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TRADE NAME(S):  
Bambec®

NAME OF ACTIVE INGREDIENTS(S) INN:  
bambuterol

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CLINICAL STUDY SYNOPSIS

Final

Title of the study: A dose-finding study with bambuterol oral solution as maintenance therapy to children (3-5 years) with asthma

Principal investigator: Eric Duiverman, M.D., Ph.D.

Study site(s): Juliana Children's Hospital, The Hague, the Netherlands

Publication (reference):

Study period: 911024-930407

Clinical phase: IIB

Objectives: The primary objective of the study was to measure the efficacy on lung function of two doses of bambuterol solution. The effect was measured after two weeks treatment with bambuterol and was compared to the effect after placebo treatment. The primary efficacy variable was total respiratory resistance measured with the multiple frequency oscillation technique (POT).

Study design: It was double-blind, randomized, placebo-controlled and of a cross-over design.

Number of patients (total and for each treatment): Twenty-six children (14 boys and 12 girls) with a mean age of 3.7 years (range: 3-5) were included in the study (21 patients on bambuterol 0.5mg/kg b.w., 22 on bambuterol 0.25 mg/kg b.w. and 22 on placebo).

Diagnosis and criteria for inclusion: 3 to 5 year old boys and girls. Children with chronic asthma symptoms and in need of bronchodilator therapy regularly or when necessary. A decrease in respiratory resistance at 6 Hz of ≥20% after inhalation of terbutaline 0.2 mg/kg body weight with a jet nebulizer. Informed consent.

27 October 1995
Investigational drugs, dose and mode of administration, batch No.: Bambuterol hydrochloride oral solution 0.5 mg/mL (batch No. DRH54) and 1 mg/mL (batch No. DRH53) (black currant taste).

Reference drugs, dose and mode of administration, batch No.: Placebo for Bambuterol hydrochloride oral solution with quinine hydrochloride (0.04 mg/mL) (batch No. DRH11) (black currant taste).

Duration of treatment: The study started with a run-in period of two weeks. There were then three treatment periods of two weeks each. The treatment periods were separated by wash-out periods of two weeks each. Placebo solution was not administered during the run-in and the wash-out periods. The three treatment periods were Bambuterol solution 0.25 mg/kg b.w., Bambuterol solution 0.50 mg/kg b.w. and placebo, with administration once in the morning during all treatments.

Assessment methods: FOT measurements (primary efficacy variable resistance \( R_{res} \)) and secondary efficacy variables reactance \( X_{res} \) and frequency dependence of resistance \( (\Delta R_{res}/\Delta f) \) and blood pressure and pulse rate measurements were made at the end of each treatment period at visits 3, 5 and 7. At each visit measurements were made before medication intake (0 h) and 4 hours after medication intake. The measurements before medication intake were to be made between 7 and 10 am, approximately at the same time of the day at all three visits. At baseline, FOT measurements were made at the end of the run-in and the wash-out periods at visits 2, 4 and 6. The measurements were to be made between 7 and 10 am, approximately at the same time of the day at all visits. A variation in the FOT measurements of \( \leq 10\% \) at visit 2, 4 and 6 was accepted. A larger variation after a second attempt was to exclude the patient from further participation in the study. Further, in the diary cards the following was recorded by the child's parents twice daily, morning and evening, during run-in and during the treatment periods: the use of inhaled \( \beta_2 \)-agonists during day and night, together with the time of inhalation, asthma symptoms during day and night, adverse events during day and night, the number and length of awakenings due to asthma during night, the time of intake of study medication and all occasionally used medication that was not recorded in the case record form as maintenance medication for asthma or any other disease.

Statistical methods: The data was analysed by ANOVA.

Summary of results: Only 13 patients completed the study due to the fact that several patients (9) were withdrawn from the study because the variation in the resistance \( R_{res} \) was not allowed to vary more than 10 % at visit 2, 4 and 6. Thus, unfulfillment of this variability condition was the most common reason for a study termination in advance, which resulted in many missing treatment periods and a considerable loss of power in the statistical analyses. Therefore, no statistical difference could be found between the treatments regarding the resistance \( R_{res} \). Further, when comparing the differences between measurements before and four hours after the last drug intake, there was a statistically significant increase in the frequency dependence of resistance \( (\Delta R_{res}/\Delta f) \) after treatment with Bambuterol 0.5 mg/kg b.w. as compared to placebo (4.72 cm H\(_2\)O s/L x 10\(^3\)). There were also statistically significant increases in the reactance \( X_{res} \) after treatment with Bambuterol 0.5 mg/kg b.w. as compared to both Bambuterol 0.25 mg/kg b.w. and placebo (0.74 and 0.91 cm H\(_2\)O s/L, respectively). For the resistance \( R_{res} \), there were no statistically significant differences between the different treatments, and this was also the case for the systolic and diastolic blood pressure, as well as, for the pulse rate. Further, for the diary variables, there were no statistically significant differences between the treatments.
Conclusion(s): Bambuterol 0.5 mg/kg b.w. once daily at steady state showed a statistically significant bronchodilating effect with respect to the differences in the reactance ($X_m$) between the measurements before and four hours after the last dose, as compared to both bambuterol 0.25 mg/kg b.w. and placebo. For the frequency dependence of resistance ($dR_m/df$), this difference was only statistically significant when compared to placebo. No statistically significant differences could be found between the treatments regarding the resistance ($R_m$). Further, both doses of bambuterol were well tolerated. The overall incidence of adverse events was similar during the three treatment periods.