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SAFETY AND PHARMACOKINETICS OF THE NOVEL ANTIMUSCARINIC DRUG FESOTERODINE IN POPULATIONS OF DIFFERENT AGE OR GENDER

Aims of Study

Fesoterodine is a novel antimuscarinic drug, which is under development for the treatment of overactive bladder. Fesoterodine is rapidly and extensively hydrolyzed in humans [1] and rats to its active metabolite SPM 7605. Both, fesoterodine and SPM 7605 have demonstrated potent specific antimuscarinic activity in rat urinary bladder *in vitro* and *in vivo* studies [2]. SPM 7605 also showed antimuscarinic activity in humans [3]. In this trial safety, tolerability, and pharmacokinetics of fesoterodine were investigated in populations of different age or gender.

Methods

In a randomized, double-blind, placebo-controlled, parallel group trial single oral doses of 8 mg fesoterodine or placebo were administered to 16 healthy young male (18-45 years), 16 healthy elderly male (>65 years) and 16 healthy elderly female (>65 years) subjects (each group: 12 active substance, 4 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.
With a highly selective LC/MS/MS method the plasma concentrations of SPM 7605, the active metabolite of fesoterodine, were detected to characterize the pharmacokinetics of SPM 7605 in human subjects. Pharmacokinetic parameters were AUC, C_{max}, $t_{½}$, t_{max}, MRT and Cl of SPM 7605.

Results

A total of 48 healthy 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 three populations.
9 adverse events (active substance: 7; placebo: 2) were reported by 5 young males (active substance: 4; placebo: 1), 7 adverse events (active substance: 6; placebo: 1) by 6 elderly males (active substance: 5; placebo: 1), and 7 adverse events (active substance: 6; placebo: 1) by 6 elderly females (active substance: 5; placebo: 1). All adverse events were classified as mild, there was no serious adverse event. The adverse event pattern was similar in the three populations.
In particular, in the elderly males and females, safety examinations such as physical examination, heart rate, systolic and diastolic blood pressure, ECG-parameters and laboratory parameters were not influenced by the study drug in a clinically relevant manner.
Mean maximum plasma levels of SPM 7605 were observed approximately 5 hours after administration. Body weight normalized maximum plasma concentration $C_{max}(w)$ and area under the curve AUC(w) were similar in all three populations. As expected, renal clearance was lower in elderly as compared to young subjects. The mean terminal half life $t_{½}$ ranged from 7 to 9.4 hours in the different populations. The mean residence time MRT of SPM 7605 was approximately 11 hours in all three populations. Overall, no differences in pharmacokinetic parameters were observed between the different populations.

Conclusions

A single oral dose of 8 mg fesoterodine was safe and well tolerated in young males, elderly males and elderly females. Different age or gender did not result in a different pharmacokinetic profile after normalization regarding individual body weights.
In conclusion, the present trial demonstrates that fesoterodine can safely be administered to elderly patients in further clinical trials and that no dosage adjustment is considered to be necessary based on tolerability and pharmacokinetic results in this population.

References

[1] Cawello et al. Naunyn-Schmiedeberg's Arch Pharmacol 365 (Suppl. 1): 428, 2002.
[2] Breidenbach et al. Submitted.
[3] Sachse et al. Naunyn-Schmiedeberg's Arch Pharmacol 365 (Suppl. 1): 413, 2002.