NAME OF COMPANY: Astra Draco AB
P.O. Box 34
S-221 00 Lund, Sweden
TRADE NAME(S): Bambec®
NAME OF ACTIVE INGREDIENT(S) INN: bambuterol

REFERENCE IN THE DOSSIER
Volume:
Ref.number:
Page:

(FOR NATIONAL AUTHORITY USE ONLY)

STUDY CODE: 009-2020
REPORT NUMBER: 843-CR-2033

CLINICAL STUDY SYNOPSIS

Final

Title of the study: A single dose study of bambuterol (Bambec®) intravenous solution and tablets in patients with obstructive airway disease

Principal/coordinating investigator(s): Gunnar Persson, M.D.

Study site(s): Department of Allergology, University Hospital, Lund, Sweden

Publication (reference):

Study period: March 1987 - June 1987

Clinical phase: II

Objectives: The primary aim was to investigate whether intravenously administered bambuterol offered any clinical advantages as compared with oral, in efficacy and/or safety. The second aim was to investigate whether bambuterol had any effect on the generation of leukotrienes in eosinophils and neutrophils isolated from peripheral blood samples.

Study design: It was a single dose, randomized (in blocks of four), double-dummy, crossover study. The study was single-blind for the first two patients for safety reasons and double-blind for the remaining patients. Two treatments were given at separate days; bambuterol intravenously 5.3 mg and bambuterol tablets 40 mg. The two treatment days were separated by at least a one-week wash-out period. There were four visits to the clinic: one screening visit, two visits when treatment was given and a follow-up visit about 1-2 weeks after the second treatment day (visit 3). Glucocorticosteroids were allowed throughout the study if the dose was kept constant while bronchodilators were not allowed on the treatment days and during a certain time prior to the treatment days.

Number of patients (total and for each treatment): In total 10 patients out-patients were included in the study. Nine patients completed both treatments and one patient discontinued the study after the first treatment day (oral bambuterol).

30 June 1596 Llri/KKa/hom

Clinical Study Synopsis
**Diagnosis:** Reversible obstructive airway disease

**Criteria for inclusion:** Men and women, 16-70 years old / Reversibility of ≥15% in FEV₁₀ 15-30 minutes after inhalation of 4 puffs of either salbutamol 0.1 mg/puff or terbutaline 0.25 mg/puff / Basal FEV₁₀ of ≥1 L

**Investigational drug:** Bambuterol hydrochloride solution for injection 12 mL (5.3 mg) (0.44 mg/mL), batch No. DMG 41 during 10 minutes. A dose of 5.3 mg corresponded to 0.075 mg/kg for a person weighing 70 kg. The corresponding placebo was sodium chloride solution (0.9 mg/mL, batch No. DMG 42).

**Reference treatment(s):** Bambuterol tablets 20 mg, batch No. DMB 102 (2 x 20 mg). The corresponding placebo tablets, batch No. DMC 104.

**Duration of treatment:** Single dose of each administration and clinical investigations until 24 hours after dose intake. The total study time for each patient was about 2-4 weeks.

**Assessment methods:** At -5 (baseline), 30, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720 minutes and at 24 hours after study drug intake the following were assessed: FEV₁₀ (L), FVC (L), blood pressure (mm Hg), pulse rate (beats/min) and adverse events (tremor, restlessness, palpitations, headache, other). Terbutaline plasma concentration (nmol/L) was measured at 0.5, 1, 2, 3, 4, 6 and 24 hours after dose. The concentration of leucotrienes were determined before drug administration at visit 1 (baseline) and two hours after drug administration on the first and the second treatment days.

**Statistical methods:** Due to the pilot type of investigation, no formal calculations of statistical power were performed. AUC was calculated for FEV₁₀, FVC, pulse rate and blood pressure and the difference was tested with Wilcoxon sign rank test. All data were analysed irrespective of whether the treatment was single-blind or double-blind. Extensive descriptive statistics were computed for all variables.

**Summary of results:** Ten out-patients (8F/2M) with bronchial asthma, all Caucasians, were randomized into the study whereof eight patients (6F/2M) were included in the per protocol analyses. Demographic and baseline data for the eight patients were: mean age 32 years, mean duration of asthma 16 years, mean basal FEV₁₀ 2.25 L, mean cent in predicted value 63%, mean reversibility in FEV₁₀ 39%, mean blood pressure 121/78 mm Hg and mean pulse rate 73 beats/min.

The mean area under the effect versus time curve (AUC, 12 hours) was after the intravenous administration 2.66 L/h for FEV₁₀ and 3.46 L/h for FVC. After the oral administration FEV₁₀ was 2.88 L/h and FVC 3.71L/h. The difference between the administrations was statistically significant (p=0.023) for both FEV₁₀ and FVC. Maximal values for FEV₁₀ were seen 2 hours (i.v.) and 5 hours (oral) after dose. The increase in terbutaline plasma concentration was accompanied by an increase in FEV₁₀ with both administration ways and the curve profiles were similar. The i.v. and the oral dose did not generate a similar concentration of plasma terbutaline as was the intention why the actual mean area under the plasma concentration time curve of terbutaline was 75% higher after the oral as compared with the i.v. dose. Therefore, no conclusions can be drawn about the difference in bronchodilating effect between the administration ways.

No statistically significant difference was seen between the treatments for blood pressure and pulse rate. Three out of 10 patients had an increase in pulse rate of 20 mm Hg or more after i.v. treatment and three out of nine after oral treatment. The mean changes from baseline were small for both variables.

Adverse events were mild to moderate except for two patients. The one patient experienced nausea and vomited on oral treatment and the other patient experienced headache on intravenous treatment. Adverse events were somewhat less frequent and intensive with i.v. treatment which is consistent with the higher terbutaline plasma concentration with oral treatment. No serious adverse events were reported and no patient discontinued from the study due to adverse events.
One patient discontinued after treatment with oral bambuterol (asthma deterioration).

No conclusive results were obtained for the effect of bambuterol on the generation of leukotrienes.

Conclusions:

Intravenous administration of bambuterol seems to offer no advantage in comparison with oral administration, neither in terms of onset of action of bronchodilation nor in degree of improvement of lung function.

A single oral dose of 40 mg bambuterol gave a better bronchodilating effect, probably due to a higher terbutaline plasma concentration.

Both oral and intravenous administrations were well tolerated.

No conclusions could be drawn about the possible leukotriene release inhibiting effect of bambuterol.

Author / Lena Lästmyr

Date / 960701

Statistician / Klas Svensson

Date / 960701