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The effects of oral isotretinoin (13-Cis retinoic acid) on the inner ear: A prospective clinical study

Abstract

Purpose: The purpose of this study was to investigate the effect of oral isotretinoin, a drug used in the treatment of acne vulgaris, on hearing function determined by serial audiology examinations.

Methods: Forty patients with acne vulgaris were included in this study. Nine patients were excluded from the study because of inconsistent follow-up. The hearing of each participant was tested with pure tone audiometry and transient evoked otoacoustic emissions before and two and four weeks after treatment with isotretinoin (0.3-0.6 mg/kg/day) in the remaining 31 patients (62 ears).

Results: The differences between the mean values of the pre-treatment and post-treatment pure tone hearing thresholds at 1000, 2000, 4000 and 6000 Hz frequencies were statistically significant ($p < 0.05$), but there was no significant difference between the pre-treatment and post-treatment values at 250 and 500 Hz frequencies ($p > 0.05$). The difference between the pre-treatment and post-treatment signal-noise ratio values of the transient evoked otoacoustic emissions was not significantly different ($p > 0.05$).

Conclusion: Our results suggest that the use of isotretinoin may cause bilateral hearing threshold changes. Further animal and human studies are required to investigate and characterize isotretinoin-induced neurophysiological alterations in hearing.

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Isotretinoin (13-cis retinoic acid) belongs to a group of drugs known as retinoids, which are derivatives of vitamin A. Isotretinoin decreases the size and activity of the sebaceous glands in the skin, thus reducing the amount of sebum produced by the sebaceous glands [1]. Acne vulgaris is common among adolescents and young adults and isotretinoin is frequently administered for this condition. It is the first-line treatment for extensive and nodulocystic acne [2]. Isotretinoin is also used in moderate acne that is unresponsive to conventional treatment and in patients with obvious scarring [1]. Isotretinoin has adverse effects on the mucosae, eyes, skin, liver and the musculoskeletal system. The most common side effects are cheilitis, retinoid dermatitis, xerosis, palmoplantar desquamation, photosensitivity, paronychia, onycholysis and delayed wound healing.

There are only a limited number of studies investigating the effects of isotretinoin on the inner ear [3-7]. The first study on the subject was an experimental study on rats, which demonstrated that retinoic acid may stimulate regeneration of rat auditory hair cells in the ototoxic-poisoned organ of Corti [7]. Later studies measured auditory evoked potentials to investigate the effects of isotretinoin on auditory nerve pathways. They reported increased latencies in the measured potentials, which indicated that isotretinoin may affect these pathways [5,6]. The two most recent studies on the subject have utilized pure tone audiometry in their analyses and found significant post-treatment changes. Among these studies, Ugur *et al.* measured post-treatment values after four months of treatment [4]. Karabulut *et al.*, on the other hand, evaluated their patients weekly after initiation of treatment but did not include otoacoustic emissions (OAE) measurements in their study [3]. It is difficult to compare these studies as they utilized different methods and produced varying results. The aim of this study was to investigate the short-term effects of systemic isotretinoin on the inner ear, using pure tone audiometry and measurement of transient otoacoustic emissions.

Methods

Patients

From September 2012 to May 2013, 40 patients consecutively diagnosed with acne vulgaris, who were unresponsive to other modes of treatment or who had nodulocystic acne or significant scarring, were offered treatment with isotretinoin at the Department of Dermatology at the Dicle University Hospital and were included in this study. The study was approved by the Ethical Committee of Dicle University Faculty of Medicine. Written informed consent for participation in the study was

obtained from all patients. During the first visit, the medical history, demographic information, skin type, body weight, isotretinoin dose, Global Acne Grading Score (GAGS) [8] were recorded and an otological examination was performed in all patients. Exclusion criteria were pregnancy, history of ototoxic drug use, chronic middle ear disease, otologic surgery, Meniere's disease, psychiatric disorder, metabolic disease, autoimmune disease and otoscopic examination revealing a perforated tympanic membrane or other middle ear pathology.

Patients were counseled on the efficacy and side effects of isotretinoin. The daily dose of isotretinoin was 0.3-0.6 mg/kg body weight. The drug was administered twice daily with meals. Laboratory screening was performed just before and one month after starting treatment. Complete blood count, serum aspartate and alanine aminotransferases, total cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein and very-low-density lipoprotein were measured. The patients were seen again 15 days after starting treatment (second visit) and after 30 days of treatment (third visit) and monthly from then on. At each follow-up visit, patients were asked if they had experienced any of the common adverse effects of isotretinoin. The adverse effects and GAGS were recorded at each follow-up visit.

Audiologic measurements

Speech discrimination ability was measured with W-22 word lists using a monitored live voice presentation rather than tape-recorded test materials.

Pure Tone Audiometry

Pure tone audiometry (PTA) (Madsen OB 822 Clinical Audiometer), tympanometry (Clinical Middle Analyzer AZ 26, Interacoustic, Denmark, calibrated to ANSI S3.39-1987 standards) and OAE (Otodynamics Ltd, EZ-screen, Interacoustic, Denmark) were performed at each of the first three visits. Pure-tone air and bone conduction audiometry (250, 500, 1000, 2000, 4000, 6000 Hz) were performed on all subjects. The pure tone average, used to determine hearing loss, was calculated by taking the average of hearing thresholds at 0.5-4 kHz.

The data were processed and evaluated with OAE software (Otoscreen OAE Screening and NOAH based Software, Denmark). Stimuli with a click of 80 μ s duration were used to achieve the transient evoked otoacoustic emissions (TEOAE). The amplitudes according to frequencies (frequency bands from 1 to 5 kHz) and percentages of reproducibility were documented. The TEOAE was considered to be a response if the amplitude reached ≥ 3 dB above the level of the noise. Five

TABLE 1. Mean pure-tone audiometry values in different frequencies

Frequency (Hz)	First visit (I)	Second visit (II)	Third visit (III)
250 Hz	12.9	14.5	13.6
500 Hz	11.4	12.6	12.7
1000 Hz	9.4	10.7	12.9
2000 Hz	12.9	8.6	10.5
4000 Hz	11.1	9.9	13.6
6000 Hz	11.2	11.7	18.5
SDS	96.2	96.1	95.2

SDS: speech discrimination scores

successive frequency bands from 1 to 5 kHz with reproducibility percentages $\geq 60\%$ were considered to be acceptable for analysis. The signal-noise ratio (SNR) for each frequency was calculated.

Statistical Analysis

Analysis of data was performed using SPSS for Windows, version 18.0. Normally distributed data were compared using the paired samples t-test and data without normal distribution were compared using the Wilcoxon Sign Rank test. Data were expressed as mean $\pm$ standard deviation or median and interquartile range, respectively. P values less than 0.05 were considered statistically significant.

Results

Patients

A total of 31 patients (62 ears) completed the study (21 non-pregnant females and 10 males). Nine patients of similar age (five females and four males) did not regularly attend their

clinic visits and were excluded from the study. The mean age of the patients was 21.00 ± 4.1 (Range 15 to 21) years. The mean length of time patients had been diagnosed with acne was 5.56 ± 3.88 (Range 1-15) years. Most patients (74%) had used either topical medications or systemic antibiotics in the past. The mean pretreatment GAGS was 17.68 ± 6.85 . The mean GAGS decreased to 13.75 ± 6.71 after one month of isotretinoin use ($p < 0.05$). The otoscopic examination was normal in all participants. All patients used isotretinoin for six to eight months. The most frequently observed side effects were cheilitis and xerosis. Liver enzymes and lipid parameters remained normal in all patients. Other rare and/or serious side effects of isotretinoin were not encountered.

Audiologic measurements

No alterations in the speech discrimination scores (SDS) were seen in any patients during treatment ($p > 0.05$).

The normal peak compliance, peak pressure, gradient, ear canal volume, and acoustic reflexes were obtained with a 226-Hz probe tone at frequencies of 250, 500, 1000, 2000, 4000

TABLE 2. Results of statistical comparison of means of pure-tone audiometry

Frequency (Hz)	Compared visits	P value*	z-value*
250 Hz	I-II/I-III/II-III	0.219	-1,272
500 Hz	I-II/I-III/II-III	0.220	-628
1000 Hz	I - III	0.020	-2,338
2000 Hz	I- III	< 0.001	-2,358
4000 Hz	I - II	0.008	-1,128
	I - III	0.003	-2,671
6000 Hz	I - II	0.008	-2,925
	I - III	0.006	-2,776
SDS	I-II/I-III/II-III	0.474	-716

* The result of Wilcoxon Sign Rank test

SDS: speech discrimination scores

FIGURE 1. Audiogram of mean values of pure-tone thresholds measured on three visits

and 6000 Hz in all patients before and after isotretinoin treatment. The mean PTA at the first visit was 10.3 ± 5 dB, it was 11.2 ± 5.7 dB on the second visit and 13.6 ± 6.6 dB on the third visit. The bone conduction threshold was taken into consideration since there was no air-bone gap. In pure-tone audiometry, the pre-treatment and post-treatment differences in the 1000, 2000, 4000 and 6000 Hz frequencies were statistically significant ($p < 0.05$). The pure tone audiometric findings and statistical analyses are shown in Table 1 and 2.

The SNR values of the TEOAE at different frequencies were compared. Changes in the TEOAE pre- and post-treatment were not statistically significant ($p > 0.05$). TEOAE findings are summarized in Table 3.

Discussion

In this study, significant differences were found between the pre-treatment and post-treatment hearing thresholds at 1000,

2000, 4000 and 6000 Hz frequencies. The mean hearing threshold of the patients increased after treatment with isotretinoin; however, the differences between the pre-treatment and post-treatment TEOAE of SNR values and SDS were not significant ($p > 0.05$).

Isotretinoin (13-cis-retinoic acid) is an effective drug in the treatment of severe recalcitrant and/or scarring acne [2]. The adverse effects of isotretinoin are well known, but ototoxic effects have also rarely been reported. Documented ototoxic side effects range from relatively benign, such as tinnitus, to more serious, such as sensorineural hearing loss [9]. Lefebvre *et al.* reported that retinoic acid stimulates the in vitro regeneration of the auditory hair cells in ototoxic-poisoned rat organs of Corti [7]. Other research has suggested that the development of the inner ear structures depends on retinoid signalling via the retinoic acid receptors [10]. The embryologic inner ear is sensitive to the effects of retinoids for a limited period of

TABLE 3. Mean SNR values of TEOAE in different frequencies

Frequency (kHz)	First visit (I)	Second visit (II)	Third visit (III)	P value*
1.0 kHz	9.6	9.8	11.3	0.347
1.4 kHz	11.4	12.6	12.7	0.558
2.0 kHz	9.4	10.7	12.9	0.626
2.8 kHz	12.9	8.7	10.5	0.754
4.0 kHz	11.1	9.9	13.6	0.083

* The result of Wilcoxon Sign Rank test

time during development [11]. During this period, either a deficiency or excess of vitamin A can cause malformations [10]. In fact, retinoic acid embryopathy is caused by isotretinoin and most commonly leads to external ear anomalies such as microtia or anotia [12], but may also include sensorineural, conductive or mixed hearing loss. [13] Thus, it seems plausible that the retinoids may have unfavorable effects on the adult ear in addition the known teratogenic effects.

Studies and case reports in the literature suggest that isotretinoin affects hearing [3-7,9,14-17]. Nikiforidis *et al.* [5] investigated auditory brainstem responses in 33 patients with severe nodulocystic acne before and after three weeks of treatment with isotretinoin. Although not statistically significant, subclinical changes were present in three patients after therapy. Aydogan *et al.* [6] observed significant changes in brainstem auditory evoked potentials in 32 patients receiving isotretinoin. Bidgy and Stern [17] described decreased hearing in a patient in a report listing the suspected adverse reactions to isotretinoin among 104 patients. Bilateral sensorineural deafness due to acitretin, another drug of the retinoid group, was documented [15]. Ugur *et al.* [4] reported that isotretinoin can change the bilateral hearing threshold.

This study was undertaken after a patient in our clinic was diagnosed with hearing loss secondary to isotretinoin treatment [9] and a literature search revealed the scarcity of publications on this issue and varying results.

The main difference in our study was the use of auditory measurements with TOAE that objectively measures outer hair cell function. The effect of isotretinoin was examined using pure-tone air and bone conduction audiometry, acoustic reflexes, tympanometry and OAE. OAEs provide objective, stable and frequency-specific information on the function of the outer hair cells in the cochlea. In our study, TOAE was not significantly different after two and four weeks of treatment with isotretinoin; however, the pure tone thresholds were significantly reduced at the middle and high frequencies (1000 Hz, 2000 Hz, 4000 Hz and 6000 Hz) and the SNR values of TEOAE levels decreased to 2.8 and 4.0 mHz levels after treatment. These results are compatible with the study by Ugur *et al.*; however, there was difference in timing of the audiologic tests. In our study, all audiometric tests were performed at after two and four weeks of treatment since our reported case developed hearing loss within days whereas in the study by Ugur *et al.*, audiometric tests were not performed until after four months of treatment. Another interesting result in our study was that there were statistically increased hearing thresholds at both the second and third visits (15 and 30 days) at the higher frequencies (4000 and 6000 Hz). Thus, it seems that the effects

of isotretinoin on hearing do not change much over time; however, there are some case reports that describe hearing loss that was reversible three weeks to two months after withdrawal of isotretinoin. [14, 15] It is possible that isotretinoin could immediately affect hearing and then have an additional long-term cumulative effect.

The term 'ototoxic' refers to any drug with the potential to result in damage to the inner ear structures, including the cochlea, vestibule, semicircular canals and otoliths. Hearing loss usually begins at higher frequencies [3]. Drug-induced damage to the structures of the auditory and balance system can result in hearing loss, tinnitus and dysequilibrium or vertigo. The ototoxic effects of drugs such as aminoglycosides and other antibiotics, platinum-based antineoplastic agents, salicylates, quinine, and loop diuretics have been well-documented and each have different ototoxic properties depending on the dosage and duration of treatment. The ototoxic properties of isotretinoin have not been characterized. Additionally, hearing loss may not be apparent until several weeks or months after the completion of treatment with the offending drug [18]; therefore, it may not be easy to determine the time at which ototoxicity may occur. Classically, isotretinoin is dosed at 0.5 to 1.0 mg/kg/day until a cumulative dose of 120-150 mg/kg has been reached. Since this dosage regimen causes many dose-dependent mucocutaneous and systemic side effects, low-dose and intermittent regimens have been developed. [19] These regimens are effective in moderate to severe acne with a low incidence and decreased severity of side effects.

In contrast to the findings described in this study, Karabulut *et al.* found that the hearing thresholds improved at all frequencies tested at the short-term follow-up visit in patients treated with isotretinoin at a dose of 0.5-0.8 mg/kg for acne vulgaris [3]. They evaluated the efficacy of isotretinoin solely with pure tone audiometers. Erturan *et al.* [16] reported that isotretinoin treatment induces oxidative stress and liver damage by decreasing plasma vitamin E levels and increasing erythrocyte GSH-Px, GSH and liver enzyme values.

In most of the studies on isotretinoin and hearing, pure tone audiometry, auditory evoked potentials and otoacoustic emissions were used to assess hearing. The results of all of the studies may be explained by the conclusion that parts of the hearing pathways other than the outer hair cells are affected by isotretinoin. Isotretinoin may cause either a synaptic malfunction or a conduction defect in the auditory nerve fibers. It is also possible that isotretinoin may have a metabolic effect that alters the retrocochlear nervous system. Although the changes reported in all these studies, including ours, are not clinically significant (i.e., a patient would have trouble differentiating a

2-3 dB change in hearing), the effects of isotretinoin used at higher dosages or for longer time periods on hearing are unknown.

Our study has some important limitations. First, the study population was mostly comprised of young adults. Second, auditory evoked potentials were not measured in our patients, as it is more difficult to obtain patient consent for this procedure. Another limitation was the lack of histopathological evidence. Additionally, the effect of isotretinoin on hearing at different dosages to determine the effect of dosage on the hearing thresholds were not examine, and the patients were not retested after the course of isotretinoin was completed to see if the changes in hearing thresholds were irreversible.

In conclusion, our results suggest that isotretinoin may cause bilateral hearing threshold changes. Screening of hearing functions both clinically and using audiological measurements before initiation of the drug and during treatment may be appropriate. Further animal and human studies with histopathological correlation are required to investigate and characterize isotretinoin-induced neurophysiological alterations in the inner ear.

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