

Effects of allergic rhinitis and desloratadine on the submandibular gland in a rat allergy model

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Background: Allergic rhinitis (AR) and antihistamine usage can cause xerostomia. The study aims to examine if AR, antihistamines, and the use of antihistamines in AR have histopathological effects on the submandibular gland. The study also investigates the effect of oxidant and antioxidant plasma parameters.

Methods: Thirty-two adult Sprague-Dawley rats were used in the study. The rats were divided into the 4 following groups: the control group (C group); the AR group; an antihistamine-treated group (AH group); and an AR plus antihistamine-treated group (AR+AH group). The AR and AR+AH groups were sensitized using ovalbumin. The AR+AH and AH groups received desloratadine. The histopathological effects of AR and desloratadine treatment on the submandibular glands (SMGs) and the values of the oxidative and antioxidative serum parameters were evaluated.

Results: Histopathological examination of sections of the SMGs from the AR and AH groups revealed that vacuolization was present in the mucous acinar and ductal cells and that the number of connective-tissue cells was greater than that of the control group. The appearances of the AR+AH-

group sections were similar to those of the control group. The superoxide dismutase activity level and the glutathione level were relatively decreased in these groups compared with those of the control group. The malondialdehyde level in the AR group was increased compared with that of the control group.

Conclusion: The AR-induced pathological changes were diminished by desloratadine treatment. Thus, the new-generation antihistamine desloratadine may be used to treatment of AR patients who have xerostomia. © 2015 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; xerostomia; desloratadine; submandibular gland; salivary glands; superoxide dismutase; glutathione; malondialdehyde

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Xerostomia is dryness of the mouth due to a decrease in the amount of saliva. Saliva is an important factor

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in local and systemic defense that has lubricating, cleansing, antibacterial, buffering, and remineralizing effects on the oral cavity, oropharyngeal region, and upper gastrointestinal tract.^{1,2} The effects of many drugs and diseases on the salivary glands have been extensively investigated. The submandibular glands (SMGs) are responsible for the production of 60% of the total saliva. The SMGs are mixed tubuloacinar glands that contain end-secretory units called acini and cells that release serous, mucous, or both serous and mucous secretions. The serous acini comprise 90% of an SMG, whereas mucous tubules with a serous crescent cap comprise 10% of this gland.^{3,4}

Allergic rhinitis (AR) is the most common manifestation of allergic diseases. AR is not a life-threatening disease, but it can impair quality of life and lead to xerostomia.^{5,6} Antihistamines are commonly used in AR treatment, though they can lead to xerostomia.⁵⁻⁷ Desloratadine, a basic

metabolite of loratadine, is commonly used in AR treatment. This drug is a new-generation agent that is highly selective for H1 receptors and is nonsedating. Recent studies have indicated that desloratadine not only had an antihistaminic effect but also exhibited an antioxidative effect.^{8,9} Although desloratadine has an antioxidative effect, it causes xerostomia because of its anticholinergic and antihistaminic effects.^{7,10}

Oxidative stress occurs due to the imbalance between the endogenous production of free reactive oxygen species (ROS) and the efficacy of the antioxidative defense mechanisms of the organism. Oxidative stress occurs in many allergic and immunological diseases, including AR.^{11,12} Oxidative stress can lead to lipid peroxidation, which causes the oxidative degeneration of lipids. Glutathione (GSH) is the major substrate of many enzymes, including the glutathione peroxidase that causes lipid peroxidation. Oxidative stress can lead to a decrease in the GSH content. Malondialdehyde (MDA) is a product of lipid peroxidase, and its level increases under oxidative stress conditions. Additionally, superoxide dismutase (SOD) is generally found in aerobic systems. It is the basic defense agent against oxygen toxicity.^{12,13} Therefore, the levels of MDA, GSH, and SOD activities are commonly used to evaluate the performance of oxidative and antioxidative systems.^{9,11–13}

It has been reported that both AR and desloratadine cause xerostomia. The use of desloratadine for AR treatment is expected to increase xerostomia, but on the contrary xerostomia has been shown to be relieved when desloratadine is used in AR patients.^{5,6} These results were obtained in clinical studies in which the histopathological and biochemical changes in the salivary glands and blood were not investigated. In this study, the histopathological effects of AR, desloratadine treatment alone, and AR plus desloratadine treatment on the SMGs were studied; and, the associated changes in the values of oxidative stress parameters were assessed.

Materials and methods

Animal studies

This study was conducted in the Animal Laboratory of Medical Pharmacology and the Embryology and Histology Department of the Ataturk University Medical Faculty. Female Sprague-Dawley rats were supplied by the Ataturk University Experimental Medical and Research Center. The Ataturk University Veterinary Faculty Animal Ethical Committee approved this study. All of the rats had free access to standard rat chow and tap water. The rats were fed with a standard rat diet up to 12 hours prior to surgery.

This study used 32 adult female Sprague-Dawley rats (200 to 250 g). The rats were randomly classified into the following 4 groups including 8 rats each: the healthy group (control; group C); the induced-AR rats (group AR); the desloratadine-treated rats without AR (group AH); and the group of induced-AR rats treated with desloratadine (group AR+AH).

Ovalbumin-induced AR animal model

The AR model was established according to the standard published protocol.¹⁴ The rats belonging to the AR and AR+AH groups were sensitized through a 1-mL intraperitoneal injection of solutions of 30 mg/mL of AL(OH)₃ and 0.3 mg/mL of ovalbumin (OVA) (Sigma, St. Louis, MO) once every second day for 14 days (a total of 7 injections). Sensitization was continued through a nasal challenge (putting drops in the bilateral nasal cavities) using 20 mL of 10% OVA once a day from the 15th day to the 21st day. On day 15 of the study, after the first nasal challenge, rats were placed in an observation cage for about 10 minutes for acclimatization. Rats were observed for 10 minutes. AR was assessed by using nasal symptom scores that include nasal scratching, sneezing, and nasal flow. The number of nasal itching and sneezes was scored as: none = 0 points; 2 times = 1 point; 4 to 6 times = 2 points; and over 6 times = 3 points. The amount of nasal flow was scored as: none = 0 points; in 1 nostril = 1 point; in both nostrils = 2 points; and out-flowing = 3 points. The development of AR was approved if total scores were more than 5 points.¹⁵ The total symptom score was over 5 points in all rats. All of the rats in the AR+AH group were orally administered 10 mg/kg of desloratadine dissolved in a saline solution once every 7 days at the same time as the nasal challenge. The rats in the AH group were administered 10 mg/kg desloratadine in a saline solution once a day for 7 days. The animals tolerated the experimental protocols well.

Blood samples were taken from each rat through a cardiac puncture under isoflurane anesthesia 12 hours after the intranasal administration of OVA and oral desloratadine. The rats were then euthanized. All of the sera samples were stored at –80°C until the biochemical analyses were performed. The SMG tissues were removed and examined for histopathological changes.

Histopathological procedures

The SMG tissues were fixed for 72 hours using 10% neutral-buffer. After fixation, the salivary-gland tissue samples were dehydrated using a series of alcohol solutions, cleared using xylene, and embedded in paraffin. Five- μ m-thick sections cut using a Leica RM2125RT microtome (Leica Microsystems, Wetzlar, Germany) were collected on positively charged slides. After the paraffin was removed from the sections using a series of xylene solutions and rehydrated through a graded alcohol series, 2 sections of each rat SMG were separately stained with Mayer's hematoxylin and eosin (H&E) stain or with Dane trichrome stain. The sections were later dehydrated, using xylene as the final treatment, and a coverslip was applied for evaluation using a light microscope (Leica Microsystems).

Semiquantitative analysis of histopathological and histochemical changes

Semiquantitative histopathological and histochemical evaluations of the sections of SMGs harvested from each rat

were conducted using a light microscope. In each section of each rat's SMG, the parenchymal and stromal portions of 5 randomly chosen $100\text{-}\mu\text{m}^2$ areas of the gland were evaluated using a $10\times$ objective. The arithmetic mean values were semiquantitatively scored. In the histopathological analysis, the number of connective-tissue cells, the density of the stained mucous acinar secretory granules, the density of the stained serous acinar secretory granules, the extent of vacuolization, and the levels of degenerative serous cells and degenerative mucous cells in the submandibular gland tissues were scored. The scoring was conducted as follows: none = 0; mild = 1; moderate = 2; and severe = 3.

Stereological procedures and analysis

Slides containing tissue specimens were placed on a motor-driven stage connected to a microscope, and images of the specimens were projected to the monitor via a camera using $\times 40$ magnification. Each acinus was examined using a systematic random-sampling method of moving the microscope stage from left to right in a stepwise manner. The mean serous acinar area was determined using the nucleator method of the Stereo Investigator software, version 9 (MBF Bioscience, Williston, VT) using the following formula that was developed by Gundersen:

$$a(\text{area}) = n(\text{the number of nucleator estimates}) \times 12(\text{length of intercepts}) \quad (1)$$

Serological analysis

The SOD activity level¹⁶ and the GSH¹⁷ and MDA¹⁸ concentrations of each sample were determined at room temperature in duplicate using a modified enzyme-linked immunosorbent assay (ELISA) method. The average absorbance of each sample and standard were calculated. Standard curves were plotted, and an equation was obtained based on the absorbance of the standards solutions. The linear SOD activity level and the GSH and MDA concentrations were calculated according to these equations. The results of the SOD, GSH, and MDA assays of the tissues were expressed as U/mL protein, mmol/mL, and nmol/mL, respectively. All of the data were presented as the mean values $\pm$ standard deviation (SD) per mg of protein.

Protein determination

The protein concentrations were determined using the Lowry method, using commercial protein standards (total protein kit-TP0300-1KT; Sigma Chemical Co. Munich, Germany).

Statistical analysis

The statistical analysis was conducted using SPSS software (IBM SPSS Statistics 20.0; IBM Corporation, Armonk, NY). The groups were compared to each other using a 1-way analysis of variance (ANOVA) followed by Tukey's

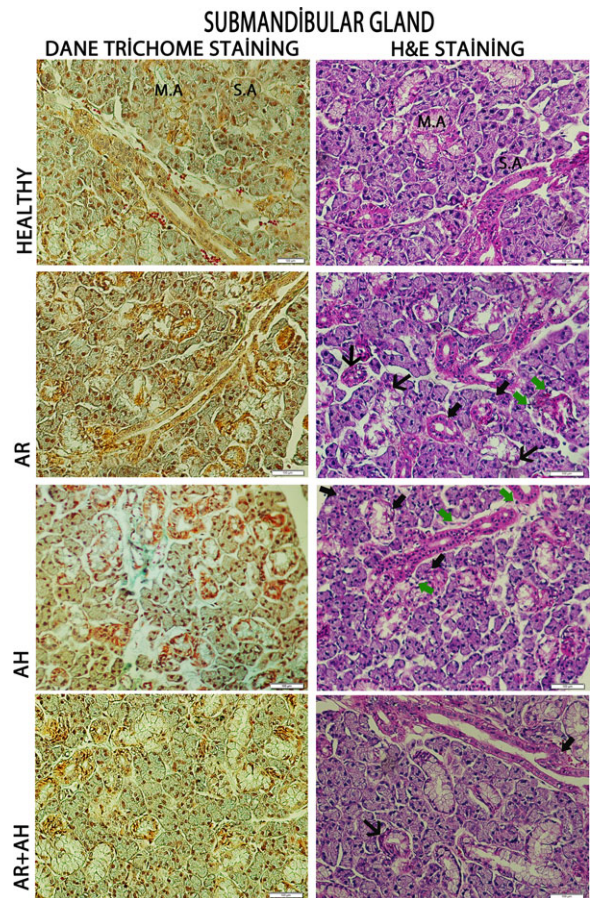


FIGURE 1. Dane trichrome–stained and H&E–stained sections of submandibular glands from the 4 groups show SM, MA, degenerative cells (thin arrows), vacuolization (thick arrows), and connective-tissue cells (green arrows). AH = antihistamine-treated group; AR = allergic rhinitis group; AR+AH = AR plus antihistamine-treated group; H&E = hematoxylin and eosin; MA = mucous acini; SM = serous mucous acini.

test. A p value of less than 0.05 was considered significant ($p < 0.05$). The values were expressed as the mean values $\pm$ SD.

Results

Histopathological and histochemical evaluations

The H&E–stained and Dane trichrome–stained sections of the submandibular tissues were examined (Fig. 1). Histopathological and histochemical analysis of the submandibular tissues showed that the serous and mucous acini, the ducts, and the connective tissue in the control-group sections appeared normal. In the AR-group sections, there was vacuolization in the mucous acinar and ductal cells, and the number of connective-tissue cells was greater than that of the control glands. The number of degenerative mucous acinar cells was increased, and the staining intensity of the secretory granules in the serous cells was more pronounced in these sections. In the AH-group sections, an increased number of connective tissue cells and vacuolization of the serous acinar, mucous acinar, and ductal cells

TABLE 1. Results of the semiquantitative histopathological and immunohistochemical evaluations of the submandibular gland tissues*

Groups	Rats (n)	CTC	DSMASG	DSSASG	V	DSC	DMC
Control	8	1.01 ± 0.15 ^b	2.01 ± 0.18 ^b	1.96 ± 0.18 ^b	1.01 ± 0.07 ^b	1.04 ± 0.14 ^c	1.01 ± 0.10 ^c
AR	8	2.01 ± 0.15 ^a	3.00 ± 0.15 ^a	2.99 ± 0.17 ^a	2.37 ± 0.14 ^a	2.97 ± 0.17 ^a	3.00 ± 0.16 ^a
AH	8	1.89 ± 0.44 ^a	1.22 ± 0.41 ^c	0.99 ± 0.46 ^c	2.14 ± 0.07 ^a	2.01 ± 0.47 ^b	2.01 ± 0.47 ^b
AR+AH	8	1.18 ± 0.11 ^b	2.02 ± 0.17 ^b	2.02 ± 0.13 ^b	1.01 ± 0.16 ^b	1.00 ± 0.15 ^c	1.05 ± 0.18 ^c

*Values with the same superscripted letters are not statistically significantly different ($p = 0.05$). Results are mean ± SD of the mean.

AH = antihistamine-treated; AR = allergic rhinitis; CTC = connective tissue cell, DSMASG = density of stained mucous acini secretory granules, DSSASG = density of stained serous acini secretory granules; DMC = degenerative mucous cell; DSC = degenerative serous cell; SD = standard deviation; V = vacuolization.

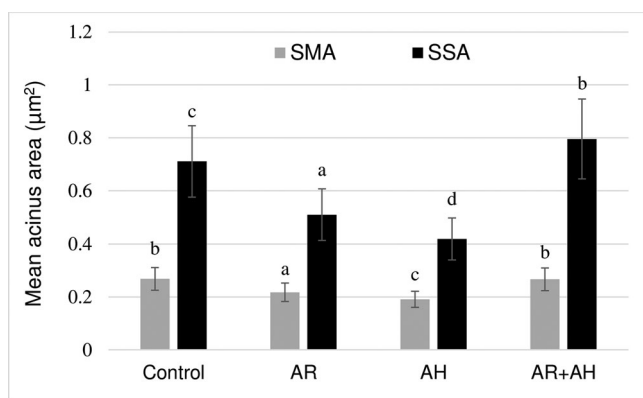


FIGURE 2. Stereological assessments of the mean mucous acinar area and the mean serous acinar area of glands from the 4 groups. Bars in the same series (SMA or SSA) shown by the same letter are not significantly different from each other at a level of 5%. AH = antihistamine-treated group; AR = allergic rhinitis group; AR+AH = AR plus antihistamine-treated group; SMA = submandibular mucous acini; SSA = submandibular serous acini.

were observed. Interstitial edema and a decreased level of staining of the serous cells were observed in sections from this group (Table 1).

The AR+AH-group sections were found to be similar to those of the control group. The mucous acini were nearly normal, and the number of connective tissue cells of vacuolated serous and ductal cells was decreased compared with those of AR group. The staining intensity of the serous and mucous acinar cell secretory granules was also similar to that of the healthy group (Fig. 1, Table 1).

Stereological evaluation

Calculating the area occupied by the mucous acinar cells in the submandibular glands showed that there was not a significant difference between the control and AR+AH groups (Fig. 2). The AR group showed a significant decrease in the area occupied by mucous acinar cells ($p < 0.05$). The AH group exhibited the greatest decrease in the mean acinar area ($p < 0.05$).

Assessment of the area of the submandibular glands occupied by serous acinar cells revealed that the values for all of the groups significantly differed ($p < 0.05$) from one another. The AH-group sections exhibited the most

greatly decreased mean serous acinar area. The value for the AR+AH group was similar to that of the control group (Fig. 2).

Serological results

The levels of SOD activity of the control and AH groups were similar, but this level was markedly decreased in the AR+AH group. The lowest level of SOD activity was observed in the AR group (Fig. 3). The GSH levels of the control and AH groups were similar, whereas the GSH level was lower in the AR+AH group. The lowest GSH level was detected in the AR group. The MDA levels of the control, AH, and AR+AH groups were similar, but this level was higher in the AR group compared with those of the other groups.

Discussion

Xerostomia generally develops when the rate of salivary secretion decreases, although a subjectively dry mouth is occasionally experienced despite a normal level of salivary secretion.^{1,2} The occurrence of certain histological changes in the salivary glands, including acinar vacuolization and changes in the secretory granular contents, accompany decreased salivary secretion.¹⁹ In studies on the effects of irradiation, apoptosis and vacuolization of the acinar cells were observed upon treatment and these changes were associated with the decreased production of saliva.²⁰ Additionally, studies of periodontitis showed that a reduction in the secretory granule content and vacuolization were related to defective salivary secretion.²¹ Using single-photon emission computed tomography, Choi et al.²² showed that decreased salivary flow rates were associated with acinar cell atrophy, cytoplasmic vacuolization, and periductal fibrosis in the salivary glands of mice. In our study, there was a marked increase in vacuolization of acinar cells and increased degeneration of both serous and mucous secretory cells in SMGs of AR and AH groups compared to the control group. Connective tissue was also increased in the SMGs of the AR and AH groups when compared to the control group. Based on these findings, we believe that both AR and antihistamine treatment can lead to decreased salivary secretion.

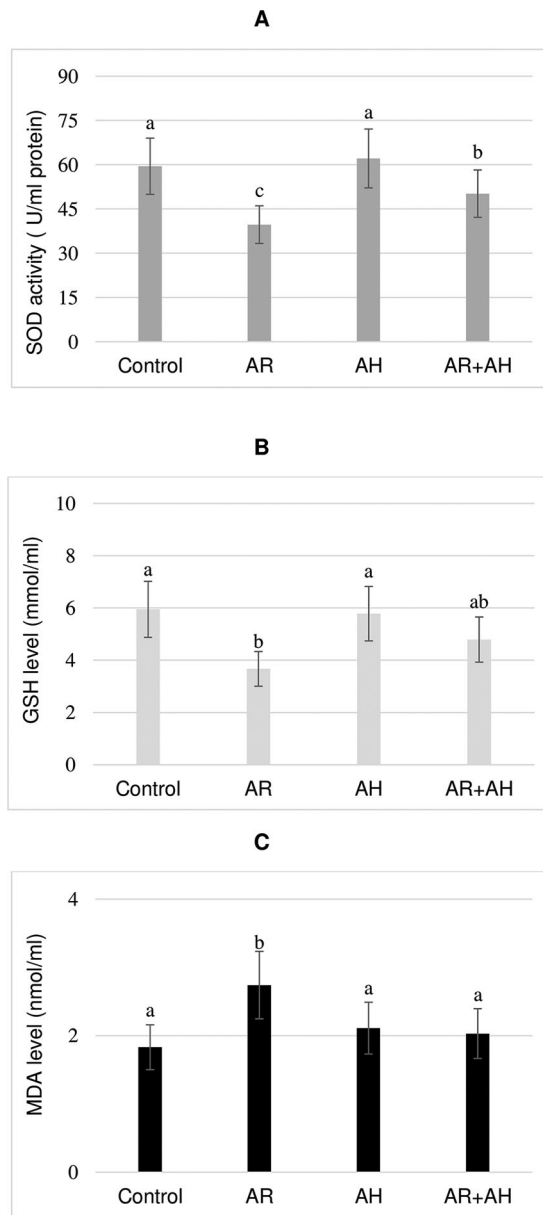


FIGURE 3. Serological results of the 4 groups are given as the mean values $\pm$ SD. (A) Levels of SOD activity; (B) GSH levels; and (C) MDA levels in the 4 groups. AH = antihistamine-treated group; AR = allergic rhinitis group; AR+AH = AR plus antihistamine-treated group; GSH = glutathione; MDA = malondialdehyde; SD = standard deviation; SMA = submandibular mucous acini; SOD = superoxide dismutase; SSA = submandibular serous acini.

The stereological analysis of the SMGs of the AR and AH groups showed that both the serous and mucous acinar areas were smaller than those of the control group. In the literature, there were no clear histopathological, histochemical, and stereological examinations on the effects of antihistamines on salivary glands. It has been concluded that the decreased mean acinus area in the AR and AH groups can occur because of alterations on the secretory granules, related to the decrease in the function of these cells.²³

Studies have demonstrated that AR leads to xerostomia and decreased salivary secretion, but the underlying mechanisms are unknown.^{5,6} The nasal mucosa has also been shown to become dry in AR patients.⁵ These studies reported that the dry-mouth sensation can develop in AR patients because of the anatomical proximity of the nasal and oral cavities. Additionally, the secretion of watery saliva (not of the normal salivary consistency) due to H1-receptor activation has been proposed to be a possible reason for the dry-mouth sensation.^{5,6}

The xerostomic effects of antihistamines are well known. The xerostomic effect of antihistamines can occur through the activation of muscarinic receptors.⁷ Kim et al.²⁴ showed the presence of H1 receptors in the SMG. They also reported that human salivary secretion can be regulated by both parasympathetic acetylcholine receptors and histamine receptors. The xerostomic effects of antihistamines were mediated not only via muscarinic receptors but also via H1 receptors. The new-generation antihistamines, which have very low antimuscarinic effects, lead to xerostomia via their H1-receptor antagonistic effects. The data obtained in this study showed that the negative H1-receptor-mediated effect of increased histamine release on the salivary glands of an AR model could be remediated by applying an antihistamine that exerted H1-receptor-antagonistic effects.²⁴ In addition, the anticholinergic effects of antihistamines used to treat AR were observed by Kim and Baraniuk.¹⁰

Although the existence of AR or antihistamine treatment alone can lead to xerostomia, there are some clinical studies that have shown recovery of decreased salivary secretion in AR patients by the use of antihistamines.^{5,6} Our histopathological data supported these claims. We determined that the level of vacuolization of the acinar cells, the levels of degeneration of the secretory cells and the connective tissue, and the secretory-granule content of the acinar cells in the AR+AH group were similar to those of the control group. The stereological analysis revealed that the average areas occupied by serous and mucous acini in the AR+AH group were similar to those of the control group.

Oxidative stress plays an important role in allergic disorders, including AR, and high levels of oxidants cause cellular damage.^{11–13,25,26} Increased values for the oxidation parameters that are signs of oxidative stress have been observed in the blood,^{25,27} erythrocytes,²⁶ exhaled air and exhaled-breath condensate in AR.¹³ An increase in oxidative stress caused histopathological changes and decreased the rate of secretion of saliva, thereby causing xerostomia. Salivary-gland hypofunction induced by radiation and periodontitis has been reported to be related to an increase in oxidative stress.^{27,28} The use of antioxidative agents reversed the irradiation-induced reduction in salivary secretion and restored the level of SOD activity and the GSH and MDA levels.^{19,29}

Desloratadine is known to possess antioxidative activity.^{8,9} In a study of pediatric patients, it was reported that the level of oxidative stress was increased

in the perennial AR patients. SOD levels, catalase activity, and MDA formation normalized when they were treated with desloratadine.³⁰ Studies of the levels of antioxidative molecules under pathological conditions have shown that antioxidant-agent treatments were effective in the recovery from pathologies caused by ROS production. Accordingly, the negative effects of the potentially AR-induced oxidative stress on the salivary glands appeared to be ameliorated by the antioxidative effect of desloratadine.

In this study, the SOD activity level and GSH concentration were decreased and the MDA concentration was increased in the AR group compared with the levels of the control group. Furthermore, the values for these parameters in the AR+AH group were similar to those of the control group. These results are compatible with the results reported in the literature demonstrating a relationship between AR and oxidative stress and the antioxidative effects of desloratadine. Although desloratadine had an antioxidative effect, the reason for the negative histopathological effects observed in the AH group could be the anticholinergic and antihistaminic effects of desloratadine. Based on the significant relationship between the histological findings and the values for the oxidation parameters of the AR and control groups, oxidative stress could be one of the reasons for the histopathological changes in the salivary glands of the AR group. The reasons for the similarity of the biochemical and histological findings of the control group and the AR+AH group could be the antihistaminic, anticholinergic, and antioxidative effects of desloratadine.

Overall, this study showed that the pathological changes due to AR could be diminished by desloratadine treatment. More research is needed to evaluate the effects of the use of desloratadine primarily for AR patients who have xerostomia. The results obtained in this study might contribute to future studies that may provide hard evidence of the remedial effect of desloratadine treatment on AR-induced xerostomia, and whether other new-generation antihistamines have the same effects as desloratadine.

Conclusion

Our study showed the following results:

- The level of oxidative stress was increased in an AR model.
- AR can have histopathological effects on salivary glands.
- Although desloratadine had an antioxidative effect, its use caused histopathologic changes of the salivary glands because of its anticholinergic and antihistaminic effects.
- Desloratadine promoted the recovery from the AR-induced effects of oxidative stress. This result indicated that desloratadine decreased the extent of AR-induced oxidative stress-related damage to the salivary glands. ③

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