Does Systemic Disease Aggravate the Severity of Dry Mouth by Anticholinergics in Overactive Bladder Patients?

Keon-Cheol Lee[1]*, Bong-Mo Seong[2]

Purpose: In overactive bladder (OAB) patients with systemic diseases, dry mouth tends to be more prominent owing to the effects of systemic diseases or related medications. We evaluated how systemic diseases affect dry mouth before and after anticholinergic treatment.

Materials and Methods: OAB patients were enrolled in this study. The patients were divided according to the presence or absence of systemic diseases. Patients with systemic diseases were sub-grouped by the number of systemic diseases (only one or more than one disease). OAB symptoms score (OABSS), visual analogue scale (VAS) score for dry mouth, and body mass index (BMI) were measured. The statistical assessments were done with independent T-tests and ANCOVAs.

Results: One hundred and four OAB patients were enrolled in this study. Seventy (67.3%) patients had systemic diseases and thirty-four (32.7%) patients did not. Age and BMI were higher in the systemic diseases group. The baseline VAS score of OAB in the systemic diseases group (15.9 ± 19.5) was higher than that in the OAB without systemic diseases group (4.1 ± 6.4) (P = .002). Even after age and BMI adjustment, the difference was significant. The follow-up VAS score was also different (P = .028), but the change in VAS score was not different (P = .280). In a sub-analysis, the change in VAS score in the group with two or more systemic diseases (23.6 ± 18.1) was higher than that in the group with only one systemic disease (12.5 ± 13.2) (P = .012).

Conclusion: The severity of xerostomia after treatment with anticholinergics in OAB increases in patients with one systemic disease parallel to its severity before starting treatment. However, in patients with two or more systemic disease the magnitude of change in xedrostomia score is higher that we would expect in patients with no or one systemic diasese.

Keywords: body mass index; cholinergic antagonists; systemic diseases; urinary bladder, overactive; xerostomia

INTRODUCTION

Anticholinergics are very useful and are currently the most commonly prescribed medication in overactive bladder (OAB) patients. However, they have a well-known side effect profile that includes dry mouth, constipation, voiding difficulty, and so on.[1] Dry mouth is the most common side effect; it occurs in 8-87% of OAB patients after administration of various anticholinergics depending on the particular formulation of each anticholinergic agent.[2-5] Anticholinergics work by blocking muscarinic receptors in the bladder, and dry mouth caused by anticholinergics appears to be the result of blocking muscarinic receptors in salivary glands.

Many systemic diseases appear to be related to dry mouth through various mechanisms. For example, diabetes, which is a common disease of the endocrine system, has a high dry mouth rate, up to 40-60%, even in children,[6] and the mechanisms are thought to be multifactorial and include dehydration, polyuria, and autonomic abnormalities.[7] The medications used to treat systemic diseases also frequently cause dry mouth.[8] Therefore, patients with systemic diseases could already be predisposed towards a risk of dry mouth before treatment with anticholinergics. Also, it may be that underlying systemic disease status affects side effect profiles in OAB patients treated with anticholinergics. The interaction between anticholinergics and some drugs that interfere with the cytochrome P450 pathway has been reported to potentiate the side effects of anticholinergics.[9] However, clinical reports proving this hypothesis are rare. We can assume that underlying systemic diseases make some patients more vulnerable to the adverse effects of anticholinergics. Therefore, we evaluated how systemic diseases affect dry mouth before and after anticholinergic treatment in OAB patients.

PATIENTS AND METHODS

OAB patients were enrolled in this study. The Institutional Review Board (IRB) of Inje University, Ilsanpaik

[1] Department of Urology, Inje University School of Medicine, Ilsanpaik Hospital, Goyang, Korea.

[2] Department of Urology, COMWEL Incheon Hospital, Incheon, Korea.

*Correspondence: Department of Urology, Inje University Ilsanpaik Hospital, 2240, Daehwa-dong, Goyang, Gyeonggi, Korea.

Postal code : 10380

Tel: +82 31 9107230. Fax: +82 31 9107239. E-mail: kclee@paik.ac.kr.

Received October 2016 & Accepted March 2017

Table 1. Patient demographics and comparisons of VAS score between the group of patients with OAB and systemic diseases and the group with OAB without systemic diseases before and after anticholinergic treatment.

Variables		OAB with Systemic Diseases(n=70)	OAB without Systemic Diseases(n=34)	*P*-Value
Age, year, mean ± SD		64.1 ± 10.2	56.7 ± 11.6	0.001
Male(%)		45.7(32/70)	23.5(8/34)	
Female(%)		54.3(38/70)	76.5(26/34)	
OAB-SS				
mean ± SD	Baseline	6.8 ± 3.5	6.5 ± 4.2	0.453
	Follow-up	4.5 ± 2.8	3.9 ± 4.2	0.258
Symptom duration, month, mean ± SD		83.5 ± 68.8	49.3 ± 44.7	0.010
BMI, kg/m2, mean ± SD		23.8 ± 3.5	22.3 ± 1.9	0.024
Baseline VAS, mean ± SD		15.9 ± 19.5	4.1 ± 6.4	0.002
Age-adjusted difference				0.023
BMI-adjusted difference				0.002
Follow-up VAS, mean ± SD		33.1 ± 26.4	21.8 ± 20.1	0.028
Changes of VAS, mean ± SD		17.0 ± 16.2	13.2 ± 14.1	0.280

Abbreviations: OAB, OverActive Bladder; OAB-SS, OAB-Symptoms Score; BMI, Body Mass Index; VAS, Visual Analogue Scale.

Hospital approved this study (IB-1108-037). It follows the guidelines of the Declaration of Helsinki and all patients provided written informed consent. Inclusion criteria were: age older than 20 years, total overactive bladder symptoms score (OABSS) more than three, including question 3 score more than two, without the presence of any exclusion criteria, such as narrow angle glaucoma, urinary retention, gastro-intestinal slow transit, myasthenia and any anticholinergics use during last three months.

The patients were divided into two groups according to the presence or absence of systemic diseases. A systemic disease is one that affects a number of organs and tissues, or affects the body as a whole and usually is dealt with in the internal medicine department. After thorough chart review, we used following categories as systemic diseases in this study (hypertension, endocrinologic diseases including diabetes, coronary artery diseases, cerebrovascular conditions, auto-immune conditions, hepato-biliary diseases, etc.). Seventy (67.3%) patients had systemic diseases and thirty-four (32.7%) patients did not. Patients with systemic diseases were sub-divided into two groups, those with only one systemic disease and those with two or more systemic diseases. Drugs taken by the patients for the treatment of those systemic diseases were recorded via a full chart review or by asking the patients.

Before anticholinergic treatment, OABSS and visual analogue scale (VAS) score ranging from 0 to 100 for dry mouth was examined using self-administered questionnaire forms. Body weight and height of the patients were measured in order to calculate body mass index (BMI). The clinical parameters of the systemic diseases group were compared with those of the non-systemic disease group. All patients received solifenacin 5 mg for the treatment of OAB. After 3 months of solifenacin treatment, VAS for dry mouth and OABSS were measured again and comparisons between the two groups were made again. To exclude the effects of age and BMI because age and BMI could be the risk factor of dry mouth, statistical adjustment for age and BMI was made and the data were re-analyzed.

The group with two or more systemic diseases was compared with the group with only one systemic disease for the above mentioned clinical parameters. The statistical program used was SPSS 12.0 for Windows and the normality of any variables was confirmed before running statistical comparison. Employed statistical methods were independent T-tests and ANCOVAs. P values less than 0.05 were regarded as statistically significant.

RESULTS

Between June 2012 and February 2013, a total of one hundred and four OAB patients were enrolled in this study. There were 40 (38.5%) male patients and 64 (61.5%) female patients in the studied group of patients. The mean age of the patients was 64.1 ± 10.2 years (range: 43-82) in the OAB with systemic diseases group and 56.6 ± 11.6 years (range: 38-80) in the OAB without systemic diseases group (P = .001). OAB symptom duration before study was 83.5 ± 68.8 months (range: 3-240) for the OAB with systemic diseases group and 49.3 ± 44.7 months (range: 3-120) for the OAB without systemic diseases group (P = .003). Baseline OABSS of the OAB with systemic diseases group (6.8 ± 3.5, range: 3-15) was not different from that of the OAB without systemic diseases group (6.5 ± 4.2, range: 3-14). Both groups showed significant improvements in OABSS after treatment. All patients completed three-month follow-up. The follow-up OABSS of OAB with systemic diseases group (4.5 ± 2.8, range: 0-12) was also not different from that of the OAB without systemic diseases group (3.9 ± 4.2, range: 0-14) (**Table 1**).

The baseline VAS scale of the OAB with systemic diseases group (15.9 ± 19.5, range: 0-50) was higher than

Table 2. Comparisons between the group with only one systemic disease and that with two or more systemic diseases before and after anticholinergic treatment.

Variables	One Systemic Disease (n=42)	Two or more Systemic Diseases (n=28)	*P*-value
Age, year, mean ± SD	62.5 ± 11.4	66.6 ± 7.7	0.104
Symptom duration, month, mean ± SD	67.0 ± 59.8	108.2 ± 74.9	0.013
BMI, kg/m2, mean ± SD	24.1 ± 3.8	23.2 ± 2.9	0.327
Number of drugs for systemic diseases, mean ± SD	2.5 ± 1.3	5.8 ± 2.6	0.001
Baseline VAS, mean ± SD	12.5 ± 17.8	20.9 ± 21.1	0.120
Follow-up VAS, mean ± SD	28.6 ± 25.4	40.0 ± 26.7	0.075
Changes of VAS, mean ± SD	12.5 ± 13.2	23.6 ± 18.1	0.012

Abbreviations: VAS, Visual Analogue Scale; BMI, Body Mass Index.

that of the OAB without systemic diseases group (4.1 ± 6.4, range: 0-20) (*P* = .002). Even after age-adjustment, the difference in baseline VAS scale between the two groups was still significant (*P* = .023). The follow-up VAS scale score of the OAB with systemic diseases group (33.1 ± 26.4, range: 0-90) remained higher than that of the OAB without systemic diseases group (21.8 ± 20.1, range: 0-60) (*P* = .028). However, the extent of change in VAS score in the OAB with systemic diseases group (17.0 ± 16.2, range: 0-60) was not different from that of the OAB without systemic diseases group (13.2 ± 14.1, range: 0-50) (*P* = .280). The BMI of the OAB with systemic diseases group (23.8 ± 3.5, range: 16.4-31.6) was higher than that of the OAB without systemic diseases group (22.3 ± 1.9, range: 17.6-26.5) (*P* = .024) and, after adjustment for BMI, the VAS score of the OAB with systemic diseases group was still higher than that of the OAB without systemic diseases group (*P* = .002) (**Table 1**).

The mean number of systemic diseases in each patient in the systemic disease group was 1.7 ± 1.0 (range: 1-4) and the mean number of drugs prescribed for the treatment of systemic diseases was 3.8 ± 2.5 (range: 1-11). Hypertension was the most common systemic disease (60%, 42/70), followed by diabetes (24/70), coronary artery diseases (20/70), cerebrovascular accidents (16/70), liver cirrhosis (8/70), autoimmune diseases (8/70), and end stage renal disease (2/70).

In the sub-divided group comparison, the number of drugs prescribed for the treatment of systemic diseases in the two or more systemic diseases group (5.8 ± 2.6) was higher than that for the one systemic disease group (2.5 ± 1.3) (P = .000). Although the baseline VAS score was comparable between the two groups, the change in VAS score of the two or more systemic diseases group (23.6 ± 18.1) was significantly higher than that of the one systemic disease group (12.5 ± 13.2) (*P* = .012) (**Table 2**).

DISCUSSION

Dry mouth, or xerostomia, is the subjective feeling experienced by patients suffering from hypofunction of the salivary glands.[10] In the elderly, the prevalence of xerostomia is 12-47%, which is higher than in the younger population, and age appears to be directly proportional to dry mouth.[11,12] In this study, the patients with systemic diseases and more severe dry mouth were older than the patients in the group without systemic diseases. So, we performed age-adjustment with statistical methods, and found that the severity of dry mouth of the OAB with systemic diseases group was still significantly higher than that of the OAB without systemic diseases group.

The causes of dry mouth have been attributed to the use of medications, chronic disorders, and radiation therapy of the head and neck region.[13] Dry mouth can cause dental and oral diseases such as dental caries, periodontal diseases, and problems with dentures, and can be accompanied by alterations in taste, speech, eating, and swallowing, so, it is an important problem that should not be overlooked.[14] Various systemic diseases or medications used to treat those diseases can cause dry mouth. For example, endocrine diseases, infections, autoimmune or granulomatous diseases, end-stage renal disease, and Parkinson's disease are known to be related with hypofunction of the salivary glands and subjective feelings of xerostomia via various mechanisms.[15] Various systemic diseases could have different effect profiles on xerostomia, so, some diseases could have more effect and some less. We analyzed one systemic disease group patients in this study and failed to find any difference among various systemic diseases. But, we think more profound analysis including patients with many types of systemic diseases would reveal this important hypothesis. Patients with systemic diseases usually take many different types of drugs, some of which have anticholinergic effects. The summation of the anticholinergic effects of these drugs could be an important factor in dry mouth in systemic disease patients.[16]

Overactive bladder is a complex of symptoms including increased frequency, urgency, and nocturia, and it has a profoundly negative impact on the psychosocial functioning and quality of life of patients.[17] Anticholinergics are the first-line agents used to treat overactive bladder[18] and have some side effects. Of these side effects, dry mouth is the most common problem and tends to be the most annoying to patients and doctors. The side effects as well as efficacy of anticholinergics increase with increased dosage,[19] so, a fixed single dose is preferable for proper analysis in studies of anticholinergics. Although recently introduced OAB drugs, such

as beta-3 agonists, have a low incidence of dry mouth compared with previous drugs that act through anticholinergic mechanisms,[20,21] anticholinergic agents are still the main treatment tools used to manage overactive bladder and dry mouth is still the main concern.

In this study, the severity of dry mouth in the group of OAB patients with systemic diseases was higher than in the group of OAB patients without systemic diseases before administration of anticholinergics, and the difference in the severity of dry mouth was maintained after 3 months of anticholinergic use. This could be because of the effects of the drugs used to treat systemic diseases or because of the diseases themselves. When we subdivided the systemic diseases group, the accumulated number of systemic diseases had a significant effect on dry mouth severity. The group with two or more systemic diseases showed increased dry mouth severity compared with the group with only one systemic disease. The number of drugs taken for systemic diseases was also greater in the group with two or more systemic diseases, which could result in those patients being more susceptible to the side effects of anticholinergics.

OAB patients with systemic diseases had higher baseline and follow-up dry mouth severity after anticholinergic treatment than did OAB patients without systemic diseases even after adjusting for the effects of age and BMI. In addition to the well-known age factor, systemic diseases themselves affect baseline dry mouth, and this already high baseline xerostomia is accompanied by significantly more severe dry mouth after anticholinergic treatment in OAB patients with systemic diseases. Although the changes in the severity of dry mouth were not different between the systemic diseases group and the non-systemic diseases group, sub-classification of the systemic diseases group revealed an association between the number of systemic diseases and the changes in dry mouth after anticholinergic treatment. Compared with the patients with only one systemic disease, those with two or more systemic diseases appear to be more susceptible to aggravation of dry mouth by anticholinergics. Therefore, when administering anticholinergics to OAB patients with systemic diseases, especially those with two or more systemic diseases, it is necessary to prepare for the aggravation of dry mouth.

This study has several limitations. Firstly, age was not comparable between the systemic diseases group and the no systemic diseases group. Age is known to be directly proportional with the rate of dry mouth, so, this difference could have caused a bias in our results. All else being equal, it is reasonable to assume that patients with systemic diseases would generally be older and in worse condition. We did not make intentional efforts to select patients as long as all inclusion criteria and no exclusion criteria were met. Simple allocation to groups was made according to the presence or absence of systemic diseases. We attempted to overcome this age discrepancy with statistical age-adjustment. Second limitation of this study is that accurate sample size was not calculated before study with the simple goal of at least 30 patients in each group for the proper statistical comparison including normality and the number of patients were not the same among groups. Another limitation of this study is that gender distribution is not even in OAB without systemic disease group compared with OAB with systemic disease group. Male predominance in OAB without systemic disease group might have the possibility of gender difference bias in xerostomia although gender difference in xerostomia was not generally proven.

CONCLUSIONS

The severity of xerostomia after treatment with anticholinergics in OAB increases in patients with one systemic disease parallel to its severity before starting treatment. However, in patients with two or more systemic disease the magnitude of change in xerostomia score is higher that we would expect in patients with no or one systemic disease.

ACKNOWLEDGEMENT

“ This work was supported by the grant from Astellas ”. All authors have contributed significantly and all authors are in agreement with the content of this manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Herbison P, Hay-Smith J, Ellis G, Moore K. Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. BMJ. 2003;326:841-4.
2. Cardozo L, Lisec M, Millard R, van Vierssen Trip O, Kuzmin I, Drogendijk TE, Huang M, Ridder AM. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol. 2004;172:1919-24.
3. Chapple CR, Arano P, Bosch JL, De Ridder D, Kramer AE, Ridder AM. Solifenacin appears effective and well tolerated in patients with symptomatic idiopathic detrusor overactivity in a placebo- and tolterodine-controlled phase 2 dose-finding study. BJU Int. 2004;93:71-7.
4. Halaska M, Ralph G, Wiedemann A, Primus G, Ballering-Bruhl B, Hofner K, Jonas U. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World J Urol. 2003;20:392-9.
5. Anderson RU, Mobley D, Blank B, Saltzstein D, Susset J, Brown JS, OROS Oxybutynin Study Group. Once daily controlled versus immediate release oxybutynin chloride for urge urinary incontinence. J Urol. 1999;161:1809-12.
6. Busato IMS, Ignácio SA, Brancher JA, Grégio AMT, Machado MÂN, Azevedo-Alanis LR. Impact of xerostomia on the quality of life of adolescents with type 1 diabetes mellitus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108:376-82.
7. Vasconcelos ACU, Soares MSM, Almeida

PC, Soares TC. Comparative study of the concentration of salivary and blood glucose in type 2 diabetic patients. J Oral Sci 2010;52:293-8.

8. Miranda-Rius J, Brunet-Llobet L, Lahor-Soler E, Farré M. Salivary Secretory Disorders, Inducing Drugs, and Clinical Management. Int J Med Sci. 2015;12:811-24.
9. Oefelein MG. Safety and tolerability profiles of anticholinergic agents used for the treatment of overactive bladder. Drug Saf. 2011;34:733-54.
10. Thomson WM, Chalmers JM, Spencer AJ, Williams SM. The Xerostomia Inventory: A multi-item approach to measuring dry mouth. Community dent health. 1999;16:12-7.
11. Thomson WM. Issues in the epidemiological investigation of dry mouth. Gerodontology. 2005;22:65-76.
12. Murray Thomson W, Poulton R, Mark Broadbent J, Al-Kubaisy S. Xerostomia and medications among 32-year-olds. Acta Odontol Scand. 2006;64:249-54.
13. Ouanounou A. Xerostomia in the Geriatric Patient: Causes, Oral Manifestations, and Treatment. Compend Contin Educ Dent. 2016;37:306-11.
14. Turner M, Jahangiri L, Ship JA. Hyposalivation, xerostomia and the complete denture. A systematic review. JADA 2008;139:146-50.
15. Mortazavi H, Baharvand M, Movahhedian A, Mohammadi M, Khodadoustan A. Xerostomia due to systemic disease: a review of 20 conditions and mechanisms. Ann Med Health Sci Res. 2014;4:503-10.
16. Reppas-Rindlisbacher CE, Fischer HD, Fung K, Gill SS, Seitz D, Tannenbaum C, et al. Anticholinergic Drug Burden in Persons with Dementia Taking a Cholinesterase Inhibitor: The Effect of Multiple Physicians. J Am Geriatr Soc. 2016;64:492-500.
17. Liberman JN, Hunt TL, Stewart WF et al: Health-related quality of life among adults with symptoms of overactive bladder: results from a U.S. community-based survey. Urology. 2001;57:1044.
18. Krhut J, Gärtner M, Petzel M, Sykora R, Nemec D, Tvrdik J, et al. Persistence with first line anticholinergic medication in treatment-naïve overactive bladder patients. Scand J Urol. 2014;48:79-83.
19. Preik M, Albrecht D, O'Connell M, Hampel C, Anderson R. Effect of controlled-release delivery on the pharmacokinetics of oxybutynin at different dosages: severity-dependent treatment of the overactive bladder. BJU Int. 2004;94:821-7.
20. Andersson KE, Martin N, Nitti V. Selective β-adrenoceptor agonists for the treatment of overactive bladder. J Urol. 2013;190:1173-80.
21. Imran M, Najmi AK, Tabrez S. Mirabegron for overactive bladder: a novel, first-in-class β3-agonist therapy. Urol J. 2013;10:935-40.