CLINICAL STUDY SYNOPSIS

Title of the study:
The efficacy and safety of bambuterol in children (6-12 years) with asthma. A dosage regimen study.

Coordinating investigator:
Göran Wettrell, M.D., Dept. of Paediatrics, Kårnsjukhuset, S-541 85 Skövde, Sweden

Study site(s):
Multicentre study in Sweden - Skövde, Jönköping, Karlskrona, Karlstad, Örebro, Norrköping, Stockholm, Ängelholm

Publication (reference): -

Study period:
27th February-23rd October 1990

Clinical phase:
II A

Objectives:
To investigate which dosing regimen of bambuterol, 20 mg daily, is most appropriate in terms of efficacy and safety

Study design:
Placebo controlled, double-blind, randomized, crossover design. A run-in period followed by three consecutive treatment periods (no washout). The treatment periods were bambuterol administered once in the evening (20 mg), bambuterol twice daily morning and evening (10 mg each time) and placebo.
Number of patients (total and for each treatment):
Sixty-four patients (34 M/30 F) entered the study; 63 into placebo period, 63 into 10 mg twice daily period and 62 into once daily period

Diagnosis and criteria for inclusion:
Boys and girls (out-patients) 6-12 years old with asthma. A reversibility in FEV$_{1.0}$ or PEF ≥15% after inhalation of 0.4 mg salbutamol (Ventolin® with Diskhaler®)

Investigational drug:
Bambuterol tablets 10 mg (DOC 29) and 20 mg (DOE 111)

Reference treatment(s):
Bambuterol placebo tablets 10 mg (DNC3) and 20 mg (DNB 108)

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

Assessment methods:
At the clinic in the afternoon: FEV$_{1.0}$, blood pressure, pulse, adverse events, acceptability of treatment, treatment preference, compliance with medication intake and plasma concentration of generated terbutaline. At home twice daily (recorded in a diary): PEF morning and evening (primary efficacy variables), asthma symptoms, use of rescue medication, awakenings due to asthma and time awake and adverse events.

Statistical methods:
Data were analyzed using ANOVA. Asthma symptoms, adverse events, number of times awake and total time awake were rank transformed before analyzed. Treatment preference was also rank transformed before analyzed with Friedman's test. For diary data, means for day 4-7 in each period were computed and used as variables in the analyses.

Summary of results:
Patients on average 8.6 years old with an FEV$_{1.0}$ of predicted normal value of about 73%. Inhaled anti-inflammatory therapy in a constant dose was used throughout the study by 72% of the patients and inhaled salbutamol as rescue medication by 83%.

Bambuterol 20 mg once daily showed an increase in PEF of 7% in the morning and 6% in the evening, over placebo. Bambuterol 10 mg twice daily showed an increase in PEF of 8% (morning) and 7% (evening) over placebo. The increases were statistically significant (p<0.001). Increases in FEV$_{1.0}$ compared with placebo were 5% (once daily; p<0.01) and 8% (twice daily; p<0.001). The differences between the active treatments were small and statistically non-significant.

The use of rescue medication night-time was less during the once daily period than during placebo (p<0.01). No statistically significant treatment differences were shown in any other efficacy variable. The acceptability (asthma control and tolerability) was higher for active treatment than for placebo (p<0.05).

Changes in blood pressure were very small throughout the study. Mean pulse showed an increase from baseline of around 7 beats/min. The difference between active treatments and placebo was statistically significant (p=0.0002) but no individual increases were judged as clinical important.
The intensity of adverse events was low and the treatment differences in intensity was statistically non-significant. No patient withdrew due to adverse events.

Two patients withdrew due to asthma deterioration. The patients were hospitalized, which is, by definition, a serious adverse event. The two patients recovered completely. The withdrawals took place during the placebo and the twice daily treatment periods.

Conclusion(s):

- administration of bambuterol 20 mg once daily in the evening and bambuterol 10 mg twice daily morning and evening to children 6-12 years old resulted in a statistically significant improvement compared with placebo, both in PEF and in FEV$_{1.0}$
- the parents' subjective judgement accompanied the objective measurements i.e. an improvement of lung function with active treatment compared with placebo
- the once daily administration was comparable in effect with the twice daily administration, both in the mornings and in the evenings
- both dosing regimens were well tolerated, in adverse events as well as in blood pressure and pulse
- bambuterol 20 mg once daily is a dosing regimen that may be recommended to children in the age group 6-12 years in terms of both efficacy and safety. It is also more simple to take than the twice daily administration, which may increase compliance.