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SMP-986, A NA+-CHANNEL BLOCKER AND A MUSCARINIC RECEPTOR ANTAGONIST, SHOWED INCREASED VOIDING EFFICIENCY IN ANESTHETIZED DOGS.

Hypothesis / aims of study

The muscarinic receptor antagonists are known to be effective in treating the symptoms of overactive bladder syndrome, but there are limitations. Recently, there has been an increasing interest in the role of Na^+-channels in the pathophysiology of detrusor overactivity (1, 2). SMP-986 is a Na^+-channel blocker as well as a non-selective muscarinic receptor antagonist, and has affinities for Na^+-channel and muscarinic receptors with K_i values around 20 - 90 nM. From previous report using anesthetized dogs, pure muscarinic receptor antagonists increase threshold volumes (bladder capacities) associated with large residual urine volume increase, resulting in unchanged voided volumes (3). Our aim was to evaluate the effect of combined muscarinic receptor antagonism and Na^+-channel block on urodynamic characteristics, especially on voided volume, in anesthetized dogs by using SMP-986.

Study design, materials and methods

Male beagle dogs were anesthetized with a continuous infusion of sodium pentobarbital (1.2 - 3 mg/kg/h, i.v.) and gallamine. Both ureters were ligated and catheterized proximal to the ligation. A catheter was inserted in a ureter at the bladder side for saline infusion and another catheter was inserted through the bladder dome for intravesical pressure measurement. Test substances were administered through the catheter inserted in the duodenum. The bladder was filled with physiological saline (7 - 13.4 mL/min) and after stabilization period, single cystometrogram was performed before (baseline) and 1, 2 and 3 hours after intradeodunal administration of vehicle (0.5% methylcellulose solution) or SMP-986 (1 mg/kg). Bladder threshold volume (TV), contraction amplitude (CA), residual urine volume (RV) and voided volume (VV) were evaluated as %change from baseline values.

Results

Table 1: Effect on Threshold Volume (%Change from baseline)

	1 hour	2 hours	3 hours
Vehicle	89 ± 5†	91 ± 3†	103 ± 7
SMP-986	136 ± 13*†	147 ± 5*†	151 ± 11*†

Data are expressed as means ± SEM (n=5), *P<0.05 (vs vehicle, Dunnett's test or Steel's test), †P<0.05 (vs baseline, paired t-test)

Table 2: Effect on Contraction Amplitude (%Change from baseline)

	1 hour	2 hours	3 hours
Vehicle	99 ± 5	100 ± 3	97 ± 2
SMP-986	101 ± 4	103 ± 2	92 ± 5

Data are expressed as means ± SEM (n=5), No statistically significant difference observed between two groups or between baseline and post-treatment values.

Table 3: Effect on Voided Volume (%Change from baseline)

	1 hour	2 hours	3 hours
Vehicle	87 ± 2†	92 ± 5	104 ± 9
SMP-986	136 ± 14*	148 ± 2*†	139 ± 9†

Data are expressed as means ± SEM (n=5), *P<0.05 (vs vehicle, Dunnett's test or Steel's test), †P<0.05 (vs baseline, paired t-test)

Table 4: Effect on Residual Urine Volume (%Change from baseline)

	1 hour	2 hours	3 hours
Vehicle	94 ± 11	91 ± 8	102 ± 7
SMP-986	137 ± 10†	151 ± 14†	189 ± 35*†

Data are expressed as means ± SEM (n=5), *P<0.05 (vs vehicle, Dunnett's test or Steel's test), †P<0.05 (vs baseline, paired t-test)

Interpretation of results

Intraduodenal administration of SMP-986 (1 mg/kg) significantly increased TV in anesthetized dogs without affecting CA. SMP-986-treated group showed only slight increase in RV therefore resulting in significant VV increase. Pure muscarinic receptor antagonist increased TV, suppressed CA, but did not increase VV because of large RV increase in anesthetized dogs in previous report (3). Thus, voiding efficiency could be improved by combination of muscarinic antagonism and Na^+-blockade, using SMP-986, compared to muscarinic receptor antagonists.

Concluding message

Combination of Na^+-blockade to clinically established muscarinic antagonism may offer a novel treatment option of overactive bladder syndrome, with greater efficacy and/or reduced side effects.

References

(1) J Neuroscience 21: 8690-8696 (2001), (2) ICS abstract 293 (2005), (3)Arzneim-Forsch/Drug Res 47: 182-189 (1997)

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