19-Dec-2010

Dear Mrs. KARABULUT:

It is a pleasure to accept your revised manuscript entitled "The Effect of Oral Isotretinoin on Hearing System in Patients with Acne Vulgaris: A prospective study" in its current form for publication in the International Journal of Dermatology. Any additional comments received by the reviewer(s) are at the foot of this letter.

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Sincerely,

Dr. Lawrence Gibson
Editor in Chief, International Journal of Dermatology
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Reviewer(s)' Comments to Author:
Referee: 1
Comments to the Author
This corrected manuscript may be accepted for publication in Int J Dermatol.
The Effect of Oral Isotretinoin on Hearing System in Patients with Acne Vulgaris: A prospective study

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Title: The Effect of Oral Isotretinoin (13-cis retinoic acid) on Hearing System in Patients with Acne Vulgaris: A prospective study

Running title: Oral Isotretinoin and Hearing

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The Effects of Oral Isotretinoin on Hearing System in Patients with Acne Vulgaris

Running Head: Oral Isotretinoin and Hearing

ABSTRACT

Objective: Isotretinoin is widely used in the treatment of extensive and nodulocystic acne. The objective of this prospective study was to investigate whether oral isotretinoin could affect the hearing system.

Methods: Thirty-eight patients with acne vulgaris (76 ears) who were diagnosed and treated in the department of dermatology were included in the current study. Study evaluation visits were performed at baseline, and at weeks 1, 2, and 3. Pure tone averages (PTA) of air conduction thresholds at 250Hz (PTA1), 500, 1000 and 2000 Hz (PTA2), 4000, 8000 and 10000 Hz (PTA3), 12500, 16000, 18000 and 20000 Hz (PTA4) for each ear were calculated separately. Assessment of the efficacy was based on the audiometric findings.

Results: Compared to pre-treatment evaluation, the PTA of patients were found significantly different at first week for PTA2 (p=0.033) and PTA3 (p=0.001), at second week for PTA1 (p=0.036) and at third week for PTA4 (p=0.002).

Conclusion: Our results suggest that the oral isotretinoin (13-cis retinoic acid) which is a derivative of retinol (vitamin A) was improved hearing level of the patients in all audiometric frequencies in a short period follow up.
Introduction

Oral isotretinoin (13- cis retinoic acid, isotretinoin) is a derivative of retinol (vitamin A), is the first-line treatment in extensive and nodulocystic acne. It is also used in moderate acne unresponsive to conventional treatment and in patients with obvious scarring \(^1\). A number of metabolites of carotenoids have been reported, and isotretinoin is one of them. Retinoids metabolized to retinal by the enzyme alcohol dehydrogenase, which is further converted into retinoic acid \(^2\). Retinoids are involved in the complex arrangements of physiological and developmental responses in many tissues of higher vertebrates that include embryonic development, vision, reproduction, bone formation, hematopoiesis, metabolism, growth and differentiation of a variety of cell types, apoptosis and processes of carcinogenesis \(^3-5\). Although it is an effective and generally well-tolerated medication, isotretinoin also has a broad side effect profile. Most of the common side effects rarely necessitate the discontinuation of treatment, and spontaneously resolve shortly after cessation of treatment \(^6\). Isotretinoin may cause adverse reactions on mucosa, skin, eye, liver, bone and the musculoskeletal system \(^6,7\). The most serious side effects are teratogenicity and the increase in the rate of spontaneous abortion \(^6\). The adverse effects of isotretinoin are well known, but ototoxic effects have rarely been reported \(^7\).

The objective of this prospective study was to investigate whether oral isotretinoin could affect the hearing system by pure tone high frequency audiometry and timpanometry. Assessment of the efficacy was based on the audiometric findings.

Materials and methods:

Thirty-eight patients with acne vulgaris (76 ears) who were diagnosed and treated in the department of dermatology were included in the current study. Study group was selected
from a group of male or non-pregnant female patients with moderate to severe nodulocystic acne. Females of childbearing potential were using at least two separate and effective methods of birth control, and had a negative serum pregnancy test 1 week before the initiation of isotretinoin therapy. Patients using any vitamin A supplements or having any following problems were excluded from study; sensitivity or allergy to parabens, recent history of psychiatric disorders, pregnancy, a history of ototoxic drug use, noise exposure, ear surgery, chronic middle ear disease, Meniere’s disease, cranial trauma, metabolic diseases, autoimmune disease and otoscopic evidence of a perforated tympanic membrane or other middle ear pathology.

Isotretinoin therapy was initiated at a dose of 0.5-0.75 mg/kg body weight. Treatment was continued for at least 3 months. The drug was administered twice daily with meal. Screening for biochemical parameters were done just before initiation and after 1 months of isotretinoin treatment. These parameters included hemoglobin, creatinine, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetate transaminase (SGOT), total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL).

The patient’s hearing status was assigned based on history, physical examination including otoscopy and audiometric test findings. Audiometric tests including pure tone, speech, high frequency audiometry, ipsi and contralateral acoustic reflexes were performed in all participants. All audiometric tests were repeated at the time of first, second and third weeks of treatment.

Pure-tone and speech audiometry were performed by using a diagnostic audiometer (Madsen Orbiter 922-2, Denmark) in a sound-treated cabin. TDH-39 standard headset was used for air conduction thresholds and speech tests. Radio ear B-71 vibrator was used in high
frequency audiometry. Air conduction pure tone thresholds were measured at the frequency of 250, 500, 1000, 2000, 4000 and 8000 Hz. Bone conduction thresholds were measured at the frequency of 500, 1000, 2000 and 4000 Hz. High frequency air conduction thresholds were measured at the frequency of 10000, 12000, 16000, 18000 and 20000 Hz. Measurements were done using an ascending-descending technique, in 5 dB steps at all frequencies. If a patient made two or more responses to a set of 3 stimuli, she/he was deemed to have heard the sound.

Typically, the degree of hearing loss is determined by averaging the pure tone hearing thresholds (in decibels) for test frequency groups. The resulting number, the pure tone average, is used to define the degree of hearing loss at low, middle, high, and ultra high frequencies. Four pure tone average (PTA) groups were calculated: PTA1 (250 Hz), PTA2 (500, 1000 and 2000 Hz), PTA3 (4000, 8000, and 10000 Hz) and PTA4 (12500, 16000, 18000 and 20000 Hz). PTA of air conduction thresholds were calculated for each ear separately.

Tympanometric measurements were done using a TDH-39 headset and Middle Ear Analyzer (TympStar GSI, Grason-Stadler Inc., Milford, USA). Ipsi and contralateral acoustic reflexes were measured using a 226 Hz probe tone at the frequencies of 500, 1000, 2000 and 4000 Hz.

Statistical analyses:

According to normal distribution of data was determined by Kolmogrov-Simirnov test. Wilcoxon and Mann-Whitney U test were used for analyses of unsuitable data in normal distribution. Independent sample T test and paired sample T test were used for analyses of suitable data in normal distribution. Paired Sample T test and Wilcoxon test were used in intra-group comparisons. Pearson correlation test, linear and logistic regression analyses were used in the relationship of data of each other. Statistical analyses were performed using the
Statistical Package for the Social Sciences version 15.0 for Windows software. A p value of < 0.05 was considered significant.

**Results:**

Forty-seven patients were enrolled in the study. Nine patients were excluded from the study because of irregular visits. Thirty-eight patients completed the study (twenty-three females and fifteen males). The mean age of patients was 19.8 ± 4 (range 15–34) years. Before and after the treatment, the otoscopic examination was normal in all participants. Normal peak compliance, peak pressure, gradient, ear canal volume and acoustic reflexes were obtained by immittance measures in all patients before and after the isotretinoin treatment.

No changes were observed in all patients during the isotretinoin treatment in speech discrimination scores.

The pure tone audiometry descriptive results for patients are shown in Table 1. Compared to before the treatment, the pure tone averages of patients were significantly different at first week for PTA 2 (p=0.033) and PTA 3 (p=0.001), at second week for PTA 1 (p=0.036) and at third week for PTA 4 (p=0.002). Pure tone average (PTA) results are shown in Table 2.

Figure 1a and 1b summarize the hearing thresholds of the low and moderate frequencies; figure 2a and 2b presenting hearing thresholds of the high frequencies of right and left ears before and after therapy. There were not significant differences in audiometric results belonging to the pre and post-treatment between genders (p>0.05).

**Discussion:**

In this study we found that hearing thresholds of the patients were raised in middle frequency at first week, in high frequency at second week and in ultra high frequency at third week of treatment.
Isotretinoin have got a lot of common and uncommon effects. The most frequent adverse reactions associated with isotretinoin are the mucocutaneous effects on lips, eyes, mouth, and other epidermal surfaces. Uncommon side effects of using isotretinoin are neurologic effect, rheumatic effects, pulmonary effects, renal system effects, gastrointestinal and genitally effects. The adverse effects of isotretinoin are well known, but ototoxic effects have rarely been reported. The ototoxic side effects ranged to from relatively benign, such as tinnitus, to more serious, such as hearing problems. Contrary to existing information, some reports showed that retinoic acid enhanced hair cell renewal after damage caused by ototoxic drugs. Since oxidative stress has been suggested to be involved in hearing impairment, antioxidants are expected to play a preventive role. Our findings demonstrated that, the following isotretinoin treatment hearing thresholds were decreased at a dose of 0.5-0.8 mg/kg/day.

There are two studies evaluating the effect of isotretinoin on hearing system in the literature. In the first of them, sub-clinical changes of the auditory brain system response have been observed in 9% of patients treated orally with isotretinoin over a period of 3 weeks. In the other study, no clinically evident adverse reactions have been observed in the treated patients with isotretinoin. A statistically significant increase of the third and fifth peak latency in both ears, and significant increase of the first peak latency and IPL I-V in the left ear were found after isotretinoin administration, as compared to the pretreatment.

A number of metabolites of carotenoids have been reported and 13-cis retinoic acid is one of them. Carotenoids have been considered to have two possible mechanisms of action: a) to be metabolized to retinoids, b) acting as lipid phase antioxidants. β-carotene directly blocks the superoxide anion preventing cell damage, and cholesterol deposits in the arteries. Phospholipids make up the cell membrane and are oxidized by free radicals in OH or COH damaging the membrane compactness. The endothelium is at major risk of free radical -
induced lesions and this damage is most manifest in microcirculation\textsuperscript{17,18}. It has been observed that reactive oxygen species (ROS) play an important microcirculatory role in the pathology of the inner ear and the peripheral and central pathways\textsuperscript{19–21}. There are some reports suggesting that oxidative stress could impair the sensorineural epithelium of the labyrinth and the acoustic and vestibular nervous system\textsuperscript{19}. Oxidative stressors induce the production of intracellular oxygen reactive products and the production of ROS, which interact with the phospholipidic membrane of the sensorial cells producing aldehyde lipids such as the 4-hydroxynonenal, a mediator of apoptosis for auditory neurons and hair cells\textsuperscript{16}.

The damage caused by ROS and the positive effect of antioxidant substances on the labyrinth have been demonstrated by an experimental study by Aubert et al\textsuperscript{22}. Since oxidative stress has been suggested to be involved in hearing impairment, antioxidants are expected to play a preventive role\textsuperscript{10}. It is also known that retinoic acid, an active metabolite of retinol, is indispensable for normal development of the Corti organ\textsuperscript{23}. The association between vitamin A (retinol) and the prevention of hearing impairment in particular has been focused because the concentration of vitamin A in the inner ear has been shown to be high\textsuperscript{12}. Retinol plays an important role in the normal development of the organ of Corti\textsuperscript{23}. An animal experiment using rats showed that retinoic acid stimulates the regeneration of hair cells in inner ear\textsuperscript{24}. Our investigation suggests that retinoic acid was decreased hearing thresholds of the patients in all frequency. Further clinical and experimental investigations will be required to impact of retinoic acid in hair cells in inner ear.

In conclusion isotretinoin, having many adverse effects on a number of systems, and has improved hearing levels of the patients with acne vulgaris in all frequency tested in a short term follow-up.
References


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Table 1: Averages of audiometric findings of patients

Table 2: Pure tone average (PTA) results

Figure legends:

Figure 1a: Pure tone thresholds for low and moderate frequencies of right ear

Figure 1b: Pure tone thresholds for low and moderate frequencies of left ear

Figure 2a: Pure tone thresholds for high frequencies of right ear

Figure 2b: Pure tone thresholds for high frequencies of left ear
Table 1: Averages of audiometric findings of patients

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<th>Baseline Std. Dev. (dB HL)</th>
<th>1st week Mean (dB HL)</th>
<th>1st week Std. Dev. (dB HL)</th>
<th>2nd week Mean (dB HL)</th>
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Hz: Hertz, dB: deciBel, HL: Hearing Level
Table 2: Pure tone average (PTA) results

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<th>Frequency (Hz)</th>
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Pure tone average thresholds of patients PTA1 (250Hz), PTA2 (500, 1000 and 2000 Hz), PTA3 (4000, 8000, 10000 Hz), and PTA4 (12500, 16000, 18000, 20000 Hz).