Synopsis of study report: 208/2001
Location in Module 5:

Study Code:
BY217/FHP027

Report Version:
1.0 (dated 30 April 2003)

Title of the study:
The possible effect of steady-state roflumilast on digoxin pharmacokinetics in healthy subjects – an open, randomized, two-period crossover design

Study center:
Swiss Pharma Contract Ltd., 4123 Allschwil, Switzerland

Publication (reference):
Not applicable.

Studied period (years):
09 April 2001 to 28 May 2001

Clinical phase:
I

Objectives:
The primary objective was the possible effect of steady state roflumilast on digoxin pharmacokinetics. Secondary objectives were the pharmacokinetics of roflumilast and roflumilast-N-oxide, as well as safety and tolerability.

Methodology:

The study was conducted according to an open, randomized, two-period crossover design. Subjects received either Treatment A (digoxin 250 µg o.d. on Days 1 and 14, and Roflumilast 500 µg o.d. on Days 1 to 14) or Treatment B (digoxin 250 µg o.d. on Day 1). The treatment periods were separated by a washout period of at least 10 days. Blood sampling for determination of pharmacokinetic parameters was done on Day 1 of Treatment A and on Days 13 and 14 of Treatment B. Clinical laboratory parameters were determined before start of each treatment, on Days 12 and 19 of Treatment A and on Days 1 and 6 of Treatment B.

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

N = 16 (PP and ITT population)

Diagnosis and criteria for inclusion:

Healthy female or male Caucasians, aged 18 to 45 years, with a normal body weight, who gave their written informed consent were eligible.

Test product:

Roflumilast together with digoxin

Dose:

Roflumilast: 500 µg
Digoxin: 0.25 mg (250 µg)

Mode of administration:

Roflumilast: o.d., oral with 240 ml water, in the morning after an overnight fast, Days 1 to 14 of Treatment A. In addition, digoxin s.i.d, oral with 240 ml water, in the morning after an overnight fast, Days 1 and 14 of Treatment A.

Batch No.:

Roflumilast: Batch No. 499110; Digoxin: Batch No. OK672A (Glaxo Wellcome)

Duration of treatment:

14 days

Reference product:

Digoxin alone

Dose:

0.25 mg (250 µg)

Mode of administration:

Digoxin: s.i.d., oral with 240 ml water, in the morning after an overnight fast, Day 1 of Treatment B.

Batch No.:

OK672A (Glaxo Wellcome)

Criteria for evaluation:

Primary variables: $AUC_{(0-\infty)}$ and C_{max} of digoxin.

Secondary variables: $AUC_{(0-24h)}$ and C_{max} of roflumilast, $AUC_{(0-24h)}$ of roflumilast-N-oxide, $t_{1/2}$ and t_{max} of digoxin and roflumilast, $t_{1/2}$ of roflumilast-N-oxide, safety measurements and adverse events.

Statistical methods:

Pharmacokinetic characteristics were evaluated using the validated 'KINTPC' program (Version 2.0). $AUC_{(0-\infty)}$ was calculated based on the trapezoidal formula up to the last sampling time with a concentration above the limit of quantitation and was extrapolated to infinity. If the extrapolated part exceeded 30%, AUC up to the last sampling point was calculated instead. C_{max} values were directly obtained from the measured concentrations.

The potential effect of concomitant roflumilast administration on digoxin pharmacokinetics was investigated by comparison of rate and extent of digoxin absorption following digoxin alone (Day 1, Treatment B, Reference) and under concomitant roflumilast treatment (Day 14, Treatment A, Test).

The biostatistical analysis was performed employing the 'BIOQPC' program (Version 1.2.2). $AUC_{(0-\infty)}$ and C_{max} values were evaluated using a multiplicative model, i.e. by the corresponding analysis of variance model after logarithmic transformation, yielding point estimates and 90% confidence intervals for the respective Test/Reference ratios.

Safety variables were analyzed descriptively, including summary statistics (mean, median, 68% range, SD, SEM, geometric mean, and geometric 68%-range.

The secondary pharmacokinetic variables t_{max} and $t_{1/2}$ were analyzed with an explorative intention. For $t_{1/2}$ a multiplicative model was applied. For t_{max} an additive model was used.

The point estimates of the $AUC_{(0-24\ h)}$ and C_{max} ratios (Day 14/Day 13) were evaluated together with the 90% confidence intervals for roflumilast and roflumilast-N-oxide.

SUMMARY - CONCLUSIONS

Summary:

For digoxin, the primary variable $AUC_{(0-\infty)}$ as well as C_{max} were not influenced by concomitant treatment with roflumilast. Point estimates for the Test/Reference ratios for $AUC_{(0-\infty)}$ and C_{max} as well as their 90% confidence intervals were within the respective equivalence ranges. The secondary variables (t_{max} and $t_{1/2}$) were also unaffected by concomitant roflumilast treatment.

No significant influence by concomitant digoxin treatment on $AUC_{(0-24\ h)}$, C_{max} and t_{max} was found for roflumilast and its metabolite roflumilast-N-oxide. For $t_{1/2}$ of roflumilast, a slight prolongation was seen, whereas a decrease of $t_{1/2}$ was observed for roflumilast-N-oxide. However, these alterations of the terminal elimination half-lives were not significant. Point estimates for the Test/Reference ratios for $AUC_{(0-24\ h)}$ and C_{max}, as well as their 90% confidence intervals were within their equivalence ranges.

In one subject (Subject #10) a marked elevation of $AUC_{(0-24\ h)}$, C_{max} and for $t_{1/2}$ was found for roflumilast and roflumilast-N-oxide. The pharmacokinetic parameters for digoxin were not increased in this subject. From the prolonged $t_{1/2}$ values found for roflumilast and roflumilast-N-oxide, it can be concluded for Subject #10 that both components are accumulated to higher steady state concentration levels than for the other study subjects. This is supported by the finding that pre-dose levels on Days 13 and 14 were significantly increased for Subject #10 for roflumilast and roflumilast-N-oxide, compared to geom. mean concentrations of the pre-dose values of all study subjects.

Both Treatments A (digoxin and roflumilast) and B (digoxin) were well tolerated in subjects aged 20 to 43 years. No serious adverse event was reported. A total of 10 subjects experienced a total of 44 adverse events. Most adverse events (28) were of mild intensity. All adverse events recovered without sequelae.

Serial recording of ECG revealed normal findings in most patients. QTc intervals were not prolonged by any of the treatments. Laboratory parameters remained unaffected by both treatments.

Conclusions:

Treatment with digoxin in combination with roflumilast was well tolerated. For digoxin, $AUC_{(0-\infty)}$ and C_{max} were not influenced by concomitant treatment with roflumilast. No significant influence by concomitant digoxin treatment on $AUC_{(0-24\ h)}$, C_{max} and t_{max} was found for roflumilast and its metabolite roflumilast-N-oxide.