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PHARMACODYNAMIC PROFILING OF THE NOVEL ANTIMUSCARINIC DRUG FESOTERODINE ON RAT BLADDER

Aims of Study

Fesoterodine is a novel antimuscarinic, developed for treatment of overactive bladder. Fesoterodine is rapidly metabolized in humans [1] and rats [Scharfenecker U. unpublished, 2001] to its active metabolite SPM 7605. The aim of the study was to characterize the in-vitro and in-vivo effects of fesoterodine and its active principle, SPM 7605, in comparison to oxybutynin and atropine.

Methods

The effects of fesoterodine, SPM 7605, oxybutynin and atropine on carbachol-induced or electrical field stimulation-induced contractions of rat bladder strips were measured in organ bath chambers. Data were presented (normalized) as % carbachol response and pA_2 values (mean ± SD) were evaluated by Schild analysis.

Fesoterodine and SPM 7605 at doses of 0.01, 0.1 and 1 mg/kg were administered intravenously to female Sprague-Dawley rats (n = 6 per group). Continuous recording of urodynamic parameters (micturition pressure, threshold pressure, basal pressure, bladder capacity, micturition volume, residual volume, intercontraction interval) for 90 to 120 min after drug administration was performed. Results were presented as mean values ± SEM. Student's paired two-tailed t-test was used for comparison between effects before and after treatments. Statistical differences between groups were assessed by ANOVA and post-hoc Scheffe's F-test with $p < 0.05$ being accepted as significant.

Results

Both, fesoterodine and SPM 7605 caused a rightward shift of the concentration-response curve for carbachol (1 µM – 1 mM). There was no significant depression of the maximum indicating a competitive antagonism. The calculated pA_2 values were 8.7 ± 0.3 for fesoterodine and 8.8 ± 0.3 for SPM 7605. The slope of the Schild plot was 1.0 and 1.3 for fesoterodine and SPM 7605, respectively. The respective pA_2 values for oxybutynin and atropine were 8.4 ± 0.1 and 9.0 ± 0.3.

Contractions induced by electrical field stimulation were inhibited in a concentration-dependent way. Maximum inhibition was achieved at 0.1 µM for both fesoterodine (60.0 ± 15.3%; n = 7) and SPM 7605 (46.6 ± 13.1%; n = 7). Corresponding figures for oxybutynin (0.1 µM) and atropine (0.1 µM) were 33.7 ± 14.0% and 39.7 ± 27.1%, respectively.

Urodynamic investigations in healthy rats revealed potent increases in bladder capacity (BC) and intercontraction intervals (ICI) with both fesoterodine (BC: 0.99 ± 0.1 mL versus 0.83 ± 0.1 mL; ICI: 5.48 ± 0.7 min versus 4.61 ± 0.5 min) and SPM 7605 (BC: 1.08 ± 0.1 mL versus 0.98 ± 0.1 mL; ICI: 6.04 ± 0.7 min versus 5.44 ± 0.8 min) given i.v. at 0.01 mg/kg. At this dose there was only a tendency of micturition volume increase. However, a significant reduction of the micturition pressure was concomitantly seen at this dose for both fesoterodine and SPM 7605 indicating that the threshold dose is still below 0.01 mg/kg.

Conclusions

Functional antimuscarinic action of both fesoterodine and SPM 7605 in-vitro and in-vivo was similar in terms of potency. This might be explained by the rapid and complete conversion of fesoterodine by ubiquitously present esterases to SPM 7605. In fact, in human and in rat plasma only SPM 7605 is measurable after oral administration of fesoterodine [1]. The following order of potency was obtained in-vitro: atropine > fesoterodine = SPM 7605 > oxybutynin (figure). Already at 0.01 mg/kg i.v. fesoterodine as well as SPM 7605 exerted potent effects on urodynamics in this rat model of incontinence. Based on the effects seen on the micturition pressure it is assumed that the threshold dose level is still below the tested dosages. This consideration is subject to further experiments.

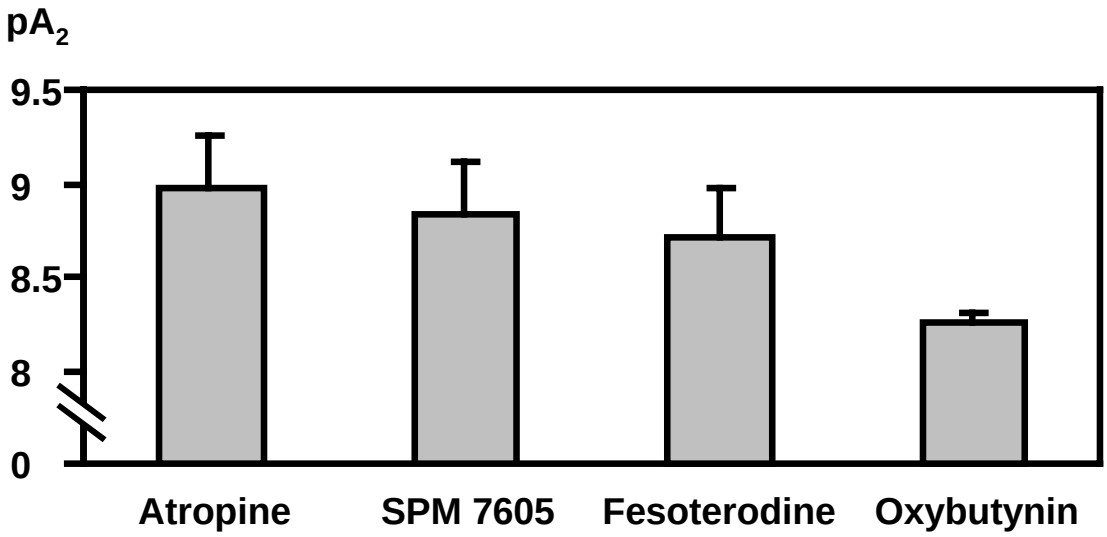

Figure: pA_2 values (mean ± SD) were calculated from concentration response curves (n = 5 – 8 preparations per concentration of antagonist)

[1] Cawello W, Auer S, Hammes W, Sachse R, Horstmann R. Multiple dose pharmacokinetics of fesoterodine in human subjects. Naunyn-Schmiedeberg's Arch Pharmacol 365 (Suppl. 1): 428, 2002.