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CONCOMITANT FOOD INTAKE DOES NOT SIGNIFICANTLY INFLUENCE THE PHARMACOKINETICS OF THE NOVEL, BLADDER-SELECTIVE ANTIMUSCARINIC FESOTERODINE

Hypothesis / aims of study

Fesoterodine is a novel bladder-selective antimuscarinic under development for the treatment of overactive bladder syndrome. Fesoterodine's active metabolite, SPM 7605, is rapidly and extensively formed by unspecific plasma esterases and shows dose-proportional pharmacokinetics [1]. The safety and pharmacokinetics of fesoterodine are similar in populations of different age and gender and no dosage adjustment is required in elderly patients [2]. Especially in an elderly population it is preferable to administer a medical treatment for overactive bladder syndrome without regard to meals. Therefore, the influence of concomitant food intake on the pharmacokinetics of fesoterodine was investigated.

Study design, materials and methods

In a single-center, open-label, two-way crossover trial 16 healthy male subjects (mean age: 31.3 ± 7.6, mean body mass index: 25.0 ± 2.1) received a single oral dose of 8 mg fesoterodine in the fasted state and after a standard high-fat and high-calorie meal [3]. There was a wash-out phase of one week between the two periods. Blood samples were taken from predose until 36 hours after administration of fesoterodine. SPM 7605 plasma concentrations were detected with a highly sensitive and selective LC-MS/MS method. The following pharmacokinetic parameters were determined using non-compartmental methods: maximum plasma concentration (C_{max}), area under the concentration time curve from zero up to the last measurable plasma concentration ($AUC_{0\text{-}tz}$) and to infinity ($AUC_{0\text{-}inf}$), time to reach C_{max} (t_{max}) and terminal half-life ($t_{½}$). The logarithms of C_{max}, $AUC_{0\text{-}tz}$ and $AUC_{0\text{-}inf}$ in the fasted and fed state were analyzed using analysis of variance (ANOVA). Based on these analyses point estimates and 90% confidence intervals for the ratio "fed" versus "fasted" were calculated by re-transformation of the logarithmic data using the intraindividual standard deviation of the ANOVA.
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.

Results

All 16 subjects completed both periods of the study and were included in the analysis. 8 subjects reported 14 mild adverse events including headache, dry mouth and dysuria. Physical examination, heart rate, blood pressure, ECG-parameters and laboratory parameters were not influenced by the study drug in a clinically significant manner.
The pharmacokinetic parameters C_{max}, $AUC_{0\text{-}tz}$ and $AUC_{0\text{-}inf}$ of SPM 7605 increased slightly after a standard high-fat and high-calorie meal. The ratios "fed" versus "fasted" [90% confidence interval] for C_{max}, $AUC_{0\text{-}tz}$ and $AUC_{0\text{-}inf}$ were 1.19 [0.95, 1.49], 1.19 [1.04, 1.37], and 1.12 [0.98, 1.29], respectively. Mean $t_{½}$ was shortened from 8.7 ± 3.0 hours in the fasting state to 6.6 ± 2.2 hours in the fed state, t_{max} was comparable for both conditions.

Interpretation of results

Fesoterodine was safe and well tolerated in healthy male subjects receiving a single oral dose of 8 mg fesoterodine in the fasted state or after a high-fat, high calorie breakfast.
Time to reach C_{max} was not influenced by the ingestion of food. The pharmacokinetic parameters C_{max} and $AUC_{0\text{-}tz}$ increased slightly in the fed condition. Bioavailability of SPM 7605 expressed as $AUC_{0\text{-}inf}$ was on average 12% higher for fesoterodine administered in the fed state than in the fasted state. This difference is judged as being of no clinical relevance.

Concluding message

Administration of fesoterodine in the fasted state or after a high-fat and high calorie meal results in similar bioavailability and similar maximum plasma concentration. This suggests

that fesoterodine may be taken without regard to meals in patients with overactive bladder syndrome.

References

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