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Bambuterol: clinical effects of three doses of bambuterol once daily in asthmatic patients

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Twenty-two asthmatics received bambuterol solution, a terbutaline pro-drug, once every evening. The following doses were each given orally for 7 days in a double-blind cross-over study: 0.185, 0.270 and 0.400 mg/kg. Bambuterol 0.270 mg/kg was preferable regarding clinical effects and side effects. The plasma concentration of generated terbutaline showed a slow linear decrease at all doses. Tests of two methods for objective measurements of tremor in five patients did not add any new data compared with the subjective recordings.

Key words: asthma; terbutaline; bambuterol; tremor.

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Bambuterol is a pro-drug of terbutaline with high metabolic stability. It functions as an "inner depot" from which terbutaline is slowly formed (6, 10). The pharmacokinetic and clinical results show that bambuterol has a good and long-lasting bronchodilating effect and the same types of side effects as terbutaline (3). Thirty mg bambuterol as tablets, approximately 0.400 mg/kg administered once daily to asthmatics produces bronchodilating effects comparable with or better then 10 mg terbutaline sustained-release tablets twice daily (7). This sustained release formulation of terbutaline has proved to have a good anti-asthmatic effect (2, 5) comparable to sustained release theophylline in the long-term treatment of asthmatics (5).

The aim of the present study was to examine the clinical effects of three doses of bambuterol. Further, a kinetic study on plasma-terbutaline was performed and three different methods of tremor measurement were evaluated.

PATIENTS AND METHODS

The trial was performed with a double-blind and cross-over design with randomized allocation of the three bambuterol doses. The study consisted of a 7-day run-in period with the patients' ordinary treatment and three consecutive periods of 7 days with different doses of bambuterol solution: 0.185, 0.270 and 0.400 mg/kg administered once daily in the evening.

Twenty-two patients (12 men and 10 women), mean age 47.6 years (range 22–69) suffering from "stable" reversible airways obstruction, completed the study. The patients fulfilled the criteria for asthma according to the American Thoracic Society (1). The mean duration of asthma was 17 years (range 3–47), mean weight 73 kg (range 49–106), mean basal forced expiratory volume in 1st s (FEV_1) 1.7 l (range 0.7–2.7). The mean increase in FEV_1 was 38% (range 20–80) 15 min after 2 puffs rimiterol aerosol (Pulmadil). Ten patients suffered from non-allergic asthma and 12 had extrinsic asthma, 4 were smokers, 7 were ex-smokers and 11 were non-smokers. During the study inhaled and oral steroids were allowed, but the dose was kept constant for 1 month before and during the trial. Twenty patients used inhaled steroids and two received prednisone tablets 2.5 and 5 mg/day respectively. Theophyllines, anticholinergics and other beta-adrenoceptor agonists were not allowed, only

Pulmadil and Ventoline aerosol, which could be used when needed but not later than 3 h (Pulmadil) or 8 h (Ventoline) before each measurement. Patients recorded PEF morning and evening, asthma symptoms day and night (breathlessness, cough and wheezing graded from 0–5: 0 = no symptoms, 1 = slight symptoms, 2 = somewhat moderate symptoms, 3 = moderate symptoms, 4 = somewhat severe symptoms, 5 = severe symptoms. Patients also recorded the number of times they woke up during the night due to asthma symptoms, use of beta-stimulating aerosol day and night (time and number of puffs), and side effects day and night (tremor, uneasiness, palpitations, headache, rash and other side effects) graded from 0–5.

On day 7 in each period in the morning (i.e. 14 h after drug intake) and in the evening (i.e. 24 h after drug intake) the following were recorded in the clinic: Blood pressure (mmHg), supine (after 5 min) and standing (after 1 min), pulse rate (beats/min) supine and standing, FVC, FEV_1 and side effects.

At the end of the study the patients were asked in which period they experienced least asthma symptoms and side effects and which period they preferred.

Twenty-eight patients were included and six were withdrawn, three during the run-in period, two during treatment with bambuterol 0.185 and 0.400 mg/kg respectively and one because of bad patient compliance.

Plasma-terbutaline. Blood samples were collected from 11 of the patients 14, 16.5, 19, 21.5 and 24 h after drug intake, and the plasma concentration of generated terbutaline was analysed by gas-chromatography and mass spectrometry.

Objective tremor measurements. Two different objective measurements were performed in five patients 14, 16.5, 19, 21.5 and 24 h after drug intake. At these times the patients also recorded subjective tremor as described above.

Finger oscillations were performed by an opto-electronic displacement transducer that measures the distance to a reflecting tape attached to the nail of the right finger. The right arm was supported from the elbow and the right hand was supported except for the middle finger. The displacement signal was amplified and electronically derivated to obtain a signal proportional to velocity. The velocity signal was then squared and averaged with a time constant of 2 s. The square root of the mean value during the last minute of a 5 min period was used for quantitative estimation of the tremor.

The patients then had to draw a line between two printed sinus-curves 5 mm apart without touching the paper with their hand. This test was repeated 4 times each time and the number of drawings outside the curves were recorded.

Statistics

A ranking was made of the bronchodilating effect during the three periods. FEV_1 amount and time of possible beta-agonist inhalations were taken into consideration. The periods were ranked from 1 to 3, with 1 indicating the best period. Statistical analysis was performed in two ways a) analysis of on raw ranking values; b) Kruskal-Wallis analysis (non-parametric analysis of variance) on raw ranking values. For all variables the results of the two approaches showed close agreement.

RESULTS

Clinical effects

The following effect parameters were statistically evaluated morning and evening: PEF, asthma score, number of beta-agonist aerosol puffs, FEV_1 and side effects recorded by the patients. Those of the variables that showed statistical significance between treatments are shown in Table 1. There was no significant difference between bambuterol 0.270 and 0.400 mg/kg as to number of beta-agonist aerosol puffs and FEV_1, but both doses were significantly better than bambuterol 0.185 mg/kg as to anti-asthmatic effect. 0.400 mg/kg caused significantly more side effects than 0.185 mg/kg. There was no significant

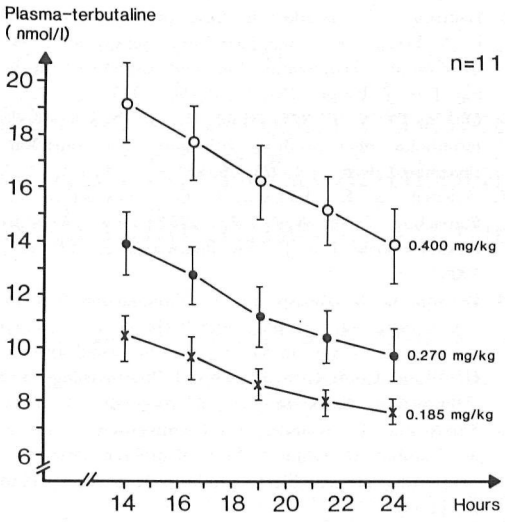

Fig. 1. The plasma concentration of terbutaline after administration of different doses of bambuterol.

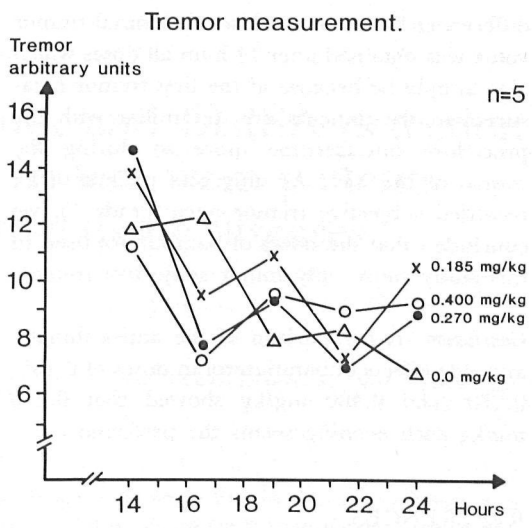

Fig. 2. Finger tremor after administration of different doses of bambuterol.

difference between blood pressure or pulse in the supine and standing positions after administration of the three doses.

Plasma-terbutaline

The plasma concentration of generated terbutaline 14, 16.5, 19, 21.5 and 24 h after administration of bambuterol 0.185, 0.270 and 0.400 mg/kg shows a linear decrease with time at all three doses (Fig. 1).

Special tremor measurement in five patients

One patient recorded subjective tremor once (grade 1), otherwise no tremor was noticed. One patient was unable to draw a line between the printed sinus-curves without crossing the predrawn lines on all three doses, the other four could draw between the lines on all three doses. There were no differences in finger tremor between the different doses, including the run-in period, but at all doses a higher tremor value was obtained 14 h after drug intake compared with the values obtained later in the day (Fig. 2).

DISCUSSION

In this study we found no significant difference between bambuterol 0.400 and 0.270 mg/kg as to anti-asthmatic effect, but both doses were better than bambuterol 0.185 mg/kg. This is in accordance with the findings of Sandstrom et al. (9). However, 0.400 mg/kg bambuterol caused significantly more subjective side effects than 0.185 mg/kg. On the basis of these data, bambuterol 0.270 mg/kg seems to be preferable. A good correlation between the bronchodilating effect and plasma-terbutaline concentration has been shown (3, 4). Further, it has been shown that bambuterol acts as an inner depot from which terbutaline is slowly generated and that bambuterol gives long-lasting and stable terbutaline concentrations (3, 4, 6, 10). The latter was confirmed in this study, which showed a slow linear decrease in plasma-terbutaline concentration for all three doses.

As tremor is one of the more common side effects with β-agonists, three different methods of measuring tremor were used in five patients. Drawing a line between two printed curves was too insensitive for outlining differences between the three bambuterol doses and no bambuterol. The finger oscillation method also showed no

differences between the doses. Maximal tremor value was obtained after 14 h on all doses which may simply be because at the first tremor measurement the patients are unfamiliar with the procedure but become more so during the course of the day. As only one patient of 22 recorded subjective tremor once (grade 1), we concluded that the doses of bambuterol used in this study cause only minor subjective tremor.

Conclusion. A comparison of the anti-asthmatic and side effects of bambuterol in doses of 0.185, 0.270, and 0.400 mg/kg showed that 0.270 mg/kg each evening seems the preferred.

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