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Matsuo T[1], Mitsunari K[1], Ohba K[1], Mochizuki Y[1], Miyata Y[1], Sakai H[1]
1. *Department of Urology, Nagasaki University School of Medicine*

QUESTIONNAIRE SURVEY ON POSSIBLE ORAL DRYNESS FOR COMPARISONS AMONG THREE A1-ADRENERGIC RECEPTOR ANTAGONISTS (NAFTOPIDIL VS. TAMSULOSIN VS. SILODOSIN)

Hypothesis / aims of study
It is clinically known that anticholinergic agents, commonly used for treating overactive bladder, etc., act on the muscarinic receptor in salivary glands, causing dry mouth as an adverse effect. Not only the muscarinic receptor but also the α1-adrenergic receptor are present in human salivary glands, and are thought to accelerate saliva production. The common adverse events associated with α1-adrenergic receptor antagonists include orthostatic hypotension and dizziness. However, clinical research focusing on the association between α1-adrenergic receptor antagonists and oral dryness is very limited. Therefore, we conducted a cross-sectional study on current oral dryness using a questionnaire in patients prescribed an oral α1-adrenergic receptor antagonist for benign prostatic hyperplasia.

Study design, materials and methods
The study included patients who were receiving an oral α1-adrenergic receptor antagonist at the usual dose in Japan (naftopidil 75 mg/day, tamsulosin 0.2 mg/day, or silodosin 8 mg/day) to treat benign prostatic hyperplasia at our institution. For comparison, a control group consisting of age-matched patients was also enrolled. Subjects who provided informed consent completed a 9-item questionnaire on oral dryness using a face scale ranging from 1 to 7 points that was validated for reliability and appropriateness (Dry Mouth Scale [DMS]). In addition, the impact of oral dryness on patient quality of life (QOL) was assessed by the Visual Analog Scale (VAS, 0 to 10 points). Patients were excluded if they had an underlying disease that may cause dry mouth (e.g., diabetes mellitus, Sjögren's syndrome, head and neck tumors) or a history of radiotherapy for head and neck tumors, or were taking oral medications that can cause dry mouth. The Kruskal-Wallis test was used for statistical analyses, and the Steel-Dwass test for multiple comparisons, with a significance level of $P < 0.05$.

Results
The questionnaire was administered to 58 patients in the control (C group), 58 in the naftopidil (N group), 55 in the tamsulosin (T group), and 62 in the silodosin (S Group) groups. Patient characteristics for each group are shown in Table 1. Patient ages did not differ significantly among the groups. Neither was there a significant difference in the International Prostate Symptom Score or Overactive Bladder Symptom Score among the 3 groups on α1-blockers.
The questionnaire results on oral dryness are shown in Table 2. The total score was significantly higher in the S group than in the C group, suggesting a possible effect of the drug on oral dryness. Compared to the N group, the total score was significantly higher in the T and S groups. The S group also had significantly higher subscale scores for dry mouth symptoms and accompanying symptoms than the C and N groups. The T group had a higher subscale score for accompanying symptoms than the N group. In a comparison to the C group by questionnaire item, the N group had significantly higher scores for Q6 and Q8, the T group for Q6, and the S group for 5 items (Q2, 3, 5, 6, 9). For the question asking about QOL, the score was higher in the S group than in the other 3 groups, indicating a lower QOL due to oral dryness in the former group.

Interpretation of results
In this clinical study, naftopidil, which is more selective for $\alpha 1_D$ receptors than other α1-adrenergic receptor antagonists, produced results comparable to the control and minimally affected the development of oral dryness. In the groups given tamsulosin and silodosin, which are selective for $\alpha 1_A$ receptors, the severity of oral dryness, especially in patients who received silodosin, was higher than that in the control and naftopidil groups. Silodosin also appeared to affect QOL most strongly. Some basic research has demonstrated that the major isoform in the submandibular gland is the $\alpha 1_A$ subtype; binding to α1 receptors in the submandibular gland is greater following administration of silodosin than tamsulosin; and silodosin exerts its inhibitory effect more selectively in the salivary gland than in the urethra. These reports may support of our observations.

Concluding message
With the use of α1-adrenergic receptor antagonists, especially silodosin, in patients with benign prostatic hyperplasia, cautions should be exercised against not only orthostatic hypotension and/or dizziness and retrograde ejaculation, but also the onset and exacerbation of oral dryness.

Table 1 Patient characteristics

	C group	N group	T group	S group	P value
Age	70.9±11.4	70.9±9.3	69.4±10.0	69.8±7.0	0.273
IPSS total score	3.4±2.5	7.8±4.5**	7.0±4.6**	7.5±4.4**	<0.0001
OABSS total score	2.5±1.9	3.6±2.2*	4.1±2.4**	4.1±2.7**	0.0002

*P <0.05, **P<0.01 VS control group

Table 2 Results of the questionnaire survey on DMS and quality of life

	C group	N group	T group	S group	P value
Q1(Oral dryness)	2.4±1.0	2.3±1.2	2.5±1.2	2.7±1.2	0.2714
Q2 (Oral dryness when wake up)	2.4±1.0	2.2±1.3	2.5±1.2	2.9±1.3*‡	0.0186
Q3 (Throat dryness)	2.2±1.1	2.0±1.2	2.7±1.3†	2.9±1.3*‡	0.0001
Q4 (Difficulty in speaking due to dryness)	1.4±0.6	1.4±1.0	1.5±0.9	1.6±0.8	0.1414
Q5 (Sticky feeling)	1.6±0.6	1.7±1.3	2.1±1.0‡	2.3±1.2*‡	0.0004
Q6 (Pain of tongue)	1.0±0.3	1.3±0.8*	1.2±0.5*	1.2±0.4**	0.0014
Q7 (Bad breath)	1.6±0.7	1.7±1.3	1.9±1.0†	1.9±1.0†	0.0094
Q8 (Taste impairment)	1.1±0.2	1.4±0.9*	1.1±0.5	1.2±0.5	0.0227
Q9 (Difficulty in eating due to dryness)	1.1±0.2	1.4±0.9	1.3±0.8	1.3±0.6**	0.00232
Total scores	14.7±4.3	15.4±8.7	16.8±6.7†	18.0±6.8*†	0.0009
Subscale scores					
Dry mouth symptoms(Q1+2+3)	6.7±2.8	6.5±3.5	7.7±3.4	8.5±3.4*‡	0.0062
Accompanying symptoms(Q4+5+9)	4.1±1.2	4.5±3.1	4.8±2.3‡	5.1±2.2*‡	0.0003
Other symptoms(Q6+7+8)	3.6±0.8	4.4±2.7	4.3±1.7	4.4±1.6	0.056
Influence on Quality of Life	1.8±1.3	2.2±1.6	2.6±2.3	4.2±2.4**‡§	<0.0001

*P<0.05, **P<0.01 VS control; †P＜0.05, ‡P<0.01 VS naftopidil, §P<0.01 VS tamsulosin

References
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