disease rather than the FEV_1 measured only at relatively few clinic visits. Observations in previous studies have indicated that PEF has a good correlation with the changes in the disease [9–11].

The present results also showed that bambuterol seemed to need more than one week to achieve the maximal bronchodilating effect, which was seen, in particular, during treatment with 10 mg bambuterol. This is illustrated by increasing improvements in FEV_1 after 1 and 4 weeks of treatment, as well as the continuous increase in mean weekly PEF during the study.

The increases in PEF (12 and 24 h after dose) from the reference period were about 5–6% above placebo. These effects may seem rather modest, but the same magnitude of increase is seen in the evening in other studies of similar design with long-acting inhaled β_2-agonists [12, 13]. One explanation could be that most patients were already rather well-treated with anti-inflammatory drugs, such as steroids. The mean daily doses of inhaled steroids before randomization were: 774, 745 and 800 µg in the placebo, 10 mg bambuterol and 20 mg bambuterol group, respectively. Another explanation could be the circadian variation in lung function resulting in a peak in the late afternoon. The maximal effect of bambuterol occurs during the night, which is shown in this study to be around 4 a.m., *i.e.* the time when patients often experience a worsening of their symptoms [14–16]. In another study, in which bambuterol was given either in the morning or in the evening, the evening administration was found to produce a maximal effect around 4 a.m. about 29% better than placebo [17].

These observations are in agreement with another study on patients with nocturnal asthma, which showed that bambuterol is a suitable treatment for patients with nocturnal problems [18]. Furthermore, there were no statistically significant differences between treatments in

nocturnal asthma symptoms in this study. Again, this might be due to many of the patients using constant doses of inhaled steroids or sodium cromoglycates. It could also be due to the fact that the patients in this study already had a low level of nocturnal asthma scores before inclusion.

The use of inhaled β_2-agonists did not show any statistically significant reduction with bambuterol treatment in this study. It has been demonstrated in other studies, however, that the need for β_2-agonist inhalations has lessened with bambuterol 10 and 20 mg [4, 6, 18].

The response to inhaled terbutaline decreased with time in both bambuterol groups, but was most pronounced with 20 mg. This is probably not due to a decrease in the responsiveness of the β_2-receptors, but rather to the better baseline FEV_1 values following bambuterol therapy, which leaves less room for further bronchodilation. The fact that the maximum values were almost the same throughout the study supports this interpretation.

In these days, there are increasing worries about side-effects of inhaled local steroids even in moderate doses used during long periods of time. Therefore, it is of great interest to find a combination therapy that means a dose-reduction of the inhaled steroids. One method of administration is long-acting β_2-agonists in powder inhalers, another, which many asthma patients would prefer, is long-acting β_2-agonist tablets, e.g. bambuterol.

We conclude that bambuterol 20 mg (tablets) administered once daily in the evening showed a significant 24 h effect duration in FEV_1 during 4 weeks of treatment. With daily PEF recordings, this was also demonstrated for both 10 and 20 mg bambuterol. Furthermore, the maximal bronchodilating effect demonstrated by PEF was seen at about 4 a.m. The adverse events were relatively few, and mainly reported to be mild or moderate. Bambuterol should, therefore, be considered as a suitable alternative for treatment of asthma.

References

1. Olsson OAT, Svensson LÅ. New lipophilic terbutaline ester prodrugs with long effect duration. *Pharmaceut Res* 1984; 1: 19–23.

2. Svensson LÅ. Bambuterol: a prodrug-prodrug with built-in hydrolysis brake. *Acta Pharm Suec* 1987; 24: 333–341.

3. Van den Berg W, Alanko K, Sahlström K, Järvinen M, Mikkola E, Jansson C. Bambuterol once every evening 10 and 20 mg compared with terbutaline 5 mg three times daily. *Eur Respir J* 1989; 2 (suppl. 8): 812S.

4. 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): 35.

5. Larsén K, Schmekel B. Tremor in healthy volunteers after bambuterol and terbutaline CR-tablets. *Eur J Clin Pharmacol* 1993; 45: 303–305.

6. Pierce R, McDonald C, Bowler S, *et al.* Bambuterol yields better effect/side-effect ratio than terbutaline in elderly patients with CROAD; multicentre study Australia. *Eur Respir J* 1993; 6 (suppl. 17): 592S.

7. Vilsvik J, Langaker O, Persson G, *et al.* Bambuterol: a new long-acting bronchodilating prodrug. *Ann Allergy* 1991; 66: 315–319.

8. Knight A, Aoki F, Grossman RF, Alexander M. Bambuterol: a long-acting β_2-agonist: a dose finding study in elderly COPD patients. *Eur Respir J* 1990; 3 (suppl. 10): 321S.

9. Molema J, Lammers JW, van Herwaarden CL, Folgering HT. Effects of inhaled beclomethasone dipropionate on β_2-receptor function in the airways and adrenal responsiveness in bronchial asthma. *Eur J Clin Pharmacol* 1988; 34: 577–583.

10. Gove RI, Bruge PS, Robertson AS. Limitations of simple spirometry. *Lancet* 1986; March 22: 676.

11. Pauli G, Bigot H, Pelletier A, Kopferschmitt-Kubler MC, Roegell E. A study of the criteria used for clinical evaluation of prophylactic treatment in bronchial asthma. *Eur J Respir Dis* 1985; 67: 369–377.

12. Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airway disease. *Eur Respir J* 1991; 4: 1178–1184.

13. Faurschou P. Chronic dose-ranging studies with salmeterol. *Eur Respir J* 1991; 4: 282–287.

14. Smolensky MH, Barnes PJ, Reinberg A, McGovern JP. Chronobiology and asthma. I. Day-night differences in bronchial patency and dypnea and circadian rhythm dependencies. *J Asthma* 1986; 23: 321–343.

15. Turner-Warwick M. Definition and recognition of nocturnal asthma. *In:* Barnes PJ, Levy J, eds. Nocturnal asthma. London, Royal Society of Medicine, 1984; pp. 3–5.

16. Lewins HC, Capel LH, Smart J. Changes in forced expiratory volume throughout the day. *Br Med J* 1960; 1: 462.

17. 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.

18. Petrie GR, Chookang J, Clark RA. Bambuterol: efficacy in nocturnal asthma. *Am Rev Respir Dis* 1991; 143 (no. 4 pt 2): A652.