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

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

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, we identified significant difference 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 cause bilateral hearing threshold changes in a period of three months.

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

ÖZET

Anahtar Kelimeler: Asitretin; işitme kaybı; izotretinoin; saft ton odiometri

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 observed side effect of retinoids is the mucocutaneous side effects, which is dose dependent.3 They may also have many side effects on other organ systems.4 Although the adverse effects of retinoids are well known, there are only few reports and studies about their ototoxic effects.1,2,5-7

The main purpose of this study was to determine if isotretinoin and acitretin have any effects 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 this study. The local ethics committee has given an approval for the study (EPKK-3870; 01.02.2012-0451). The study has been carried out according to Helsinki Declaration Criteria. Patients with moderate acne were included for the first group. 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 of birth control other than oral contraceptives. There was some excluding criteria from the study, as follows: those younger than 18 years, those having alcohol abuse or smoking history, a history of using any vitamin A supplements, 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. Their otoscopic examinations were performed carefully before the initiation of the therapy, and the ones who have the otoscopic evidence of any pathology were not included in the study. After all of 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 therapy 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 initiation of the therapy 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. All of the patients’ hearing status were evaluated by anamnesis, physical examination and audiometric findings. Audiometric tests were performed for all of the patients. The hearing of every patient 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. 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. But in this study, these frequencies were also examined in 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 answers 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 separately.

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 intra-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 accepted to the study. Five patients suffering from adverse effects other than hearing abnormalities and inconsistent follow-up were excluded and finally 55 patients were enrolled in the study. Of the 55 patients, 32 were women (56.1%) and 23 (40.4%) were men. In the isotretinoin group, 20 (60.7%) were women and 10 (33.3%) were men. In the acitretin group, 12 (48%) were women and 13 (52%) were men. 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 groups. No significant difference was determined between the mean values of the pretreatment and posttreatment pure tone hearing thresholds of acitretin group (p>0.05). But 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) (Tables 1, 2). A total of 15 patients had hearing threshold changes in the isotretinoin group, 9 of which were women and 6 of them were men.

DISCUSSION
Isotretinoin is a drug that is considered to be the first choice in the course of 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 of the drugs 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, it was found that the mean hearing thresholds of the patients increased 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. In a series of 32 patients receiving isotretinoin, significant changes in brainstem auditory evoked potentials have been detected. In another series of 104 patients, detecting the adverse reactions to isotretinoin from an adverse drug reaction reporting system; among all the patients, only one patient was reported to develop decreased hearing.

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. 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 embryologic inner ear is very sensitive to the effect of retinoids, and during this period, either deficiency or excess of vitamin A can cause malformations. Karabulut et al. claimed that the hearing levels of the patients using isotretinoin is improved in all audiometric frequencies in a short time period.

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. We may theorize 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 in the literature 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 of the literatures. 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 although the opposite was thought. 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. It has similar adverse effects like isotretinoin, but its ototoxic effects are not currently known. As far as our knowledge, there is only one case report in the literature suggesting that a patient developed simultaneous bilateral sudden sensorineural hearing loss after taking acitretin and improved after shifting to a reduced dose. 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 the end of the treatment course of isotretinoin and acitretin to be able to detect the 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.

**CONCLUSIONS**

In conclusion, according to the results of our study, it can be declared 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 on hearing status should be investigated in wider patient groups, which are commonly used in the daily practice.

**Acknowledgements:** There was no funding sources that supported the work. There was no conflict of interests.

**Source of Finance**

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

**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 Eksioglu; **Data Collection and/or Processing:** Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Eksioglu; **Analysis and/or Interpretation:** Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Eksioglu; **Literature Review:** Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Eksioglu; **Writing the Article:** Nermin Karaosmanoğlu, Özlem Akkoca, Hatice Meral Eksioglu; **Critical Review:** Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Eksioglu; **References and Funding:** Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Eksioglu; **Materials:** Nermin Karaosmanoğlu, Ahmet Akkoç, Özlem Akkoca, Hatice Meral Eksioglu.

**REFERENCES**


