Synopsis of study report: 21/2003
Location in Module 5:

Study Code:
BY217/CP-053

Report Version:
Version 1.0 (dated 10 June 2003)

Title of the study:
Determination of cytochrome P450 1A2 activity in Subject No. 10 of Study BY217/FHP 027 - a case control study

Study center(s):
Swiss Pharma Contract Ltd., Allschwil, Switzerland

Publication (reference):
Not applicable

Studied period (years):
23 July 2002 – 30 July 2002

Clinical phase:
Phase I

Objectives:
The main objective of the present study was to determine the enzyme activity of cytochrome P450 1A2 in a single female subject who recorded high levels of roflumilast and roflumilast-N-oxide in her plasma during Study No BY217/FHP027 (Subject No. 10) in comparison with the cytochrome P450 1A2 activity determined in six healthy female subjects.

Methodology:
This study was conducted as a monocenter case control study. The study consisted of a pre-study medical examination (including blood pressure, heart rate, and ECG) within one week prior to study start, one treatment period of eight hours (subjects were hospitalized the

afternoon before study start and remained in hospital until the study's conclusion), and a post study medical examination conducted immediately after study termination (including blood pressure, heart rate, and ECG). Urine samples were collected predose (before intake of caffeine) and during the treatment period (after caffeine intake) at two defined time intervals: 0 to 4 h and 4 to 8 h. Blood pressure, heart rate and ECG were also recorded at 0.5 h and 1 h after intake of the study drug.

No. of subjects (total and for each treatment):

Total number of subjects: 7
Case: 1 case subject (Subject No. 10 from Study BY217/FHP 027)
Control: 6 control healthy female subjects

Diagnosis and criteria for inclusion:

The case subject was included in this study after showing high levels of roflumilast and roflumilast N-oxide in the plasma during Study No. BY217/FHP027 as compared with other participants in that study. For inclusion in the control group (n = 6) of this study, subjects had to be female, aged between 18 and 45 years, Caucasian, within the normal weight range according to Broca's index, and assessed as healthy based on the pre-study medical examination (including blood pressure, heart rate, and ECG). All subjects provided written informed consent.

Test product:

Caffeine

Dose:

caffeine 200 mg taken once only

Mode of administration:

Tablet, taken orally

Batch No.:

26295 01 (Merck)
The study medication was caffeine, supplied as Coffeinum 0.2 g Compretten® N by Cascan, Wiesbaden, Germany.

Duration of treatment:

The study period lasted 8 h.
At the start of the study period, a single tablet (200 mg caffeine) was administered in the morning to fasted subjects.

Reference product:

None

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Pharmacokinetics:
The primary variable of this study was to determine the enzyme activity of cytochrome P450 1A2, evaluated by the ratio of the caffeine metabolites (1X + 1U + AFMU)/17U, in the urine. The secondary variables of the study were the enzyme activities of N-acetyl transferase and xanthine oxidase, evaluated by the ratios AFMU/1X and 1U/1X, respectively.

Safety and tolerability:
Physical examinations, including vital signs such as blood pressure and heart rate, use of 12-lead ECG, and clinical laboratory examinations (blood chemistry, hematology, coagulation and urinalysis) were used as safety variables during this trial. In addition, adverse events were monitored during the entire trial.

Statistical methods:

The ratio of caffeine metabolites in the urine of the case subject was compared with the median of the respective ratios in the control subjects. Adverse events were analyzed descriptively and safety variables were analyzed using summary statistics (e.g. median, 68%-range, mean, standard deviation).

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetic results:
Cytochrome P450 1A2 activity was reduced by a factor of 2.6 in the case subject when compared with the median activity of the control group. N-acetyl transferase activity was similar for the case subject and the subjects in the control group. However, the case subject's N-acetyl transferase activity was increased by a factor of 2 if one control subject (whose N-acetyl transferase activity was increased by a factor of 10 compared with the other control subjects) was excluded from the control group. For XO, the activity of this enzyme in study subject AL was similar to that of the control group.

Safety results:
During treatment one subject reported one adverse event. The event (dizziness) was mild in intensity and was not of a serious nature. Its relationship to the study drug was assessed as 'unlikely' by the investigator.

Conclusions:

Cytochrome P450 enzyme 1A2 is one of the important enzymes involved in the metabolism of roflumilast and roflumilast N-oxide. In the previous study BY217/FHP027, female Subject No. 10 was found to have high levels of roflumilast and roflumilast N-oxide in the plasma. For this reason, this subject was reevaluated in the present study (BY217/CP-053). Caffeine, which is metabolized by cytochrome P450 enzyme 1A2, was used as a marker compound for this enzyme.

Based on the data obtained with caffeine, the results of the present study show that the enzyme activity of cytochrome P450 1A2 was reduced in the case subject when compared with the median activity of this enzyme in the control group. This finding may explain the high plasma levels of roflumilast and roflumilast N-oxide found for this subject in the previous study BY217/FHP027.