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The effects of isotretinoin on the inner ear in patients with acne vulgaris

Akne vulgaris hastalarında oral izotretinoinin kullanımının iç kulak sistemi üzerine etkileri

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Abstract

Background and Design: Systemic isotretinoin (ISO) is one of the most important treatment agents that are used in nodulocystic acne treatment. It has many effects on many systems of the body. Previous studies reported positive and negative results related to systemic ISO and its effects on hearing. Thus, this study aimed to investigate the effects of systemic ISO on hearing functions.
Materials and Methods: This study included 53 patients with acne vulgaris (106 ears) that were treated with 0.8 mg/kg oral ISO for 6 months. Pure tone audiometry (PTA), speech discrimination test (SD), and distortion product otoacoustic emission (DPOAE) tests were performed.
Results: No significant differences were found in the mean SD and PTA threshold values between the pre-treatment period, after 3 months of treatment, and 4 months after the end of treatment. Statistically significant increases were detected in the amplitudes at 6,000, 8,000, and 10,000 Hz frequencies when DPAOE values in 3 months of treatment were compared with the pre-treatment DPAOE values; however, no significant differences were detected in the DPAOE values between the pre-treatment and 4 months after the end of treatment.
Conclusion: Systemic ISO increased DPOAE amplitudes during the treatment in patients with acne; however, these changes returned to pre-treatment levels in 4 months after the end of treatment. Our results indicate that ISO treatment has temporary effects on DPOAE values, which is an important parameter in measuring the cochlear function. Therefore, ISO seems a safe and well-tolerated agent for the auditory system.
Keywords: Isotretinoin, acne vulgaris, inner ear

Öz

Amaç: Sistemik izotretinoin (İSO), nodülokistik akne tedavisinde kullanılan en önemli tedavi ajanlarından biridir. Pek çok sistem üzerine birçok yan etkisi vardır, bunlardan biri nadiren bildirilen işitme sistemidir, ayrıca önceki çalışmalarda sistemik İSO ve işitme sistemi üzerine etkisi ile ilişkili olumlu ve olumsuz sonuçlar bildirilmiştir. Bu çalışmada sistemik İSO'nun işitme fonksiyonu üzerine olan etkilerini araştırmayı amaçladık.
Gereç ve Yöntem: Çalışmaya 6 ay süreyle 0,8 mg/kg oral İSO ile tedavi edilen 53 akne vulgaris hastası (106 kulak) dahil edildi. Saf ses odyometrisi, konuşmayı ayırt etme testi (SD) ve bozulma ürünü otoakustik emisyon (DPOAE) değerleri sağ ve sol kulak için ayrı ayrı bakılarak ortalama değerleri alındı.
Bulgular: SD ve ortalama saf ses eşiklerinde (PTA) tedaviden önce, tedavinin 3. ayı ve tedaviden sonra 4. ay arasında anlamlı bir fark bulunmadı. Ek olarak, tedavinin üçüncü ayındaki DPAOE değerleri, tedavi öncesi DPAOE değerleri ile kıyaslandığında 6.000, 8.000 ve 10.000 Hz frekanslarda istatistiksel olarak anlamlı bir amplitüd artışı görüldü ancak tedaviden sonraki 4. ay ile tedavi öncesi DPAOE değerleri arasında anlamlı bir fark saptanmadı.
Sonuç: Sonuçlarımız bize İSO tedavisinin koklear fonksiyonu ölçme açısından önemli bir parametre olan DPOAE değerleri üzerine geçici bir etki yaparken, SD ve PTA üzerinde herhangi bir değişikliğe yol açmadığını göstermiştir. Sonuç olarak, İSO'nun işitme sistemi açısından güvenli ve iyi tolere edilebilen bir ajan olduğu görülmektedir. Bu nedenle, sistemik İSO'nun kalıcı ototoksik etkilerinin olmadığı ve hatta işitmeyi geçici olarak olumlu yönde etkilediği için klinisyenlerin şiddetli akne tedavisinde çok etkili olan bu ilacı işitme sistemi açısından güvenle kullanabileceğini düşünmekteyiz.
Anahtar Kelimeler: İzotretinoin, akne vulgaris, iç kulak

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Introduction

Acne vulgaris is an inflammatory disease of the pilosebaceous unit and has multiple pathogeneses along with follicular epidermal hyperproliferation, increased sebum production, inflammation, and presence of *Propionibacterium acnes (P. acnes)*. Isotretinoin [(ISO), 13-cis retinoic acid] is a retinoid and a synthetic vitamin A analog[1], which reduces sebum production from the sebaceous glands and the size of these glands at significant levels, normalizes follicular keratinization and prevents the development of micro- and macro-comedones. Additionally, the suppression in sebum production causes follicular micro-surface changes, indirectly causing a decreased number of *P. acnes*[2,3]. ISO is the most important agent that is effective in all these stages; however, its effect on many systems remains controversial[1].

Retinoids play roles in embryonic development, vision, reproduction, bone formation, hematopoiesis, metabolism, growth, and differentiation of various cells, apoptosis, and carcinogenesis[4]. ISO, which is a retinoid, has been widely used in severe cystic or persistent acne vulgaris treatment since 1982[2,4]. The use of ISO is increasing day by day; however, several case reports regarding its side effects are presented in the literature, and new studies are needed.

The pure tone audiometry (PTA) is the basis of audiology, evaluates the whole hearing system, and provides data in all hearing systems from the external auditory canal to the auditory cortex.

Otoacoustic Emissions (OAEs) are very low-intensity sound waves that originate from the outer hair cells (OHCs) in the cochlea and can be recorded with a microphone that is inserted in the external auditory canal. They were first suggested by Kemp[5], and acoustic energies are measured from the cochlea in the presence of normal or near-normal hearing. A loudspeaker is inside the inserted probe in the outer ear canal that gives stimuli, and a microphone records the responses generated in the cochlea and transmitted to the outer ear as a response to these stimuli. This sound energy coming from the OHCs is reflected from the middle ear and outer ear canal and recorded in the presence of a healthy outer ear, middle ear, ear ossicles, and cochlea. It is then converted into an electrical signal and averaged and analyzed on a computer. The OAEs test is a noninvasive, highly reliable, cheap, and objective audiological test, which does not require the active participation of the patient, and gives results in a short time.

The OHCs of the cochlea are the first part of the auditory system[6]. Thus, changes in OAE amplitude may reflect early damage in the cochlear OHCs. Lutman and Hall[7] reported that the OAE test was two-fold more sensitive compared to PTA in detecting hearing threshold level changes.

Nair and Kashyap.[8] revealed that OAE could reflect the changes in the OHCs even when they were still undetectable in PTA. Therefore, OAE can be used as a superior diagnostic predictor for hearing losses compared to PTA. Abnormally low OAE response amplitudes may indicate higher risks of hearing loss development[9].

ISO is known to have negative effects on the mucosa, eyes, skin, liver, and musculoskeletal system[10]. However, studies in the literature that explain its effects on the inner ear are limited[11,12]. Some studies assert that ISO affects hearing positively, whereas some argue that it has adverse effects. Therefore, this study aimed to determine the effects of oral ISO on the inner ear and auditory system with a larger number of participants and determine the persistence of these effects after the end of treatment.

Materials and Methods

Patients

This study included 59 patients aged 18-28 years, who received oral ISO treatment for acne vulgaris between August 2020 and April 2021. One patient was excluded from the study since the drug was discontinued because of its side effects (liver enzyme elevation) and five patients since they did not arrive for follow-ups. After obtaining the approval of the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval number: 2020/6-47, date: 23.06.2020), all participants were informed about the side effects of oral ISO, and written consent forms were obtained. Those who had suspected pregnancy, psychiatric disease history, liver and kidney dysfunction or a serious systemic disease, history of ototoxic drug use, ear surgery history, and eardrum perforation or middle and external ear pathologies at the otoscopic examination were excluded from the study. A total of 53 patients and 106 ears were included in the study. The demographic characteristics, acne duration, skin type, and medical disease history of patients were noted and acne severity scored according to the Global Acne Severity Score with a detailed dermatological examination. PTA (125 Hz to 8000 Hz) and speech discrimination test (SD) were performed to determine the hearing loss in participants. Then, the distortion product otoacoustic emission (DPOAE) test was performed on all patients at 500-10000 Hz. Tests were repeated at 3 months of treatment and in 4 months after the end of treatment.

The daily oral ISO dose was initiated at 0.5 mg/kg/day, continued at 0.80 mg/kg/day after 1 month, and this dose was continued for 5 months. The hemogram, liver and kidney function tests, and lipid profiles were regularly evaluated before and every month after the treatment initiation. Female patients were tested for beta-human chorionic gonadotropin. Patients were evaluated every month by the same doctor during the treatment period, possible side effects were questioned, and patients were informed about the emerging side effects.

Audiologic measurements

PTA and SD were performed using a diagnostic audiometer (Interacoustics AC 40, Clinical Audiometer, Denmark) in a sound-treated cabin. Air conduction pure tone thresholds were measured from 250 to 8000 Hz, and bone conduction thresholds were measured from 500 to 4000 Hz for both ears. Speech discrimination ability was measured with a Single-Syllable Words List using a monitored live voice presentation.

DPOAEs were measured using Madsen Capella[2] equipment (GN Otometrics, Denmark). Data were processed and evaluated with OAE software (OtoscreenOAE Screening and NOAH-based Software, Denmark). Frequencies were examined from 500 to 10000 Hz (500, 1000, 2000, 4000, 6000, 8000, and 1000 Hz). A ±2 standard deviation signal-noise ratio (SNR) was achieved for each frequency by calculating the difference between distortion products and noise.

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences version 22 program. The distribution pattern of data was analyzed using the Kolmogorov-Smirnov test and the Histogram Normality test. Non-parametric tests were used for data that did not comply with the normality test criterion.

Considering that the administered drug was systemic and without clinical and statistical difference between the two ears, a comparison was made by taking the average measurements of both ears.

The comparisons of SD and PTA values before the treatment, in 3 months of treatment, and 4 months after the end of treatment were made using the Friedman-Rank Two-Way Analysis of Variance. DPOAE amplitude values before and 4 months after the treatment were analyzed using the Wilcoxon signed ranks test because the data were not normally distributed. Statistical significance was taken as p-values of <0.05. The spearman correlation test was used for the relationship between acne severity and duration with DPOAE test.

Results

No significant side effects were detected based on 6-month oral ISO use in the patients. The most common side effects were cheilitis, dryness, and xerosis. The mean age of participants was 20.51±2.486 (18-27) years, and 38 (71.7%) of them were females and 15 (28.3%) were male.

The otoscopic examinations of patients were normal before the treatment, 3 months of treatment, and 4 months after the end of treatment. The right and left ears of patients were separately tested in all three periods, and the obtained mean values from the PTA and SD test of the right and left ears were noted. SD scores and mean PTA scores were within normal limits in all patients at all periods.

The mean values of the PTA and SD before the treatment, after 3 months of treatment, and 4 months after the end of treatment are shown in Table 1. No statistically significant difference was found (p>0.05).

Statistically significant increases were detected in DPOAE amplitudes at 6000, 8000, and 10000 Hz in 3 months of treatment compared to the pre-treatment values (p<0.05) (Table 2). No statistically significant differences were detected in DPOAE amplitude values between pre-treatment and 4 months after the end of treatment (p>0.05) (Table 3).

The results of the correlation analysis between global acne score severity and acne duration, with DPOAE amplitudes, are shown in Table 4. No significant correlations were detected between acne severity, acne duration, and DPAOE values (p>0.05) (Table 4).

Table 1. Comparison of PTA values (mean pure tone audiometry values in different frequencies) and SD values between pre-treatment, 3 months of treatment, and 4 months after the end of treatment

	SD	PTA
Pre-treatment	94.0 (91.0-99.0)	11.5 (6.0-18.0)
After 3 months of treatment	94.0 (90.0-98.0)	11.0 (6.50-17.0)
4 months after the end of treatment	94.0 (89.0-98.0)	11.0 (6.0-17.0)
P-value[a]	0.15	0.08

Median (minimum-maximum) values were presented in cases because not normally distributed data. Analyzed by[a] Friedman test. P<0.05 is significant, SD: Speech discrimination, PTA: Pure tone audiometry

Table 2. Comparison DPOAE amplitudes and SNR according to frequencies between pre-treatment and after 3 months of treatment

	Average values of both ears		
Frequency (Hz)	**Pre-treatment**	**After 3 months of treatment**	**p**
500 SNR	5.0 (-11-14)	4.0 (-9-14)	0.33
500 DP	13.5 (-3.50-38.00)	16.5 (-10.0-38.5)	0.41
1000 SNR	15.5 (-7.00-37.00)	15.5 (-8.0-36.0)	0.62
1000 DP	13.5 (-6.00-37.00)	16.0 (-5.5-37.0)	0.31
2000 SNR	21.0 (-8.0-40.0)	18.0 (-3.5-45.0)	0.11
2000 DP	11.5 (-10.5-34.5)	13.0 (-19.0-34.0)	0.74
4000 SNR	15.5 (1.5-41.0)	12.5 (-6.5-29.5)	<0.06
4000 DP	2.0 (-22.5-17.0)	2.0 (-11.5-20.5)	0.09
6000 SNR	13.0 (-11.5-40.5)	11.0 (-8.5-35.5)	0.73
6000 DP	-0.5 (-21.0-20.5)	2.5 (-19.0-25.5)	**0.02**
8000 SNR	11.0 (-8.0-27.5)	8.5 (-5.5-26.5)	0.19
8000 DP	-5.0 (-18.0-15.5)	-3.5 (-19.5-15.0)	**0.04**
10000 SNR	9.0 (-11.5-23.0)	7.0 (-6.5-20.0)	0.33
10000DP	-2.0 (-25.5-16.5)	2.0 (-15.5-21.5)	**0.01**

Median (minimum-maximum) values were presented in cases because the data were not normally distributed. Analyzed by Wilcoxon sign rank test. P<0.05 is significant. DPOAE: Distortion product otoacoustic emission, SNR: Signal-noise ratio

Discussion

Acne vulgaris is an inflammatory dermatosis that affects the quality of life in the vast majority of the population. Many treatment modalities were suggested for this dermatosis; however, oral ISO is an effective agent and its treatment success improves the socialization and quality of life in patients with acne at a great deal[13,14].

Oral ISO has effects on cellular growth, differentiation, and immune-modulatory functions[15,16]. The inner ear can be affected by retinoids for a short duration during embryological development. Studies reported that low or excessive vitamin A in the embryological period may cause inner ear malformation[16]. Some other studies in the literature reported that retinoids can negatively affect the hearing of adults[17], whereas some speculated that retinoic acid may yield positive results for hearing restoration in hearing loss that results from noise exposure[12].

ISO is routinely administered as 0.5-1 mg/kg/day and 120-150 mg/kg as a cumulative dose in treatment[18]. This dose has the highest effect in acne treatment with the least side effect. Our study administered the treatment at an average dose of 0.8 mg/kg/day for 6 months. We tried to detect the effects of ISO on the inner ear by administering the treatment for a long time at a higher dose than the average dose.

The effects of some medical agents on the inner ear can be seen within weeks after the treatment ends. Following the patients for longer times after the end of treatment is necessary to evaluate the drug effects on hearing since the elimination time of ISO from the body is long. Therefore, our study reevaluated the hearing at 4 months after the end of 6-month ISO treatment in the young patient group who did not have any hearing loss complaints.

PTA, which is the gold standard method in hearing evaluation, is subjective and time-consuming and is also based on patient

Table 3. Comparisons of DPOAE amplitudes and SNR according to frequencies between pre-treatment and 4 months after the end of treatment

	Average values of both ears		
Frequency (Hz)	**Pre-treatment**	**4 months after the end of treatment**	**p**
500 SNR	5.0 (-11-14)	5.5 (-10-18)	0.63
500 DP	13.5 (-3.50-38.00)	12.5 (-2.5-39.0)	0.16
1000 SNR	15.5 (-7.00-37.00)	15.5 (-8.0-38.0)	0.13
1000 DP	13.5 (-6.00-37.00)	13.0 (-5.5-37.0)	0.39
2000 SNR	21.0 (-8.0-40.0)	21.0 (-9.0-42.0)	0.25
2000 DP	11.5 (-10.5-34.5)	11.0 (-10.5-34.5)	0.19
4000 SNR	15.5 (1.5-41.0)	15.0 (1.5-41.0)	0.28
4000 DP	2.0 (-22.5-17.0)	2.0 (-23.5-18.0)	0.11
6000 SNR	13.0 (-11.5-40.5)	13.0 (-12.5-41.0)	0.48
6000 DP	-0.5 (-21.0-20.5)	-0.5 (-23.0-21.5)	0.45
8000 SNR	11.0 (-8.0-27.5)	11.0 (-11.0-28.5)	0.24
8000 DP	-5.0 (-18.0-15.5)	-5.0 (-20.0-15.5)	0.58
10000 SNR	9.0 (-11.5-23.0)	9.0 (-12.5-25.0)	0.92
10000 DP	-2.0 (-25.5-16.5)	-2.0 (-27.5-15.5)	0.41

Median (minimum-maximum) values were presented in cases because the data were not normally distributed. Analyzed by wilcoxon sign rank test. Analyzed by Wilcoxon sign rank test $p<0.05$ is significant. DPOAE: Distortion Product Otoacoustic Emission, SNR: Signal-noise ratio

Table 4. The relationship between hearing frequencies and disease duration, severity in patients with acne vulgaris

Hertz	Acne severity score		Acne duration (year)	
	Spearman's R	**p**	**Spearman's R**	**p**
500 DP	-0.19	0.15	-0.22	0.10
500 SNR	0.12	0.23	0.09	0.53
1000 DP	-0.07	0.60	-0.07	0.57
1000 SNR	0.06	0.65	0.08	0.56
2000 DP	-0.07	0.60	0.02	0.88
2000 SNR	0.10	0.43	0.09	0.48
4000 DP	-0.07	0.60	-0.10	0.47
4000 SNR	-0.14	0.28	-0.12	0.36
6000 DP	-0.09	0.50	-0.15	0.27
6000 SNR	-0.14	0.31	-0.18	0.19
8000 DP	0.10	0.47	0.05	0.71

Analyzed by spearman correlation test. DPOAE: Distortion Product Otoacoustic Emission, SNR: Signal-noise ratio

compliance, and the device must be calibrated by specialists at certain intervals[19].

PTA has become routine clinical practice at frequencies ranging between 250 and 8000 Hz, and the evaluation of hearing sensitivity beyond 8000 Hz is less preferred. High-frequency (>8000 Hz) PTA is used to determine the severe threshold changes caused by ototoxicity[20,21]. Therefore, we believe that the evidence value is low in studies that only used routine PTA, wherein high frequencies are not evaluated, and objective hearing tests, such as OAE, are not employed. Our study examined the audiometry values in the range of 250 and 8000 Hz and evaluated the extended hearing scores within the range of 500-10000 Hz with the DPAOE test for patients with normal hearing thresholds, unlike other studies.

DPOAE test is an objective, noninvasive, fast, and easy audiological test to apply. Extended DPOAE, which also includes high frequencies, is more sensitive and has a high negative predictive value in detecting early changes in the cochlea in high-frequency hearing loss. DPOAE was reported to predict the onset of hearing loss, and amplitude changes occur in DPOAE in healthy adults before detecting the changes in PTA[22]. We did not find any significant differences in PTA thresholds in all three measurements in our study; however, the differences in DPOAE values between pre-treatment and after 3 months of treatment were statistically significant.

Few studies investigated the effects of ISO on the inner ear. Some studies speculated that oral ISO intake positively affects the hearing values[12], whereas some others argue that they have adverse effects[17,23]. Our study revealed that the use of oral ISO had temporary partial and positive effects on hearing functions at some frequencies (6000, 8000, and 10000); however, this returned to the pre-treatment values 4 months after treatment termination.

Retinoids play roles as endogenous signaling molecules at different stages of inner ear development[23], not only in the embryological development of the inner ear but also as a protective agent after birth. Some sources speculated that retinoic acid regenerates cochlear hair cells due to ototoxic drug damage. This role of retinoids can provide us a clue on why and how the use of ISO, which is a retinoid analog, affects hearing thresholds[24,25].

The animal trial by Lefebvre et al.[25] reported that retinoic acid provided inner hair cell regeneration. Another animal experiment, which used rats, reported that retinoic acid stimulated hair cell regeneration in the inner ear, and was necessary for a normal Corti organ development[24]. Our study revealed that DPAOE amplitudes increased after 3 months of treatment compared to the pre-treatment values.

Akdag et al.[11] planned 6-8-month ISO treatment for 31 patients. They applied 250-6000 Hz PTA, SD, and transient evoked otoacoustic emissions (TEOAE) in the pre-treatment, 15 days after treatment initiation, and after 30 days of treatment[11]. In PTA, the differences in 1000, 2000, 4000, and 6000 Hz frequencies were statistically significant. However, they detected no significant differences in the TEOAEs that were examined between SD and 1000-4000 Hz. Our study revealed significant differences at 6000, 8000, and 10000 Hz DPOAE frequencies above 4000 Hz; however, no differences were detected in PTA thresholds and SD values.

Additionally, our study was the first in comparing DPOAE and SNR test values, which are among more important parameters to determine hearing functions, before, at 3 months of treatment, and 4 months after the end of treatment.

Nikiforidis et al.[26] performed an Auditory Brainstem Responses investigation on 33 patients who received ISO treatment before and 3 weeks after treatment initiation. They detected an increase in latencies and interpeak latencies and a decrease in amplitudes; however, these were not statistically significant. They speculated that these subclinical changes might have occurred because of the effects of ISO on auditory nerve fibers. However, their measurements were not repeated in the later months or after the treatment; and the continuation of the long-term effects of the drug was not shown.

Ugur et al.[17] treated 23 patients with acne vulgaris using systemic ISO at 5 mg/kg. PTA, TEOAE, and DPOAE were evaluated before using ISO and after 4 months of treatment. They revealed significant differences in all frequencies in PTA, which was examined at 25-16000 Hz frequencies. They could not detect any significant differences in DPOAE and SNR values at frequencies between 500 and 8000 Hz and in TEOAE amplitudes at frequencies between 1000 and 5000 Hz[17]. However, post-treatment evaluations were not made in this study, and data of continuous effects after drug discontinuation is unavailable.

A study by Yaldız et al.[27] included 30 patients with acne and performed DPOAE (750-8000 Hz) and PTA (500-8000 Hz) tests before and at the end of 6 months. No statistically significant differences were detected at any frequencies in the pre-treatment and post-treatment result comparison[27]. However, the frequencies above 8000 Hz were not evaluated in this study, and measurements were not repeated after drug termination.

Karabulut et al.[12] examined the effects of PTA at 250-20000 Hz frequencies in 38 patients with acne before the treatment, and in 1, 2, and 3 weeks and revealed that ISO improved the hearing levels of patients in all frequencies. However, their measurements were not repeated at the end of the treatment or after drug termination, and no data were reported on the permanent or temporary positive effects of the treatment.

As mentioned above, the data published on the systemic effects of ISO on the auditory system is contradictory. Additionally, important variables that affect the study results might occur at different times of hearing measurement procedures during the treatment, and audiometric tests, such as PTA, may be subjective. To the best of our knowledge, the only study that evaluated the effects of ISO systemic on the hearing system after the end of treatment was conducted by Kemeriz et al.[28]. Pure tone thresholds were found to increase at significant levels at 8000 Hz in the third-month measurement, and this change improved in the measurement at 6 months after drug termination. Thus, they speculated that ISO might have a temporary short-term ototoxic effect[28]. However, they examined only PTA values between 250 and 8000 Hz, and high frequencies and OAEs were not evaluated.

Studies in the literature revealed the effects of many dermatological diseases and treatments on hearing. The evaluation of studies in acne treatment revealed that the most important purpose in planning our study was to evaluate the effect of ISO in a larger number of patients and longer follow-ups. While doing this, we wanted to use a diagnostic test that is both objective and can detect changes in the earlier period. Additionally, the effect of cochleotoxic drugs in the early period is more seen in high frequencies (4000 Hz and above), and the patient does

not notice hearing loss when there is no loss in speech frequencies (at 250-4000 Hz). Therefore, high frequencies are extremely important in studies where hearing is evaluated. Our study used the DPAOE test in addition to PTA and SD tests and frequencies between 250 and 10000 Hz were measured. A significant difference was also detected in these high frequencies. Additionally, patients were evaluated with the same test 4 months after the end of the treatment unlike other studies, and the continuous effects of ISO after the treatment were evaluated and its effect was found to be reversible. Therefore, we think that our study is the most comprehensive and objective study among all acne-hearing studies.

As a result, our study was the first study conducted in patients with acne using oral ISO, with the highest number of patients, in which PTA and DPOAE tests were examined before, during, and after the end of treatment. According to our results, systemic ISO treatment caused increased DPAOE amplitudes, especially at high frequencies (6000, 8000, and 10000 Hz). We found that oral ISO had partial positive effects on hearing and inner ear functions, which recovered 4 months after the end of the treatment. From our result evaluations, we believe that oral ISO does not permanently affect hearing and inner ear structures, positively or negatively.

Therefore, we believe that systemic ISO will not have permanent ototoxic effects, and clinicians can safely use this very effective drug in the treatment of patients with severe acne. Additionally, we believe that routine audiometric hearing tests are unnecessary before and during ISO treatment unless patients have hearing symptoms.

Study Limitations

The most important limitation of our study was that the high-frequency audiometry was not evaluated. However, significant differences were found in high-frequency DPAOE, thus new studies can be designed to evaluate high-frequency PTAs. Additionally, different doses were not investigated to determine the dose-dependent effects of ISO on hearing thresholds.

Conclusion

Therefore, further histopathological studies can be conducted to elucidate the action mechanisms of systemic ISO on hearing function and investigate the neurophysiological changes in the inner ear. Additionally, studies that compare different ISO doses with a higher number of patients may contribute to the literature.

Ethics

Ethics Committee Approval: The study was approved by the Adıyaman University Non-Interventional Clinical Research Ethics Committee (approval number: 2020/6-47, date: 23.06.2020).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.İ.D., Concept: E.İ.D., Design: E.İ.D., Data Collection or Processing: Ö.Y.A., Analysis or Interpretation: Ö.Y.A., Literature Search: Ö.Y.A., Writing: E.İ.D.

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References

1. Layton A: The use of isotretinoin in acne. Dermatoendocrinol 2009;1:162-9.
2. Brelsford M, Beute TC: Preventing and managing the side effects of isotretinoin. Semin Cutan Med Surg 2008;27:197-206.
3. Thielitz A, Krautheim A, Gollnick H: Update in retinoid therapy of acne. Dermatol Ther 2006;19:272-9.
4. Lotan R: Retinoids and apoptosis: Implication for cancer chemoprevention and therapy. J Natl Cancer Inst 1995;87:1655-7.
5. Kemp DT: In active processes and otoacoustic emissions in hearing. Otoacoustic emissions: Concepts and origins. New York. Springer; 2008; pp. 1-38.
6. Bohne BA, Kimlinger M, Harding GW: Time course of organ of Corti degeneration after noise exposure. Hear Res 2017;344:158-69.
7. Lutman MH, Hall AJ: Novel methods for early identification of noise-induced hearing loss. Sudbury: HSE Books; 2000.
8. Nair S, Kashyap RC: Prevalence of noise induced hearing loss in indian air force personnel. Med J Armed Forces India 2009;65:247-51.
9. Merve Batuk, Batuk İT: Otoakustik emisyon uygulamaları. In: Sennaroglu G, Yücel E, Türkyılmaz MD, Çiçek Çınar B, Batuk M, (eds). Odyoloji Klinik Uygulama Protokolleri. Türkiye: Hipokrat Kitabevi; 2019.
10. Charakida A, Mouser PE, Chu AC: Safety and side effects of the acne drug, oral isotretinoin. Expert Opin Drug Saf 2004;3:119-29.
11. Akdag M, Akkurt ZM, Gul A, et al.: The effects of oral isotretinoin (13-Cis retinoic acid) on the inner ear: A prospective clinical study. Clin Invest Med 2014;37:E102-7.
12. Karabulut H, Karadag AS, Acar B, et al.: The effect of oral isotretinoin (13-cis retinoic acid) on hearing systems in patients with acne vulgaris: a prospective study. Int J Dermatol 2011;50:1139-43.
13. Yesilova Y, Bez Y, Ari M, Turan E: Effects of isotretinoin on social anxiety and quality of life in patients with acne vulgaris: A prospective trial. Acta Dermatovenerol Croat 2012;20:80-3.
14. Brito Mde FM, Sant'Anna IP, Galindo JCS, de Melo Rosendo LHP, dos Santos JB: Evaluation of clinical adverse effects and laboratory alterations in patients with acne vulgaris treated with oral isotretinoin. An Bras Dermatol 2010;85:331-7.
15. Bigby M, Stern RS: Adverse reactions to isotretinoin. A report from the adverse drug reaction reporting system. J Am Acad Dermatol 1988;18:543-52.
16. Romand R, Hashino E, Dolle P, Vonesch JL, Chambon P, Ghyselinck NB: The retinoic acid receptors RARalpha and RARgamma are required for inner ear development. Mech Dev 2002;119:213-23.
17. Ugur KS, Erpolat S, Kurtaran H, Ark N, Sarifakioglu E, Gunduz M: The effects of oral isotretinoin (13-Cis retinoic acid) on the inner ear: A clinical study. J Int Adv Otol 2012;8:339-44.
18. Selçuk LB, Arıca DA, Şahin HB, Yaylı S, Bahadır S: The prevalence of sacroiliitis in patients with acne vulgaris using isotretinoin. Cutan Ocul Toxicol 2017;36:176-9.
19. International Standardization Organization (ISO) 389-1. Acoustics-Reference zero for the calibration of audiometric equipment-Part 1: Reference equivalent threshold sound pressure levels for pure tones and supra-aural earphones. (1998, accessed 30 May 2014). www.iso.org/obp/ui/#iso:std:iso:389:-:ed-1:v1:en
20. Fausti SA, Larson VD, Noffsinger D, et al.: High-frequency audiometric monitoring strategies for early detection of ototoxicity. Ear Hear 1994;15:232-9.
21. Fausti SA, Henry JA, Helt WJ, et al.: An individualized, sensitive frequency range for early detection of ototoxicity. Ear Hear 1999;20:497-505.
22. Murthy VA, Kalyan GK: Effects of ageing on otoacoustic emission. Indian J Otolaryngol Head Neck Surg 2013;65:477-9.
23. Aydogan K, Karli N: Effects of oral isotretinoin therapy on peripheral nerve functions: A preliminary study. Clin Exp Dermatol 2007;32:81-4.
24. Romand R: The roles of retinoic acid during inner ear development. Curr Top Dev Biol 2003;57:261-91.

25. Lefebvre PP, Malgrange B, Staecker H, Moonen G, Van de Water TR: Retinoic acid stimulates regeneration of mammalian auditory hair cells. Science 1993;260:692-5.
26. Nikiforidis G, Tsambaos D, Karamitsos D, Koutsojannis C, Georgiou S: Effects of oral isotretinoin on human auditory brainstem response. Dermatology 1994;189:62-4.
27. Yaldız M, Kara A, Güven M, Solak B, Kara R, Erdem MT: Assessment of auditory function and lipid levels in patients receiving oral isotretinoin (13-cis retinoid) therapy for acne vulgaris. Postepy Dermatol Alergol 2020;37:360-3.
28. Kemeriz F, Kayabaşı S, Cemil B, Hızlı Ö: Evaluation of oral isotretinoin effects on hearing system in patients with acne vulgaris: Reversible or not? Dermatol Ther 2021;34:e14640.