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SAFETY AND PHARMACOKINETICS OF THE NOVEL BLADDER-SELECTIVE ANTIMUSCARINIC FESOTERODINE IN POPULATIONS OF DIFFERENT ETHNIC ORIGIN

Aims of Study

The novel bladder-selective antimuscarinic drug fesoterodine is under development for the treatment of overactive bladder syndrome. It is rapidly and extensively hydrolyzed in humans to its active metabolite SPM 7605. In this trial safety, tolerability, and pharmacokinetics of fesoterodine were investigated in populations of different ethnic origin.

Methods

In a randomized, double-blind, placebo-controlled, parallel group trial single oral doses of 8mg fesoterodine or placebo were administered to 16 healthy male Caucasian or Black African subjects, aged 18-45 years. In each group, 12 subjects received active substance and 4 subjects received placebo. 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. Salivary secretion was measured by a cotton swab test as a pharmacodynamic effect.

To characterize the pharmacokinetics of SPM 7605 in human subjects, the plasma concentrations of SPM 7605, the active metabolite of fesoterodine, and further metabolites were detected with a highly sensitive and selective LC-MS/MS method. Pharmacokinetic parameters were AUC, C_{max}, $t_{½}$, t_{max} and CL of SPM 7605.

Results

A total of 32 healthy male subjects were randomized in this trial. There were no dropouts, all of the randomized subjects completed the trial. In general, fesoterodine was safe and well tolerated in the two populations. Physical examination, heart rate, blood pressure, ECG-parameters and laboratory parameters were not influenced by the study drug in a clinically significant manner. Two adverse events, which were classified as mild, were reported by two Caucasian subjects, both receiving fesoterodine. No adverse event was reported by the Black Africans. There were no serious adverse events reported.

In line with the antimuscarinic effect, a reduced salivary secretion was observed in both ethnic groups at 5 hours after treatment with fesoterodine compared with the placebo group. There was no report on dry mouth.

The maximum plasma concentration (C_{max}) of SPM 7605 and further metabolites, the area under the curve (AUC) and the renal clearance (CL) of SPM 7605 were similar for both populations. Mean maximum plasma levels of SPM 7605 were observed between 5 and 6 hours after administration. The mean terminal half-life ($t_{½}$) ranged between 6 and 7 hours. The t-test used to compare the the parameters C_{max}, t_{max}, and AUC in Caucasians and Black Africans showed no difference between both groups. Overall, no differences in pharmacokinetic parameters of SPM 7605 and further metabolites were observed between the different populations.

Conclusions

A single oral dose of 8mg fesoterodine was safe and well tolerated in healthy male Caucasian and Black African subjects. Different ethnic origin did not result in a different pharmacokinetic profile.

In conclusion, the present trial demonstrates that fesoterodine can safely be administered to Caucasian and Black African patients. No dosage adjustment is considered to be necessary between these two populations of different ethnic origin.