

Saliva Secretion in Patients with Allergic Rhinitis

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Key Words

Allergy · Fexofenadine · Loratadine · Saliva · Xerostomia

Abstract

Background: Allergic rhinitis is manifested by watery discharge; however its clinical effect on the watery volume in the oral cavity is unknown. In addition, the low incidence of dry mouth due to treatment with the new generation antihistamines is based on subjective patients' reports only. This study aimed to examine the effect of loratadine and fexofenadine on the salivary gland function in patients diagnosed with allergic rhinitis compared to untreated allergic patients and healthy individuals. **Methods:** A comparative observational study assessed parameters related to the patients' perception of dry mouth as well as clinically observed parameters in fexofenadine-treated patients (group A) and in loratadine-treated patients (group B). Allergic patients without pharmacological treatment (group C) and healthy individuals (group D) served as a double control in order to evaluate the effect of allergy itself on dry mouth. A total of 36 patients were enrolled. **Results:** Patients in groups A and C reported the highest intensity of xerostomia. Sialometry values were significantly lower in these 2 groups compared to the healthy controls ($p = 0.02$ and 0.03 , respectively). Average sialometry was over 0.2 ml/min in all groups and subjective dry mouth sensation ranged in the lower quarter of the visual analogue scale. **Conclusions:** In this pilot study, pa-

tients diagnosed with allergy presented a significant difference in salivary flow rate compared to healthy controls. Unlike the effect of loratadine, fexofenadine-treated patients showed significantly lower salivary flow rates compared to healthy individuals. In all cases the intensity of dry mouth was low.

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Introduction

Xerostomia is defined as a subjective feeling of dry mouth that may result from a decrease in the production of saliva. However it is not always associated with salivary gland hypofunction [1].

A number of factors, including medications, may play a role in the cause of xerostomia. Over 500 drugs have been reported to produce xerostomia or salivary hypofunction as a side effect [2]. Antihistamines were suggested to be related to a subjective complaint of dry mouth [3]. In the 1940s, as soon as the first generation of antihistamines was introduced (chlorpheniramine maleate, hydroxyzine hydrochloride), side effects of inhibition of excretion of the exocrine glands were noted.

In the 1980s a new generation of antihistamines such as loratadine and terfenadine was introduced. Unlike the first generation of antihistamines that inhibited acetylcholine through the muscarinic receptors, the new gen-

eration does not have this effect. Goets et al. [3] compared first generation antihistamines (hydroxyzine) to the new generation (terfenadine) and showed that patients treated with terfenadine complained less of dry mouth than patients treated with hydroxyzine. However, this study presents a partial view of the new-antihistamine-related salivary function, since the assessment of dry mouth side effects is based exclusively on the patients' reports. Considering this partial clinical evidence and the findings in animal model studies, it is unclear whether the new generation of antihistamines spare the salivary function [4, 5].

The aim of this pilot study was to compare the patients' subjective reports and the clinical salivary function in patients treated with new generation antihistamines with untreated allergy patients and healthy individuals.

Patients and Methods

Patient Selection

Patients who were diagnosed based on previous allergic diseases of the upper respiratory tract or eyes, including persistent or intermittent allergic rhinitis or eye inflammation, were consecutively enrolled in the study. Inclusion criteria were age of 18 years or older, mild-to-moderate allergic disease and treatment with new generation antihistamines for at least 7 days. The Institutional Review Board approved the study and informed consent was obtained from all patients in accordance with the precepts established by the Helsinki Declaration.

Patients suffering from one of the systemic diseases known to cause dry mouth, including primary and secondary Sjögren syndrome (connective tissue disease, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease), were excluded.

Patients with other conditions that may also lead to dry mouth (e.g. radiation therapy, primary biliary cirrhosis, vasculitis, chronic active hepatitis, HIV, AIDS, bone marrow transplantation, graft-versus-host disease, renal dialysis, anxiety or depression, diabetes type I or II) were also excluded [2].

A third group of patients that were excluded from the study were those taking any of the following systemic medications: anticholinergics, antidepressants, antihypertensives, diuretics, β -blockers, NSAIDs, antihypoglycemics and antiparkinsonians.

Consumption of food 30 min prior to the examination was an exclusion criterion as well.

Untreated allergic patients were enrolled in a first control group and age-matched healthy individuals were consecutively enrolled in another control group.

Study Design

Subjects were grouped into 4 arms: (A) allergic patients administered the antihistamine fexofenadine (Telfast®, Patheon France SA, France); (B) allergic patients administered the antihistamine loratadine (Lorastine®, Schering-Plough Labo NV, Bel-

gium); (C) allergic patients not receiving any treatment; (D) non-allergic patients not receiving any treatment. Since the hypothesis was that none of these medications induce dry mouth in the therapeutic dose, 2 doses were allowed for fexofenadine (120 or 180 mg/day) [6]. The loratadine dose used was 10 mg/day.

Participants were prospectively interviewed using a uniformed questionnaire and clinically evaluated.

Patient Evaluation and Clinical Assessment

The questionnaire elicited information about the patient's demographic characteristics such as age, sex and occupational environment. The general medical history of the patient was documented including underlying diseases and drug intake. A subjective score – 11-step visual analogue scale (VAS) – of dry mouth, skin and eyes, as well as satisfaction with the antihistamine were the subjective parameters used to reflect the patient's evaluation. The questionnaire was constructed in such a way that there was no bias. Behavioral parameters that may affect dryness (daily fluid intake, place of work, type of breathing) were also collected.

Sialometry was used to assess the secretory flow rate of the major salivary glands. Unstimulated whole saliva flow rate of ≤ 0.2 ml/min was considered low [7]. Patients were requested to refrain from swallowing. Whenever saliva accumulated in their mouth, specifically in the floor of the mouth, they were instructed to expectorate the saliva into a standard disposable container. The container was fabricated from a 10-ml disposable plastic syringe without internal piston and sealed at its apex with dental impression wax. The plastic containers were calibrated at intervals of 0.1 ml. The serous and mucous fractions of secretions were measured.

Unstimulated salivary secretions were collected over a period of 5 min. During these 5 min the patient was not allowed to speak in order to avoid mechanical stimulation of the salivary glands. This is preferably done within a certain time interval after a meal in order to avoid salivary stimulation by food consumption. In addition, it was emphasized that the expectoration should be without any intense activation of the mastication muscles. The container was held extraorally close to the lips and was brought in contact with the lips whenever the patient felt sufficient saliva volume was ready for expectoration.

In addition, signs of dry mouth, based on mucosal color, mucosal wetness and mucosal palpation, were documented [2]. Mucosal lesions associated with dry mouth (atrophy of the mucosa, candidiasis and angular cheilitis) were reported. Dental status suggesting dry mouth (such as multiple cervical carious foci) was documented as well.

Statistics

Comparison of the mean ages between the 4 groups was performed with one-way ANOVA. For all measurements, Kolmogorov-Smirnov's test of normality with the Liliefors significance correction led to the use of the nonparametric method. An adaptation of Fisher's protected significance p value to the nonparametric setting was used for multiple comparisons. First Kruskal-Wallis ANOVA was applied. Whenever the p value for this test was < 0.10 , the Mann-Whitney test was used for pair-wise comparisons between groups. Associations between categorical variables were tested by χ^2 tests. $p < 0.05$ in Mann-Whitney and χ^2 was considered significant.

Table 1. Patient characteristics

	Groups			
	A	B	C	D
Number of patients	9	6	11	10
Antihistamine treatment	fexofenadine	loratadine	none	none
Diagnosis of allergy	yes	yes	yes	no
Age (mean $\pm$ SD), years	39.9 $\pm$ 19.5	24.9 $\pm$ 8.9	37.2 $\pm$ 15	32.8 $\pm$ 13
Age (range), years	18–8	18–0	19–9	25–0
Sex (M:F)	3:6	3:3	4:7	5:5

Table 2. Patients' subjective scoring of dryness

	Groups			
	A (fexofenadine)	B (loratadine)	C (allergic)	D (healthy)
Average VAS for dry mouth	2.7 $\pm$ 3.8	1.6 $\pm$ 3.2	2.45 $\pm$ 2.87	0.8 $\pm$ 1.62
Average VAS for dry skin	4.5 $\pm$ 4.6	1.5 $\pm$ 3.2	3.6 $\pm$ 3.5	0.8 $\pm$ 1.9
Average VAS for dry eyes	3.6 $\pm$ 4.6	1.3 $\pm$ 3.2	3.9 $\pm$ 3.7	0.6 $\pm$ 1.9

Results

Patients

Between March 2002 and December 2004, 39 patients were screened and enrolled in the study. Thirty-six patients matched the inclusion criteria for the comparative analysis. The baseline characteristics of the patients were comparable in the 4 groups (table 1). The age difference between the groups was not statistically significant ($p = 0.22$).

Patients' Subjective Scoring of Satisfaction with the Antihistamines

Average VAS of satisfaction was 7.4 ± 1.66 with Telfast (group A) and 7 ± 0.63 with Lorastine (group B). There were no complaints of nonoral side effects in 35 patients. One patient in group B reported feeling general dryness and fatigue. When patients were asked specifically about oral dryness as a side effect, 2 patients answered positively: 1 in group A, and 1 patient in group B (the same patient who complained about general dryness and fatigue).

Patients' Subjective Scoring of Dryness

A subjective feeling of dryness of the mouth was reported by patients in all groups. Patients in group B scored lower VAS for dryness than patients in group A for all 3 parameters (table 2). No significant difference was found

in regard to VAS for xerostomia ($p = 0.69$). Patients' scores for dryness were the lowest in group D for all 3 parameters: mouth, skin and eyes (table 2).

Most patients reported that dry mouth occurred in the morning hours.

Patients' Behavioral Parameters

Patients' reports about an estimated daily consumption of liquid are presented in table 3. There was no statistically significant difference between groups A and B in regard to hydration ($p = 0.78$).

Most of the patients (32 of 36) work in an air-conditioned environment. One patient from group B works outdoors in the sun. Two patients from group C and 1 patient from group A work both indoors and outdoors.

Most patients in groups B, C, and D breathe through the nose. When comparing groups A and B, there was no significant difference concerning the type of breathing ($p = 0.81$) (table 3).

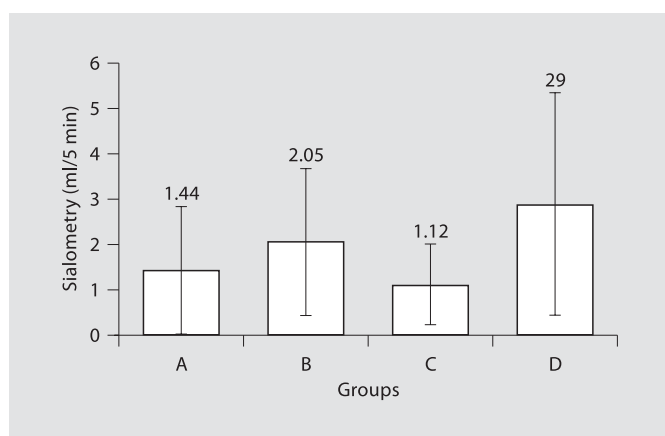
Oral Findings

There were no oral mucosal pathologies in any of the patients, except for 1 from group B who had clinical candidiasis on the dorsum of the tongue. Cervical dental caries were not found in any of the patients.

In the tactile test, only 1 patient from group C was found to have dry oral mucosa.

Table 3. Patients' behavioral parameters

	Group type			
	A (fexofenadine)	B (loratadine)	C (allergic)	D (healthy)
Hydration, l/day	1.8 ± 0.96	2.18 ± 2.18	1.5 ± 0.38	1.99 ± 1.22
Type of breathing, number of patients				
Nose	3 (33%)	3 (50%)	10 (91%)	9 (90%)
Mouth	2 (44%)	4 (33%)	1 (9%)	0
Both	1 (22%)	2 (16.7%)	0	1 (10%)

**Fig. 1.** Comparison of the salivary flow between patients treated with fexofenadine (group A), patients treated with loratadine (group B), allergic untreated patients (group C) and healthy individuals (group D).

Average sialometry was over 0.2 ml/min in all 4 groups (fig. 1). In pair-wise comparisons a significant statistical difference was found between groups A and D ($p = 0.02$) and between groups C and D ($p = 0.03$).

Discussion

Antihistamines are listed among the drugs that cause dry mouth [8]. However, the documentation of this side effect is based mainly on patients' subjective reports rather than on clinical examination [5, 8, 9]. Considering the scarce information about the adverse effects of new generation antihistamines on salivation, this pilot study aimed to examine the effect of loratadine and fexofenadine on salivary gland function in patients diagnosed with allergic rhinitis. A comparative observational study assessed parameters related to the patients' perception of

dry mouth as well as clinically observed parameters. The study design included a double control (healthy individuals and allergic patients not receiving pharmacological treatment) in order to evaluate the possible effect of allergy on dry mouth.

Patients in both treatment groups (A and B) had a lower salivary flow rate than the healthy control group (D). However, only patients receiving fexofenadine were significantly different from the healthy control. There was no statistically significant difference in salivary flow rate between patients treated with fexofenadine (group A) and patients treated with loratadine (group B). These trends were reflected in the patients' subjective scoring of dryness. Fexofenadine- and loratadine-treated patients complained of dry mouth more than healthy controls. Yet there was no statistically significant difference between the 2 treatment groups. The observation was in accordance with the patients' scoring of dry skin and dry eyes. This positive correlation between dry mouth and dryness in nonoral organs has previously been reported [8].

In this study the values of subjective mouth dryness score (VAS) were relatively low, ranging in the lower quarter of the scale. These findings reflect the fact that most patients were relatively satisfied with the antihistamines. In addition, no clinical findings supporting extreme dry mouth, such as mucosal change and cervical dental caries, were present in most of the patients.

The rank of selectivity for histamine receptors over muscarinic receptors was estimated to be higher for the new generation of antihistamines in comparison to the first generation of antihistamines [10]. No anticholinergic effects have been observed with loratadine in an animal model [11]. This pharmacological action may yield the low level of spontaneous dry mouth complaint and the absence of marked objective clinical findings observed in our study. Nevertheless, subclinical objective hyposalivation was detected in the fexofenadine group.

Interestingly, in this study, patients diagnosed with allergy presented a significant difference in salivary flow rate compared to healthy controls. Patients with allergic rhinitis typically experience sneezing, watery rhinorrhea and excess lacrimation [12]. In addition, dryness of the mucous membrane in the nasal cavity is described [13]. Therefore, it is reasonable to assume that subsequent to the allergic watery discharge, a dry mouth sensation develops. Moreover, the anatomical proximity between the nasal cavity and the oral cavity implicates it in the patient's perception of dry mouth [8]. Accordingly, the antiallergic treatment groups presented better salivary flow rates than the untreated allergic patients. A larger group may confirm these results.

In conclusion, in this pilot study, patients treated with fexofenadine showed a significantly lower salivary flow rate in comparison to healthy individuals. However, no such difference was observed for the loratadine-treated patients. The effect of allergy on salivary function should be further investigated in a large-scale study.

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