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Comparison between a new once-daily, bronchodilating drug, bambuterol, and terbutaline sustained-release, twice daily

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Comparison between a new once-daily, bronchodilating drug, bambuterol, and terbutaline sustained-release, twice daily. G. Persson, Y. Gnosspelius, S. Anehus.

ABSTRACT: Bambuterol is a prodrug, from which terbutaline is slowly generated. The objectives of the study were to evaluate whether bambuterol, given once daily, can control symptoms in asthmatic patients and to compare the bronchodilating effect and the side effects with those of terbutaline sustained-release (SR) tablets given twice daily. Twenty-five out-patients with bronchial asthma were treated during two consecutive 14-day periods with either 30 mg bambuterol tablets once every evening or 2 × 5 mg terbutaline SR tablets morning and evening. The study had a double-blind, cross-over and randomized design. The mean evening peak expiratory flow rate (PEFR) (*i.e.* 24 h after intake of bambuterol and 12 h after intake of terbutaline SR) was significantly ($p < 0.001$) higher during bambuterol than during terbutaline treatment (432 *vs* 415 *l*/min). The need for β-adrenoceptor agonist aerosol in the daytime was significantly ($p < 0.05$) lower during treatment with bambuterol once daily (0.70 puffs) than with terbutaline SR *b.i.d.* (1.04 puffs). The type and intensity of the side effects were the same during both treatments.

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Bambuterol is a new bronchodilator prodrug in the form of bisdimethyl-carbamate of terbutaline [1]. The terbutaline part of this prodrug is protected from being metabolized during absorption and during the first-pass through the liver. This means that bambuterol can act as an inner depot from which terbutaline is slowly generated. Human pharmacological and clinical studies have shown that bambuterol provides safe and reliable generation of terbutaline [2, 3].

Sustained-release (SR) terbutaline (administered twice daily) has a good bronchodilating effect [4, 5]. The bronchodilation obtained is comparable to that of oral sustained-release preparations of theophylline [6].

In the first clinical studies, bambuterol was administered twice daily [2, 3]. When compared to terbutaline SR, the generated terbutaline plasma concentration curve and bronchodilation showed a more prolonged profile after bambuterol [2]. A good correlation was found between the plasma concentration of terbutaline and the bronchodilating effect. Bambuterol given once daily to healthy volunteers produced a plasma profile of generated terbutaline from bambuterol with a peak/trough ratio of 1.9 compared to a ratio of 2.4 for terbutaline SR given twice daily (Nyberg *et al.*, personal communication). These results indicate that bambuterol administered only once daily may have a good bronchodilating effect.

The aim of the present study was to evaluate whether bambuterol is suitable for once daily administration in asthmatic patients, with regard to the duration of its bronchodilating effect and its side effects, compared to terbutaline SR treatment twice daily.

Patients and methods

Twenty-five outpatients (eleven males and fourteen females) with bronchial asthma participated in the study. All patients received written and verbal information and gave their informed consent to participation. The study was approved by the local Ethics Committee at the University of Lund.

The study consisted of two consecutive treatment periods, each lasting for fourteen days: bambuterol tablets 30 mg once every evening and terbutaline SR 10 mg (two 5 mg tablets) *b.i.d.* The treatments were given by using a randomized, double-blind, cross-over design with a double-dummy technique. Each patient's medication was provided in blister-packs, in order to obtain maximal patient compliance.

The patients were between 18 and 60 yr old (mean 40.6 yr) with a mean weight of 72.3 kg (range 54 to 95 kg). The mean duration of asthma was 21 yr (range 3–45 yr) and the mean basal forced expiratory volume in one second (FEV_1) 2.18 *l* (range 0.75–3.95 *l*). The mean increase in FEV_1 was 44% (19–147%) 15 min

after the last inhalations of terbutaline (Bricanyl®) aerosol or salbutamol (Ventoline®) aerosol (1+5 puffs, with an interval of 15 min). Patients receiving inhaled or oral corticosteroids were allowed to continue this treatment, provided that the dosage was kept constant during the study. Theophyllines, anticholinergics and other β-adrenoceptor agonists were discontinued, but rimiterol (Pulmadil®) aerosol was permitted, if needed, but not later than four hours before each PEFR recording.

The PEFR was recorded (highest of three values) on the morning and evening before drug intake, using a Wright mini-Peak Flow Meter. The patients also recorded their asthma symptoms throughout the day and night (breathlessness, cough, wheezing), the number of times they woke during the night because of asthma, the use of rimiterol aerosol and the side effects (tremor, palpitations, headache and uneasiness) during the day and night. Asthma symptoms and side effects were scored using a six-graded scale: 0 = no symptoms; 1 = slight; 2 = slight to moderate; 3 = moderate; 4 = moderately severe; 5 = severe symptoms.

At the end of the study, the patients were asked in which of the two periods they experienced the fewest asthmatic symptoms and the fewest side effects and which of the two periods they preferred.

The statistical evaluations were based on the last ten days in each 14-day period. A steady state had then been obtained and the risk of any carry-over effect was considered to be eliminated. The student's paired t-test was used to compare the PEFR and the number of rimiterol puffs in the two periods. The Wilcoxon signed rank test was used in the evaluation of the subjective grading of asthmatic symptoms, the side effects, the number of times the patients awoke, and the patient's preference for one of the preparations. In this study, the power of the statistical evaluation was 80%, using the paired two-tailed t-test and a p-value of less than 0.05 to reveal a true difference of at least 10% in the mean PEFR between treatments.

Results

The mean morning PEFR (±SEM) was almost the same during the two treatments (bambuterol: 425±23 *l*/min; terbutaline: 415±22 *l*/min), but the mean evening PEFR was significantly higher ($p < 0.001$) during bambuterol (432±23 *l*/min) than during terbutaline SR treatment (415±23 *l*/min). The day-to-day variations in the morning and evening PEFR during the two periods are shown in figure 1. The need for a β-adrenoceptor agonist aerosol was small during both treatments (table 1). However, in the daytime the number of puffs was significantly ($p < 0.05$) lower when bambuterol was used.

The patients scored their asthma symptoms as mild-to-moderate during both treatment periods (table 1). No statistically significant difference was found between the treatments, but there was a

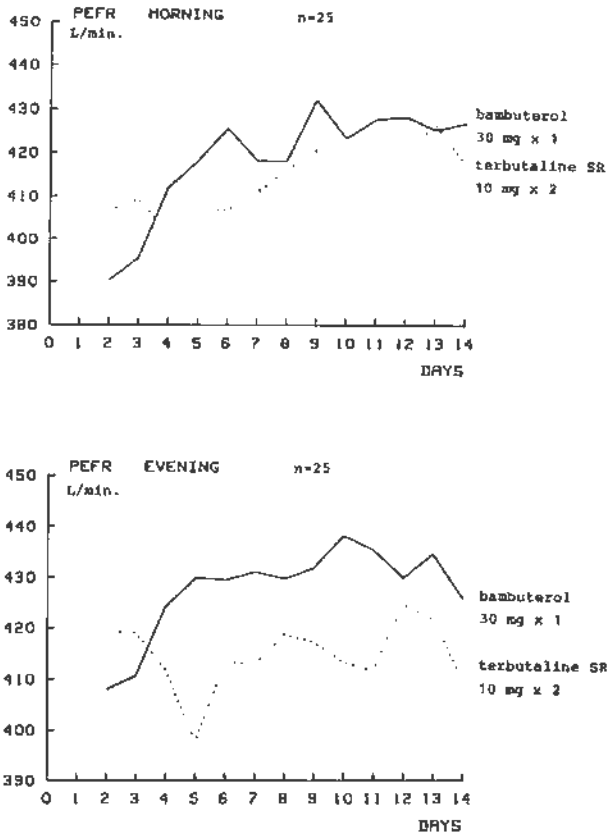

Fig. 1. Day-to-day variations in the morning PEFR (upper panel) and the evening PEFR (lower panel) during 14 days of treatment with bambuterol once daily or sustained-release terbutaline twice daily. Statistical calculations were made on days 5–14.

tendency towards fewer asthma symptoms during treatment with bambuterol. Five patients reported sleep disturbances due to asthma during the bambuterol period and seven during treatment with terbutaline SR (table 1).

Very few patients experienced any side effects and those who did scored them as mild-to-moderate (table 1). There was no difference between the two treatment periods.

Fifteen, out of 25 patients, preferred the period with bambuterol and only one patient failed to distinguish between the two periods (table 2).

Discussion

The results in healthy volunteers indicated that bambuterol should be suitable for once-daily administration. One objective of the present study was to evaluate this in patients with bronchial asthma. The next was to find out at what time of day bambuterol should be administered. To achieve an effective protection against early morning wheezing, which is very troublesome for many asthmatic patients, bambuterol should be administered in the evening.

The reference drug used in this study was terbutaline SR. This β-agonist was chosen because of the long duration of its effect and its twice-daily dosage

Table 1. - Asthma symptom score, sleep disturbances, side effect score and number of ß-aerosol puffs during the last ten days in each period (mean values, n=25)

	DAY				NIGHT			
	bambuterol		terbutaline SR		bambuterol		terbutaline SR	
	30 mgx1		10 mgx2		30 mgx1		10 mgx2	
Asthma symptoms*	0.24	(13)	0.36	(13)	0.11	(9)	0.16	(10)
No. of awakenings					0.04	(5)	0.08	(7)
Tremor*	0.06	(3)	0.10	(4)	0	(0)	0.02	(1)
Palpitations*	0.01	(1)	0.02	(3)	0	(0)	0	(0)
Headache*	0.07	(6)	0.05	(5)	0.04	(4)	0.06	(7)
Uneasiness*	0	(0)	0.01	(1)	0	(0)	0.02	(2)
Mean no. of puffs	0.70±0.29		1.04±0.39		0.18±0.08		0.32±0.16	
	——— p<0.05 ———							

* Score using a six-grade scale (0—5). Number of patients reporting asthma symptoms, sleep disturbances and/or any side effect is in brackets.

Table 2. - Preferences for the two treatments (number of patients, n=25)

	bambuterol 30 mgx1	terbutaline SR 10 mgx2	no preference
Fewest side effects	12	7	6
Fewest asthma symptoms	15	6	4
Preference	15	9	1

regimen. Terbutaline SR has been shown to have a more prolonged duration of effect than plain tablets [7] and it can prevent early morning dyspnoea [8]. Compared to plain terbutaline tablets, treatment with terbutaline SR tablets increases the morning lung function values in asthmatic patients [4, 5].

The administration of bambuterol once daily to asthmatic patients produced better bronchodilation and fewer asthma symptoms than terbutaline SR given twice daily. The PEFR, recorded in the evening (24 h after administration of bambuterol and 12 h after the morning dose of terbutaline SR), was significantly higher during bambuterol treatment, which indicates a clinically significantly prolonged duration of effect without any increase in the frequency and intensity of side effects. No significant difference in PEFR was seen between the two drugs in the morning. This probably reflects the slow absorption of terbutaline from terbutaline SR during the night, compared with the day, resulting in a high plasma concentration of terbutaline in the morning and consequently a good morning lung function. Thus, the present study is in accordance with the results in healthy volunteers where bambuterol given once daily produced a more prolonged and stable terbutaline plasma concentration curve than did terbutaline SR (*b.i.d.*). (NYBERG *et al.*, personal communication).

In contrast to the present study, the results of another study in asthmatic patients revealed that treatment with bambuterol given once daily produced the same bronchodilation and the same incidence of side effects as did terbutaline SR given twice daily [9]. The doses and dosage regimens used were the same as those in the present study. However, the patients were somewhat older and had a lower mean basal FEV_1 value than those in the present study. They also used more β-adrenoceptor agonist aerosol during both treatments. About two-thirds of the patients were also dependent on corticosteroid treatment, as compared to about one-third in the present study. These differences may have contributed to the discrepancy in results between the two studies.

In conclusion, bambuterol seems to be suitable for a once daily administration to asthmatic patients. When administered once daily, 30 mg bambuterol provides better bronchodilation, with the same frequency and intensity of side effects, than does 10 mg terbutaline SR given twice daily.

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RÉSUMÉ: Le Bambutérol est une pro-drogue de la Terbutaline qui libère lentement ce dernier produit. Les objectifs de l'étude étaient d'évaluer si le Bambutérol, administré une fois par jour, peut contrôler les symptômes chez les patients asthmatiques et de comparer son effet broncho-dilatateur et ses effets collatéraux avec ceux des comprimés de Terbutaline à libération continue, administrée deux fois par jour. 25 patients ambulatoires, atteints d'asthme bronchique, ont été traités pendant deux périodes consécutives de quatre jours, soit par 30 mg de Bambutérol en comprimés, à administrer en une fois le soir, soit au moyen de deux comprimés de Terbutaline à 5 mg, administrés le matin et le soir. L'étude était en double aveugle avec permutation croisée et randomisation. Le débit expiratoire de pointe moyen du soir (c'est-à-dire 24 h après la prise de Bambutérol et 12 h après la prise de Terbutaline à libération lente) était significativement plus élevé ($p < à 0.001$) au cours du traitement par le Bambutérol par rapport au traitement à la Terbutaline 432 *vs* 415 *l*/minute). L'emploi moyen d'aérosols d'agonistes bêta-adréno-récepteurs pendant la journée s'avère significativement plus faible ($p < à 0.05$) au cours du traitement au moyen de Bambutérol à administration une fois par jour (0.70 puffs) qu'avec la Terbutaline, deux fois par jour (1.04 puffs). Le type et l'intensité des effets collatéraux furent similaires pendant les deux traitements.