EXPERIMENTAL STUDY

EFFECT OF ACITRETIN ON HEARING CAPACITY IN RATS

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SUMMARY

Introduction: Acitretin is a widely used drug for various skin diseases, despite its high risk of toxicity. Although the effect of isotretinoin (a first generation retinoid) on hearing has been investigated, there is limited research on the effects of acitretin, a second generation retinoid, on hearing. The available data consist of case reports. Therefore, we aimed to investigate the relationship between acitretin treatment and hearing loss using distortion product otoacoustic emission (DPOAE) testing.

Methods: Twenty-seven rats (nine rats in each group) were included in the study. The rats were divided into three groups as control, acitretin 1mg/kg and acitretin 5mg/kg. DPOAE was obtained in all groups and signal-to-noise ratio (SNR) values were evaluated at the 4th and 8th weeks of the study.

Results: There was no statistically significant difference between the measurements of DPOAE SNR values in all groups. Acitretin treatment did not affect the SNR values in DPOAE measurements between control and acitretin groups and between acitretin 1mg/kg and acitretin 5mg/kg dose groups.

Conclusion: Acitretin has no adverse effect on the inner ear and is not considered ototoxic. This indicated that it can be used safely, especially in multidrug users and in various other clinical conditions.

Keywords: Acitretin; Distortion Product Otoacoustic Emissions; Signal-to-Noise Ratio; Ototoxicity; Rational Drug Therapy

ASİTRETİNİN SIÇANLARDA İŞİTME KAPASİTESİ ÜZERİNE ETKİSİ

ÖZET

Giriş: Asitretin, yüksek toksisite riskine rağmen, çeşitli cilt hastalıkları için yaygın kullanılan bir ilaçtır. İzotretinoinin (birinci nesil bir retinoid) işitme üzerindeki etkisi araştırılmış olsa da, ikinci nesil bir retinoid olan asitretinin işitme üzerindeki etkileri hakkında sınırlı sayıda araştırma vardır. Mevcut veriler vaka sunumlarından oluşmaktadır. Bu nedenle, distorsiyon product otoakustik emisyon (DPOAE) testi kullanılarak asitretin tedavisi ve işitme kaybı arasındaki ilişkinin araştırılması amaçlanmıştır.

Yöntemler: Yirmi yedi sıçan (her grupta dokuz sıçan) çalışmaya dahil edilmiştir. Sıçanlar kontrol, asitretin 1mg/kg uygulanan ve asitretin 5mg/kg uygulananlar olmak üzere üç gruba ayrılmıştır. Tüm gruplarda DPOAE elde edilmiş ve çalışmanın 4. ve 8. haftalarında sinyal-gürültü oranı (SNR) değerleri değerlendirilmiştir.

Bulgular: Tüm gruplarda DPOAE SNR değerlerinin ölçümleri arasında istatistiksel olarak anlamlı bir fark bulunmamıştır. Asitretin tedavisi DPOAE ölçümlerinde SNR değerlerini kontrol ve asitretin grupları arasında ve asitretin 1mg/kg ve asitretin 5mg/kg doz uygulanan gruplar arasında etkilememektedir.

Sonuç: Asitretinin iç kulak üzerinde olumsuz bir etkisi olmadığı ve ototoksik olarak kabul edilmediği görülmüştür. Bu, özellikle çoklu ilaç kullanan hastalar ve diğer çeşitli klinik koşullarda güvenli olarak kullanılabileceğini göstermiştir.

Anahtar Sözcükler: Asitretin; Distorsiyon Produkt Otoakustik Emisyonlar; Sinyal-Gürültü Oranı; Ototoksisite; Akılcı İlaç Tedavisi

INTRODUCTION

Retinoids like acitretin and isotretinoin are structural and functional analogues of vitamin A. Isotretinoin, a well-known first-generation retinoid, is used to treat acne. Acitretin, a second-generation oral retinoid, is a common treatment for a range of dermatological conditions, including psoriasis, lichen planus, Darier's disease, hidradenitis suppurativa, pityriasis rubra pilaris, ichthyosis, and keratodermas[1-3]. Acitretin use is limited by serious systemic side effects, including liver toxicity, birth defects, high cholesterol, and mucocutaneous toxicities[4,5]. While isotretinoin has been reported to affect hearing, with side effects such as hearing impairment and tinnitus, reports on the effect of acitretin on hearing are limited to a few case studies[6-9]. One case reported sudden bilateral hearing loss in a patient after only one week of acitretin treatment, which improved when the dose was lowered[10]. Another case described tinnitus after four months of acitretin use; the tinnitus resolved when acitretin

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was stopped and returned when it was restarted[11].

It's often difficult to determine the cause of adverse drug effects due to confounding factors such as patient age, co-existing conditions, multiple medications, and the subjective nature of reported side effects like tinnitus and dizziness. Nevertheless, understanding potential drug side effects is crucial for rational drug therapy. The widespread use of a medication can sometimes create problems in other clinical contexts.

Therefore, the aim of this experimental animal study was to investigate whether there is a relationship between acitretin treatment and hearing loss using the distortion product otoacoustic emission (DPOAE) test.

MATERIAL and METHODS

Animals

Female Wistar rats aged 4-6 months were obtained from Experimental Animal Center of Aydin Adnan Menderes University (ADU) and all experiments were performed in accordance with the principles and guidelines of ADU Animal Ethical Committee's guidelines. International standards regarding the animal care and handling have been followed during the study. ADU Animal Ethical Committee approved the study (Approval number: HADYEK 64583101/2016/29).

This study was planned mainly to evaluate the ovarian toxicity of acitretin[3], but in the meantime, in order to reduce the number of animals used in medical research, the hearing function of rats was evaluated after obtaining the relevant animal ethics approval. The evaluation was performed simultaneously with the other study and the two studies did not affect each other scientifically.

Total 27 rats were planned to be included in this study, with nine rats per group. Rats were held in 24±2 °C room temperature with 12 hour of light, 12 hour of darkness, free food and water access, and background noise levels of less than 50 dBA.

Experimental design

The rats were examined, randomly assigned in to three groups with 9 rats per group and weighted on the first day of study. The experimental groups were as follows:

Control: The rats in this group were not administered any medication and served as a healthy animal group.

ACI 1: The rats received daily 1 mg/ kg oral acitretin (Neotigason®, Actavis, Istanbul, Turkey) treatment for 28 days.

ACI 5: The rats received daily 5 mg/ kg oral acitretin treatment for 28 days.

Every Monday, acitretin doses were revised according to actual body weight of the rats. Rats receiving acitretin continued to the medication for four weeks. At the end of 4th week of the study, under the anesthesia of Ketamine and Xylasine (50 mg/kg and 5 mg/kg, respectively), the rats examined with otoscope and DPOAE tests were performed in all three groups. After cessation of drug, second evaluation with otoscope and DPOAE was performed at the 8th week of the study. With the second measurements, it was aimed to evaluate whether discontinuation of the drug could correct the possible acute effect of acitretin and to determine whether there was a long-term persistent harmful effect of acitretin.[12]

DPOAE measurement

DPOAE measurements were made with Madsen Capella® (Otometrics, MADSEN, Natus Medical Denmark ApS). Measurements were made in a room, where the noise level did not exceed 50 dBA. Measurements began by observing that the probe mark and waveform were in the proper configuration on the monitor of the device. DP-gram measurements were taken between 500 and 10.000 Hertz. Seven frequency points were sampled: 986 Hz, 1503 Hz, 2001 Hz, 2998 Hz, 4003 Hz, 5996 Hz, and 7998 Hz in DP-gram. DPOAE signal-to-noise ratio (SNR) values were recorded at these frequencies. Stimulus parameters of DPOAE measurements were the ratio between frequencies f2 and f1 (f2/f1) was 1.22 and the stimulus intensity of L1 was 65 and that of L2 was 65.

Statistical analysis

Data were analyzed using the SPSS version 21 program (Statistical Package for Social Sciences v.21, IBM, Chicago, IL). Kruskal-Wallis tests were used to compare between-group measurements, and Wilcoxon's test was used to compare within-group

measurements. p values below 0.05 were considered as significant.

Patient Consent

Since our study was an animal study, patient consent was not obtained.

RESULTS

Twenty-seven rats (nine rats in each group) were included in the study. At the 4th week measurements, there were no statistically significant differences between control and acitretin applied groups, in terms of DPOAE SNR values for each frequency (986 Hz, 1503 Hz, 2001 Hz, 2998 Hz, 4003 Hz, 5996 Hz, and 7998 Hz). At the 8th week of the study, there were no significant differences between groups in terms of DPOAE SNR values for each frequency (Table 1, Table 2) and Figure1.

In all groups, no statistically significant differences were found between groups, at the 4th week of the study in terms of DPOAE SNR values for 986 Hz, 1503 Hz, 2001 Hz, 4003 Hz, and 5996 Hz. There were statistically significant differences between 4th and 8th week measurements of the study in DPOAE SNR values for 7998 Hz and 2998 Hz in 1 mg/kg acitretin group. In control group and 5 mg/kg acitretin group, there was no difference between 4th and 8th week measurements of the study for 7998 Hz and 2998 Hz. There was an increase in SNR values for 7998 Hz and 2998 Hz in acitretin 1 group (Table 1, Table 2) and Figure 1.

Table 1. The comparison of DPOAE SNR values of groups at 4th and 8th week. p value was not found significant according to all frequencies in any measurement.

DPOAE SNR values	Control Group	ACI 1 Group	ACI 5 Group	p*
4th week measurements				
7998 Hz Amplitude (dB)	25.2±10.8 (29.3)	22.5±7.8 (20.6)	28.8±7.6 (28.7)	0.194
5996 Hz Amplitude (dB)	21.5±7.2 (22.8)	20.3±7.3 (20.4)	20.3±9.1 (18.6)	0.887
4003 Hz Amplitude (dB)	10.4±9.2 (10.0)	9.0±3.3 (8.8)	8.1±6.6 (9.1)	0.858
2998 Hz Amplitude (dB)	6.6±9.5 (7.5)	5.6±3.6 (6.2)	5.1±8.8 (6.3)	0.858
2001 Hz Amplitude (dB)	2.4±4.7 (1.8)	5.5±5.4 (6.8)	2.9±8.3 (4.1)	0.262
1503 Hz Amplitude (dB)	2.7±4.9 (2.6)	1.8±6.3 (2.2)	1.6±5.6 (3.3)	0.986
986 Hz Amplitude (dB	2.2±6.0 (5.4)	2.9±6.0 (2.2)	-1.7±7.6 (-2.6)	0.273
8th week measurements				
7998 Hz Amplitude (dB)	30.1±11.2 (33.1)	34.5±3.9 (34.9)	31.4±5.2 (31.4)	0.520
5996 Hz Amplitude (dB)	23.6±9.3 (23.9)	25.1±6.7 (24.4)	21.7±6.1 (22.9)	0.598
4003 Hz Amplitude (dB)	14.3±6.9 (12.6)	11.4±2.9 (13.3)	8.4±8.5 (9.1)	0.327
2998 Hz Amplitude (dB)	11.0±5.2 (10.3)	11.7±4.9 (12.6)	7.5±7.0 (6.6)	0.368
2001 Hz Amplitude (dB)	5.9±5.2 (7.0)	3.4±5.4 (3.1)	4.5±7.8 (5.9)	0.558
1503 Hz Amplitude (dB)	-1.1±7.8 (-0.8)	0.2±4.5 (0.6)	-0.6±3.5 (0.8)	0.922
986 Hz Amplitude (dB	2.7±6.0 (6.3)	1.9±5.9 (1.4)	-0.2±6.2 (0.3)	0.399

p*: Group comparisons were made with Kruskal Wallis test.

ACI: Acitretin

DPOAE: Distortion Product Otoacoustic Emission

SNR: signal-to-noise ratio

Table 2. The comparison of DPOAE SNR values within groups at all frequency. In all groups no statistically significant differences were found amongst the measurements at the 4th and the 8th week, except two frequencies (7998 Hz and 2998 Hz) in ACI 1 mg/kg group. At these frequencies, an increase, not a decrease, was detected in SNR values. The improvement was not taken into account since there was no significant deterioration in the 4th week drug use compared to the control group.

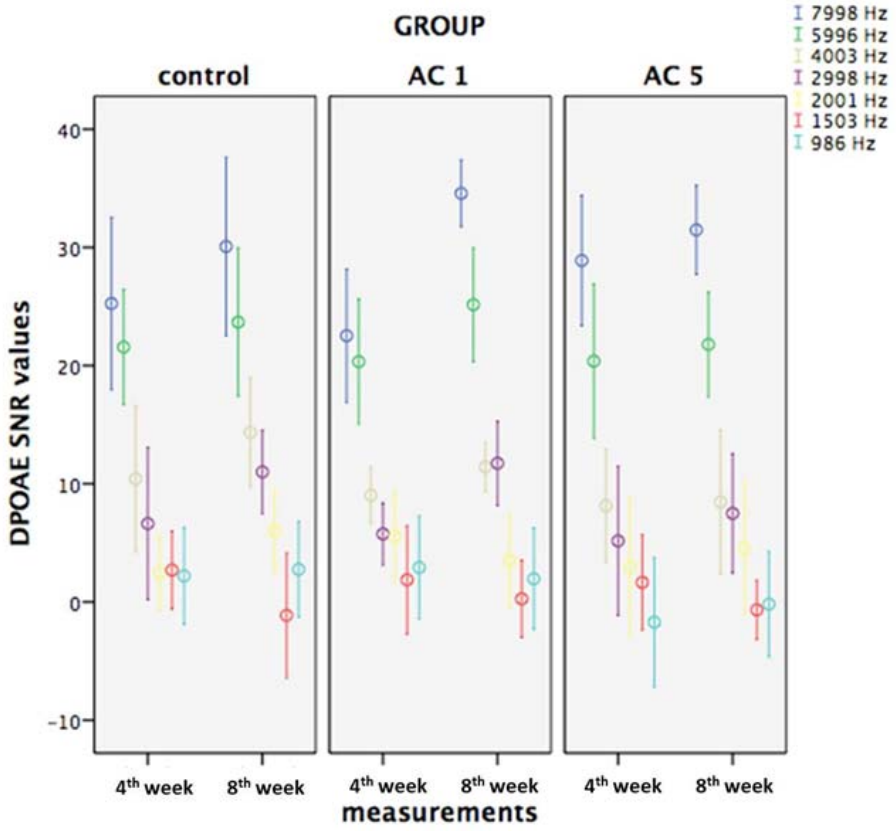
DPOAE SNR values	**4th week**	**8th week**	**p****
1 mg/kg ACI Group			
7998 Hz Amplitude (dB)	22.5±7.8 (20.6)	34.5±3.9 (34.9)	**0.007**
5996 Hz Amplitude (dB)	20.3±7.3 (20.4)	25.1±6.7 (24.4)	0.185
4003 Hz Amplitude (dB)	9.0±3.3 (8.8)	11.4±2.9 (13.3)	0.093
2998 Hz Amplitude (dB)	5.6±3.6 (6.2)	11.7±4.9 (12.6)	**0.017**
2001 Hz Amplitude (dB)	5.5±5.4 (6.8)	3.4±5.4 (3.1)	0.385
1503 Hz Amplitude (dB)	1.8±6.3 (2.2)	0.2±4.5 (0.6)	0.646
986 Hz Amplitude (dB	2.9±6.0 (2.2)	1.9±5.9 (1.4)	0.646
5mg/kg ACI Group			
7998 Hz Amplitude (dB)	28.8±7.6 (28.7)	31,4±5,2 (31,4)	0,327
5996 Hz Amplitude (dB)	20.3±9.1 (18.6)	21,7±6,1 (22,9)	0,721
4003 Hz Amplitude (dB)	8.1±6.6 (9.1)	8,4±8,5 (9,1)	0,878
2998 Hz Amplitude (dB)	5.1±8.8 (6.3)	7,5±7,0 (6,6)	0,575
2001 Hz Amplitude (dB)	2.9±8.3 (4.1)	4,5±7,8 (5,9)	0,646
1503 Hz Amplitude (dB)	1.6±5.6 (3.3)	-0,6±3,5 (0,8)	0,333
986 Hz Amplitude (dB	-1.7±7.6 (-2.6)	-0,2±6,2 (0,3)	0,575

p**: Within group comparisons were made with the Wilcoxon test.

ACI: Acitretin

DPOAE: Distortion Product Otoacoustic Emission

SNR: signal-to-noise ratio



ACI 1: Acitretin 1mg ACI 5: Acitretin 5mg

DPOAE: Distortion Product Otoacoustic Emission

SNR: signal-to-noise ratio

Figure 1: *DPOAE SNR values of groups in basal measurements and the measurements taken on the 4 th week. There is no statistically significant difference was observed.*

DISCUSSION

The main adverse effects of acitretin are hepatotoxicity and teratogenicity[5]. Hearing loss side effect of acitretin has been reported in one case report in the literature so far[10]. In that report, 37 years old woman under the psoriasis treatment, developed simultaneous bilateral sudden hearing loss after one week of acitretin treatment and hearing loss improved after reducing the acitretin dose. Also, it has been reported that acitretin caused peripheral neuropathy in two patients, 57 years old female and 37 years old male[13]. A study conducted with a total of thirty patients with moderate acne vulgaris and another thirty patients diagnosed with psoriasis vulgaris supports our findings that acitretin has no significant effect on hearing systems, while isotretinoin may cause bilateral hearing threshold changes within a three-month period[14]. A more recent study, which included 23 patients with psoriasis vulgaris, has also reported that acitretin does not have an ototoxic effect[15]. Case reports and clinical trials often involve patients with complex medical histories, including varying ages, coexisting conditions, and multiple medications, which can make it difficult to isolate the specific causes of adverse

effects of drugs. Animal studies, conversely, allow researchers to assess the impact of a single variable. Therefore, the current study was designed to investigate the effects of low and high doses of acitretin on the auditory system over two different time periods. To our knowledge, this is the first in vivo experimental animal study to investigate the ototoxic effects of acitretin using DPOAE measurements.

It was determined that there were no statistically significant differences amongst groups in the 4th week of the study in terms of SNR values in DPOAE test, at all frequency. SNR values of both the rats using 1 mg/kg acitretin and the rats using 5 mg/kg acitretin were the same as the control group. In all groups, no statistically significant differences were found amongst the measurements at the 4th and the 8th week, except two frequencies (7998 Hz and 2998 Hz) in acitretin 1 mg/kg group. At these frequencies, an increase, not a decrease, was detected in SNR values. The improvement in 7998 and 2998 Hz frequencies observed in the 8th week in the acitretin 1 mg/kg group was not taken into account since there was no significant deterioration in the 4th week drug use compared to the control group. In terms of assessment of long-term effects, no adverse drug-related effects were observed between the 4th and 8th weeks of discontinuation of the drug.

Acitretin had no disruptive effect on DPOAE measurement. Various ototoxic drugs are capable of damaging the sensory hair cells in the cochlea[16,17]. DPOAE testing provides to monitor the outer hair cell damage associated with ototoxicity and it was accepted that DPOAEs are most sensitive test to evaluate ototoxicity[18,19]. In this study, it was determined that acitretin did not impair DPOAE values. In the light of these findings, it can be said that acitretin does not cause outer hair damage in the cochlea. Consistent with this finding, some reports showed that retinoic acid enhanced hair cell renewal after damage caused by ototoxic drugs[20]. In addition, the dose of acitretin used in rats in this study is much higher than the dose used in humans. Acitretin also seems to be safe for the cochlea at high doses.

The reason why one case of hearing loss and one case of tinnitus were reported due to acitretin treatment may be the neuropathic effect of acitretin treatment[5,10]. It has been shown that acitretin may cause peripheral neuropathy[13]. Therefore, the hearing loss effect of acitretin may be due to retrocochlear hearing loss rather than cochlear hearing loss. Auditory evoked response test can be performed to investigate the effect of peripheral neuropathy. However, speech discrimination scores in the case with hearing loss in literature[10] are quite good compared to hearing loss due to peripheral neuropathy[21].

In the current study, it has been shown that acitretin did not cause cochlear damage and loses of hearing acuity. At some point, it can be very important finding in the clinical practice if the patient has under polypharmacy; acitretin may not be the first suspicious medication to be ceased in case of hearing loss. Our study provides valuable insights into rational drug treatment, specifically regarding maximizing therapeutic benefits, minimizing adverse effects, and improving patient outcomes by ensuring individuals receive the most appropriate and effective therapies for their specific conditions.

Main limitations of this study are using only DPOAE tests to examine the effects of acitretin on hearing and absence of pathological examination for the detection of cochlear damage. It can be recommended that auditory evoked response test could be performed to detect retrocochlear hearing pathology in the further studies.

CONCLUSION

In the present study, acitretin did not produce any detrimental effect on hearing acuity in two different doses and seems safe when used in high doses. Acitretin may not be the first drug to suspect in case of hearing loss or tinnitus in multidrug users.

CONFLICT OF INTEREST

The research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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