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Antiseptic mouthwashes could worsen xerostomia in patients taking polypharmacy

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Abstract

Objective. Polypharmacy is a common cause of xerostomia. This study aimed to investigate whether xerostomia could be an adverse drug event of mouthwashes, when they are used for longer than 2 weeks by patients taking polypharmacy. ***Materials and methods.*** This cross-sectional observational study included 120 hospitalized patients (60 middle-aged and 60 elderly patients), taking polypharmacy (≥4 drugs daily) and at risk of drug-induced xerostomia. Xerostomia was assessed by questioning participants. ***Results.*** A total of 62.5% of patients complained of xerostomia. In the middle-aged group (mean age = 44.0 (8.7) years; 35.0% women) xerostomia seemed independently associated to mouthwashes, at the limit of significance (OR = 5.00, 95% CI = 0.99–25.3, $p = 0.052$). Active principles in mouthwashes were mainly quaternary ammonium compounds (91.9%). Mouthwashes may disturb the healthy balance of the biofilm moisturizing the oral mucosa. The biofilm contains mucins, salivary glycoproteins with oligosaccharides side chains able to sequester water and endogenous bacteria surrounded by a glycocalyx. Oral bacteria are fully susceptible to quaternary ammonium (chlorhexidine, hexetidine, cetylpyridinium chloride) and to other antiseptics used in mouthwashes, such as betain, resorcin, triclosan, essential oils and alcohol. However, caregivers currently recommend such dental plaque control products to patients suffering from xerostomia in order to reduce the risk of caries and periodontitis. ***Conclusion.*** This study is the first report that use of antiseptic mouthwashes for more than 2 weeks could worsen xerostomia in patients taking polypharmacy. Oral care protocols should avoid this iatrogenic practice, particularly when xerostomia alters the quality-of-life and worsens malnutrition.

Key Words: *adverse drug event, biofilm, iatrogenic disease, xerostomia*

Introduction

Alterations of saliva physiology include xerostomia, hyposalivation and altered saliva composition. Xerostomia is a subjective feeling of oral dryness. Mouth dryness is a term regarding dryness in the oral cavity, objectively diagnosed by for instance a dental mouth mirror sticking to the buccal mucosa of the cheek due to dryness. Xerostomia varies substantially between individuals [1,2]. According to Glore et al. [3], dry mouth is not necessarily related to decreased salivary flow. Some patients experience a feeling of oral dryness, despite seemingly normal, objectively measured levels of saliva secretion [4], whereas others do not complain about dry mouth, despite objectively diagnosed hyposalivation [5]. However, most individuals experience a sensation of oral dryness when their salivary output is less than about half of the normal output in health, but with great variation [2].

The prevalence of xerostomia reaches 10–20% in the general population, primarily in women, and 50% in the elderly [1,6]. Symptoms of mouth dryness include a sensation of thirst, soreness and dryness of the lips and oral mucosa [7,8]. It is associated with an increased risk of caries, oral candidiasis, removable denture intolerance, taste disturbance and pneumonia, with a subsequent risk of eating difficulties,

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choking, loss of appetite and malnutrition [6,8–10]. Treatment protocols may include: general and local hydration, saliva substitutes and lubricants, central (pilocarpine, cevimeline) and local (sugar-free chewing-gums and candies) secretagogues, antifungal treatment, topical analgesics before meals, suppression or replacement of xerogenic drugs, dietary modification and/or dietary supplements and oral hygiene reinforced with antiseptic oral care products. No treatment or combination treatment is fully satisfactory in combating xerostomia [1,2,11–13].

Common causes of xerostomia include dehydration, autoimmune (Sjögren's syndrome) and endocrine (diabetes) diseases, hepatitis C virus (HCV) infection and radiation therapy of head and neck tumors [12,14,15]. Many commonly prescribed medications are associated with the feeling of mouth dryness, despite normal saliva production [1,2]. In the elderly, the main cause of xerostomia is medication and, in particular, the use of ≥4–5 drugs per day [2]. More than 500 medications are associated with xerostomia, with special emphasis placed on psychotropic drugs (anticholinergic drugs/atropinics, neuroleptics, tricyclic antidepressants, antipsychotics, benzodiazepines), followed by anti-hypertensives, diuretics, anti-neoplastics, opiates, bronchodilators, proton pump inhibitors, antihistamines and others [6–9,16,17]. However, few medications except for true anticholinergic drugs have been demonstrated to affect salivary function and polypharmacy remains the most prevalent cause of mouth dryness [4,14,16]. Actually, xerostomia is not listed either among indications of antiseptic mouthwashes or among their side-effects. However, we observed that, in all the previous series investigating polypharmacy and xerostomia, no attention had ever been paid to topical medications such as antiseptic mouthwashes [2,16,17].

Antiseptic mouthwashes are efficient against bacterial species colonizing the oral biofilm and their use must not exceed 2 weeks [18]. However, misuse of antiseptic mouthwashes for longer than a 2-week period is frequently reported by patients, with the risk to unbalance the oral bacterial biofilm coating oral mucosa. Besides, the biofilm contains salivary and bacterial glycoproteins, the primary function of which are to retain water [19].

Due to the absence of consensual treatment for xerostomia [2,6], it might be necessary to combat iatrogenic factors. We hypothesized that, in addition to low saliva secretion induced by systemic drugs, mouth dryness could be worsened by biofilm alterations induced by local antimicrobial medications.

The objective of the present work was to investigate the link between xerostomia and the use of antiseptic mouthwashes for a duration of time longer than 2 weeks, in patients taking polypharmacy.

Materials and methods

Study design and patients

This cross-sectional observational study included 120 patients from Nice University Hospital: 60 middle-aged patients (Mean age = 44 (8.7)) from the Department of Infectious Diseases and 60 elderly patients (Mean age = 84.5 (8.0)) from the Department of Geriatrics. Patients recruited in the Infectious Diseases Department suffered mainly from human immunodeficiency virus (HIV) infection or HCV chronic hepatitis. Patients recruited in the Geriatrics Department suffered from various cardiovascular, endocrine, psychiatric and other chronic disorders. Both of these populations had a high probability to be given polypharmacy. Such patients frequently complained of xerostomia and exhibited mucosal dryness. We enrolled consecutive patients seen at the Department of Dentistry for routine dental examination. All participants taking four drugs or more daily were eligible for the study and there was no exclusion criterion. All participants gave written informed consent. The study was approved by the Clinical Research Department of Nice University Hospital and by the local Ethics Committee (May 6, 2013; registration number 20100108).

Data collection

The main variable was subjective xerostomia. According to the protocol described by Thomson et al. [20], participants were asked the question 'How often does your mouth fell dry?' with four possible answers: 'Always', 'Frequently', 'Occasionally' or 'Never'. Patients who answered 'Always' or 'Frequently' were considered as suffering from xerostomia.

Other data were obtained from patient interviews, routine dental examinations and hospital medical files. Collected data includes gender, age and common known associations with xerostomia: Sjögren's disease, dehydration, head and neck radiation therapy, tobacco use, previous or current illicit drug addiction, HIV or HCV infection, depressive disorders, diabetes mellitus, Parkinson's disease, number of drugs taken per day and loss of appetite. Recent non-voluntary weight loss and body mass index (BMI: [mass in kg]/[height in m]^2) were also noted. Xerostomia and use of antiseptic mouthwashes for longer than 2 weeks duration were recorded. Routine oral parameters were charted: oral candidiasis (denture stomatitis, acute stomatitis, erythematous stomatitis), oral pain, oral ulcerations, active dental caries, edentulousness, removable denture(s) and masticatory ability [21].

Patients' medications were also recorded. Each psychotropic agent was categorized as follows: muscarinic antagonists (true anticholinergic/atropinic

drugs), adrenergic alpha-antagonists, opioid agonists, serotonin 5-HT2 blockers, histamine H1 antagonists, dopamine D2 receptors blockers or GABA-A receptor agonists. Some were classified in more than one category; for instance, risperidone is a selective blocker of dopamine D2 receptors and serotonin 5-HT2 receptors and it was attributed to both categories. Other drugs were charted as follows: paracetamol, glucocorticoids, antibacterial agents, antifungal agents, anti-HIV agents, diuretics, adrenergic beta-blockers, angiotensin-converting enzyme inhibitors, sodium potassium pump inhibitors, iron supplements, calcium channel blockers, platelet aggregation inhibitors, coumarin anticoagulants, heparin, proton pump inhibitors, anti-diabetic agents, etc.

Data analysis

Analysis was performed separately for the middle-aged patients group and for the elderly patients group, using SAS statistical package, version 9.1.3 (SAS Institute, Inc., Cary, NC). In univariate analysis, the association between xerostomia and quantitative parameters were assessed using Student's *t*-test or Wilcoxon test if Student's *t*-test hypothesis was not verified. Association between xerostomia and qualitative variables were assessed using the chi-square test or Fisher's exact test in case of small expected frequencies.

Multivariate analysis was performed using logistic regression. The analysis was adjusted on risk factors known to be associated with xerostomia ('woman', 'number of drugs taken per day' and 'use of psychotropic drugs') [1,2]. In addition, the variables associated with $p < 0.1$ in the univariate analysis were included in the multivariate model. Statistical significance was accepted at 5% ($p \leq 0.05$).

Results

Patients of both groups were heavily medicated with up to 18 drugs per day. Seventy-five out of the 120 patients (62.5%) suffered from subjective xerostomia and 37 patients (30.8%) reported regular use of antiseptic mouthwashes. They used them once or more daily at home for more than 2 months and they continued this habit during their hospitalization. Most of the antiseptic mouthwashes contained quaternary ammonium compounds (34/37: 91.9%): chlorhexidine gluconate (n = 19, combined with chlorobutanol, alcohol and levomenthol), hexetidine (n = 12, combined with alcohol and menthol), cetylpyridinium chloride (n = 3, combined with chlorobutanol, eugenol, menthol and castor oil). Other mouthwashes contained sodium bicarbonate (n = 1), alcohol and anethole combined with other essential oils (mint, cinnamon, clove and benzoin) (n = 1) and salicylic acid combined with alcohol, levomenthol, resorcinol and veratrol (n = 1). No patient reported the use of antimicrobial oral care products specifically designed for daily oral hygiene. For the inclusive patients, no element in favour of dehydration at the clinical or biological level was noted in the medical record. In this study, we observed only denture stomatitis and no acute or erythematous stomatitis. However, we did not make an oral sample in search of *Candida*.

The two groups of patients are described in Tables I and II. In the group of middle-aged patients, risks factors for xerostomia were as follows: younger age (42.5 (9.4) years vs 46.5 (6.9) years; $p = 0.08$), woman (46.0% vs 17.4%; p = 0.024), use of antiseptic mouthwashes for a duration of time longer than 2 weeks (43.2% vs 17.4%; p = 0.039), tobacco use (83.8% vs 60.9%; p = 0.046) and use of GABA treatment (43.2% vs 17.4%; $p = 0.039$). In the group of elderly patients, risks factors for xerostomia were as follows: number of drugs taken per day (9.0 (2.9) vs 6.6 (3.2); $p = 0.005$), use of sodium potassium pump inhibitors (36.4% vs 13.6%; p = 0.055) and use of psychotropic drugs (57.9% vs 22.7%; p = 0.008).

In the group of middle-aged patients, multivariate analysis showed an association between xerostomia and the variable 'use of antiseptic mouthwashes', at the limit of significance (adjusted odds ratio (OR) = 5.00, 95% CI = 0.99–25.3; p = 0.052) (Table III). However, in the group of elderly patients, the association between xerostomia and the variable 'use of antiseptic mouthwashes' was not statistically significant (OR = 1.70, 95% CI = 0.44–6.62; $p = 0.44$).

In the younger population, the multivariate model included, in addition to the forced variables cited above, the variable 'age' (year), 'tobacco use' (yes/no) and 'use of GABA treatment' (yes/no). The variable 'use of GABA treatment' was no longer associated to xerostomia after adjustment (p = 0.53) and did not modify the association between 'use of antiseptic mouthwashes' and xerostomia, therefore the variable was removed from the final model. As previously described, we observed in younger patients an association between xerostomia and female gender or tobacco. In this series, a younger age was also associated to xerostomia.

In the group of elderly patients, multivariate analysis confirmed a significant association between xerostomia and the number of drugs taken per day. The multivariate model included, in addition to the forced variables, the variable 'use of sodium potassium pump inhibitor' treatment. This variable was no longer associated to xerostomia after adjustment (p = 0.28) and did not modify the association between 'use of antiseptic mouthwashes' and xerostomia, therefore it was removed from the final model (Table III). In elderly patients we only observed a tendency of association between xerostomia and psychotropic drugs consumption (Table III).

Table I. Description on the population included in the study.

	Middle-aged group (n = 60)	Elderly group (n = 60)
Mean age, years	44.0 (8.7)	84.5 (8.0)
Women	21 (35.0)	43 (71.7)
Tobacco use	45 (75.0)	1 (1.7)
Previous or current illicit drug addiction	26 (43.3)	1 (1.7)
HIV infection	41 (68.3)	1 (1.7)
HCV infection	41 (68.3)	1 (1.7)
Depressive disorders	29 (48.3)	13 (21.7)
Diabetes mellitus	2 (3.3)	10 (16.7)
Alzheimer's disease	0	2 (3.3)
Parkinson's disease	0	1 (1.7)
Sjögren's syndrome	0	1 (1.7)
Dehydration	0	0
Head and neck radiation therapy	0	0
Mean number of drugs taken per day	5.2 (1.2)	8.1 (3.2)
Loss of appetite	22 (36.7)	28 (46.7)
Recent non-voluntary weight loss	28 (46.7)	37 (61.7)
Mean Body Mass Index (BMI), kg/m2	22.8 (4.1)	23.6 (4.5)
Subjective xerostomia	37 (61.7)	38 (63.3)
Use of antiseptic mouthwashes >2 weeks	20 (33.3)	17 (18.3)
Oral candidiasis	8 (13.3)	1 (1.7)
Oral pain	13 (21.7)	12 (20.0)
Oral ulcerations	4 (6.7)	4 (6.7)
Active dental cariesa	25 (49.0)	1 (2.7)
Edentulousness (no residual tooth)	9 (15.0)	23 (38.3)
Removable denture(s)	27 (45.0)	25 (41.7)
Mean masticatory ability,b %	50.9 (31.5)	22.8 (30.6)

Results are expressed as mean (standard deviation) or number (%).
[a]The percentage of active dental caries was calculated in dentate patients only (51 younger and 37 elderly patients).
[b]Masticatory ability, expressed as a percentage, was recorded without removable dentures: an index to quantify the couples of antagonistic teeth (100%: 32 healthy teeth; 0%: no couple of antagonistic teeth).

Discussion

This study showed that, in a population of hospitalized adults taking polypharmacy (mean age = 44), the regular use of antiseptic mouthwashes was independently associated to xerostomia. Despite a high prevalence of xerostomia in patients who are administered polypharmacy (62.5% in the present series of 120 subjects), antiseptic mouthwashes had never been included in the list of the drugs associated with xerostomia. Apart from antiseptic mouthwashes, in the group of middle-aged patients we could not attribute xerostomia to any specific medication or pharmacodynamic pathway. Only 14 patients were given true anti-cholinergic drug (muscarinic antagonists), which was insufficient to correlate these drugs to xerostomia. These results are in line with those of previous authors with larger series, who did not evidence any association between xerostomia and xerogenic medications, other than true anti-muscarinic medications [3,16].

Many risk factors may be involved in xerostomia and the present study faced several difficulties. First, it is difficult to validly and reliably assess the degree of xerostomia [20,22]. Second, drugs classification is complex and we proposed a coding system based on pharmacodynamic rather than therapeutic classes. Finally, the present study was a cross-sectional study and causality between the use of mouthwashes and secondary mouth dryness or conversely the feeling of mouth dryness and secondary use of mouthwashes can be debated. However, a microbiological approach would favor the first hypothesis. Actually, antiseptic mouthwashes efficiently fight bacterial proliferation. The impact of antiseptic mouthwashes on mouth dryness could be explained by an unbalance of the endogenous microbial biofilm coating the oral mucosa. Eliasson et al. [23] showed that a feeling of xerostomia was related to a deficiency in minor salivary gland secretions. Mucin-rich saliva moistens the oral mucosal surfaces more efficiently than the salivary flows produced during meals by the parotid, submandibular and sublingual glands. Salivary mucins are glycoproteins with large oligosaccharides side chains able to sequester water and lubricate the oral mucosa [11]. They contribute to the extracellular matrix of the oral biofilm [24]. However, the healthy biofilm is also composed of bacteria, such as *Streptococcus salivarium*, *Streptococcus mitis*, *Rothia mucilaginosa*, *Gemella haemolysans* and *Fusobacterium nucleatum*, themselves enveloped by glycoproteic capsules or glycocalyx able to retain water [25,26]. These bacterial species are fully susceptible *in vitro* to antiseptics commonly used in oral care products, including quaternary ammonium, betain, resorcin, triclosan, essential oils and alcohol [6]. Fluorides also display antimicrobial properties against cariogenic and other viridans streptococci [27,28]. The unbalanced bacterial biofilm can in turn be colonized by *Candida albicans* [29], which is able to produce secretory aspartyl proteinases (Sap2), specifically known to disrupt mucins [30]. Use of antiseptic mouthwashes for a duration of time of more than 2 weeks could, thus, initiate or worsen mouth dryness by a direct action on the oral biofilm. Considering these preliminary results, microbial biofilm analysis would help to understand whether use of

Table II. Drug treatment of the population included in the study.

Drug treatment	Middle-aged group (n = 60)	Elderly group (n = 60)
Muscarinic antagonists	7 (11.7)	7 (11.7)
Adrenergic alpha-antagonists	11 (18.3)	14 (23.3)
Opioid agonists	21 (35.0)	15 (25.0)
Serotonin 2 (5-hydroxy-tryptamine 2, 5-HT2) blockers	5 (8.3)	9 (15)
Histamine 1 (H1) inhibitors	11 (18.3)	10 (16.7)
Dopamin 2 (D2) receptors blockers	7 (11.7)	7 (11.7)
Gamma-amino-butyric acid -A (GABA-A) receptor agonists	20 (33.3)	29 (48.3)
Paracetamol	2 (3.3)	37 (61.7)
Glucocoticoids	3 (5.0)	4 (6.7)
Antibacterial agents	8 (13.3)	4 (6.7)
Antifungal agents	4 (6.7)	3 (5.0)
Anti-HIV agents (non-nucleosidic reverse transcriptase inhibitors, NNRTI)	13 (21.7)	0
Anti-HIV agents (nucleotidic reverse transcriptase inhibitors, NRTI)	37 (61.7)	0
Anti-HIV agents (protease inhibitors, PI)	21 (35.0)	0
Diuretics	2 (3.3)	21 (35.0)
Adrenergic 1 beta-blockers	5 (8.3)	15 (25.0)
Angiotensin converting enzyme (ACE) inhibitors	0	25 (41.7)
Sodium potassium pump inhibitors (SPPI)	0	17 (28.3)
Iron supplements	1 (1.7)	9 (15.0)
Calcium channel blockers	0	13 (21.7)
Platelet aggregation inhibitors	2 (3.3)	13 (21.7)
Coumarin anticoagulants	2 (3.3)	8 (13.3)
Heparin	0	9 (15.0)
Proton pump inhibitors (PPI)	1 (1.7)	18 (30.0)
Antidiabetic agents	2 (3.3)	10 (16.7)
Psychotropic drugs[a]	17 (28.3)	27 (45.0)

Results are expressed as number (%).
[a]Psychotropic drugs: patients receiving muscarinic antagonists, adrenergic alpha-antagonists, opioid agonists, 5-HT2 blockers, H1 inhibitors, D2 receptor blockers and/or GABA-A receptor agonists.

mouthwashes exacerbates xerostomia among persons taking polypharmacy.

This study showed that hospital stay did not prevent tobacco smoking and confirmed that it was a risk factor of xerostomia [31]. In parallel with the present results, smoking could have systemic and topical effects on xerostomia. It is possible that the hospitalization contributes to reduce the tobacco consumption but we have no quantified data allowing us to compare before and after. The results are given according to the answers of patients and maybe under-estimated in particular for the sick of the Department of Geriatrics.

Among elderly people (mean age = 85), we did not find a significant link between complaints of mouth dryness and the regular use of antiseptic mouthwashes. The first explanation was that elderly patients were more heavily medicated than younger patients (average = 8.2 drugs/day vs 5.2 drugs/day) and the risk of xerostomia increases with the number of drugs taken daily [2]. However, other causes of mouth dryness among elderly could have been taken in account, such as age-related saliva alterations and mouth breathing [1,2]. Besides, elderly people in their 80s frequently suffer from swallowing problems. In order to avoid choking, they are given crushed medicines or opened capsules mixed with food [32]. A topical antimicrobial action of active ingredients on the oral biofilm cannot be excluded to explain the high prevalence of xerostomia among elderly patients taking polypharmacy. This would be in line with literature data, confirmed by the present study, assessing that the risk of dry mouth increases when patients are prescribed four or more drugs per day, whatever drugs are prescribed, except for true atropinic drugs which have a clear pharmacodynamic action on salivary secretory cells [3,16]. In other words, topical factors directly in contact with the oral mucosa, such as tobacco smoking, alcohol (in drinks or in mouthwashes), antiseptic mouthwashes or crushed medicines, could be inducers of xerostomia by disrupting the endogenous microbial biofilm [31–33].

According to recommended regimens, the duration of use of antiseptic mouthwashes should not exceed 2 weeks. However, in this study, many patients used them as if they were common hygiene products. They reported the 'expectation of improving dry mouth symptoms' or 'slowing down the progression of caries or periodontal diseases'. Antiseptic mouthwashes are also commonly recommended as daily oral care products to fight mouth dryness, dental caries and gingival inflammation in hospitals or at home [6,12,27,28]. As far as xerostomia may severely alter the quality-of-life of chronically ill or elderly patients [34–36], the use of antiseptic mouthwashes should be taken into account in patients taking polypharmacy.

In conclusion, patients and caregivers should be aware that long-term, routine use of the most common mouthwashes might be harmful and increase the risk of xerostomia, especially in patients taking polypharmacy. These antimicrobial products should be left aside and replaced by conventional oral hygiene procedures whenever xerostomia worsens quality-of-life or nutritional status, particularly with frail chronically ill patients.

Table III. Multivariate analysis for association with xerostomia in the middle-aged and in the elderly populations.

	Middle-aged patients (n = 60)		Elderly patients (n = 60)	
	OR (95% CI)	p	OR (95% CI)	p
Women	6.57 (1.1; 38.3)	0.036	1.06 (0.27; 4.2)	0.93
Age	1.14 (1.02; 1.28)	0.024	–	–
Use of antiseptic mouthwash >2 weeks	0.2 (0.04; 1.0)	0.052	0.59 (0.15; 2.3)	0.44
Tobacco use	0.09 (0.01; 0.63)	0.016	–	–
Number of drugs taken per day	0.83 (0.67; 1.0)	0.105	0.75 (0.57; 0.99)	0.042
Psychotropic drugs[a]	0.76 (0.15; 3.8)	0.74	0.30 (0.08; 1.11)	0.072

OR, Odds Ratio.
[a]Psychotropic drugs: patients receiving muscarinic antagonists, adrenergic alpha-antagonists, opioid agonists, 5-HT2 blockers, H1 inhibitors, D2 receptor blockers and/or GABA-A receptor agonists.

Additional studies would be necessary on the biofilm in the case of xerostomia. Research and quantification of bacterial species of the healthy oral biofilm capable of maintaining hydration due to their glycocalyx such as *Rothia mucilaginosa*, *Prevotella intermedia* or *Micrococcus luteus* would be particularly interesting. Usually these bacterial markers are not isolated and quantified in the studies on the oral mucosal flora.

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