CLINICAL STUDY SYNOPSIS

Title of the study: A pharmacokinetic study of Bambuterol oral solution at two dosage regimens in pre-school children with asthma symptoms

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Study period: February 1991 - June 1991

Clinical phase: I

Objectives: Primary: to investigate the bambuterol and terbutaline concentration levels in blood plasma and urine. Secondary: efficacy on lung function by asthma symptoms assessments and, when possible, PEF measurements.

Study design: Randomized, double-blind and of a cross-over design. The study included two treatment periods preceded by a run-in period.

Number of patients (total and for each treatment): 12 patients (8 boys/4 girls) entered and completed the study. The mean age was 4.8 years (range 3-6).

Diagnosis and Criteria for Inclusion: The patients should have recurrent asthma symptoms and a need of bronchodilators, regularly or at need.

Investigational drug: Bambuterol oral solution (black currant flavour) once daily in the evening (10 mg, batch no. DQK 46) and twice daily morning and evening (5 mg, batch no. DQK 53).

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Reference treatment(s): Placebo for bambuterol oral solution (black currant flavour; batch no. DQK 10).

Duration of treatment: The two treatment periods and the run-in period were each one week.

Assessment methods: Blood and urine sampling for determination of bambuterol and terbutaline concentrations after one week of treatment. Blood samples were collected just before intake of last dose and at 3 and 6 hours after. Urine was collected between 3 and 6 hours after intake of last dose. Clinical chemistry and haematology were evaluated before and after the two weeks of active treatment. Diary cards were filled in by the parents and PEF (by 9 patients), asthma symptoms, use of fenoterol and adverse events were recorded.

Statistical methods: Descriptive statistics were given for all variables.

Summary of results:

Pharmacokinetics

Bambuterol 10 mg once daily: terbutaline mean steady state plasma concentration (Cₚ) was 11.0 nmol/L (range: 6.22-14.6), mean peak plasma concentration 15.4 nmol/L (range: 8.80-22.4), mean plasma concentration peak/trough ratio 2.44 and mean renal clearance 65.6 mL/min (3.27 mL/min/kg). Bambuterol mean peak plasma concentration was 5.63 nmol/L (range: 1.30-13.2) and mean renal clearance 53.2 mL/min (2.69 mL/min/kg).

Bambuterol 5 mg twice daily: terbutaline mean steady state plasma concentration (Cₚ) was 10.9 nmol/L (range: 7.12-15.6), mean peak plasma concentration 13.4 nmol/L (range: 9.60-18.4), mean plasma concentration peak/trough ratio 1.61 and mean renal clearance 62.5 mL/min (3.05 mL/min/kg). Bambuterol mean peak plasma concentration was 4.68 nmol/L (range: 1.50-11.7) and mean renal clearance 49.1 mL/min (2.40 mL/min/kg).

Clinical efficacy

Run-in: mean morning and evening PEF were 168 and 180 L/min, respectively. Mean asthma symptoms day and night were 0.35 and 0.33, respectively. The number of inhalations of fenoterol daytime were 1.67 while only one patient inhaled during the nights.

Bambuterol 10 once daily vs run-in: mean increase in morning and evening PEF were 18 and 14 L/min, respectively. Decrease in mean score of asthma symptoms day and night were 0.25 and 0.17, respectively. The use of fenoterol during daytime decreased with on average 1.17 inhalations while no patient used fenoterol during the nights.

Bambuterol 5 mg twice daily vs run-in: mean increase in morning and evening PEF were 16 and 15 L/min, respectively. Decrease in mean score of asthma symptoms day and night were 0.27 and 0.23, respectively. The use of fenoterol during daytime decreased with on average 1.17 inhalations while only one patient used fenoterol during the nights.

Safety

Restlessness was reported by 8 patients, headache by 5 patients and palpitations and tremor by each two patients. Other symptoms were reported by 9 patients. The adverse events were mostly mild to moderate and reported in about the same frequency during all study periods. A statistically significant decrease in B-haemoglobin (6.73; p<0.01) and increase in B-glucose (0.65; p<0.02) were shown.

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Conclusion(s): There were no differences in basal pharmacokinetics between the once and twice daily dosing. Renal clearance of terbutaline was about 75% of that of children 6-12 years old given the same dose. This is somewhat higher than the about 60% that was anticipated from the body weight relation between the two age groups. The mean steady-state plasma concentration of terbutaline was about 20% higher and the peak plasma concentration of terbutaline about the same as compared to children 6-12 years old. This means that for pharmacokinetic reasons the dosage of bumenterol in children should be very much the same in different age groups regardless of differences in body weight.

The once and twice daily dosing showed about the same magnitude of improvement in lung function compared to run-in. Adverse events were reported with about the same frequency and intensity during the two dosage regimens. The changes in clinical chemistry and haematology were small and of no clinical relevance.

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