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THE EFFECT OF ASP5633 ON URETHRAL PRESSURE IN HEALTHY FEMALES – A RANDOMIZED, PLACEBO CONTROLLED CROSSOVER STUDY WITH MIDODRINE AS ACTIVE CONTROL

Hypothesis / aims of study

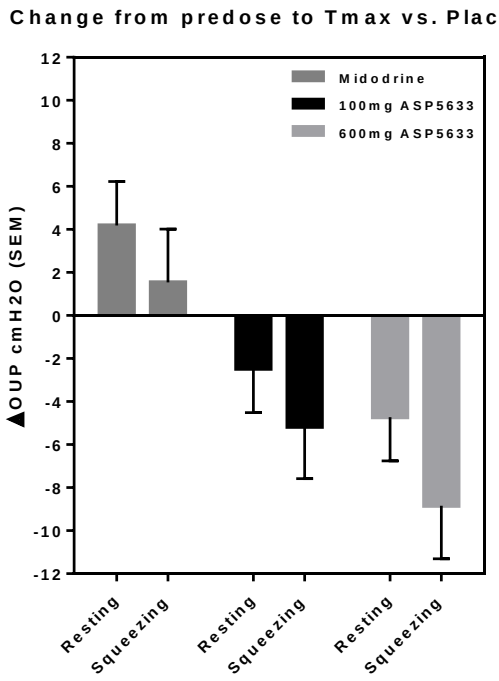
Midodrine is used off label in stress urinary incontinence patients by its virtue to activate α1a-adrenoceptors on urethral smooth muscles (USM). ASP5633 has shown to increase urethral pressure (UP) in relevant animal models, possibly by acting on USM. Urethral pressure reflectometry (UPR) is a reliable technique for evaluation of the urethral closure function measuring the opening urethral pressure (OUP). The OUP is the pressure exactly needed to open the urethra. This parameter is reproducible, without movement artefacts, can discriminate between continent and SUI women and is sensitive to pressure changes in the urethra during pharmacological treatment (1). The examination has minimal influence on the urethra as only a very thin and highly flexible plastic bag is placed in the urethra during the examination and is well-tolerated.
The aim of this study was to evaluate the effect of single oral doses of ASP5633 and midodrine against placebo on the OUP in healthy females using UPR.

Study design, materials and methods

Adult healthy female subjects (18-55 years old), recruited by advertising, were included in this placebo-controlled, investigator- and subject-blinded, randomized, 4-period crossover study, receiving a sequentially randomized single dose of ASP5633 100 mg, ASP5633 600 mg, midodrine 10 mg and matching placebo. The subjects had consecutive randomization numbers which specified the treatment sequence. The plasma concentrations of ASP5633 cover the exposure levels shown to increase UP in relevant animal models. The dose of midodrine has shown to increase the OUP using the UPR method (2). During each treatment period, the subjects underwent UPR assessments to measure OUP. UPR was performed at baseline and at 1, 2, 4 and 8 hours after dosing to cover the reported Tmax of both ASP5633 and midodrine (2 hr) in a supine position with a filled bladder (150ml 0.9% saline), without (resting) and with squeezing of the pelvic floor. With an assumed standard deviation (SD) of 13.3 cmH_2O, a total of 24 subjects would be needed to detect a difference of 8 cmH_2O in the resting OUP between placebo and ASP5633 with a power of 80% at the 2-sided 5% significance level. The study was conducted between April 2015 and June 2015.

Results

All 24 subjects (median age 24 [range 21-53] years) gave written informed consent and performed all 4 periods. Observed adverse events (AEs) were mild. The number of subjects with AEs was 10 (42%), 15 (63%), 11 (46%), and 12 (50%) during the 100mg ASP5633, 600mg ASP5633, midodrine and placebo period, respectively. The most common AEs were fatigue (in 2, 7, 6 and 3 subjects, respectively) and headache (in 4, 5, 2 and 0 subjects, respectively). In the resting condition the mean change in OUP from pre-dose to Tmax versus placebo was -2.5 cmH_2O (95% CI -6.5 to 1.5, p=0.224) for ASP5633 100mg, -4.7 cmH_2O (95% CI -8.7 to -0.7, p=0.021) for ASP5633 600mg, and 4.2 cmH_2O (95% CI 0.2 to 8.2, p=0.040) for midodrine. When the pelvic floor was squeezed the mean change in OUP from predose to Tmax vs. placebo was -5.2 (95% CI -10.0 to -0.3, p=0.037), -8.8 (95% CI -13.7 to -4.0, p<0.001) and 1.5 (95% CI -3.3 to 6.4, p=0.533), respectively.



Interpretation of results

Both doses of ASP5633 were generally safe and well-tolerated. Midodrine 10mg showed a modest but statistically significant increase in OUP in the same scale as previously reported (2). ASP5633 in contrary appeared to, albeit modestly, decrease OUP in the resting as well as the squeezing condition. There was a tendency toward a dose depended decrease in OUP and the largest effect was seen during squeezing of the pelvic floor. The mechanism behind the pressure decrease is, at the moment, unknown.

Concluding message

In contrast to midodrine, ASP5633 does not appear to increase OUP using UPR under conditions of resting and squeezing of the pelvic floor.

References

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Disclosures

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