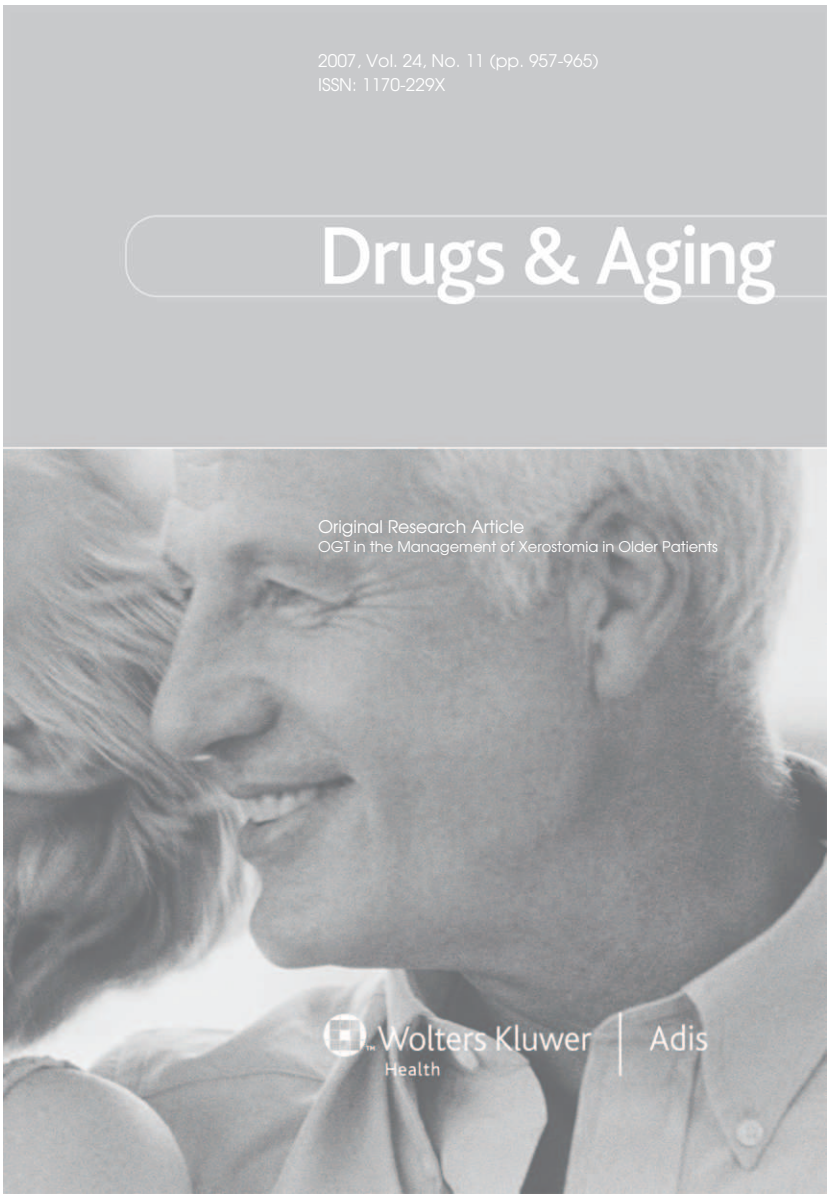

ORIGINAL RESEARCH ARTICLE

Drugs Aging 2007; 24 (11): 957-965
1170-229X/07/0011-0957/$44.95/0

Management of Xerostomia in Older Patients

A Randomised Controlled Trial Evaluating the Efficacy of a New Oral Lubricant Solution

Stéphane Mouly,[1] *Michel Salom*,[2] *Yves Tillet*,[3] *Anne-Claude Coudert*,[4] *Frantz Oberli*,[5] *Philip M. Preshaw*,[6] *Stéphane Desjonquères*[4] and *Jean-François Bergmann*[1]

1 Assistance Publique-Hôpitaux de Paris, Unit of Therapeutic Research, Department of Internal Medicine, Lariboisière Hospital, Paris, France
2 Department of Geriatry, Clinique Leopold Bellan, Magnanville, France
3 White-Tillet Consultants & Experts, Chelles, France
4 Laboratoires Carilène, Montesson, France
5 Dermscan-Pharmscan, Lyon, France
6 School of Dental Sciences, University of Newcastle, Newcastle, UK

Abstract

Background: Xerostomia is a subjective sensation of mouth dryness that may frequently occur in older patients.

Objective: To compare the clinical efficacy and acceptability of a new oxygenated glycerol triester (OGT) oral spray taken five times daily with that of a commercially available saliva substitute (Saliveze®) in the treatment of xerostomia.

Methods: Forty-one institutionalised patients (28 women, 13 men; mean age 84 ± 7 years) were randomly assigned to receive either OGT or Saliveze® in a 2-week, randomised, parallel-group study. Clinical assessment of xerostomia included evaluation of mouth dryness using a self-rated, 10cm long visual analogue scale (VAS), objective assessment of oral tissue condition using a four-point ordinal scale and subjective assessment of symptoms of xerostomia using dichotomous responses to a questionnaire. The primary endpoint was the day (D) 14 patient-based mouth dryness score measured on a self-rated VAS.

Results: At D14, OGT resulted in significantly greater efficacy with respect to mouth dryness (mean between-treatment difference 2.1 ± 0.1, 95% CI 1.9, 2.3; p = 0.001), swallowing difficulty (1.8 ± 0.3, 95% CI 1.5, 2.1; p = 0.001), speech difficulty (1.1 ± 0.2, 95% CI 1.0, 2.4; p = 0.04) and overall sensation of symptom relief (2.7 ± 1.2, 95% CI 1.9, 3.8; p = 0.001). Objective assessment of oral tissues also showed significantly better improvement with OGT spray with respect to dryness (p = 0.01), stickiness (p = 0.005) and dullness (p = 0.001) of oral mucosa; severity of mucositis (p = 0.01); and thickening of the tongue (p = 0.03). A significant difference in taste acceptability was also noted in favour of OGT (1.4 ± 0.6, 95% CI 1.2, 1.9; p = 0.04).

Conclusion: OGT lubricant oral spray was superior to Saliveze® in improving xerostomia and oral tissue condition in older institutionalised patients.

Introduction

Saliva plays a fundamental role in the maintenance of oral health.[1] Salivation is dependent on parasympathetic, especially muscarinic-dependent, stimulation that induces dilation of the oral mucosal blood vessels and contraction of the myoepithelial cells.[2,3] In addition, β-adrenergic-dependent sympathetic as well as serotonin stimulation by the CNS control saliva secretion in response to several common stimuli, for example, taste and smell, further enhancing glycoprotein secretion in the saliva, which in turn increases lubrication of the oral cavity.[2,3] Numerous drugs[4-6] act directly on the sympathetic and parasympathetic pathways, hence decreasing salivary output and modifying saliva quality without directly affecting the structure of the salivary glands, with resultant effects in the oral cavity.[7-9] Moreover, an additive effect has previously been observed[4] when several drugs are taken concomitantly by the same patient, as is often observed in the geriatric population. Unfortunately, drug-induced xerostomia is often neglected by physicians because it has long-term rather than immediate severe dental consequences.[10-14]

Xerostomia is defined as the subjective sensation of dryness of the mouth that usually implies a marked decrease in saliva secretion.[1] Mouth dryness is not a normal consequence of old age but may occur in as many as 90% of older patients due to the growing use of medications, including psychotropic drugs and β-adrenoceptor antagonists, and/or during the course of several pathological conditions, for example, dehydration, hypothyroidism, Parkinson's disease, early- and end-stage dementia, chronic obstruction of nasal breathing, Sjögren's syndrome and/or diabetes mellitus.[1,10-12,15-17] As a result, retention of dental prostheses is decreased,[18] and mucosal dehydration and reduced lubrication in the oral mucosa may occur.[19] Other complications include bad breath and mouth ulcers;[11] extensive dental caries; mucosal atrophy and burning sensation; compromised speech, chewing and swallowing; and reduced or altered taste sensation, with resultant restrictions in daily activities and social life.[11,12,17-21] While <6% of older patients spontaneously complain of dry mouth[11,12,16,17] and xerostomia has theoretically not been considered part of aging, up to 50% of glandular tissue undergoes involution in older patients in conjunction with decreased concentrations of sodium, mucin and immunoglobulin in saliva.[22,23] Hence, studies of the management of xerostomia should specifically address older individuals.

Management of xerostomia includes symptomatic relief, prevention or correction of the sequelae of saliva hypofunction and treatment of any underlying disease.[15,16,20] Adequate hydration of oral tissues (frequent sips of water) is the standard treatment for xerostomia. The different modalities available in the management of xerostomia include products destined to stimulate the production of saliva (e.g. sialogogues such as pilocarpine and cevimeline [potent muscarinic receptor agonists that enhance saliva secretion], masticatory stimulants, and administration of gustatory substances), artificial saliva and saliva substitutes.[15] However, use of oral pilocarpine may not be suitable in the geriatric population because of numerous associated parasympathomimetic adverse effects observed, for example, hyperhidrosis, urgent micturition, rhinitis, tachycardia and even hypertension.[24] Saliva substitutes, which are typically based on aqueous electrolyte solutions, can contain animal mucins or carboxymethylcellulose, are associated with variable results and have poor acceptability to some patients.[25] In addition, prolonged administration of citric or malic acid contained in some of these formulations may lead to dental demineralisation and dental loss, especially in the older patient with often poor denture hygiene.[13]

Oxygenated glycerol triester (OGT) oral spray (Aequasyal®, Eisai SAS, Paris, France)[1] is a new oral lubricant for the treatment of dry mouth that is neither a saliva substitute nor a saliva stimulant. OGT spray has the property of adherence to the oral mucosa, forming a lipid film that protects against mechanical trauma, and may help to reduce moisture loss from oral tissue. OGT contains no pharmacological ingredients and consists only of the lubricant compound OGT (94.4%), silicon dioxide (1.5%) and alimentary grade flavouring agents

1 The use of trade names is for product identification purposes only and does not imply endorsement.

(4.1%). In the current study, we hypothesised that OGT oral spray might be effective in the relief of the subjective symptoms and objective signs of dry mouth in older people hospitalised in long-term care facilities.

Patients and Methods

Materials

OGT oral spray was kindly provided by the sponsor (Laboratoires Carilène, Montesson, France). The positive control Saliveze® was an aqueous electrolyte-containing solution (calcium chloride 0.15 mg/mL, magnesium chloride 0.05 mg/mL, sodium chloride 0.05 mg/mL, potassium chloride 1.2 mg/mL, sodium phosphate 0.28 mg/mL and sorbitol 30 mg/mL in purified water) purchased from Wyvern Medical Limited (Herefordshire, UK). Each bottle of OGT oral spray contained 20mL and each bottle of Saliveze® contained 50mL of solution.

Subjects, Aim and Study Design

Our objective was to evaluate the clinical efficacy and acceptability of OGT oral spray in the relief of signs and symptoms of xerostomia compared with Saliveze®. The latter was chosen as the reference product because it is a standard, commercially available treatment for dry mouth and is supplied as an oral spray similar to OGT spray. A 2-week, randomised, open-label, parallel-group design was employed. Forty-one patients with xerostomia aged ≥70 years and hospitalised in long-term care facilities were included in the study. Patients were enrolled after written informed content was obtained and then randomly assigned to either OGT or Saliveze® spray treatment for 2 weeks. Patients with oral candidiasis (as diagnosed by *Candida* counts obtained from an unstimulated whole saliva sample), dental infection, recent and/or ongoing head or neck radiotherapy, Sjögren's syndrome, a life-threatening pathological condition and those participating in another clinical trial at the time of the study were excluded from the trial.

Xerostomia was diagnosed by means of a patient-based questionnaire and measurement of saliva volume using a sialometer (test of saliva weight absorbed ≤0.5g/5 min) at baseline and after stimulation by chewing gum (showing a mean saliva flow rate of ≤0.2 mL/min and ≤0.5 mL/min, respectively).[20,21,26,27] Patients in the study also completed a questionnaire to assess symptoms of xerostomia at baseline. In addition, an oral soft tissue examination was conducted by a dental hygienist in a blinded fashion and included an objective evaluation of the lips, tongue, hard and soft palate, gingiva, mucobuccal fold areas, buccal mucosa and floor of the mouth using a four-point ordinal scale as follows: 0 = normal, 1 = mild, 2 = moderate, 3 = severe defect.[20,21]

Application of the oral lubricant and the saliva substitute was standardised. In brief, each patient was instructed to use one or two sprays of the assigned product at least five times per day, with nursing help as necessary to ensure that both treatments were applied correctly and consistently. The frequency of each product use was recorded. Spray bottles were weighed prior to dispensing to the patients and at the end of the treatment period to assess the quantity of the product used and treatment adherence. This study was approved by the Local Research Ethics Committee of Versailles, France and was registered on the ClinicalTrials.gov registry (NTC00350350).

Clinical Measurements and Questionnaires

The primary outcome variable was patient-based dry mouth scores as evaluated by a self-rated, 10cm long visual analogue scale (VAS) score recorded on day (D) 0 and D14. The latter was chosen as the primary endpoint because it was a specific, sensitive and reproducible criterion,[24-28] consistent with the main objective of the current clinical trial. Anchor points for the VAS score were 0 representing normal (i.e. no dry mouth symptoms) and 10 representing "the worst imaginable" dry mouth symptoms. Secondary outcome variables included patient-based perception of changes in other dry mouth symptoms (i.e. chewing, swallowing and speech difficulties as well as taste and burning sensations) using a self-rated, 10cm long VAS. In addition, oral tissue condition (redness and dryness of the tissues, degree of inflammation) was recorded on a four-point ordinal scale at D14 by the dental hygienist in a blinded fashion.[20,21]

Subjective assessment of xerostomia was performed at baseline and at D14 as dichotomous responses to a questionnaire and included several criteria such as diurnal and nocturnal mouth dryness, sleep disturbances due to mouth dryness, bad taste sensations, use of saliva substitutes, as well as questions about restrictions in social life, i.e. "Do you avoid speaking to people because of your dry mouth?" and "Do you stay in your room because of your dry mouth?". Other variables, such as the number of sprays required by patients per day and the time interval between each spray, were also recorded.

Evaluation of Treatment Tolerance and Acceptability

Taste was evaluated using a 10cm long VAS. Adverse events were recorded by the investigators.

Statistical Analysis

Based on previously published studies[26,28] and assuming a within-group standard deviation (SD) of 1cm in VAS score, a power of 85% and a type 1 error rate of 0.05, a sample size of 20 patients in each treatment arm was calculated as being necessary to demonstrate an effect size of 0.75.

Statistical analysis was conducted using the SPSS version 12.0 for Windows (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD or median ± SD, as appropriate, for continuous variables. Two-tailed comparisons were made between treatment groups with respect to demographics and efficacy parameters, according to the intent-to-treat principle, and between-treatment differences were presented as 95% confidence intervals. Analysis of covariance (ANCOVA), using the study group assignment as factor and baseline dry mouth VAS scores as covariate, was performed to reveal whether adjusted D14 dry mouth scores differed significantly between treatments. This was followed by Scheffe's test adjusted for multiple comparisons to determine the level of significance of differences (if any) between the two treatment groups in VAS scores relating to the effectiveness of the spray at D14 for the respective variable. Results were presented as percentages for nominal variables, and chi-squared (χ^2) or Fisher's Exact tests, as appropriate, were used to determine the significance of differences (if any) between dichotomous response variables. Between-treatment comparisons at D14 regarding mouth condition overall acceptability, oral spray taste and acceptability as evaluated by VAS score were performed using the non-parametric Mann-Whitney U test. For all comparisons, a p-value of ≤0.05 was considered statistically significant.

Results

Demographic and Baseline Characteristics

Between November 2003 and December 2004, 41 patients (22 in the OGT group, 19 in the Saliveze® group; 28 women and 13 men, sex ratio = 2.15) with xerostomia, as assessed by the questionnaire and measurement of saliva output, were enrolled and all but one completed the entire study. However, the only patient (OGT group) lacking data for D14 was included in the final analysis on the intent-to-treat principle and baseline values were assigned for the missing data. Mean (± SD) age (84 ± 7 years, range 70–94 years), weight (64 ± 12kg, range 43–90kg), height (161 ± 7cm, range 145–178cm) and saliva flow rate (0.03 ± 0.01 mL/min, range 0.01–0.05 mL/min) did not differ between treatment groups (p = 0.08, 0.96, 0.94 and 0.92, respectively, on the two-tailed, unpaired Student's t-test). Likewise, the sex ratio did not differ between treatment groups (p = 0.99, χ^2 test). Medical history taking revealed cardiovascular disease in 68% of patients, hypertension in 41%, psychiatric disorders in 34%, irritable bowel syndrome in 34%, arthritis in 34%, cancer in 12% and chronic obstructive pulmonary disease in 10% of patients. Eighty-one drugs, accounting for a total of 173 prescriptions (i.e. 4.22 drugs per patient), were taken by patients at the time of the study and the rate of such medication use did not differ between groups. Among these, 148 drugs usually associated with dry mouth symptoms[4] were prescribed; these included diuretics, antihypertensive and anti-arrhythmic drugs (furosemide, n = 40, hydrochlorothiazide, n = 15, rilmenidine, n = 10, metoprolol, n = 5, amiloride, n = 1), psychotropic drugs (alimenazine, n = 12, zopiclone, n = 10, acepromazine, n = 8,

Table I. Baseline and day (D) 14 degree of xerostomia as determined by patients using a self-rated, 10cm long visual analogue scale (VAS)[a]

Item	Baseline (cm)		D14 (cm)		Treatment difference at D14
	OGT (n = 22)	Saliveze® (n = 19)	OGT (n = 22)	Saliveze® (n = 19)	[cm] (95% CI)
Mouth dryness	7.4 ± 1.5	6.6 ± 1.5	2.5 ± 1.5	4.6 ± 1.3	2.1 ± 0.1 (1.9, 2.3)*
Chewing difficulties	4.9 ± 3.7	4.0 ± 3.9	1.3 ± 1.2	1.9 ± 1.8	0.7 ± 0.2 (−0.4, 0.9)
Swallowing difficulties	6.5 ± 2.5	6.1 ± 2.3	1.8 ± 1.5	3.6 ± 1.8	1.8 ± 0.3 (1.5, 2.1)*
Speech difficulties	5.1 ± 3.4	4.3 ± 3.4	1.8 ± 1.4	2.9 ± 1.6	1.1 ± 0.2 (1.0, 2.4)**
Taste alteration	5.1 ± 3.5	4.0 ± 3.5	1.8 ± 1.4	1.8 ± 1.5	0.1 ± 0.1 (−0.2, 0.2)
Burning sensation	4.2 ± 3.3	3.2 ± 2.8	2.0 ± 1.5	2.6 ± 2.1	0.6 ± 0.5 (−0.3, 0.9)

a Data are presented as mean ± SD.

OGT = oxygenated glycerol trimester; * p = 0.001, ** p = 0.04, at D14 (analysis of covariance using baseline VAS scores as covariate).

clomipramine, n = 5, mianserin, n = 3, chlorpromazine, n = 2, tianeptine, n = 1) and proton pump inhibitors (omeprazole, n = 22, lanzoprazole, n = 8, pantoprazole, n = 6). Other medications taken included laxatives (n = 15) and cholesterol-lowering drugs (n = 10).

Most patients complained of moderate to severe dry mouth at baseline, as measured on the 10cm long VAS (table I). No difference was noted between the two treatment groups (p > 0.16, ANCOVA). Analysis of the dichotomous responses recorded in the subject questionnaire revealed no statistically significant difference between the two treatment groups at baseline. Overall, 98% (40/41) of patients complained of diurnal mouth dryness and 76% (31/41) complained of nocturnal mouth dryness, which was associated with sleep disturbances and early wake-up in 48% (20/41) of patients (p = 0.45 between groups, Fisher's Exact test). Thirty-one percent (7/22) of patients in the OGT group and 16% (3/19) of patients in the Saliveze® group complained of bad taste in the mouth (p = 0.29 between groups, Fisher's Exact test). Consequently, 10% of patients declared that they usually avoid speaking to people but only 2.4% of them declared staying in their room because of dry mouth. Eighty-three percent of patients (34/41) were wearing a denture (18 in the OGT group vs 16 in the control group). Denture retention was affected by mouth dryness in 53% (21/41) of patients (p = 0.31 between treatment groups at baseline, Fisher's Exact test).

The objective assessment of patients' oral condition recorded by the dental hygienist in a blinded fashion using a four-point ordinal scale is presented in table II. At baseline, 100% of patients presented with dry mouth, considered by the dental hygienist to be moderate or severe in 85% of cases. Mild or moderate oral mucositis was documented in 39% (16/41) of patients. Overall, the oral mucosa was red and/or sticky and presented with at least one lesion in 49% of patients at baseline (20/41). Up to 59% of patients (24/41) had damaged lips and/or a thickened tongue and 76% of patients (31/41) had viscous and/or foamy saliva leading to moderate difficulties with speech related to dry mouth. No differences were noted between treatment groups at baseline (p > 0.4 for all comparisons, Fisher's Exact test).

Efficacy of Oxygenated Glycerol Triester Spray Based on the Primary and Secondary Endpoints at Day (D) 14

Of the six symptoms assessed by the VAS, OGT was significantly superior to Saliveze® in three items, i.e. mouth dryness (the primary endpoint), swallowing difficulties and speech difficulties, after adjustment for differences that existed at baseline using the ANCOVA model (table I). Likewise, the mean VAS score for overall sensation of symptom relief at D14 was significantly lower in the OGT spray group compared with Saliveze® (4.6 ± 2.9 vs 7.3 ± 3.9, respectively; mean difference, 2.7 ± 1.2, 95% CI 1.9, 3.8; p = 0.001). The sensation of improvement started on the first day of treatment in 23% versus 18% of patients and on the second day of treatment in 53% and 27% of patients treated with OGT and Saliveze®, respectively (p = 0.49 between groups, χ^2 test), and did not differ between day and night in 73% of patients (p = 1.00, Fisher's Exact

Table II. Baseline and day (D) 14 objective assessment of the oral tissue condition as recorded by a dental hygienist in a blinded fashion using a four-point ordinal scale[a]

Item	Baseline (cm)		D14 (cm)		95% CI for the	p-Value[b]
	OGT (n = 22)	Saliveze® (n = 19)	OGT (n = 22)	Saliveze® (n = 19)	difference at D14	
Overall dryness of mouth	2.1 ± 0.7	2.0 ± 0.6	0.9 ± 0.6	1.5 ± 0.6	0.4, 0.8	0.001
Dryness of oral mucosa	2.0 ± 0.7	1.8 ± 0.5	0.8 ± 0.6	1.3 ± 0.6	0.3, 0.9	0.01
Inflammation of oral mucosa	1.7 ± 0.9	1.2 ± 0.8	0.8 ± 0.5	0.8 ± 0.8	−0.2, 0.3	0.63
Redness of oral mucosa	1.5 ± 0.8	1.5 ± 1.1	0.6 ± 0.5	0.6 ± 0.6	−0.03, 0.1	0.66
Stickiness of oral mucosa	1.5 ± 0.7	1.5 ± 0.8	0.4 ± 0.5	0.8 ± 0.5	0.2, 0.5	0.005
Dullness of oral mucosa	1.3 ± 0.4	1.7 ± 0.7	0.3 ± 0.5	1.0 ± 0.5	0.6, 0.8	0.001
Severity of mucositis	0.5 ± 0.7	0.6 ± 0.9	0.0 ± 0.0	0.3 ± 0.4	0.1, 0.5	0.01
Oral mucosal abrasion	0.8 ± 0.8	0.6 ± 0.8	0.2 ± 0.4	0.3 ± 0.4	−0.1, 0.1	0.53
Damaged lips	0.8 ± 0.8	0.9 ± 1.0	0.3 ± 0.5	0.5 ± 0.6	−0.2, 0.25	0.11
Thickened tongue	0.8 ± 0.8	0.7 ± 0.7	0.1 ± 0.3	0.4 ± 0.5	0.2, 0.4	0.03
Deficiency of saliva	1.9 ± 0.7	2.0 ± 0.7	0.9 ± 0.5	1.1 ± 0.6	−0.2, 0.3	0.14
Viscosity of saliva	0.9 ± 0.8	1.3 ± 0.8	0.3 ± 0.5	0.7 ± 0.6	0.3, 0.6	0.01
Foamy saliva	0.4 ± 0.7	0.5 ± 0.7	0.1 ± 0.3	0.2 ± 0.4	−0.1, 0.2	0.28
Halitosis (bad breath)	0.4 ± 0.6	0.4 ± 0.6	0.1 ± 0.3	0.2 ± 0.4	−0.1, 0.2	0.28
Speech difficulties	0.6 ± 0.7	0.7 ± 0.9	0.2 ± 0.4	0.5 ± 0.5	0.2, 0.4	0.04
Saliva and crusting at corners of mouth	0.4 ± 0.5	0.5 ± 0.7	0.0 ± 0.0	0.2 ± 0.4	−0.1, 0.3	0.06

a Data are presented as median ± SD of the score obtained by either treatment group at baseline and D14, respectively.

b p-Value for the respective item (analysis of covariance using baseline score as covariate).

OGT = oxygenated glycerol triester.

test). However, OGT spray prevented patients from night awakening in 33% of patients compared with only 5% of patients treated with Saliveze® (p = 0.03, Fisher's Exact test). After a single administration, both oral sprays were effective for 2–4 hours in 85% of patients in each group (p = 0.88, χ^2 test) and no additional oral spray was administered on any day by 60% of patients (p = 0.67 between treatment arms, Fisher's Exact test).

Patient-Based Assessment of Symptoms at D14 Using Responses to a Dichotomous Questionnaire

Eighty-one percent of patients treated with OGT declared that their mouth dryness had been substantially improved compared with 68% of patients treated with Saliveze® (p = 0.76, Fisher's Exact test). Likewise, OGT spray improved chewing, swallowing and speech in 48%, 71% and 38% of cases, respectively, versus 16%, 15% and 26% of patients treated with Saliveze® (p = 0.15, 0.002 and 0.67, respectively, Fisher's Exact test). Taste, burning sensation and items related to social life restriction, including dichotomous responses to questions such as "Do you stay in your bedroom more because of your dry mouth?" and "Do you avoid speaking to people because of your dry mouth?" were overall improved by both oral sprays in up to 71% of patients according to a patient-based assessment of symptoms (p > 0.33 for all comparisons, Fisher's Exact test). At D14, 68% of patients treated with Saliveze® still preferred to stay in their room because of mouth dryness, as compared with 38% of patients treated with OGT, but this difference did not reach statistical significance (p = 0.06, Fisher's Exact test). Among patients wearing a denture, OGT spray improved denture retention in 44% of patients treated with OGT versus 36% of those treated with Saliveze® (p = 0.38, Fisher's Exact test). Overall, 81% of patients felt better often using OGT as compared with only 58% of those treated with Saliveze® (p = 0.03, Fisher's Exact test). Likewise, 76% of patients treated with OGT experienced quality-of-life improvement compared with 21% of patients receiving Saliveze® (p = 0.002, Fisher's Exact test).

Objective Assessment of Oral Tissue at D14

Table II presents data relating to the objective assessment of the patients' oral tissue condition as recorded by the dental hygienist in a blinded fashion at D14 using a four-point ordinal scale. Among the 16 items objectively measured and shown in table II, local improvement in dryness (95% CI 0.4, 0.8; p = 0.001), stickiness of the oral mucosa (95% CI 0.2, 0.5; p = 0.005), dullness of the oral mucosa (95% CI 0.6, 0.8; p = 0.001), severity of mucositis (95% CI 0.1, 0.5; p = 0.01), thickened tongue (95% CI 0.2, 0.4; p = 0.03) and viscosity of saliva (95% CI 0.3, 0.6; p = 0.01) were significantly more improved with OGT than with Saliveze® at D14. Consequently, speech difficulties were also significantly improved with OGT (95% CI 0.2, 0.4; p = 0.04) [table II].

Treatment Tolerance and Acceptability

No serious adverse events that could be related to either study product were reported. Minor adverse events were reported in four patients (9.8%) and included nausea (one patient in the Saliveze® group) and unpleasant taste (two patients in the Saliveze® group and one in the OGT group).

Both oral sprays were rated easy to use by 83% of patients. At the end of the study, 76% of patients using OGT said they were willing to continue using OGT after the study versus 47% of patients treated with Saliveze® (p = 0.06, χ^2 test). The taste of OGT was preferred by patients over that of Saliveze®, according to the mean VAS results (7.2 ± 2.2 vs 5.8 ± 2.9, respectively; mean difference, 1.4 ± 0.6, 95% CI 1.2, 1.9; p = 0.04).

Discussion

In clinical practice, xerostomia is often neglected by both clinicians and patients, presumably because the efficacy of currently available therapeutic options is highly unpredictable.[14] In the current study, extensive evaluation of clinically relevant, accessible and reproducible subjective and objective symptoms of xerostomia[4,12,14,16,20] in older institutionalised patients with severe hyposalivation leading to sticky oral mucosa, mucositis, damaged lips and impaired quality of life as a result of taste alteration, speech difficulties, bad breath and social life restrictions demonstrated that OGT oral spray was significantly superior to Saliveze® in improving mouth dryness, swallowing and speech. Furthermore, OGT also resulted in significantly greater improvements in oral tissue condition and saliva viscosity as assessed by a blinded dental hygienist after 14 days of treatment. Both oral sprays were also well tolerated although OGT was perceived to have a better taste than Saliveze®.

There is considerable difficulty in making the initial clinical decisions as to whether a given patient has salivary gland hypofunction and hence requires additional salivary gland evaluation and may be eligible for treatment. In this regard, we used previously validated measures (e.g. dryness of lips and buccal mucosa), previously validated tools (e.g. a 10cm long VAS and a four-point ordinal scale) and a validated cut-off of salivary flow-rate to identify and enrol patients with dry mouth into the current clinical trial.[29] Thus, the enrolled population had clinical relevance because patients were included primarily on the basis of saliva production, as measured by a sialometer to confirm hyposalivation at D0 (but not at D14 as OGT is not a saliva stimulant). Nevertheless, the current study has several limitations, partly related to the difficulties inherent in designing a clinical trial in older institutionalised patients and evaluating treatments in a condition as subjective as xerostomia. Consideration of the short-term parallel-group design of the current trial points to the need for a further longer clinical study to demonstrate the long-term benefit of OGT oral spray in older patients. Furthermore, a randomised, double-blind, controlled trial conducted in a larger cohort of older patients would have been more methodologically sound; however, this is unrealistic in the current setting because of the different textures of the two products (Saliveze® is an aqueous solution while OGT is a viscous oral lubricant). Finally, the purpose of the current study was to compare the efficacy of OGT oral spray in the relief of symptoms of xerostomia with that of a currently marketed saliva substitute, rather than to the reference drug pilocarpine.[15] This reflects the fact that OGT is not a saliva stimulant and treatment efficacy cannot be correlated with increase in saliva output, to the best of our knowledge.[1,15,16,20,26,28]

Although more than 500 medications have been reported to cause dry mouth as an adverse effect, only a small number have been demonstrated to result in actual reduced salivation; these include tricyclic antidepressants, histamine H_1 receptor antagonists (antihistamines), antihypertensives and diuretics.[4] Most of these drugs are often concomitantly prescribed in older patients,[5,6,16] as observed in the current study. Moreover, an additive dry mouth adverse effect has previously been observed[4] when several such drugs are co-administered in the same patient, a situation that is often observed in the geriatric population and was documented in the current study. Increasing use of medication in this particular patient population is clearly exacerbating mouth dryness and patients' oral condition, although this was not evaluated in our study of daily life in institutionalised patients taking numerous concomitant medications.

As shown in the current study, in which several validated assessment scales were utilised in addition to measurement of saliva output, evaluation of dry mouth symptoms should be carried out in a systematic fashion, especially in older adults.[9,12,16,20] The goals are to relieve symptoms, prevent or correct the sequelae of salivary dysfunction and treat any underlying disease. Adequate hydration of the oral mucosa in order to moisten and cleanse the mucosal surface and hydrate the oral tissue is essential but not sufficient. European formulations (not available in the US) of saliva substitutes that contain animal mucins have been preferred to products with a carboxymethycellulose base alone in some but not all patients.[9,30] However, in some authors' experience,[9,30] most patients find that frequent sipping of fluids is superior and more aesthetically acceptable than use of saliva substitutes. The current study does not confirm these observations, as 83% of our patients rated both oral sprays as easy to use, product acceptability was high and 76% of patients were willing to continue using the oral sprays after the end of the study. In a previous study conducted in patients with advanced cancer who had undergone radiation therapy, the efficacy of an animal mucin-based saliva substitute was not significantly different from that of chewing gum, a salivary stimulant, in the management of xerostomia.[26] However, this study was underpowered, lacked many data in the final analysis, and enrolled patients with moderate mouth dryness (mean VAS score obtained in each group at baseline was 3.25cm). In addition, the mucin contained in the study product was derived from porcine gastric mucosa, and therefore may not be suitable for Jews, Muslims and various other groups.[28]

Conclusion

Dry mouth is a common complaint and a significant problem in geriatric clinical practice that deserves to be as aggressively evaluated as it is in younger people. Given the numerous mechanisms involved in xerostomia in older patients, use of an oral lubricant might be suitable for the treatment of dry mouth. In this regard, OGT oral spray was superior to a currently marketed aqueous saliva substitute containing electrolytes (Saliveze®) in improving mouth dryness, oral tissue condition and social life in a long-term hospitalised geriatric population. This treatment may therefore be proposed in older institutionalised patients with symptoms of dry mouth, even in those treated with multiple concomitant medications known to induce xerostomia. With the number of older patients expected to increase worldwide,[31] further studies will be welcomed to confirm that the benefit of OGT may be prolonged over time in the treatment of xerostomia. Maintenance of adequate oral hygiene and hydration to prevent clinical complications such as increased dental caries, monilial infection, dysgeusia and tooth sensitivity, all of which are often observed in older patients with xerostomia, is an important goal.

Acknowledgements

This study was funded by Laboratoires Carilène, Montesson, France. The authors are indebted to the nurses at the Department of Geriatry, Clinique Leopold Bellan, Magnanville, France for their precious contribution to the study. Dr Stéphane Mouly received an honorarium from Laboratoires Carilène for preparation of the article. Dr Anne-Claude Coudert and Dr Stéphane Desjonquères are employees of Laboratoires Carilène. The other authors have no conflicts of interest that are directly relevant to the content of this study.

References

1. Navazesh M, Denny P, Sobel S. Saliva: a fountain of opportunity. J Calif Dent Assoc 2002; 30: 783-8

2. Mason DK, Chishlom DM. Salivary glands and their secretions. In: Mason DK, Chishlom DM, editors. Salivary glands in health and disease. London: Saunders, 1975: 3-69
3. Wilborn WH, Schackleford JM. Microanatomy of human salivary glands. In: Manaken L, editor. The biologic basis of dental caries. Hagerstown: Harper & Row, 1980: 3-62
4. Madinier I, Jehl-Pietri C, Monteil RA. Les hyposialies d'origine medicamenteuse. Ann Med Int 1997; 148: 398-405
5. Handelman SL, Baric JM, Espeland MA, et al. Prevalence of drugs causing hyposalivation in an institutionalized geriatric population. Oral Surg Oral Med Oral Pathol 1986; 62: 26-31
6. Hendelman SL, Baric JM, Saunders RH, et al. Hyposalivary drug use, whole stimulated salivary flow and mouth dryness in older long-term care residents. Spec Care Dent 1989; 1: 12-8
7. Mornstad H, Von Knorring L, Forsgren L, et al. Long-term effects of two principally different antidepressant drugs on saliva secretion and composition. Scand J Dent Res 1986; 94: 461-70
8. Sreeby LM, Valdini A, Yu A. Xerostomia: part II. Relationship to nonoral symptoms, drugs, and diseases. Oral Surg Oral Med Oral Pathol 1989; 68: 419-27
9. Fox PC. Management of dry mouth. Dent Clin North Am 1997; 41: 863-75
10. Matear DW, Locker D, Stephens M, et al. Associations between xerostomia and health status indicators in the elderly. J R Soc Health 2006; 126: 79-85
11. Rejnefelt I, Andersson P, Renvert S. Oral health status in individuals with dementia living in special facilities. Int J Dent Hyg 2006; 4: 67-71
12. Locker D. Xerostomia in older adults: a longitudinal study. Gerodontology 1995; 12: 18-25
13. Peltola P, Vehkalahti MM, Wuolijoki-Saaristo K. Oral health and treatment needs of the long-term hospitalized elderly. Gerodontology 2004; 21: 93-9
14. Sreenby LM, Valdini A. Xerostomia: a neglected symptom. Arch Int Med 1987; 147: 1333-7
15. Guijarro Guijarro B, Lopez Sanchez AF, Hernandez Vallejo G. Treatment of xerostomia: a review. Med Oral 2001; 6: 7-18
16. Navazesh M. Dry mouth: aging and oral health. Compend Contin Educ Dent 2002; 23: 41-8
17. Andersson G, Johansson G, Attstrom R, et al. Comparison of the effect of the linseed extract salinum and a methyl cellulose preparation on the symptoms of dry mouth. Gerodontology 1995; 12: 12-7
18. Niedermeier W, Huber M, Fischer D, et al. Significance of saliva for the denture-wearing population. Gerodontology 2000; 17: 104-18
19. Epstein JB, Emerton S, Le ND, et al. A open-labelled crossover trial of oral balance gel and biotene toothpaste versus placebo in patients with xerostomia following radiation therapy. Oral Oncol 1999; 35: 132-7
20. Navazesh M, ADA Council on Scientific Affairs and Division of Science. How can oral health care providers determine if patients have dry mouth? J Am Dent Assoc 2003; 134: 613-20; quiz 633
21. Epstein JB, Scully C. The role of saliva in oral health and the causes and effects of xerostomia. J Can Dent Assoc 1992; 58: 217-21
22. Vered M, Buchner A, Boldon P, et al. Age-related histomorphometric changes in labial salivary glands with special reference to the acinar component. Exp Gerontol 2000; 35: 1075-84
23. Moreira CR, Azevedo LR, Lauris JR, et al. Quantitative age-related differences in human sublingual gland. Arch Oral Biol 2006; 51: 960-6
24. Nyarady Z, Nemeth A, Ban A, et al. A randomized study to assess the effectiveness of orally administered pilocarpine during and after radiotherapy of head and neck cancer. Anticancer Res 2006; 26: 1557-62
25. Sweeney MP, Bagg J, Baxter WP, et al. Clinical trial of a mucin-containing oral spray for treatment of xerostomia in hospice patients. Palliat Med 1997; 11: 225-32
26. Davies AN. A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer. Palliat Med 2000; 14: 197-203
27. Moritsuka M, Kitasako Y, Burrow MF, et al. Quantitative assessment for stimulated saliva flow rate and buffering capacity in relation to different ages. J Dent 2006; 34: 716-20
28. Davies AN, Daniels C, Pugh R, et al. A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer. Palliat Med 1998; 12: 105-11
29. Navazesh M, Christensen C, Brightman V. Clinical criteria for the diagnosis of salivary hypofunction. J Dent Res 1992; 71: 1363-9
30. Meyer-Lueckel H, Kielbassa AM. Utilisation de succedanes salivaires chez les patients souffrant de xerostomie. Rev Mens Suisse Odontostomatol 2002; 112: 1049-58
31. Navazesh M. Xerostomia in the aged. Dent Clin North Am 1989; 33: 75-80

Correspondence: Dr *Stéphane Mouly*, Assistance Publique-Hôpitaux de Paris, Hôpital Lariboisière, Unité de Recherches Thérapeutiques – Service de Médecine Interne A, 2 rue Ambroise Paré, 75010 Paris, France.
E-mail: stephane.mouly@lrb.aphp.fr