Original paper

Assessment of auditory function and lipid levels in patients receiving oral isotretinoin (13-*cis* retinoid) therapy for acne vulgaris

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Adv Dermatol Allergol 2020; XXXVII (3): 360–363
DOI: ttps://doi.org/10.5114/ada.2018.79566

Abstract

Introduction: Isotretinoin (13-*cis* retinoid) is a synthetic retinoid. It was approved by the FDA in 1982 for use of oral isotretinoin in severe acne. It is also used in moderate-severe acne that does not respond to conventional treatments. Isotretinoin is the only available drug that affects all stages of acne pathogenesis.
Aim: To prospectively investigate whether there is an effect of isotretinoin therapy on auditory function and, if so, to demonstrate its association with simultaneous blood lipid levels.
Material and methods: Thirty patients (60 ears) with acne vulgaris, who received 0.5 mg/kg of isotretinoin therapy, were included in the study. Distortion product otoacoustic emissions (DPOAEs) and pure tone audiometry tests were performed to evaluate auditory function at the beginning of the procedure and the 6th month of treatment. In addition, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) cholesterol levels were recorded.
Results: There was no statistically significant difference between pre-treatment and post-treatment mean pure tone audiometry threshold and DPOAE values; however, the increase in total blood cholesterol, triglyceride and LDL levels and the decrease in HDL levels were statistically significant.
Conclusions: According to our study findings, isotretinoin did not cause worsening of the bilateral hearing threshold, but increased blood lipid levels. There is no need for follow-up auditory functions in routine practice during therapy, but blood lipid levels should be monitored.

Key words: auditory function, acne vulgaris, isotretinoin.

Introduction

Isotretinoin (13-cis retinoid) is a synthetic retinoid. It was approved by the Food and Drug Administration (FDA) in 1982 for use of oral isotretinoin in severe acne. It is also used in moderate-severe acne that does not respond to conventional treatments. Isotretinoin is the only available drug that affects all stages of acne pathogenesis. Although isotretinoin is effective and generally well tolerated, it has a wide side effect profile. Like other retinoids, isotretinoin has side effects on the mucosa, skin, eye, liver, bone and musculoskeletal system [1, 2]. Most of the common side effects rarely require cessation of treatment, and will recover spontaneously shortly after the treatment is terminated [1]. Side effects of isotretinoin are well known, but ototoxicity is rarely reported, and its mechanism is not clear [1].

There have recently been reports of adverse effects of hyperlipidemia on auditory function [3, 4]. In addition, Boztepe *et al*. found a decrease in the pure tone audiometry thresholds at the 6th month of isotretinoin therapy, and this finding was associated with an increase in triglyceride and total cholesterol levels [5].

Aim

The purpose of this prospective study is to investigate the effect of oral isotretinoin therapy on auditory function using pure tone audiometry (PTA) and distortion

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Received: 24.10.2018, **accepted:** 28.10.2018.

product otoacoustic emission (DPOAE) tests, and to show its association with simultaneous blood lipid levels.

Material and methods

The study group consisted of 30 (60 ears) patients selected from men or non-pregnant women with severe acne. Women with reproductive potential used at least two contraceptive methods and had a negative pregnancy test result 1 week prior to treatment. Isotretinoin therapy (0.5 g/kg) was initiated and continued until reaching cumulative doses of 120 mg/kg.

Before assessing the auditory functions of patients, detailed anamnesis was obtained from all patients and patients having the following criteria were excluded from the study: ototoxic drug use, exposure to noise, history of otologic surgery, Meniere's disease, cranial trauma, metabolic disease, autoimmune disease, allergy or susceptibility to paraben, being younger than 18 years and older than 35 years. Additionally, patients with acute or chronic otitis media findings on otoscopic examination were not included in the study. All audiologic evaluations were performed at the beginning of the treatment and at the end of the 6th month using DPOAE and PTA tests for each patient and every measurement. In addition, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels were measured at the beginning of the treatment and in monthly assessments. Local ethics committee approval was obtained before the study (SUEK.16214662/05001.04/100).

Audiological evaluations

The DPOAE tests were performed using a Madsen Capella Distortion Product Otoacoustic Emission System (Madsen Capella, Taastrup, Denmark) in the standard default mode. With this technique, a wide frequency range of the cochlea can be evaluated by providing two different sound stimuli termed F1 and F2 to the external ear channel to obtain a frequency-specific response from the cochlea. High frequencies are more likely to suffer from ototoxicity. In the current study, we studied both low and high frequencies (0.75–8 kHz).

Pure tone audiological tests were performed with an AC 40 clinical audiometer (Inter acoustics, Assens, Denmark). The audiometer was calibrated according to the ISO standards. Hearing thresholds were determined in the range 0.5–8 kHz. Contralateral masking was carried out during measurements.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20.0 for Windows statistical software (IBM Corporation, Armonk, New York, USA). Continuous variables were expressed as mean ± standard deviation. For distribution normality analyses, Kolmogorov-Smirnov analysis was performed, and non-parametric tests were preferred according to the results of this analysis. The Wilcoxon test was used for the comparisons. *P*-values less than 0.05 were accepted as significant.

Results

Forty patients were included in the study. Of these patients, 10 were excluded due to incomplete follow-up and 30 completed the study. Six of patients were male and 24 were female. Mean age of patients was 20.5 ±2.7 years. There was no serious side effect due to use of oral isotretinoin. Audiologic complaints (hearing reduction, hearing loss, tinnitus, etc.) were not observed in any of the cases. The otoscopic examination of all participants before and after the procedure was normal. Air conduction hearing thresholds were considered as there were no differences in the air and bone conduction thresholds between the patients. Mean PTA value was 6.5 ±3.6 before the treatment and it was 6.2 ±3.5 after the treatment. When the specific mean values of the frequencies were evaluated, it was found that only the difference in the frequency of 500 Hz was statistically significant. No significant differences were observed between other frequencies. The data for the PTA measurements are presented in Table 1. No statistically significant difference was observed at any frequency or mean value for the

Table 1. Pure audiometry test results evaluated before and after treatment

Value	First measurement	Second measurement	*P*-value
500 Hz	8.0 ±5.2	7.0 ±6.1	0.041
1000 Hz	6.1 ±4.6	6.2 ±4.0	0.853
2000 Hz	4.9 ±4.7	4.4 ±3.8	0.356
4000 Hz	6.1 ±5.7	6.0 ±5.1	0.736
8000 Hz	7.2 ±6.6	7.6 ±7.9	0.812
Mean	6.5 ±3.6	6.2 ±3.5	0.546

Table 2. DPOAE test results evaluated before and after treatment

Value	First measurement	Second measurement	*P*-value
750 Hz	5.1 ±4.1	4.8 ±3.9	0.881
1000 Hz	9.1 ±5.1	8.5 ±5.8	0.331
2000 Hz	10.3 ±4.3	10.3 ±4.7	0.805
4000 Hz	15.2 ±5.6	15.6 ±5.6	0.639
8000 Hz	15.5 ±7.8	15.7 ±7.9	0.958
Mean	11.0 ±3.4	11.0 ±3.4	0.827

Table 3. Biochemical test results evaluated before and after treatment

Parameter	First measurement	Second measurement	*P*-value
ALT	15.8 ±7.5	13.4 ±4.7	0.02
AST	16.7 ±4.4	18.2 ±3.6	0.01
Total cholesterol	159.9 ±25.2	175.4 ±27.8	< 0.001
Triglycerides	77.1 ±29.8	108.9 ±51.5	< 0.001
HDL	50.2 ±9.9	48.0 ±9.1	< 0.02
LDL	87.3 ±19.0	103.3 ±25.5	< 0.001

DPOAE test, which was a frequency-specific otoacoustic emission test. The results are summarized in Table 2.

Although isotretinoin therapy had a statistically significant effect on the liver when tested with AST and ALT values, it resulted in decreased ALT levels and increased AST levels. Significant increases in total cholesterol, triglyceride and LDL levels and a decrease in HDL levels proved its negative effect on blood lipid profile. The results of the biochemical test are summarized in Table 3.

Since there was no statistically significant deterioration in the hearing threshold values of volunteers included in the study, the association between changes in the blood lipid level and hearing impairment was not statistically evaluated.

Discussion

In this study, we did not find a statistically significant difference between mean pure tone audiometry threshold values and DPOAE with isotretinoin treatment, but we detected a statistically significant increase in total blood cholesterol, triglyceride and LDL levels and a decrease in HDL level.

Isotretinoin is a retinoid derivative used for acne treatment. Retinoids are natural or synthetic analogs of vitamin A, and modulate cellular growth, differentiation and immunomodulatory functions [1, 2]. Retinoic acid is also an endogenous signaling molecule, which can also play an important role during different phases of inner ear development [6]. Retinoic acid can affect several genes associated with mesenchymal epithelial interaction. Thus, it controls the morphogenesis of the inner ear [7, 8]. Romand reported that retinoic acid signaling was critical not only for embryogenic development but also for postnatal preservation of the inner ear [8]. Isotretinoin has many common and uncommon side effects [1]. Side effects of isotretinoin are well known, but ototoxic side effects are rarely reported, and their mechanism is not clear. Ototoxic side effects range from relatively benign, such as tinnitus, to more serious, such as sensorineural hearing loss [9].

There are also opposite views. In some studies, retinoic acid was found to be a treatment option for hearing loss due to recurrent otitis media and noise exposure [10, 11]. Lefebvre *et al.* reported that retinoic acid stimulated the regeneration of auditory hair cells after ototoxic drug-induced damage in rats [12]. The main mechanism of retinoic acid in the treatment of hearing loss involves its anti-inflammatory and anti-oxidant features. Moreover, the effect of retinoic acid in the regulation of connexin (Cx) expression, which is essential for normal hearing, is well known [10, 13]. Our findings showed that isotretinoin therapy at a 0.5 mg/kg dose did not affect hearing thresholds.

There is a limited number of studies regarding the effects of isotretinoin on hearing. Aydogan *et al.* observed a significant increase in brain stem auditory evoked potentials of 32 patients receiving isotretinoin therapy [14]. Nikiforidis *et al.* investigated the auditory brain stem response in 33 acne vulgaris patients using isotretinoin, before and at the 3rd week of treatment, and they found subclinical changes after treatment in 3 patients, although not statistically significant [15]. Ugur *et al.* reported that the use of isotretinoin in acne vulgaris patients may alter the bilateral hearing thresholds, although there was no significant change in the DPOAE and TEOAE amplitude levels [16]. Akdağ *et al.* determined a significant increase in mean hearing threshold values (except for 250–500 MHz frequency) of patients using isotretinoin but found no significant difference in the signal-to-noise ratio of TEOAE before and after treatment [17]. Karabulut *et al.* reported improvement in hearing levels of patients with acne vulgaris at all audiometric frequencies in the short-term follow-up period [18]. In our study, we found that changes in pure tone audiometry results at all frequencies except 500 Hz and the differences for all frequencies and mean values for the DPOAE test did not show a statistically significant result. The contradiction between the study results might be due to the small size of the study population, the absence of hearing loss in all study populations and using different methods for assessment of hearing function.

There are recent studies regarding the negative impact of hyperlipidemia on hearing. There are also publications reporting that a low cholesterol diet and antihyperlipidemic treatment improve sudden hearing loss [3, 4, 19, 20]. In the study of Boztepe *et al.* [5] conducted with patients with acne vulgaris, it was found that isotretinoin therapy influenced hearing, and triglyceride and cholesterol levels, and that increased blood lipid levels were associated with hearing impairment. The authors concluded that these two effects might occur due to the indirect consequence of a concurrent side effect of the drug and elevated blood lipid levels [5].

In our study, we found a statistically significant increase in total blood cholesterol, triglyceride and LDL levels and a decrease in HDL levels with the treatment

of isotretinoin. These results were consistent with the literature [2, 21]. However, since there was no statistically analyzed impairment in the hearing thresholds of the volunteers included in the study, the association between changes in the blood lipid level and hearing impairment was not statistically analyzed.

The PTA, auditory evoked potentials and otoacoustic emissions were used in most of the studies on isotretinoin and hearing. Changes reported in the hearing thresholds in these studies, including our study, were not clinically significant, and most changes were determined by a subjective test, pure tone audiometry measurement. In addition, all the studies were small-scale. The contradiction between our findings and the results of other studies can be explained by these reasons.

Conclusions

According to our study results, we concluded that isotretinoin did not cause worsening of the hearing thresholds, but increased blood lipid levels. We believe that there is no need to follow up hearing functions in routine practice during the treatment period; however, blood lipid levels should be monitored. Due to the contradiction between studies on the effects of isotretinoin in the literature about hearing, there is a need to measure hearing function and verify this information with human and animal studies by means of large-scale and objective methods.

Conflict of interest

The authors declare no conflict of interest.

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