586

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SAFETY, TOLERABILITY AND PHARMACOKINETICS OF FESOTERODINE AFTER CO-TREATMENT WITH THE POTENT CYTOCHROME P450 3A4 INHIBITOR KETOCONAZOLE

Hypothesis / aims of study

The novel bladder-selective antimuscarinic fesoterodine is rapidly and extensively hydrolyzed in humans to its active metabolite SPM 7605 [1]. SPM 7605 is eliminated both via hepatic metabolism and renal excretion. The hepatic metabolism involves different cytochrome P450 (CYP) enzymes such as CYP3A4 and CYP2D6. CYP3A4 is one of the most important human enzymes as approximately 60% of oxidized drugs are biotransformed, at least in part, by this enzyme [2]. Therefore, the effects of a concomitant treatment with the potent CYP3A4 inhibitor ketoconazole on the safety and pharmacokinetics of fesoterodine were investigated in extensive and poor metabolizers for CYP2D6.

Study design, materials and methods

Single oral doses of 8 mg fesoterodine alone or together with a pre- and co-treatment with ketoconazole were administered to 18 healthy male subjects (12 extensive and 6 poor metabolizers for CYP2D6) in a randomized, non-blind, two-way crossover design. Pre- and co-treatment were performed with 200mg ketoconazole once daily for six days with fesoterodine administration taking place on day 5.

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.

To characterize the pharmacokinetics of SPM 7605, the plasma concentrations of SPM 7605 were detected with a highly sensitive and selective LC-MS/MS method. Primary pharmacokinetic parameters were area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of SPM 7605. Secondary parameters were terminal half-life ($t_{½}$) and time of maximum plasma concentration (t_{max}). To investigate a potential effect of the ketoconazole co-administration, an exploratory analysis using ANOVA was performed on the log-transformed values of AUC 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. 63 mild or moderate adverse events (AE) were reported during the study. There were no severe AEs. The most frequent AE was dry mouth, detected in 5 subjects after fesoterodine alone and in 9 subjects after combination therapy. Tolerability was similar in poor and extensive CYP2D6 metabolizers.

Bioavailability of SPM 7605 expressed as AUC was approximately doubled both in poor and extensive CYP2D6 metabolizers by the co-treatment with ketoconazole. C_{max} of SPM 7605 increased 1.5-fold and 2.2-fold in poor and extensive CYP2D6 metabolizers, respectively. Mean $t_{½}$ of SPM 7605 was 7.4 hours after fesoterodine alone and 7.5 hours after co-administration with ketoconazole. Also median t_{max}, which was 6 hours for both treatment regimen, was not affected by the co-treatment with ketoconazole. Both parameters, $t_{½}$ and t_{max}, were not different between poor and extensive CYP2D6 metabolizers.

Interpretation of results

In this trial, fesoterodine was safe and well tolerated alone or together with ketoconazole both in poor and extensive CYP2D6 metabolizers. Concomitant ketoconazole treatment resulted in an increase of SPM 7605 plasma concentrations caused by CYP3A4 inhibition. However, as particularly shown by a slight 1.5-fold increase of C_{max} in poor CYP2D6 metabolizers and by the unchanged terminal half-life, other elimination pathways are able to compensate even a blockade of two important hepatic metabolism steps. Despite the statistical significance of this pharmacokinetic interaction, the increase of plasma levels is small and is not considered of clinical relevance.

Concluding message

Based on these results it seems to be justifiable not to adjust the dose of fesoterodine when co-administered with CYP3A4 inhibitors.

References

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

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