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EFFECTS OF CHRONIC ADMINISTRATION OF TAMSULOSIN AND TADALAFIL, ALONE OR IN COMBINATION, IN RATS WITH BLADDER OUTLET OBSTRUCTION INDUCED BY CHRONIC NITRIC OXIDE DEFICIENCY

Hypothesis / aims of study

In rats with bladder outlet obstruction induced by chronic nitric oxide deficiency tadalafil did not cause impairment in detrusor muscle and seems to have an addictive effect to tamsulosin

Study design, materials and methods

Thirty-one male rats were randomized to following groups: 1 - control; 2 - L-Nitroarginine methyl ester (L-NAME); 3 - Tamsulosin + L-NAME, 4 Tadalafil+L-NAME; and 5 - Tamsulosin + Tadalafil + L-NAME. At the end of the treatment period (30 days), all animals were submitted to urodynamic study.

Results

The administration of L-NAME increased the number of non voinding contractions (NVC) (1.04 ±0.22), volume threshold (VT) (1.86 ±0.35), and micturition cycle (MC) (1.34 ±0.11) compared with control (0.52 ±0.06, 0.62 ±0.06, and 0.67 ± 0.30), respectively. The administration of tamsulosin reduced the number of NVC (0.57 ± 0.42) and VT (0.76 ± 0.24) compared with L-NAME group. Co-treatment with tadalafil decreased the number of VT (0.85 ±0.53) and MC (0.76 ±0.22) compared with L-NAME group. The combination of tamsulosin with tadalafil improved the number of NVC (0.56 ±0.18), VT (0.97 ±0.52) and MC (0.68 ±0.30) compared with L-NAME group.

Variables	Group 1 (n=6) Mean ± SD	Group 2 (n=6) Mean ± SD	Group 3 (n=6) Mean ± SD	Group 4 (n=7) Mean ± SD	Group 5 (n=6) Mean ± SD	P value (ANOVA)
NVC	0.52 ± 0.06	1.05 ± 0.23†	0.58 ± 0.43‡	0.67 ± 0.21	0.56 ± 0.19‡	0.0101
VT	0.62 ± 0.06	1.86 ± 0.35†	0.76 ± 0.24‡	0.85 ± 0.53‡	0.97 ± 0.52‡	0.001
PT	26.67 ± 4.50	24.17 ± 5.04	26.71 ± 4.11	30.00 ± 8.32	28.83 ± 2.14	0.3637
PP	29.17 ± 7.83	27.50 ± 4.76	27.14 ± 6.77	29.67 ± 2.94	31.33 ± 3.56	0.6725
MC	0.68 ± 0.31	1.35 ± 0.12	0.96 ± 0.54	0.76 ± 0.22‡	0.68 ± 0.30‡	0.0101
BP	14.67 ± 8.07	18.83 ± 3.13†	16.14 ± 6.96	11.00 ± 4.29	11.00 ± 4.82	0.1135

Interpretation of results

The administration of tadalafil reduced the number of NVC, VT and MC. However, compared with L-NAME only reduction of VT and MC was significant. The exact mechanism through which PDE inhibitors act in the lower urinary tract remains unclear. Nonetheless, there are several theories to explain it. It is likely that there is an overlap between the roles of each of these candidate mechanisms. However, probably the hypothesis of the reduction of NO is the best explanation. This theory can be supported by the increase in the number of NVC, VT, and MC observed in the animals with chronic deficiency of NO in this study. Nitric oxide can activate guanylate cyclase, the enzyme that produces cGMP. The accumulation of intracellular cGMP triggers a cascade, leading to decreased intracellular calcium level and subsequent relaxation of smooth muscle cells. As previously known, the amount of cGMP results from the balance between production (NO) and degradation made by phosphodiesterase enzymes that hydrolyze and inactivate cyclic nucleotides. Thus, PDE5i increasing cGMP can probably explain the reduction in VT (decrease urethral resistance) and MC (relaxation of detrusor) observed in this study. As tadalafil did not decrease detrusor pressure (LP or PP) become evident that PDE5i do not cause impairment in detrusor muscle. This finding is important because it has been hypothesized that PDE5i could cause impairment in contractility of detrusor muscle.

It was also noted that the tadalafil seems to have an addictive effect to tamsulosin because beyond to improvement in VT, the combination markedly decrease NCV and MC. This finding in a experimental study could be an possible explanation why this combination was more effective to improve LUTS compared with the administration of tamsulosin or tadalafil alone in a randomized, double blind and placebo controlled clinical trial. PDE5i effect is likely to be due to a subsequent increase in cGMP resulting relaxation of detrusor (NVC and MC) and urethral (VT) smooth muscle. In addition, α1-blockers are known to favor the cyclic cAMP-dependent signaling pathway involved in relaxation mediated by adrenoceptors. If cAMP-dependent signaling is favored in the presence of a α1-blocker, this could increase cGMP levels initially stimulated by tadalafil, which had until then remained functionally silent. Such positive cross-talk mechanism between cGMP and cAMP signaling previously described in other systems, could be the origin oh the enhanced relaxant effect of the combination

Concluding message

Rats with BOO induced by chronic nitric oxide deficiency, tadalafil did not cause impairment in detrusor muscle and seems to have an addictive effect to tamsulosin because the combination decreased non voiding contractions as well the number of micturition cycles.

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Disclosures
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