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The Effects of Oral Retinoids on Hearing Status: A Prospective Clinical Study

Oral Retinoidlerin İşitme Düzeyi Üzerine Olan Etkileri: Prospektif Bir Klinik Çalışma

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ABSTRACT Objective: The main purpose of this study was to analyse the effects of oral isotretinoin and acitretin, on hearing functions detected by serial odiometric examinations. **Material and Methods:** A total of thirty patients with moderate acne vulgaris and other thirty patients diagnosed as psoriasis vulgaris with a PASI score between 30-50% were included in this study. Isotretinoin and acitretin were prescribed for acne vulgaris and psoriasis vulgaris, respectively. The hearing of patients were tested with pure tone odiometric examination before, at the first and third months of the treatment in the remaining 55 patients (110 ears). The differences between the mean values of pretreatment and posttreatment pure tone hearing thresholds at 500, 1000, 2000, 4000, 8000 and 10000 Hz frequencies were evaluated for each group. **Results:** No significant difference was detected between the mean values of the pretreatment and posttreatment pure tone hearing thresholds of acitretin group ($p>0.05$); while in the isotretinoin group, a significant difference was detected between the pretreatment and posttreatment values at 500 Hz frequencies at first and third months of the treatment which was progressively decreasing ($p<0.05$). **Conclusion:** It can be concluded that, according to the results of our study, acitretin has no significant effect on hearing systems, while isotretinoin may lead to bilateral hearing threshold changes in a period of three months.

Keywords: Acitretin; hearing loss; isotretinoin; pure tone audiometry

ÖZET Amaç: Bu çalışmanın amacı, oral izotretinoin ve asitretinin işitme fonksiyonları üzerine olan etkilerinin seri odyometrik incelemelerle değerlendirilmesidir. **Gereç ve Yöntemler:** Orta şiddetli akne vulgaris tanısı olan 30 hasta ve PASI skoru % 30-50 arasında değişen 30 psoriazis vulgaris tanılı hasta çalışmaya dahil edildi. Akne vulgaris tanılı hastalara izotretinoin, psoriazis tanılı olanlara asitretin tedavileri verildi. Asitretin grubunda beş hasta yan etkiler ve düzensiz takipler nedeniyle çalışmadan çıkarıldı. Hastaların işitme düzeyleri tedavinin başlangıcı, birinci ve üçüncü aylarında saf ton odyometrik inceleme ile değerlendirildi. Her grup için tedavi öncesi ve tedavi sonrası saf ses işitme eşikleri ortalamaları arasındaki fark 500, 1000, 2000, 4000, 8000 ve 10000 Hz frekanslarında değerlendirildi. **Bulgular:** Asitretin grubunun tedavi öncesi ve tedavi sonrası saf ton işitme eşik değerlerinin ortalama değerleri arasında anlamlı fark bulunmazken ($p>0,05$); izotretinoin grubunda , tedavinin birinci ve üçüncü aylarında 500 Hz frekanslarında tedavi öncesi ve tedavi sonrası değerler arasında anlamlı bir fark olduğu saptandı ($p <0,05$). **Sonuç:** Sonuç olarak, çalışmamızın bulguları, asitretinin işitme sistemleri üzerinde anlamlı bir etkisi olmadığını, izotretinoinin ise üç aylık bir süre içinde bilateral işitme eşiği değişikliklerine neden olabileceğini göstermiştir.

Anahtar Kelimeler: Asitretin; işitme kaybı; izotretinoin; saf ton odyometri

Isotretinoin and acitretin are derivatives of vitamin A. Isotretinoin is a first line treatment in nodulocystic acne, while acitretin is one of the first option treatments in moderate to severe psoriasis.[1,2] Retinoids, which are functional and structural analogues of vitamin A, have multiple

effects on cellular differentiation and proliferation, the immune system and embryonic development. There are three generations of synthetic retinoids and isotretinoin belongs to the first and acitretin belongs to the second generation, respectively.[3]

Isotretinoin and acitretin are both effective medications which are commonly used in daily practice, but they also have many side effects. Teratogenicity and an increase in the rate of spontaneous abortion are the most serious and annoying side effects.[4] The most common side effect of retinoids is the mucocutaneous side effects which is dose dependent.[3] They may also have many side effects on the other organ systems.[4] Although the adverse effects of retinoids are well known, only few reports and studies are available about their ototoxic effects.[1,2,5-7]

The main purpose of the present study was to determine the influence of isotretinoin and acitretin on hearing status, by using serial pure tone audiometric measurements.

MATERIAL AND METHODS

Thirty patients with acne vulgaris and other 30 patients with psoriasis vulgaris diagnosed and treated in the Department of Dermatology were included in the study. The local ethics committee approval was obtained prior to the study (EPKK-3870; 01.02.2012-0451). The study has been carried out in accordance to Helsinki Declaration Criteria. Patients with moderate acne were included in the first group and psoriasis patients with a PASI score of 30-50% were included in the second group. Male or non-pregnant female patients were included in the study. Young female patients had a negative serum pregnancy test before starting the therapy, and they were also informed to use at least two effective methods during the treatment of birth control other than oral contraceptives. Exclusion criteria were as follows: being younger than 18 years, having alcohol abuse or smoking history, a history of using any vitamin A supplements, presence of any psychiatric disorders, ototoxic drug usage, noise exposure, a history of ear surgery or chronic middle ear disease, Menier's disease, cranial trauma; metabolic and autoimmune diseases. Otoscopic examinations were performed carefully prior to the treatment, and the ones who have the otoscopic evidence of any pathology were not included in the study. After the careful investigations and physical examination, a dose of 0.5-0.75 mg/kg isotretinoin was prescribed for the first group; and 0.5-0.75 mg/kg acitretin was prescribed for the second group. The duration of treatment was at least three months. The drugs were administered twice a day with or after the meals. A detailed biochemical analysis was performed just before commencement of treatment and monthly thereafter. Five patients in the second group (acitretin group) were excluded from the study because of adverse effects of the drug and inconsistent follow-up. Hearing status of all patients were evaluated by anamnesis, physical examination and audiometric tests. Hearing status was tested with pure tone odiometric examination before, at the first and third months of the treatment in the remaining 55 patients (110 ears).

Pure tone and speech audiometry were performed by using a diagnostic audiometer (Interacoustics AS DK-5610, Denmark) in a sound-treated cabin. Air conduction pure-tone thresholds were measured at frequencies of 250, 500, 1000, 2000, 4000, 8000 and 10000 Hz. While the bone conduction thresholds were measured at 250, 500, 1000, 2000, 4000, 8000 and 10000 Hz. The bone conduction thresholds at 8000 and 10000 Hz are not routinely examined in all patients, they were also examined in the present study order to evaluate the effect of the drugs to the hairy cells in the inner ear. In all frequencies, measurements were performed using an ascending-descending technique in 5-dB steps. If patients gave different responses at the same frequency and decibel, it was evaluated as simulation and then the test was repeated again for each of them.

The degree of hearing loss was assessed by averaging the pure-tone hearing thresholds (in decibels) for test frequency groups. The resulting number; the pure-tone average (PTA) was used to

define the degree of hearing loss at low (250 Hz), middle (500, 1000 and 2000 Hz) and high frequencies (4000, 8000 and 10000 Hz). PTA values of air conduction thresholds were calculated for each ear seperately.

STATISTICAL ANALYSES

Statistical analyses were carried out using SPSS 15.0, the statistical software package for Windows (SPSS Inc., Chicago, IL, USA). The normal distribution of the data was assessed using the Kolmogorov-Smirnov test. Continuous and normally distributed variables were presented as means ± standard deviations and in group differences were investigated using the Student's t-test. Continuous variables with non-normal distribution were expressed as medians (minimum–maximum), and differences between variables were analyzed using the Mann-Whitney U test. Categorical variables were expressed in percentages.

RESULTS

Initially sixty patients were included in the study. Five patients suffering from adverse effects other than hearing abnormalities and inconsistent follow-up were excluded and the study was completed with 55 patients. Of 55 patients, 32 were women (56.1%) and 23 (40.4%) were men. In isotretinoin group, 20 (60,7%) were women and 10 (33,3%) were men. In acitretin group, 12 (48%) were women and 13 (52%) were men. While the mean age of all the patients was 28.8±14.9. The mean age was 19.6±4.2 in the isotretinoin group and 39.9±15.7 in the acitretin group. The otoscopic examinations were normal in all participants before, in every visit, and after the treatment. The differences between the mean values of pretreatment and posttreatment pure tone hearing thresholds at 500, 1000, 2000, 4000, 8000 and 10000 Hz frequencies were evaluated for each group. While no significant difference was found between the mean values of the pretreatment and posttreatment pure tone hearing thresholds of acitretin group (p>0.05), the mean values were statistically significantly decreased in isotretinoin group at first and third months of the treatment at 500 Hz frequency (p<0,05) (Table 1, Table 2). A total of 15 patients had hearing threshold changes in the isotretinoin group, 9 of which were women and 6 were men.

TABLE 1: Averages of audiometric findings of isotretinoin patient.

	0. month	1st month	3rd month
Frequency(Hz)	Mean (Db HL)	Mean (Db HL)	Mean (Db HL)
250 Hz	13.1	14.2	13.8
500 Hz	9.2	7.66	6.82
1000 Hz	6.99	5.78	5.4
2000 Hz	5.4	4	4.8
4000 Hz	5.4	3.9	3.65
8000 Hz	10.3	10.1	9.80
10000Hz	12.8	13.1	12.9

Hz: hertz; Db: decibel; HL: hearing level.

TABLE 2: Averages of audiometric findings of acitretin patients.

	0. month	1st month	3rd month
Frequency(Hz)	Mean (Db HL)	Mean (Db HL)	Mean (Db HL)
250 Hz	12.6	13.1	12.9
500 Hz	12	12.4	11.4
1000 Hz	12	12.8	11.6
2000 Hz	12.4	12.4	11.4
4000 Hz	15.2	16.4	16
8000 Hz	10.2	9.8	10
10000Hz	11.4	11.8	10.89

Hz: hertz; Db: decibel; HL: hearing level.

DISCUSSION

Isotretinoin is a first choice drug for treatment of acne vulgaris, which is prudent and prone to scarring. The drug is already known to have some various side effects, but ototoxic effects are not clear. There are some reports notifying the ototoxic side effects from benign; such as tinnitus, to more serious, such as sensorineural hearing loss.[8]

There are a few reports studying different effects of isotretinoin on hearing systems. In a recent

prospective clinical study, the mean hearing thresholds of the patients were found to elevate after treatment with isotretinoin at 1000, 2000, 4000 and 6000 Hz frequencies.[5] Nikiforidis et al. evaluated the human auditory brainstem responses in order to demonstrate the possible effects of oral isotretinoin along the nerve fibers. The auditory brainstem response of a total of 33 patients at the beginning and third week of treatment were evaluated and found that the results were not statistically different, but, subclinical changes for both ears were seen in three patients. The authors concluded that these subclinical changes may be due to an isotretinoin-induced neurophysiological defect in the auditory nerve fibers.[9] In a series of 32 patients receiving isotretinoin, significant changes in brainstem auditory evoked potentials have been detected.[10] In another series of 104 patients, detecting the adverse reactions to isotretinoin from an adverse drug reaction reporting system; only one patient was reported to develop decreased hearing.[11]

Contrary to all of these studies; Lefebvre et al. have found that, retinoic acid is a stimulator of in vitro regeneration of the auditory hair cells in ototoxic-poisoned rat organs of Corti.[12] In another in vitro study, Romand et al. reported that retinoid signaling via the retinoic acid receptors is necessary in the development of the inner ear structures. They emphasize that there is a limited time period that the embriologic inner ear is very sensitive to the effect of retinoids, and during this period, either deficiency or excess of vitamin A can cause malformations.[13] Karabulut et al. claimed that the hearing levels of the patients using isotretinoin is improved in all audiometric frequencies in a short time period.[1]

Clerici et al. reported that the impairment of the sensorineural epithelium of the labyrinth and also the acoustic and vestibular nervous system may be related with oxidative stress.[14] We may theorise that retinoic acid may have an important role as an antioxidant in preventing the oxidative stress which is claimed to be involved in hearing impairment.

It seems that, according to a small number of reports published until now, isotretinoin may effect the hearing systems either in a positive or negative way. It can be concluded that isotretinoin effects the hearing pathways, especially the inner hair cells. In this study, the finding that isotretinoin decreases the hearing threshold levels at 500 Hz frequency is an interesting result, supporting some literature. Although two decibel reduction in the hearing threshold is not clinically noticeable by the patient, and even though we did not expect such a result; this finding is still surprising and intriguing. It is still a piquant question that isotretinoin has an effect on human hearing status or not.

The prescription of isotretinoin, which is a commonly used and effective drug in dermatology practice, can be restricted because of its many known systemic side effects. In this study, it was observed that the drug had no ototoxic side effect on the contrary to expectations. The most important result of this study is that isotretinoin can be used safely without ototoxic side effects.

Acitretin is a second generation oral aromatic retinoid which is an effective treatment option for severe keratinizing skin diseases like psoriasis and ichthyosis.[15,16] It has similar adverse effects like isotretinoin, but its ototoxic effects are not currently known. To the best of our knowledge, there is only one case report in literature reporting a patient who developed simultaneous bilateral sudden sensorineural hearing loss after taking acitretin and improved after shifting to a reduced dose.[7] This is the first study investigating the effects of acitretin on hearing systems. It was found that, the drug had no significant changes on the mean hearing thresholds of the patients in any frequencies detected by serial pure tone audiometric measurements. It's an interesting finding that acitretin had no effect on hearing systems; while isotretinoin, a very similar drug with similar mechanism of action, decreased hearing thresholds at some frequencies without clinical significance. In order to elucidate this point, the effects of acitretin on hearing systems

should be investigated by more extensive and detailed investigations.

This study has some limitations. Firstly, the effects of isotretinoin and acitretin were not examined at different dosage regimens to determine the impact of dosage on hearing thresholds, and the patients were not reassessed after completing the treatment course of isotretinoin and acitretin in order to detect the whether changes in hearing thresholds were irreversible or not. Secondly, since it is more difficult to obtain patient consent for the procedure, auditory evoked potentials were not measured in our patients.

CONCLUSION

In conclusion, it can be stated that isotretinoin may cause bilateral hearing threshold changes at some frequencies, while acitretin has no significant effects on hearing systems. We recommend that, in further studies, the effects of retinoids which are commonly used in daily practice on hearing status should be investigated in larger patient groups.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Author Contributions

Idea/Concept: *Nermin Karaosmanoğlu;* ***Design:*** *Nermin Karaosmanoğlu;* ***Control/Supervision:*** *Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Ekşioğlu;* ***Data Collection and/or Processing:*** *Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Ekşioğlu;* ***Analysis and/ or Interpretation:*** *Nermin Karaosmanoglu, Ahmet Akkoc, Özlem Akkoca, Hatice Meral Eksioglu;* ***Literature Review:*** *Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Ekşioğlu;* ***Writing the Article:*** *Nermin Karaosmanoğlu, Özlem Akkoca, Hatice Meral Ekşioğlu;* ***Critical Review:*** *Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Ekşioğlu;* ***References and Funding:*** *Nermin Karaosmanoglu, Ahmet Akkoc, Ozlem Akkoca, Hatice Meral Eksioglu;* ***Materials:*** *Nermin Karaosmanoglu, Ahmet Akkoc, Özlem Akkoca, Hatice Meral Eksioglu.*

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