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Br J Clin Pharmacol; 48: 299-308 (review article)

STUDY PERIOD
Date of first enrolment  September 14, 1996  IIB
Date of last completed  November 14, 1996

OBJECTIVES
The primary objective of the investigation was to determine the pharmacokinetics of bambuterol administered as oral solution in Filipino children with stable asthma, aged 2 to 5 years. This was done under steady state conditions at two dose levels, 2.5 mg and 5 mg once daily for 14 days. Specifically, the $C_{\text{max}}$, $C_{\text{min}}$, $C_{\text{ss}}$ and $t_{\text{max}}$ of plasma bambuterol and terbutaline were estimated over a 12-hour period. Safety was the secondary objective.

STUDY DESIGN
The study was a randomised double-blind, crossover study. The duration of the study was approximately 5 weeks.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION
The children were to be diagnosed with stable asthma and be between 2 and 5 years of age.
TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Bambuterol black currant flavoured solution administered orally at doses of 2.5 mg and 5 mg
Bambuterol hydrochloride oral solution 0.5 mg/mL, batch number DXF 55
Bambuterol hydrochloride oral solution 1.0 mg/mL, batch number VI 13

DURATION OF TREATMENT

7-day run-in period (range; 7-14)
14 days treatment per dose (range; 10-21)
Total duration was 5 weeks (range; 5-10)
No washout period between treatment periods

COMPARATOR DRUG

None

MAIN VARIABLE(S):

PHARMACOKINETICS

The primary pharmacokinetic variable was plasma concentration of terbutaline. The secondary
pharmacokinetic variables were plasma concentration of bambuterol and urinary excretion of
terbutaline.

SAFETY

The main safety variable was frequency of adverse events.

STATISTICAL METHODS

The study was analysed according to the “All Patients Treated” (APT) approach. A “Per Protocol (PP)
analysis was also to be performed.

C_{max} (peak plasma concentration), C_{min} (lowest plasma concentration), C_{ss} (mean steady state
centration), t_{max} (time to reach C_{max}), and AUC (area under the curve) for bambuterol and
terbutaline concentrations were calculated. Treatment differences were evaluated using multiplicative
analysis of variance models.

For safety analysis, all patients who had been treated with at least one dose of study drug were
included.

PATIENTS

The planned number of patients was 12 of either sex. 18 patients were enrolled and 17 were
randomised. Of randomised patients one was withdrawn due to a serious adverse event and 4 were
lost to follow up after visit 2. Thus, 12 patients completed the study, which was requested in the study
protocol.
SUMMARY - CONCLUSION(S)

Peak plasma concentration was observed within 6 hours after dosing for bambuterol and within 12 hours for terbutaline. AUC for terbutaline but not for bambuterol was proportional to the administered dose. Mean plasma C_{max} and AUC_{0-24} of terbutaline indicate that the 5 mg treatment should be clinically superior to the 2.5 mg treatment. The plasma terbutaline concentration resulting from the 2.5 mg bambuterol treatment seems to be too low to be of any therapeutic value. Renal clearance of terbutaline was about 40 mL/min, and not dose-dependent.

The most common adverse events reported were fever and coughing. All adverse events were scored as mild. No significant difference between treatments was observed. One patient experienced asthma exacerbation and was withdrawn from the study.

The present study suggests that, from a pharmacokinetic point of view, the initial target dose of bambuterol in Filipinos, 2-5 years of age, should be 5 mg per day.

DATE OF THE REPORT

30 November, 1999