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Location in Module 5:

Study Code:
BY217/FHP019

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Title of the study:

Pharmacokinetics of roflumilast after single oral dose administration of 0.25 mg to patients with liver cirrhosis Child Pugh A in comparison to healthy subjects

Study center(s):

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Publication (reference):

Not available

Studied period (years):

18 June 1999 – 03 December 1999

Clinical phase:

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Objectives:

Primary:

- The investigation of the pharmacokinetics of roflumilast (B9302-107) in patients with liver cirrhosis Child-Pugh A in comparison to a matched control group of healthy subjects.

Secondary:

- To assess the safety and tolerability of roflumilast and to investigate the pharmacokinetics of its active metabolite B9502-044.

Methodology:

Open label parallel group comparison

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

Total: 24
12 hepatically impaired patients
12 healthy control subjects

Diagnosis and criteria for inclusion:

For each patient with moderate liver impairment one healthy subject was included according to the following matching criteria: Same sex, age within ± 5 years, weight within ± 10%, height within ± 10%

Duration of treatment:

Single dose

Test product:

Roflumilast

Dose:

0.25 mg

Mode of administration:

p.o.

Batch No.:

020498

Reference product:

Not applicable

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Pharmacokinetics:

$AUC_{(0-\infty)}$ and C_{max} of roflumilast

$t_{½}$ and t_{max} of roflumilast

$AUC_{(0-\infty)}$ and $t_{½}$ of the metabolite B9502-044

Safety and tolerability:

Clinical laboratory, urinalysis, ECG, blood pressure, heart rate and adverse events

Statistical methods:

Point estimates and 90%-confidence limits for the ratio of the population medians of $AUC_{(0-\infty)}$ and C_{max} of Test (patients with liver cirrhosis) and Reference (healthy subjects).
Safety data were evaluated descriptively.

SUMMARY – CONCLUSIONS

Summary:

Pharmacokinetic evaluation:

The following tables show a summary of the pharmacokinetic characteristics of roflumilast (B9302-107) and the metabolite B9502-044 after single oral administration of 0.25 mg roflumilast to patients with liver impairment (n=12) and healthy control subjects (n=12). Values are given as geometric means with 68%-range except for t_{max} which is given as mean ± SEM (n=12).

Patients with liver impairment:

		B9302-107	**B9502-044**
$AUC_{(0-\infty)}$	(µg x h/l)	29.11 (20.55, 41.24)	282.32 (189.94, 419.63)
C_{max}	(µg/l)	2.926 (1.827, 4.684)	3.787 (2.594, 5.528)
$t_{½}$	(h)	32.36 (17.09, 61.29)	37.35 (27.35, 51.02)
t_{max}	(h)	1.21 ± 0.18	28.70 ± 8.74

Healthy control subjects:

		B9302-107	B9502-044
$AUC_{(0-\infty)}$	(µg x h/l)	13.59 (9.51, 19.43)	161.76 (117.80, 222.11)
C_{max}	(µg/l)	2.690 (1.825, 3.964)	3.751 (3.053, 4.608)
$t_{½}$	(h)	9.82 (4.84, 19.93)	25.87 (17.40, 38.48)
t_{max}	(h)	1.67 ± 0.30	5.54 ± 1.16

Comparison of the two groups for roflumilast was assessed by using AUC (extent of absorption) and C_{max} (rate of absorption) as primary criteria. The point estimates (90%-Cl) for these characteristics were as follows: AUC: 2.142 (1.636, 2.805) and C_{max}: 1.088 (0.804, 1.472). The point estimate (90%-Cl) of $t_{½}$ as a secondary criterion (explorative intention) was 3.295 (2.055, 5.286).
The secondary characteristics AUC and $t_{½}$ of metabolite B9502-044 were also analyzed in an explorative intention, yielding the following point estimates and 90%-confidence intervals: AUC: 1.745 (1.310, 2.326) and $t_{½}$: 1.444 (1.081, 1.929). The point estimate (90%-Cl) of t_{max} was –0.458 (-1.054, 0.138) for roflumilast and 23.158 (6.999, 39.318) for the metabolite B9502-044.

Safety and tolerability:
A total of three adverse events were reported by one patient and two healthy controls. There were no individual subjects with adverse events that were reason for discontinuation. Two of the adverse events were considered moderate and their relation to test drug as “likely” and “unlikely” (diarrhea and headache) while one was considered as mild and unrelated to test drug (back pain).
None of the hematology, biochemistry, urinalysis, vital signs and ECG assessments showed any relevant changes from baseline. No trends could be discerned, neither within subjects nor over subject groups.

Conclusions:

Pharmacokinetic evaluation:
This study showed that plasma AUCs and half-lives for both roflumilast and its metabolite B9502-044 were significantly increased in hepatic impairment patients compared to healthy controls, while peak plasma concentrations did not change significantly.
Roflumilast and metabolite B9502-044 AUC in patients with liver disease was increased by about 114% and 75% respectively. In addition, a prolongation of the half-life by 230% and 44% was observed for roflumilast and its metabolite respectively.
Therefore, clearance is reduced when liver function is impaired.

Safety and tolerability:

A single dose of 0.25 mg of roflumilast was well tolerated both in patients with liver impairment and in healthy control subjects. No drug related changes were observed in any of the safety parameters studied.