AstraZeneca

SD-037-0684

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Oxis®

ACTIVE INGREDIENT: formoterol

Trial title (number): On the bronchodilating effect of inhaled (R;R)- and (S;S)- formoterol compared with the bronchodilating effect of inhaled rac-formoterol in asthmatic patients.

Development phase:II

First subject recruited: 28 February 2000

Last subject completed: 11 October 2000

Approval date: 10 December 2001

OBJECTIVES

Primary: To estimate the relative bronchodilating potency for (R;R)-formoterol and (S;S)-formoterol compared with Rac-formoterol. To compare duration of bronchodilation between (R;R)- and Rac-formoterol. The variable was forced expiratory volume in one second (FEV_1).
Secondary: To estimate the relative pulse increasing potency for (R;R)-formoterol and (S;S)-formoterol compared with Rac-formoterol. The variable was pulse.

METHODS

STUDY DESIGN
The study had a double-blind, crossover, and randomised design with six drugadministration days (visits 2-7).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION
Diagnosis of asthma as defined by the American Thoracic Society. The disease should be in a stable condition (no change in the treatment for the last 4 weeks).

TEST PRODUCT, DOSAGE AND MODE OF ADMINISTRATION
(R;R)-formoterol solution for nebulisation, single doses corresponding to the fine particle fractions of the nominal doses of 2.25 and 18μg of formoterol fumarate dihydrate delivered via Turbuhaler; (S;S)-formoterol solution for nebulisation, single dose corresponding to the fine particle fraction of the nominal dose 18μg of formoterol fumarate dihydrate delivered via Turbuhaler.

COMPARATOR PRODUCT, DOSAGE AND MODE OF ADMINISTRATION
Rac-formoterol solution for nebulisation, single doses corresponding to the fine particle fractions of the nominal doses 4.5 and 36μg of formoterol fumarate dihydrate delivered via Turbuhaler.

DURATION OF TREATMENT
Six single doses at intervals of at least 48 hours.

MAIN MEASUREMENTS AND VARIABLES:

- PHARMACODYNAMIC
The primary end-points for evaluating relative potencies were maximum and 12-h average $FEV_1$and maximum pulse. The primary end-point for evaluating duration of effect was the 22-24 h average FEV_1.

- SAFETY
Adverse events were collected by means of standard questions: “Have you had any health problems since the previous visit?” and “Have you had any health problems since you were last asked?”. The first question was asked to the patients upon arrival at the clinic at visits 2-7. The second question was asked before the patients left the clinic at visits 2-7, i.e., after the last FEV_1 measurement, 24 hours after administration of study drug. A follow-up telephone call was performed at least two but not more than 14 days after Visit 7.

METHODS FOR DATA EVALUATION
Analysis of variance models with patient, period and treatment as factors and baseline value as covariate were fitted to data. Multiplicative models were used for FEV_1derived data. Treatments were compared pairwise. The basic assumption was that the effect of Rac-formoterol would be related to the (R;R)-enantiomer. Straight lines were fitted to the adjusted mean pharmacodynamic parameters for (R;R)- and Rac-formoterol on the log-dose scale using weighted least square regression. Treatment differences with respect to potency (maximum and 12-h average FEV_1; maximum pulse) were assessed from the horisontal shift between appropriate lines and the 95% confidence intervals for the shift were calculated using Fieller’s method. (S;S)-formoterol is expected to have a very low effect and therefore the analysis focused on comparisons with placebo.

RESULTS

PATIENTS
A total of approximately 50 out-patients at five centers were to be enrolled to ensure that at least 40 patients completed the study. A total of 77 patients were enrolled in the study. Of these, 46 patients were randomised at five centres and 43 patients completed the study.

	Total
No. planned	50
No. randomised and treated	46
Males/Females	20/26
Mean age (range)	45
Baseline values FEV_1	2.37 L; 75.6 % of predicted normal
No. analysed for efficacy	45
No. analysed for safety	46
No. completed	43

PHARMACODYNAMIC RESULTS
The relative dose bronchodilating potency between inhaled nebulised solutions of (R;R)-and Rac-formoterol indicated to be approximately 2 with respect to maximum and 12-h average FEV_1, and at 3.6 with respect to 22-24-h average FEV_1 - confidence intervals for the estimates generally included 2. Active treatments increased pulse, but only the effect of the two high dose regimens of (R;R)- and Rac-formoterol differed statistically significantly from placebo. The effects of (S;S)-formoterol were generally not statistically significant compared with placebo.

SAFETY RESULTS
The treatments were well tolerated by the patients in this study. Mainly expectedβ_2-agonist mediated effects were recorded after administration of investigational products. No clinically important safety related findings were identified.

REFERENCES

Lotvall J, Palmqvist M, Ankerst J, Persson G, Rosenborg J, Bengtsson T, Rott Z, Poczi M, Devai A, Waldeck B. The effect of formoterol over 24 h in patients with asthma: The role of enantiomers. Pulm Pharmacol Ther 2005;18(2):109-113.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Oxis® (formoterol), Healthcare Professionals should view their specific country information.