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Evaluation of the effects of oral isotretinoin on nasal function, taste, and smell

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Abstract. *Evaluation of the effects of oral isotretinoin on nasal function, taste, and smell. Objectives:* Oral isotretinoin is commonly used to treat recalcitrant nodular acne. This study's purpose is to explore the effects of oral isotretinoin on nasal patency, taste, and smell.
Methodology: This study enrolled 39 patients who had acne vulgaris. Patients were treated with isotretinoinat a daily dose of 0.5-0.8 mg/kg body weight per day in divided doses over a 3-month period. All patients underwent both objective and subjective testing of nasal obstruction, olfaction, taste, and mucociliary clearance before treatment and at week 1 and month 3 of treatment.
Results: We found that the nasal obstruction, taste and olfactory visual analog scores began to decrease even in the first week of drug treatment, and was even lower by month 3 ($p<0.01$).
In the first week,the mucociliary clearance time also decreased and continued to fall at month 3 ($p<0.01$).It was revealed by the peak nasal inspiratory flow measurements that obstruction developed even during week 1 ($p<0.01$). Sinonasal outcome test scores significantly increased at the third-month results ($p<0.01$).
Significant taste loss was evident by month 3 ($p<0.05$). However, although olfaction decreased somewhat by month 3, the fall was not significant.
Conclusion: Isotretinoin triggers loss of nasal function, reducing the mucociliary clearance and taste sensations. Subjective deteriorations occurred earlier than the objective deteriorations.

Introduction

Retinoids (synthetic analogs of vitamin A) are used to prevent chemically induced carcinogenesis.[1] In the 1980s, isotretinoin (13-cis-retinoic acid) began to be used to manage acne vulgaris and other skin disorders.[2] Oral isotretinoin is commonly used to treat severe, recalcitrant nodular acne unresponsive to conventional therapy including topical and systemic antibiotics.

The mucocutaneous and systemic toxicities of retinoids are well-recognized.[3,4] The most common adverse effects are changes in skin and mucosa in the form of cheilitis, facial dermatitis, dryness of nasal, oral and throat mucosa, eyelid inflammation and conjunctivitis, reversible corneal opacity, atopic skin and generalized skin dryness. Generally, the side-effects are dose-dependent and resolve after treatment cessation.

Isotretinoin triggers dry-nose syndrome and also affects nasal function.[5] Systemic drug administration affects the upper airway, triggering patient complaints. A few case studies have explored the effects of isotretinoin on olfaction and taste.[6] However, more data are required.

Mucociliary clearance (MCC) is the main self-clearing system of the nasal cavity and paranasal sinuses. This system is very important for non-specific defence against continuous organic and inorganic contamination. The absence or deficiency of this self-clearing system renders patients more vulnerable to infection and disease. Oral isotretinoin may alter water and electrolyte balance, resulting in altered nasal mucociliary clearance.

Taste and smell are important to motivate food intake; the body requires energy derived from nutrients. The nasal and mouth mucosae are important for smell and taste respectively.[7,8] Patients on isotretinoin often experience a dry mouth or nose. Changes in taste and smell sensations have received little attention compared to the other side-effects of isotretinoin. We thus explored the effects of oral isotretinoin on nasal function, taste, and smell.

Materials and methods

This study was carried out at the Okmeydanı Training and Research Hospital Department of

Otolaryngology and Head and Neck Surgery between March 2015 and December 2015. All study protocols and informed consent forms were collected and approved by the institutional review board. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local Ethical Committee.

The study enrolled patients who had acne vulgaris and were prescribed isotretinoin for the treatment of acne vulgaris. Exclusion criteria include nasal septal deviation, previous nasal surgery, nasal polyposis, pre-existing sinus disease or nasal allergies of any sort, preexisting subjective olfactory disturbance, smokers, any neurological disease and intracranial pathology, intranasal drug abusers and systemic disease such as diabetes mellitus, rheumatologic disorders and patients considering pregnancy.

Hemogram, liver, and kidney function tests, cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, and urine analyses were performed initially at each month. Patients were treated with isotretinoin at a daily dose of 0.5-0.8 mg/kg body weight per day in divided doses over a 6-month period.

We studied 39 patients taking isotretinoin to treat acne vulgaris. All patients underwent complete head-and-neck examinations before treatment. The nasal cavity, nasopharynx, and oropharynx of all patients were examined via flexible nasopharyngoscopy. All patients underwent both objective and subjective testing of nasal obstruction, olfaction, taste, and MCC before treatment and at week 1 and month 3 of treatment.

1. Obstruction, Olfactory and Taste Evaluation tests

Visual Analogue Scale (VAS) was used for all patients to show obstructive, taste and olfactory symptoms subjectively. There are numbers on the scale from 0-10; 0 reflects total obstruction, while 10 represent a fully opened passage. The value which best reflects the nasal obstruction indicated the patient's VAS result.

Sinonasal outcome test 22 (SNOT 22), which was validated by Hopkins et al.[9] was used to evaluate sinonasal symptoms. Data were collected by means of a self-administered questionnaire. SNOT 22 is composed of 22 questions that are scored from 0–5. A lower score implies a better result.

Peak nasal inspiratory flowmeter (PNIF) measurement was performed using a nasal inspiratory flowmeter (Clement Clark International, Harlow, Essex, UK). The value of forced inspiration was expressed as liters per minute. The patients were asked to expire forcefully while sitting and inspire forcefully through the nose with an anesthesia mask placed over the mouth. Of the three consecutive measurements with a maximum difference of 10 %, the highest measurement was recorded as the final value.

The Connecticut Chemosensory Clinical Research Center (CCCRC) test was conducted in an odorless room under standard conditions using a commercially available smell test kit for the patients. This test is composed of n-butanol odor threshold test and odor identification test.[10] For both parts of the test, each nostril is tested separately by having the subject occlude the opposite nostril.

Odor threshold is measured using nine serial dilutions of butanol. The strongest butanol concentration (bottle 0) was 4% butanol in deionized water. Each subsequent dilution (bottles1-9) was 1:3 dilutions with deionized water. Each concentration is presented along with a water control in a double-blind, forced-choice paradigm. The threshold is defined as the dilution at which the butanol bottle is correctly identified in four consecutive trials. There are seven olfactory stimuli (baby powder, chocolate, cinnamon, coffee, mothballs, peanut butter, and soap) and three stimuli (ammonia, Vicks, and wintergreen) used to test trigeminal nerve sensory function. Olfactory tests were conducted individually and were scored out of 7 (0: worst, 7: best olfaction).[10]

Nasal mucociliary clearance (MCC) was assessed for all individuals by the blinded researcher. Saccharin transit time test was used to measure the nasal MCC, as previously described.[11] Subjects were seated in an upright position. Granulated sodium saccharin (250 mg) was deposited under visual control. A saccharin granule was placed 2 cm in the right nostril lateral to inferior turbinate by the tester. They were instructed to swallow every 30 seconds with a chronometer. The time when the subjects first percepted the sweet taste of the saccharin was recorded in minutes.

Gustatory sensitivity evaluation taste strips (Burghart Messtechnik GmbH, Wedel, Germany) for the complete mouth test were used for gustatory sensitivity evaluation.[12] Subjects were asked not to

eat or drink anything other than water, no smoking and no teeth brushing 1 hour before testing. The order of sixteen taste strips in increasing concentrations of four different tastes offered to subjects are given to each patient. A double-blind approach where both subjects and examiners were blinded to the order of the tastant being tested and its concentration was used during evaluation. The taste solutions were freshly prepared with the following concentrations: sweet, 0.4, 0.2, 0.1, 0.05 g/ml sucrose; sour, 0.3, 0.165, 0.09, 0.05 g/ml citric acid; salty, 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride; and bitter, 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride. Subjects were asked to place the taste strips on the anterior region of the tongue, suck for 20 seconds, and then identify the taste in the following 10 seconds. Subjects were asked to rinse their mouth with water between each administration. Each correct answer was granted as one point (maximum 4 points for each taste score and 16 points for the whole test score).

1.2 Statistical Analysis

Statistical analyses of the data were conducted using SPSS ver. 17.0. Shapiro Wilks test was used to evaluate the normal distribution of the parameters. Data were analyzed using descriptive statistical methods (mean and standard deviation). Repeated ANOVA test for repeated data and Bonferroni test for intergroup comparison were used to compare the normally distributed data in the pretreatment, first week and 3rd-month results. Friedman test for repeated data and Wilcoxon Sign for intergroup comparison tests were used for non-parametric data. Results were evaluated using the 95% confidence intervals (CI), and the level of significance was set at $p<0.05$.

Results

The study group comprised 39 consecutive patients. Seventeen of them (43.6 %) were male and 22 (56.4%) were female. The mean age was 18.36±2.86 years (range: 13-30 years). There were no differences with regard to age or gender distribution ($p>0.05$).

The average VAS measurements for nasal obstruction differed significantly between the measurements ($p<0.01$). The average nasal obstruction score at the third month was significantly lower than the pretreatment and first-week scores consecutively (p:0.023; p:0.028). There was no significant difference between the pretreatment and first-week measurements of the VAS for nasal obstruction ($p>0.05$).

The average VAS measurements for taste sensation differed significantly at the beginning, first week and third-month results of the study ($p<0.01$). The average taste sensation score at the third month was significantly lower than the pretreatment and first-week scores consecutively (p:0.001; p:0.031). VAS score at the week 1 was also significantly lower than the pretreatment score ($p<0.05$).

There was a significant difference in average VAS scores for smell sensation at the beginning, first week and third-month results of the study ($p<0.01$). The average olfactory score at the third month was significantly lower than the pretreatment and first-week scores consecutively (p:0.002; p:0.001). The average VAS score at the week 1 was also significantly lower than the pretreatment score ($p<0.05$) (Table 1).

The average SNOT measurements differed significantly at the beginning, first week and third-month results of the study ($p<0.01$). The

Table 1

Subjective VAS values for nasal obstruction, taste and olfaction

VAS score	Pretreatment	1st week	3rd month	p
	Mean±SD (n=39)	Mean ±SD (n=39)	Mean ±SD (n=39)	
Nasal Obstruction	8.10±2.12	7.80±1.89	7.36±2.06	0.005*
Taste	9.59±0.85	9.18±1.5	8.90±1.67	0.001*
Olfaction	9.36±1.31	8.97±1.72	8.61±1.87	0.001*

Friedman Test
SD (Standard deviation)
n (Number of patients)
*p<0.01

average SNOT measurement at the month 3 was significantly higher than the measurements at the beginning and first week of the treatment (p:0.038; p:0.001). There was no significant difference between the pretreatment and first-week results of the SNOT measurements (p>0.05).

The average PNIF measurements differed significantly at the beginning, first week and third-month results of the study (p<0.01). The average PNIF measurement at the third month of the treatment was significantly lower than the measurements at the beginning and first week of the treatments (p<0.01). The average PNIF measurement at the week 1 was also lower than the pretreatment measurements (p<0.05).

There was a significant difference of MCC measurement at the beginning, first week and third-month results (p<0.01). The average MCC measurement at the beginning of the treatment was significantly lower than the first week and third-month measurements (p:0.001; p:0.001). There was no significant difference between the week 1 and month 3 measurements (p>0.05).

The taste scores differed significantly at the beginning, first week and third-month results of the study (p<0.01). The average taste score at month 3 was significantly lower than the pretreatment and first-week measurements (p:0.001; p:0.001). There was no significant difference between the week 1and month 3 measurements (p>0.05)

The average olfactory test measurements did not differ significantly at the beginning, first week and third-month results (p>0.05) (Table 2).

Discussion

Retinoids are natural or synthetic analogs of vitamin A affecting cell growth, differentiation, and morphogenesis. They inhibit tumor promotion and malignant cell growth and exhibit immunomodulatory activities.[13]

The mucocutaneous side-effects of isotretinoin in terms of nasal function remain poorly understood. Oral retinoids decrease sebum production and trigger epidermal changes, particularly a reduction in the thickness of the stratum corneum, in turn drying the mucous membranes. The nasal mucosa is very sensitive to environmental conditions. The fact that mucosal dryness impairs nasal function has long been known.[11] Gorpelioğlu et al.[5] found that nasal clearance was significantly prolonged during treatment, and a significant correlation was evident between drug dose and MCC impairment. However, neither nasal obstruction nor the smell and taste functions, were explored in that study.

We found that the nasal obstruction VAS score began to significantly decrease even in the first week of drug treatment, and was even lower by month 3. The MCC time also decreased in the first week and continued to fall at month 3. The PNIF score revealed that obstruction developed even during week 1. The increasing SNOT scores indicated that nasal functional impairment and nasal complaints increased upon isotretinoin use. Nasal cavity dryness creates nasal obstructions; the nasal MCC then deteriorates.

The effects of isotretinoin on smell and taste have been reported in only a few case series.[6,14] Olfactory

Table 2

The evaluation of the patients at the 1st week and 3rd months of the measurements

	Pretreatment	1st week	3rd month	p
	Mean±SD (n=39)	Mean ±SD (n=39)	Mean ±SD (n=39)	
SNOT score	18.54±12.1	18.15±13.32	21.59±15.3	[1]0.001*
PNIF	105.38±53.99	97.18±49.36	91.28±50.11	[1]0.001*
MCC	10.67±5.2	12±5.47	11.9±5.02	[1]0.001*
Taste score	12.56±3.04	12.21±3.14	11.42±2.95	[2]0.001*
Olfactory score	4.88±1.13	4.71±1.04	4.6±1.00	[2]0.082

[1]Friedman Test
[2]Reapted ANOVA
SD (Standard deviation)
n (Number of patients)
*p<0.01

loss was evident at the end of month 4 and taste loss by month 6. It was suggested that the taste and smell nerve fibers of the ventroposteromedial nucleus of the thalamus might be injured by the drug.[6] However, no relevant histological evidence has been presented. Yee et al.[15] showed that retinoid acid facilitated the recovery of olfaction after olfactory nerve transaction. Thus, the drug is probably not neurotoxic, as has been previously argued.

In the present study, the subjective VAS for taste and smell decreased during the first week. We used taste strips to measure sensitivities to sweet, salty, sour, and bitter materials. Significant taste loss was evident by month 3. The subjective deteriorations in taste occurred earlier than the objective deteriorations. Although olfaction decreased somewhat by month 3, the fall was not significant in objective findings. However, the decrease in the subjective findings indicated the deterioration of the olfactory function. Dryness of the nasal and oral cavities affects patient quality-of-life, explaining why the SNOT scores decreased.

Taste and smell disorders reduce dietary intake and encourage the development of food aversion.[16] Good oral hygiene, avoidance of metallic silverware, and prescription of sialagogues (sugar-free or sour drops) reduce smell and taste problems in patients taking oral isotretinoin. Topical salivary lubricants (or substitutes thereof) may alleviate the sicca symptoms of the mouth and nose and protect the mucous membranes. However, the effects of topical moisturizers require further study.

Usually, both patients and their physicians have focused on dermatological complaints to the relative exclusion of nasal complaints. Our patients reported a significant loss of nasal function and of their taste and smell sensations. Such problems should be treated. Patients prescribed isotretinoin require access to an ENT specialist.

Although this research was carefully prepared, there are few limitations. First of all, the objective test results were to be patient dependent and a certain degree of subjectivity can be found. However, these tests are easy, cost-effective and reliable. Second, test results can be more reliable in a placebo-controlled study. Therefore, it would be better if it was done with a placebo control.

Conclusion

Isotretinoin triggers loss of nasal function, reducing the MCC and smell and taste sensations. The subjective deteriorations occurred earlier than the objective deteriorations. Medical support is required if this medication is prescribed.

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