CLINICAL STUDY SYNOPSIS

Title of the study: A placebo controlled dose-finding study with bambuterol in children with reversible obstructive airway disease. A multicentre trial performed in Sweden

Co-ordinating Investigator: Dr Viggo Graff-Lonnevig, Sachsska Children's Hospital, S-116 69 STOCKHOLM, Sweden

Study centre(s): Multicentre study in Sweden - Stockholm, Nacka, Huddinge, Jönköping and Danderyd

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Study period: September 1986 - June 1987

Clinical phase: IIA

Objectives: To find an appropriate clinical dose of bambuterol tablets administered once daily (evening) to children. The dose should give a 24-hour bronchodilation with few adverse events.

Study design: Placebo controlled, double-blind, randomized, cross-over design. A run-in period followed by four consecutive treatment periods (no washout).

Number of patients (total and for each treatment): Seventy-two patients (50M/22F) entered the study; 70 into placebo, 70 into 2.5 mg, 69 into 5 mg and 68 into 10 mg.

Diagnosis and criteria for inclusion: Boys and girls (out-patients) 6-12 years old with stable reversible (COAD). A reversibility in FEV₁₀ ≥15% after inhalation of 0.50 mg terbutaline (Bricanyl®) via Nebuhaler®.

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Investigational drugs, dose and mode of administration, batch No.:
Bambuterol tablets 2.5 mg (DMA 101), 5 mg (DMB 25) and 10 mg (DMB 26).

Reference drugs, dose and mode of administration, batch No.:
Placebo for bambuterol tablets 2.5, 5 and 10 mg, (DMF 2).

Duration of treatment:
Run-in period one week, treatment periods each one week.

Assessment methods:
At the clinic: FEV₁, FVC, blood pressure, pulse rate, adverse events and plasma concentration of terbutaline on the last day in each treatment period. Haematology and clinical chemistry at entry and after each treatment.
At home twice daily (diary): PEFR, asthma symptoms, adverse events, number of awakenings due to asthma and use of a β₂-agonist aerosol.

Statistical methods:
Two-way ANOVA followed by pairwise comparisons between treatments concerning FEV₁, FVC, PEFR, blood pressure, pulse rate and no. of β₂-agonist puffs. For subjectively graded variables non-parametric methods based on sign-rank were used.

Summary of results:
Patients were on average 9 years old with an FEV₁ of normal predicted value of about 63%. An inhaled steroid or disodium cromoglycate in a constant dose was used by 69% and 97% used inhaled salbutamol when needed. None of the doses showed a 24 hours effect-duration. The changes in FEV₁, FVC and PEFR were small and statistically not significant as compared to placebo. The largest improvements were seen in PEFR with 5 and 10 mg bambuterol (3%) 12 hours after medication intake. Other efficacy variables showed no clinically significant changes after the treatment periods as compared to placebo. Only with 10 mg bambuterol had most children a detectable plasma concentration of terbutaline (95%). The cardiovascular effects and the changes in haematology and clinical chemistry after the treatments were small and of no clinical relevance. Four patients were withdrawn due to asthma deterioration. No serious adverse events was reported.

Conclusion:
Bambuterol 2.5, 5 and 10 mg once every evening are safe but not effective in children between 5 and 14 years of age. Investigation of pharmacokinetics of bambuterol in children has to be performed.

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