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Evaluation of the effect of isotretinoin on salivary gland function by Tc-99m pertechnetate imaging in acne vulgaris patients

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Background/aim: Isotretinoin is an effective drug utilized in the management of acne vulgaris and is known to cause dry mouth. In this study, we aimed to evaluate this effect of isotretinoin on the salivary gland function in patients with acne vulgaris using technetium-99m (Tc-99m) pertechnetate imaging of the salivary glands.

Materials and methods: The study population consisted of 28 patients with acne vulgaris (6 males and 22 females, mean age 20.2 ± 2.3 years), who were treated with isotretinoin for 6 months. We performed radionuclide imaging of the salivary glands pretreatment and at months 3 and 6 of treatment. After 185 MBq (5 mCi) of Tc-99m pertechnetate was intravenously administered, imaging of the salivary glands was performed over a 25-min period. We measured the following glandular function parameters for the parotid and submandibular salivary glands via time-activity curves: uptake ratio, maximum accumulation, and ejection fraction.

Results: Statistically significant differences were observed in the values obtained at months 3 and 6 of treatment, compared with the pretreatment values.

Conclusion: This study demonstrated that radionuclide imaging of the salivary glands can clearly show the glandular functions that are affected by drugs such as isotretinoin.

Key words: Radionuclide imaging of salivary glands, technetium-99m pertechnetate, isotretinoin, acne vulgaris

1. Introduction

The subjective feeling of dry mouth, xerostomia, has a variety of causes, such as Sjögren's syndrome, external radiation to the head and neck, chemotherapy, various drugs, and some viral infections, and it may derive from a decrease in the production of saliva (1–3). Acne vulgaris of unknown etiology is a chronic inflammatory disease of the pilosebaceous follicles that is seen in young adulthood. Although it is not life-threatening, it can leave long-term physical and psychological damage. Therefore, early and effective treatment is important to reduce the severity and recurrence of the disease (4). Isotretinoin is an effective drug against the factors involved in acne pathogenesis and provides long-term disease remission. However, it is a common cause of dryness of the mouth and changes in the oral and lip mucosa (5). Radionuclide imaging of salivary glands with high sensitivity is a valuable technique for use in the definition of the etiology and the degree of salivary dysfunction. This technique is noninvasive and is suitable for normal physiology. Uptake of technetium-99m (Tc-99m) pertechnetate by the salivary glands is observed following intravenous (i.v.) injection. Quantitative functional data, for example uptake ratio, concentration, and excretion fraction, can be obtained via radionuclide imaging of the salivary glands (6–8). Evaluation of salivary gland function according to objective criteria, rather than subjective complaints, may provide an accurate assessment of patients taking isotretinoin and suffering from dry mouth. Therefore, the aim of this study was to compare the quantitative parameters of salivary gland functions in patients taking isotretinoin for acne vulgaris, both before treatment and at the 3rd and 6th months of treatment, using Tc-99m pertechnetate imaging.

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2. Materials and methods

2.1. Patients

The study population consisted of 28 patients with acne vulgaris (22 females and 6 males), with a mean age of 20.2 ± 2.3 years (range: 18 to 27 years). We performed radionuclide imaging of the patients' salivary glands before they began treatment, after which all patients received the clinically recommended oral dose of isotretinoin, 0.5 mg kg^{-1} day^{-1}, for 6 months (9). Controlled radionuclide imaging of the salivary glands was then performed at months 3 and 6 of treatment. The patients had neither a history of radiation treatment and head or neck surgery nor any connective tissue or systemic disease. All patients provided written informed consent prior to the study, which was approved by the ethics committee of Atatürk University.

2.2. Radionuclide imaging of salivary glands

All patients were placed in the supine position and the head was hyperextended prior to i.v. administration of 185 MBq (5 mCi) of Tc-99m pertechnetate. A single-head gamma camera (GE-Starcam 4000 XR/T, UK) with a parallel-hole, low-energy, and high-resolution collimator was used, and this was centered on a photo peak of Tc-99m. The data were acquired as 25 frames of 60 s per frame in a 1.33 zoom and a 128 matrix × 128 matrix. Lemon juice was orally administered for salivary gland stimulation at 20 min after the injection. Similar protocols have been used in other studies (7,8,10,11). The repeated measurements were well tolerated in all patients.

2.3. Semiquantitative analysis

Regions of interest (ROIs) were drawn around the parotid and submandibular glands on collected images for semiquantitative analysis. In addition, a background ROI was placed in the temporal area, and time-activity curves of salivary glands were generated (Figure 1).

Figure 2 shows the definition of the following points on the time-activity curve: a) vascular perfusion, at 1 min; b) the maximum prestimulation count; c) the background count at the time of peak activity; d) the minimum poststimulation count. The following functional glandular parameters were measured for the salivary glands: uptake ratio (UR) = b / c, maximum accumulation (MA%) = (b – a) / b × 100, and ejection fraction (EF%) = (b – d) /b × 100 (6,10,17).

2.4. Statistical analysis

We used SPSS for statistical analysis and calculated weighted means and standard deviations. Groups were compared using repeated measures analysis of variance. For variables without a normal distribution (i.e. MA% and EF% of the left parotid gland, MA% and UR of the right submandibular gland) we used Friedman analysis and carried out further analysis using the Wilcoxon test. The significance level was taken as $P < 0.05$.

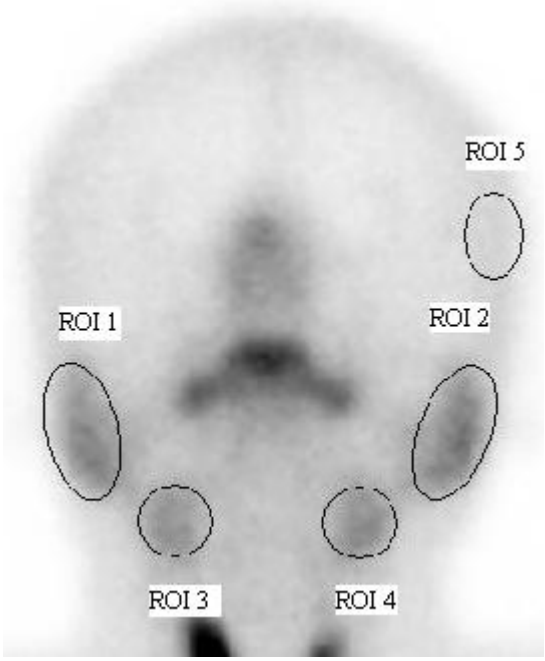

Figure 1. ROIs on the summation image obtained by radionuclide imaging of salivary glands. ROI 1- Right parotid gland, ROI 2- Left parotid gland, ROI 3- Right submandibular gland, ROI 4- Left submandibular gland, ROI 5- Background.

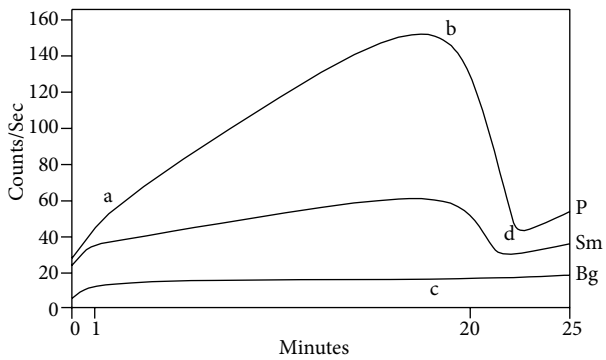

Figure 2. Time-activity curves obtained by radionuclide imaging of salivary glands. a- Vascular perfusion at 1 min, b- Maximum prestimulation count, c- Background count at the time of peak activity, d- Minimum poststimulation count, P- Parotid gland, Sm- Submandibular gland, Bg- Background.

3. Results

We included 28 patients (6 males and 22 females) treated with isotretinoin for acne vulgaris this study. The UR, MA%, and EF% values measured for the salivary glands are presented in the Table. The values obtained at months 3 and 6 of treatment were compared with pretreatment values. The UR, MA%, and EF% outcomes of the right and left parotid glands were decreased at months 3 and

Table. The values obtained at months 3 and 6 of treatment were compared with pretreatment values. *: Friedman analysis of variance. UR, Uptake ratio; MA%, maximum accumulation; EF%, ejection fraction; RP, right parotid; LP, left parotid; RSbm, right submandibular; LSbm, left submandibular. Data are expressed as mean ± standard deviation.

Parameter	Gland	Pretreatment (n = 28)	Third month of treatment (n = 28)	Sixth month of treatment (n = 28)	P
UR	RP	6.76 ± 1.31	4.57 ± 1.34	3.63 ± 1.41	0.0001
	LP	6.45 ± 1.38	4.46 ± 1.41	3.71 ± 1.44	0.0001
	RSbm	3.04 ± 1.13	2.04 ± 0.82	1.58 ± 0.72	0.0001*
	LSbm	2.63 ± 1.51	1.86 ± 1.34	1.47 ± 1.31	0.0001
MA%	RP	60.21 ± 8.99	50.17 ± 10.98	45.15 ± 11.95	0.0001
	LP	59.52 ± 8.85	50.31 ± 11.34	44.18 ± 10.81	0.0001*
	RSbm	37.05 ± 11.72	24.81 ± 10.97	16.46 ± 8.03	0.0001*
	LSbm	38.64 ± 12.69	27.61 ± 13.54	20.16 ± 9.97	0.0001
EF%	RP	55.62 ± 9.32	44.18 ± 11.55	38.12 ± 10.11	0.0001
	LP	55.00 ± 9.41	41.95 ± 12.75	35.84 ± 12.92	0.0001*
	RSbm	36.30 ± 1.31	25.70 ± 1.53	21.87 ± 1.54	0.002
	LSbm	36.88 ± 10.99	27.76 ± 11.04	21.72 ± 8.3	0.0001

6 of treatment ($P < 0.0001$ for all). In addition, there were significant decreases in the UR, MA%, and EF% of the right and left submandibular glands at months 3 and 6 of treatment when compared to pretreatment values ($P < 0.002$ for all).

4. Discussion

Drug usage is one of the most common reasons for reduced salivation. Systemic retinoids, used in the treatment of acne vulgaris, are a common cause of dryness of the mouth and changes in oral and lip mucosa (2). Isotretinoin is a drug that can be safely utilized to treat cases of acne vulgaris, with sufficient monitoring, when the benefits outweigh the risks (13). Recently, dermatologists have increasingly used isotretinoin to treat acne vulgaris that has not responded to other systemic therapies (12). Isotretinoin is effective, but some patients may experience a side effect of dry mouth due to a decrease in salivary secretion. The changes in salivary secretion may be due to the effect of retinoids on epidermal cell turnover rate (14). Lupi-Pegurier et al. (15) conducted salivary tests in patients treated with isotretinoin for acne vulgaris using whole stimulated saliva samples. To obtain these samples, the patients chewed a piece of paraffin wax for 5 min and spat into a small graduated tube, after which the flow rate was calculated. The salivary flow gradually decreased with time. Oikarinen et al. (16) assessed changes in salivary flow during treatment in patients treated for acne vulgaris with systemic isotretinoin for 3 months. They found that the flow rate of stimulated saliva diminished during treatment. In our study, we observed similar findings; gradual decreases in salivary gland function were determined in acne vulgaris patients during isotretinoin treatment.

The salivary glands may be assessed using computerized tomography and sialography. However, neither of these techniques enables quantitative evaluation of salivary gland functions. Furthermore, sialography is hard and painful for the patients, due to cannulization of the salivary gland ducts (8). An alternative useful technique is radionuclide imaging, which allows a functional assessment of the salivary glands. Radionuclide imaging may be carried out easily and is of low dosimetry. It is well tolerated by patients because it is suitable for normal physiology (17–22). A literature review of the quantitative evaluation of salivary gland functions created from dynamic studies showed that most functional parameters, for example percentage uptake, concentration, and excretion fractions, were generated from individual salivary gland time-activity curves (6–8,23–25). Booker et al. (6) studied the diversity of UR, MA, and EF in a group of 83 patients with xerostomia, including a subset of 40 patients with Sjögren's syndrome and a group of 26 healthy volunteers. Anjos et al. performed radionuclide imaging of salivary glands

to acquire reference values of salivary gland uptake and excretion fraction in 50 healthy volunteers (7). In our study, evaluation of salivary gland function was performed by radionuclide imaging, and we found that there were significant decreases in the salivary gland functions of patients using isotretinoin at months 3 and 6 compared to pretreatment values. This study was the first to conduct an objective evaluation of salivary gland function with radionuclide imaging in patients taking isotretinoin for acne vulgaris.

In conclusion, we recommend salivary gland scintigraphy as an effective, easy, and reproducible diagnostic method that can be used to assess the effects of drugs such as isotretinoin, which affect salivary gland functions.

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