585

Sachse R[1], Krastev Z[2], Mateva L[2], Gatchev E[3], de Mey C[4], Cawello W[1], Horstmann R[1]
1. Department of Clinical Pharmacology, Schwarz Biosciences, Monheim, Germany, 2. Department Hepatology, Sofia University, Bulgaria, 3. Department Clinical Pharmacology, Sofia University, Bulgaria, 4. ACPS, Mainz-Kastel, Germany

SAFETY, TOLERABILITY AND PHARMACOKINETICS OF FESOTERODINE IN PATIENTS WITH HEPATIC IMPAIRMENT

Hypothesis / aims of study

The novel bladder-selective antimuscarinic fesoterodine is under development for the treatment of overactive bladder syndrome. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by unspecific plasma esterases to its active metabolite SPM 7605 [1]. Besides from direct renal excretion, the liver is significantly involved in the elimination of SPM 7605 by biotransformation of SPM 7605 into inactive metabolites. Thus, hepatic impairment may alter the pharmacokinetics of fesoterodine affecting safety and tolerability. It is estimated that about 10 % of the population above 50 years have some degree of overactive bladder syndrome and as many as 50 million persons in the developed world may be affected [2]. Some patients may suffer from concomitant liver disease. Therefore, safety, tolerability and pharmacokinetics of fesoterodine were investigated in patients with hepatic impairment.

Study design, materials and methods

In a single-center, open-label, parallel group trial single oral doses of 8mg fesoterodine were administered to 8 patients with moderate hepatic impairment (Stage B according to Child-Pugh classification) and 8 healthy subjects matched for age, body weight and body mass index. All patients with hepatic impairment (mean age: 54.4 ± 7.1 years; mean body weight: 79.5 ± 7.1 kg; mean body mass index: 26.7 ± 3.5 kg/m^2) or healthy subjects (55.8 ± 4.9 years; 81.1 ± 7.9 kg; 27.3 ± 3.3 kg/m^2) were male Caucasians.
Safety was investigated by means of physical examination, measurement of heart rate and blood pressure, ECG and laboratory parameters. Subjective tolerability was assessed by non-leading questions.
Blood samples for determination of SPM 7605 plasma concentrations were taken from predose until 48 hours after administration of fesoterodine. Pharmacokinetic parameters were area under the concentration time curve from zero up to the last measurable plasma concentration ($AUC_{0\text{-}tz}$) and to infinity ($AUC_{0\text{-}inf}$), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), terminal half-life ($t_{½}$). Point estimates and 95% confidence intervals were calculated for the ratio of the group means for patients with hepatic impairment relative to healthy subjects with regard to $AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$ and C_{max}.

Results

Physical examination, heart rate, blood pressure, ECG-parameters and laboratory parameters were not influenced by the study drug in a clinically significant manner. 4 subjects (2 in each group) reported 4 treatment-emergent adverse events, all of them were mild dryness of the mouth. No further treatment-emergent adverse events were recorded.
Patients with moderate hepatic impairment showed an approximately twice higher total exposure and about 1.4 times higher peak exposure to SPM 7605 as compared to healthy subjects. The estimated ratios [90% confidence interval] in patients with hepatic impairment versus healthy subjects for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}inf}$ and C_{max} were 2.13 [1.43, 3.16], 2.16 [1.45; 3.20], and 1.39 [0.99, 1.95], respectively. Mean t_{max} was delayed from 5.4 hours in healthy subjects to 7.4 hours in patients with hepatic impairment. Mean $t_{½}$ of 8.4 ± 1.5 hours and 8.9 ± 2.1 hours in healthy subjects and in patients with hepatic impairment, respectively, was comparable in both populations.

Interpretation of results

In this trial, a single oral dose of 8mg fesoterodine was safe and well tolerated in patients with moderate liver impairment and in healthy subjects.
Dose-dependent pharmacokinetic parameters C_{max} and AUC of SPM 7605 increased 1.4-fold and 2.1-fold, respectively, in patients with moderate liver impairment as compared to healthy subjects. These findings together with the unchanged terminal half-life of SPM 7605 in

patients with moderate liver impairment, support the hypothesis that the reduced cytochrome P450 enzyme activity in patients with liver impairment is sufficient for metabolic elimination or that alternative elimination pathways without involvement of cytochrome P450 enzymes exist.

Concluding message

The pharmacodynamic effects of fesoterodine correlate with plasma concentrations of SPM 7605 [3]. Maximum plasma concentration in patients with moderate liver impairment is only 1.4-fold increased. The unchanged terminal half-life in patients with liver impairment suggests no accumulation of SPM 7605. Therefore, it seems to be justifiable not to adjust the dose of fesoterodine when given to patients with mild or moderate liver impairment.

References

[1] Multiple dose pharmacokinetics of fesoterodine in human subjects. Naunyn-Schmiedeberg's Arch Pharmacol 2002; 365 (Suppl. 1): 428

[2] Urinary incontinence in both sexes: prevalence rates and impact on quality of life and sexual life. Neurourol Urodyn. 2000;19: 259-71

[3] Pharmacodynamics and pharmacokinetics of ascending multiple oral doses of the novel bladder-selective antimuscarinic fesoterodine. Eur Urol 2003; Suppl. 2: 111