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ORIGINAL ARTICLE

The Effects of Oral Isotretinoin (13-Cis Retinoic Acid) on the Inner Ear: A Clinical Study

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Objective: To report a clinical study of detailed audiological examinations of acne vulgaris patients treated with oral isotretinoin.

Materials and Methods: Twenty-five patients (50 ears) with acne vulgaris who were treated with isotretinoin 5mg/kg were included in this study. Two patients gave up using isotretinoin after two months. Pure tone audiometry, TEOAE and DPOAE were evaluated before the use of isotretinoin and after 4 months of treatment. DPOAE was recorded as a DPgram.

Results: Pre-treatment and post-treatment pure tone threshold average changes for all frequencies were statistically significant. The difference between the pre-treatment and post-treatment distortion product amplitudes and signal–noise ratio values were not significantly different. When the pre-treatment and post-treatment TEOAE amplitudes according to frequencies were compared, there was no significant difference between pre-treatment and post treatment values.

Conclusion: The results support the conclusion that acne vulgaris patients using isotretinoin has bilateral hearing threshold changes despite the absence of significant DPOAE and TEOAE amplitude levels. Further animal and human studies with histopathological findings are required to investigate the effect of isotretinoin on the inner ear.

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Introduction

Retinoic acid is an active metabolite of vitamin A. It coordinates several processes, such as cell proliferation and differentiation. The reduction of hair cell loss and hearing deterioration in mice with early post-noise exposure treatment with all-trans retinoic acid (ATRA) has been described in some studies [1-3]. ATRA has been shown to inhibit the apoptosis of T cells, leukemia cells, and hematopoietic cells and to attenuate hydrogen peroxide-induced apoptosis in mesangial cells and fibroblasts [1]. We therefore decided to study the effect of oral isotretinoin on the inner ear. Isotretinoin is also a derivative of vitamin A and is routinely prescribed in dermatology clinics [4,5]. Isotretinoin (13-cis-retinoic acid) is a synthetic oral retinoid that is the first line treatment of recalcitrant, nodulocystic acne vulgaris [6,7]. Isotretinoin controls the disease, being the only medication that has an affect on the major etiological factors in acne vulgaris.

Retinoids are compounds that include vitamin A and also its chemically related derivatives. The side effects of oral isotretinoin are effects on mucosa, eye, skin, liver, bone, and the musculoskeletal system. The most common side effects are chelitis, retinoid dermatitis, xerosis, palmoplantar desquamation, photosensitivity, paronychia, onycolysis, and delayed wound healing. Isotretinoin causes signs and symptoms of dry nose and disturbed mucociliary clearance [8]. The most

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serious side effect is teratogenicity [6,7]. Although oral isotretinoin side effects are well known, to the best of our knowledge an impact of oral isotretinoin on the inner ear has rarely been observed. Otoacoustic emissions (OAE) are non-invasive measures that enable clinicians to observe the outer cell function of the inner ear in a frequency specific manner. OAE are sounds detected in the external auditory canal that come from the vibratory motions of the outer hair cells of the cochlea transmitted to the middle ear, tympanic membrane and external auditory canal. These emissions can be measured and recorded by a small sensitive microphone placed in the external auditory canal.

The aim of the this study was to present a clinical study of audiological examinations of acne vulgaris patients treated with oral isotretinoin using pure tone audiometry, distortion product otoacoustic emission (DPOAE) and transient-evoked otoacoustic emissions (TEOAE).

Materials and Methods

Patients

From September 2010 to July 2011, 25 patients (50 ears) with acne vulgaris who were diagnosed and treated with isotretinoin in the Department of Dermatology at University hospital, were included in the present study. Two patients gave up using isotretinoin after two months. The study was approved by the Ethics Committee of the Medical Faculty of Uuniversity. Written informed consent for participation was obtained from all patients. Patients were male or non-pregnant female patients with moderate to severe nodulocystic acne. A detailed history was taken and otological examination was performed on all patients. Otoscopic examinations of the patients yielded normal results. One week before the use of isotretinoin, all childbearing potential females who had a negative serum pregnancy test were given effective means of birth-control. Exclusion criteria were: a history of ototoxic drug use; noise exposure; ear surgery; chronic middle ear disease; a history of otologic surgery; Meniere's disease; cranial trauma; metabolic diseases; autoimmune disease; and otoscopic evidence of a perforated tympanic membrane or other middle ear pathology; sensitivity or allergy to parabes; a history of psychiatric disorder. Isotretinoin was given 5 mg/kg.

Audiologic mesurements

Pure Tone Audiometry

Pure tone audiometry (Interacoustics AC 40, Clinical Audiometer, Denmark) and tympanometry (Interacoustics AZ T, Impedance Auidometer, Denmark, calibrated to ANSI S3.39–1987 standards) were performed before the use of isotretinoin and after 4 months of treatment. Pure-tone air and bone conduction audiometry including high frequencies (250, 500, 1000, 2000, 4000, 8000, 9000, 10000, 12500, 14000, and 16000 Hz) were performed on all subjects. Pure tone average was calculated as the average of 0,5-4 kHz to determine the hearing loss.

Otoacoustic emissions (OAE)

DPOAEs and TEOAEs were measured using Madsen Capella equipment (GN Otometrics Ltd, Taastrup Danimark). The data were processed and evaluated with otoacoustic emission (OAE) software (Otoscreen OAE Screening and NOAH based Software, Danimark). DPOAEs and TOAEs were performed before oral isotretinoin treatment and repeated after 4 months following oral isotretinoin treatment in a sound proof room. The probe was placed in the ear canal properly and measurements were achieved. The DPOAE at 2f1 -f2 were elicited. Two equilevel (L1 = L2 = 65 dB) primary signals (f1 and f2) were fixed at f2/f1 = 1.21. The intensities for the DPgram were set as equilevel at 65 dB. DPOAE were marked as a function of f2. The frequencies examined for the DPgram ranged from 750 to 8,000 Hz (750, 1,000, 1,500, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz). By calculating the difference between distortion products and noise, a ± 2 standard deviation signal–noise ratio (SNR) for each frequency was achieved.

The TEOAEs were achieved with stimuli with a click of 80-μs duration. The click rate was 50/second, and post-stimulus analysis was in the range of 2–20 miliseconds. The stimulus level in outer air was set at 80 ± 2 dB sound pressure level (SPL). A total of 260 sweeps was averaged above the noise rejection level of 47 dB. Stimuli were presented in the nonlinear mode, in which every fourth click stimulus was inverted and three times greater in amplitude than the three preceding clicks. The amplitudes according to frequencies (frequency bands from 1 to 5 kHz) and reproducibility percentages were recorded. TEOAE was defined as a response if its amplitude was ≥3 dB

above the level of the noise. Reproducibility percentages ≥60% were taken into account as acceptable for analysis at five successive frequency bands from 1 to 5 kHz.

Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distributions of continuous variables were normally or not was determined by using Shapiro Wilk test. Data were expressed as mean ± standard deviation or median (Interquartile Range, IQR) according to distribution of data. While, the differences between pre- and post-treatment measurements regarding for normally distributed data were compared by Paired Samples t test, otherwise, Wilcoxon Sign Rank test was applied for the comparisons of not normally distributed measurements. A p value less than 0.05 was considered statistically significant.

Results

All patients used isotretinoin for at least 4 months. There were no significant side effects due to the oral isotretinoin usage. The most common side effects were chapped lips, dryness and xerosis. Mild elevation of liver enzymes was observed in two patients. Because of the mild liver enzyme elevation 2 patients gave up using isotretinoin after two months. There were dose-related side-effects, particularly dryness of the skin and mucous membranes.

The mean age of the patients with acne vulgaris was 23.00 ± 4.4 (Range 16 to 32). There were 15 (65.2%) female and 8 (34.8%) male patients. The pure tone audiometric findings are shown in Table 1. The mean PTA pre-treatment was 10.2 ± 4 dB, the mean PTA post treatment was 8.7 ± 3.5 dB respectively. Since there was no air bone gap in the patients, the bone conduction threshold was taken into consideration.

The pre-treatment and post-treatment pure tone average changes according to all frequencies were statistically significant (P=0.001) (Table 1). There was a significant difference between the pre-treatment and post-treatment hearing thresholds at 250, 500, 8000, 10000, 12000, and 16000 Hz frequencies (Fig 1) (Table 1).

DPOAE findings as pre-treatment and post-treatment distortion product amplitudes and SNR for all frequencies are shown in Table 2. The difference between the pre-treatment and post-treatment distortion product amplitudes and SNR values were not significant (p>0.05). TEOAE findings of the patients are summarized in Table 3. TEOAE changes were not statistically significant when the pre-treatment and post-treatment TEOAE amplitudes according to frequencies were compared (p>0,05).

Discussion

Isotretinoin (13-cis-retinoic acid) is an effective medication for the treatment of severe recalcitrant acne[6]. Retinoids are natural or synthetic vitamin A analogs, normally derived from dietary carotenoids and retinol [9]. They affect cellular growth, differentiation, and also maintain immune modulatory function. Several studies of synthetic retinoids have supported the continued expansion of oral retinoids both within and beyond the field of dermatology. RA is also an endogenous signaling molecule that may play a role during different phases of inner ear development,

Table 1. Comparisons of pre-treatment and post-treatment hearing thresholds of patients according to frequencies

Variables	Pre-treatment	Post-treatment	z-value	p-value a
250 Hz	10,0 (10,0-15,0)	10,0 (7,5-10,0)	-2,355	0,019*
500 Hz	10,0 (7,5-12,5)	7,5 (5,0-10,0)	-2,932	0,003*
1000 Hz	10,0 (5,0-10,0)	7,5 (5,0-10,0)	-1,676	0,094
2000 Hz	7,5 (5,0-10,0)	7,5 (5,0-10,0)	-1,580	0,114
4000 Hz	10,0 (5,0-10,0)	7,5 (5,0-10,0)	-1,783	0,075
8000 Hz	10,0 (10,0-15,0)	10,0 (5,0-10,0)	-3,058	0,002*
10000 Hz	10,0 (7,5-17,5)	10,0 (5,0-10,0)	-2,428	0,015*
12000 Hz	10,0 (10,0-15,0)	10,0 (5,0-10,0)	-2,892	0,004*
16000 Hz	10,0 (10,0-17,5)	10,0(7,5-10,0)	-2,840	0,005*
PTA	10,0 (8,0-11,0)	8,0 (6,5-10,0)	-2,586	0,010*

*a Wilcoxon Sign Rank test, * p<0,05.*

Table 2. DPOAE amplitudes and SNR according to frequencies

Variables	Pre-treatment	Post-treatment	Statistics	p-value
500 Hz Amplitude (dB)	-7,2±7,8	-7,3±7,6	t=0,007	0,994a
500 Hz SNR	1,9±5,0	0,01±5,4	t=1,089	0,288a
1000 Hz Amplitude (dB)	2,8±7,9	1,1±8,7	t=1,124	0,273a
1000 SNR	6,9±5,0	7,2±5,8	t=-0,264	0,794a
2000 Hz Amplitude (dB)	6,3 (2,0-9,5)	6,8 (3,0-10,8)	z=-1,628	0,104b
2000 Hz SNR	11,3±4,8	11,4±4,3	t=-0,087	0,932a
4000 Hz Amplitude (dB)	10,2 (7,2-12,5)	10,3 (8,6-15,1)	z=-1,202	0,229b
4000 Hz SNR	19,5±5,8	17,4±5,5	t=1,480	0,153a
6000 Hz Amplitude (dB)	21,5 (10,8-23,6)	21,0 (15,5-23,5)	z=-0,162	0,871b
6000 Hz SNR	27,1 (16,3-30,6)	22,7 (18,0-29,4)	z=-0,552	0,581b
8000 Hz Amplitude (dB)	9,2 (2,3-11,9)	8,8 (4,9-12,8)	z=-0,195	0,846b
8000 Hz SNR	20,0±6,8	20,5±6,4	t=-0,401	0,692a

a Paired Samples t test, b Wilcoxon Sign Rank test.

Table 3. Pre-treatment and post-treatment TEOAE amplitudes of patients

Variables	Pre-treatment	Post-treatment	Statistics	p-value
1000 Hz Amplitude (dB)	6,1±4,8	6,3±4,6	t=-0,197	0,846a
2000 Hz Amplitude (dB)	8,4±5,7	9,3±5,5	t=-1,386	0,180a
3000 Hz Amplitude (dB)	8,6±5,2	8,9±5,7	t=-0,989	0,333a
4000 Hz Amplitude (dB)	9,6±3,5	9,8±3,2	t=-0,502	0,621a
5000 Hz Amplitude (dB)	9,0 (7,8-13,3)	8,5 (7,5-14,0)	z=-1,431	0,153b

a Paired Samples t test, b Wilcoxon Sign Rank test.

as shown from pathological observations.[10,11] RA may regulate several genes involved in mesenchymal-epithelial interactions, thereby controlling inner ear morphogenesis[12-16]. Romand et al suggested that RA signaling is a critical component not only of embryonic development, but also of postnatal maintenance of the inner ear[13]. The signal transduction pathway of retinoic acid during inner ear development is not clear, but Ramond et al demonstrated that RAR (retinoic acid receptor) alpha and RAR gamma play an essential role in the initial differentiation of otic placode derivatives, whereas RAR beta plays a minimal role in this process[14]. Synthetic retinoids may be capable of affecting the differentiation and growth of nervous tissue in vivo and in vitro. Although Nikiforidis et al, suggested that some subclinical changes may be due to an isotretinoin-induced synaptic malfunction or to a conduction defect in the auditory nerve fibers[17], Lefebvre et, al demonstrated a stimulation of regeneration of in vitro mammalian auditory hair cells in ototoxic-poisoned organ of Corti explants in the rat by retinoic acid[18].

In the present study apart from these findings we decided a clinical study and investigated the effects of isotretinoin on auditory function by using both pure tone audiometry and OAE measurements after a 4 month treatment with isotretinoin (5mg/kg). There are a limited number of studies concerning the effect of isotretinoin on hearing. Two of these studies measured the hearing by auditory brainstem response (ABR) and one of them was conducted with pure tone audiometry, which is a subjective test[17,19,20]. Those studies observed an effect of isotretinoin after 3 weeks of treatment. The main difference of our study was the use of objective outer hair cell function measurement and the other difference was a demonstration of a long term effect of isotretinoin. Aydogan et al, found a statistically significant increase of the third and fifth peak latency in both ears, and a significant increase of the first peak latency and the wave I to V interpeak latency (I–V IPL) of the ABR response after isotretinoin administration, as compared with pre-treatment[19]. Aydogan et al performed neurological examination and electroneuromyographic studies on 18 patients with various skin diseases before, at the third month,

and at the end of (mean ±SD duration of treatment 6.5±1.0 months) isotretinoin treatment [21]. Abnormal neurophysiological findings in this study point towards a typical distal, length-dependent and predominantly sensory polyneuropathy [21]. Nikiforidis et al observed the auditory brainstem response of 33 patients with severe nodulocystic acne before and 3 weeks after the onset of oral isotretinoin administration and found a marked increase in latencies and interpeak latencies and a decrease in amplitudes for both ears in 3 patients after therapy [17]. Karabulut et al found that oral isotretinoin (13-cis retinoic acid), which is a derivative of retinol (vitamin A), improved the hearing level of the patients in all audiometric frequencies in a short-period follow-up [20]. The discrepancy between the results of the studies is because of the small size of the study populations and all studies of populations did not have hearing loss.

In this study, we examined the effect of isotretinoin using OAEs, which are objective, not relying on a behavioral response, providing information about the cochlear, mostly the outer hair cell damage. OAEs provide stable and frequency specific information on the function of the outer hair cells. In the present study, TOAE and DPOAE were not affected significantly after four months of isotretinoin, however the pure tone thresholds were significantly reduced and the amplitudes of TEOAE levels were increased for 1000, 2000, 3000, and 4000 Hz levels after isotretinoin treatment. The results may explain that the outer hair cells may not be affected by isotretinoin effects in the cochlea.

Our study has some important limitations. Firstly the populations in the study were under age of 35. Secondly study population had no hearing loss. While the main reason to choose this group was patients with acne vulgaris using isotretinoin were young, we have to configure the study population with hearing loss in the future studies to understand the exact isotretinoin effect on inner ear. The other reason to use this group in our study was there were a very small amount of patients with acne vulgaris using isotretinoin and with hearing loss to conduct a study. Thirdly, this clinical study is lacking definite support from histopathological evidence.

In conclusion we reported a clinical study of audiological examinations of acne vulgaris patients using isotretinoin. The results support the conclusion that acne vulgaris patients using isotretinoin had bilateral hearing threshold changes despite the absence of significant DPOAE and TEOAE amplitude levels. So for the precise clinical significance of the isotretinoin-induced neurophysiological alterations on the inner ear, still further animal and human studies are required.

We declare that there has been no conflict of interest regarding this clinical study.

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