Audiometry results and TEOAE and DPOAE amplitudes in men taking a phosphodiesterase type 5 inhibitor for erectile dysfunction

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Abstract

We conducted a prospective study of transient evoked otoacoustic emissions (TEOAEs) and distortion-product otoacoustic emissions (DPOAEs) in men who were taking an oral phosphodiesterase type 5 (PDE5) inhibitor for erectile dysfunction. Our study group was made up of 30 men (60 ears), aged 34 to 60 years (mean: 50.9). They were randomly divided into three groups; 10 men were given sildenafil (Viagra) at 50 mg twice a week, 10 were given tadalafil (Cialis) at 20 mg twice a week, and 10 were given vardenafil (Levitra) at 20 mg twice a week. All patients took their drug for 3 weeks, for a total of 6 tablets for each patient. Audiometric tests and TEOAE and DPOAE measurements were performed before and after treatment. Post-treatment audiometry demonstrated improvement in hearing in all three groups. However, post-treatment TEOAE amplitudes and DPOAE amplitudes differed among the three groups; they were significantly higher in the sildenafil group at 1.0 kHz and the same in the tadalafil group; in the vardenafil group, the DPOAE amplitude was significantly lower at 3.0 kHz while there was no change in the TEOAE amplitude. We speculate that the possible mechanism for these findings is that PDE5 inhibitors block degradation of cyclic guanosine monophosphate (cGMP) and induce dilation of the cochlear microcirculation, resulting in an increase in cochlear blood flow. We also believe that the decrease in DPOAE amplitudes at 3.0 kHz seen in the vardenafil group may be related to an accumulation of nitric oxide/cGMP complex, which is toxic to the cochlea; however, since there was no change in TEOAE amplitude in the vardenafil group, this influence may be minimal. Further studies are needed to obtain a more comprehensive assessment of the effects of PDE5 inhibitors on hearing with the use of higher doses and longer durations of therapy.

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Introduction

The prevalence and severity of erectile dysfunction increase in men aged 40 to 70 years, as does the incidence of comorbidities.[1,2] It is expected that more than 300 million men worldwide will experience erectile dysfunction by 2025.[1,3] Erectile dysfunction can be caused by psychogenic or organic factors or a combination thereof. The most common organic cause is vascular disease.[1,2,4]

The physiologic mechanism of penile erection during sexual stimulation involves release of nitric oxide (NO) from the cavernous nerves and vascular endothelial cells of the corpus cavernosum.[5] Vascular dilation occurs via relaxation of vascular smooth muscle, mediated by intracellular cyclic nucleotide/protein kinase messenger systems. NO activates the enzyme guanylate cyclase, which leads to an increase in the level of cyclic guanosine monophosphate (cGMP) and activation of cGMP-dependent protein kinase 1 phosphorylate proteins, which inhibit the calcium pump in the membrane of the sarcoplasmic reticulum. Free cytoplasmic calcium is reduced, smooth-muscle relaxation occurs, and blood

flow increases.[5] Type 5 phosphodiesterase (PDE5) inhibitors inhibit cGMP degradation by PDE5, increasing blood flow to the penis during sexual stimulation.[6]

The PDE5 inhibitors sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) have been used widely for about a decade to safely and effectively treat erectile dysfunction.[1] Sildenafil is a selective inhibitor of PDE5, which cleaves cGMP; cGMP amplifies parasympathetic neural stimulation. By inhibiting cGMP breakdown, sildenafil augments the effects of NO released in response to sexual stimulation, and it promotes smooth-muscle relaxation in the corpus cavernosum and ultimately penile erection.[7,8]

Tadalafil is a novel PDE5 inhibitor that enhances the smooth-muscle relaxation effects of NO which, again, play a central role in vasodilation of erectile tissues.[9] Tadalafil is distinguished from sildenafil and vardenafil by its prolonged duration of action, which can reach 36 hours after a single dose,[10] compared with about 4 to 5 hours for sildenafil[6,10] and vardenafil.[6]

Vardenafil specifically inhibits cGMP hydrolysis and significantly enhances sodium-nitroprusside–induced relaxation of human trabecular smooth muscle.[11]

In addition to their effect on the penis, PDE5 inhibitors also cause congestion of nasal erectile tissue, thereby elevating middle ear pressure.[12,13] It has also been suggested that PDE5 inhibitors may intensify the effects of NO, which has been implicated in several otologic diseases, or may simulate such effects by increasing the levels of intracellular cGMP.[14,15] PDE5 inhibitors function by blocking cGMP degradation. An accumulation of cGMP induces gene expression via phosphorylation of transcription factors by specific kinases, which are per se associated with damage to cochlear hair cells.[14]

Otoacoustic emissions (OAEs) are byproducts of cochlear function. An analysis of OAE characteristics over a range of stimuli yields information on cochlear status.

Transient evoked OAEs (TEOAEs) might be recorded in as many as 98% of normal ears.[16-18] The presence of TEOAEs indicates that a patient's hearing threshold is 20 dB HL or better. In patients with hearing losses greater than 40 dB HL, TEOAEs cannot be detected.[19]

Distortion-product OAEs (DPOAEs) are evoked with stimulation by tones at two frequencies (f1 and f2); they are also evoked at frequencies that combine these primary tones, because the tones interact in a nonlinear manner. DPOAE analysis is complex and data interpretation is difficult, but DPOAE testing is a valuable component of advanced clinical investigations in adults.[20] DPOAEs have previously been used as indicators of cochlear status.[21,22]

In this article, we describe our study of the cochlear effects of PDE5 inhibitors in men with erectile dysfunction.

Patients and methods

We conducted this prospective study in the ENT Department and Urology Department at the Kırıkkale University Faculty of Medicine. TEOAE and DPOAE recordings were prepared in the ENT Department's audiology unit.

Patients. The study group was made up of 30 men aged 34 to 60 years (mean: 50.9) who had erectile dysfunction. All had an International Index of Erectile Function (IIEF) score of 25 or less,[19,23,24] and their total testosterone and luteinizing hormone levels were within the range of normal.

Patients who had an eardrum perforation, acute otitis externa, or acute otitis media, and those who had previously used an ototoxic drug were not eligible for study participation.

All patients exhibited normal tympanic membranes on otoscopic examination. No patient had any contraindication to the use of a PDE5 inhibitor. No systemic complications caused by chronic disease were evident in any patient, and no symptom or finding of infectious ear disease was noted.

Patients were randomly and evenly assigned to one of three groups based on the order in which they presented to the Urology Department's outpatient clinic. Ten patients were given sildenafil in one 50-mg tablet twice weekly, 10 were given tadalafil in one 20-mg tablet twice weekly, and 10 were given vardenafil in one 20-mg tablet twice weekly. There were no significant differences in mean age among the three groups (53.2, 53.1, and 46.5 yr, respectively; $p = 0.116$). All patients were treated for 3 weeks, and thus each took six tablets throughout the course of the study.

IIEF scoring, ENT examinations, audiometry measurements, and TEOAE and DPOAE measurements, reflecting the functional status of outer hair cells,[23] were performed before and after treatment all 30 patients (60 ears).

Audiometry measurements. Audiometry measurements were performed with an AC40 Audiometer (Interacoustics; Middelfart, Denmark). Air- and bone-conduction thresholds were examined at 0.5 to 4.0 kHz. Pure-tone averages (PTAs) for both air and bone conduction were also calculated.

TEOAE measurements. TEOAE responses were recorded on an ILO292 DPE cochlear emission analyzer (Otodynamics Audiology Systems; Hatfield, U.K.). Recordings were made in a quiet room while patients were motionless and exhibiting regular spontaneous breathing. Plastic tube adapters were fitted over probes that housed sound sources and microphones to ensure that the probes fit well in the external auditory canals.

In each assessment, 260 stimuli (nonlinear clicks) were delivered. The responses were recorded in the

quick-screen mode using an 80-dB SPL (the dB peak-equivalent SPL) click stimulus. The frequency spectrum of each TEOAE response was in the range 1.0 to 4.0 kHz (1.0, 1.5, 2.0, 3.0, and 4.0 kHz). The magnitudes of the TEOAE responses were recorded as amplitudes in dB SPL.

DPOAE measurements. DPOAE recordings were made on the same cochlear emission analyzer in the same way as the TEOAE recordings. The acoustic stimulus consisted of two simultaneous continuous pure tones of different frequencies: f1 and f2 (f2/f1 = 1:22). The intensities were L1 and L2 for tones at frequencies f1 and f2, respectively, with L1 minus L2 = 10 dB SPL (L1 = 65 dB SPL, L2 = 55 dB SPL). DPOAEs were measured from 1.0 to 6.0 kHz.

Statistical analysis. Statistical analysis was performed with the Statistical Package for the Social Sciences software (v. 16.0). A p value of <0.05 was considered to represent statistical significance.

Ethical considerations. All aspects of the study were planned and executed according to the principles outlined in the Declaration of Helsinki.[24] All patients provided written informed consent, and our local Ethics Committee approved the work. The Good Clinical Practice Guidelines were followed.[25] Data from the specialization thesis of the first author (S.Ö.) were used in this study.[26]

Results

Audiometry results. For the audiometric measurements, the difference between the pre- and post-treatment findings at each frequency among the three groups was determined by Kruskal-Wallis variance analysis. When a statistically significant difference was detected, a pairwise comparison was performed with the Mann-Whitney U test with Bonferroni correction to identify the value that was responsible for the difference; in these cases, an adjusted value of $p < 0.0175$ was considered to be statistically significant. In each of the PDE5 groups, the difference between their pre- and post-treatment findings was analyzed by the Wilcoxon signed-rank test.

Post-treatment audiologic test results demonstrated an improvement in hearing in all three drug groups:

- air conduction at 4.0 kHz in the sildenafil group;
- air and bone conduction at 4.0 kHz the tadalafil group; and
- air conduction at 2.0 kHz, air conduction PTA and bone conduction at 0.5 kHz, and bone conduction PTA in the vardenafil group.

This improvement in hearing was believed to be the result of an increase in cochlear blood flow secondary to vasodilation caused by the drugs (data available in table form upon request from the corresponding author).

TEOAE results. For the TEOAE amplitudes, differences in pre- and post-treatment values at each frequency from 1.0 to 4.0 kHz in increments of 0.5 or 1.0 kHz among the three groups were determined by Kruskal-Wallis variance analysis. We found no statistically significant differences in pre- and post-treatment values among the groups.

The Wilcoxon signed-rank test was used to compare differences between pre- and post-treatment data in each group for each frequency from 1.0 to 4.0 kHz in increments of 0.5 or 1.0 kHz.

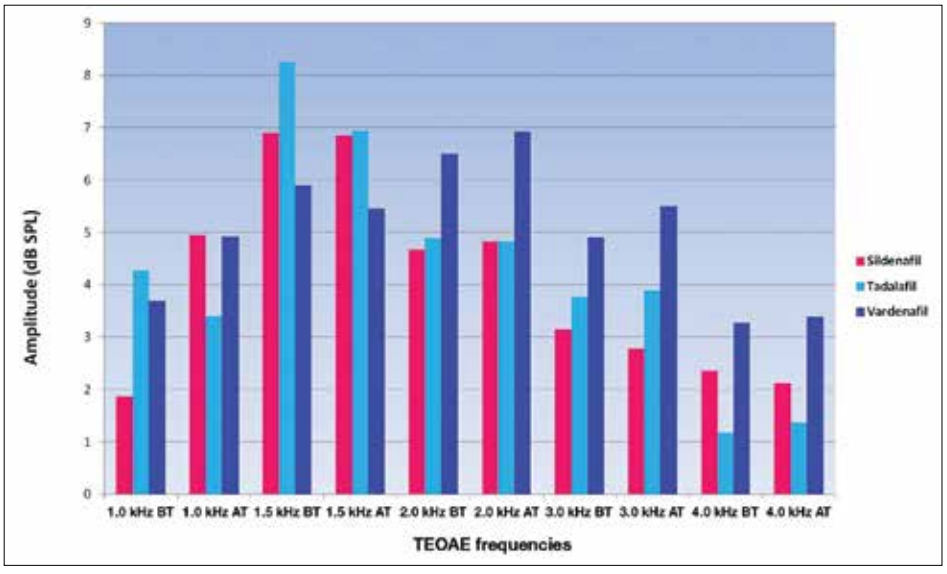

Figure 1. Graph shows comparison of TEOAEs in the three drug groups (BT = before treatment; AT = after treatment).

In the sildenafil group, the post-treatment TEOAE amplitude at 1.0 kHz was significantly higher than the pretreatment amplitude (4.95 ± 3.93 vs. 1.87 ± 2.47 dB SPL; p = 0.003). Differences at the other frequencies were not significant.

There were no significant differences in the tadalafil and vardenafil groups (figure 1; also, more data are available in table form upon request from the corresponding author).

DPOAE results. Differences in pre- and post-treatment DPOAE

amplitudes at each frequency from 1.0 to 4.0 kHz in increments of 0.5 or 1.0 kHz among the three groups were determined by Kruskal-Wallis variance analysis. We found no statistically significant differences among the groups.

The Wilcoxon signed-rank test was used to compare differences between pre- and post-treatment data in each group for each frequency from 1.0 to 4.0 kHz in increments of 0.5 or 1.0 kHz.

In the sildenafil group, the post-treatment DPOAE amplitude at 1.0 kHz was significantly higher than the pretreatment amplitude (4.66 ± 4.05 vs. 2.27 ± 3.45 dB SPL; $p = 0.015$). Differences at other frequencies were not statistically significant.

There were no statistically significant differences in the tadalafil group.

In the vardenafil group, the post-treatment DPOAE amplitude at 3.0 kHz was significantly lower than the pretreatment amplitude (6.37 ± 5.26 vs. 8.98 ± 6.26 dB SPL; $p = 0.048$). At 1.0 to 2.0 and 4.0 to 6.0 kHz, the differences were not significant (figure 2; also, more data are available in table form upon request from the corresponding author).

Discussion

PDE5 inhibitors block the action of PDE5 on cyclic GMP in the smooth-muscle cells that line the blood vessels that supply the corpus cavernosum of the penis. These drugs were the first effective oral treatments for erectile dysfunction.[6] Since PDE5 degrades cGMP, the inhibition of PDE5 slows such degradation, thereby increasing cGMP levels and triggering smooth-muscle relaxation in the blood vessels that supply the corpus cavernosum. Then blood flow through the corpus cavernosum increases, which is necessary for penile erection.[1,6]

In our study, post-treatment audiologic test results demonstrated an improvement in hearing in the sildenafil group (4.0 kHz air conduction), in the tadalafil group (4.0 kHz air and bone conduction), and in the vardenafil group (2.0 kHz air conduction, 0.5 kHz bone conduction, and PTAs). This improvement in hearing was believed to result from an increase in cochlear blood flow secondary to the vasodilation caused by these drugs.

In the sildenafil group, the post-treatment amplitudes of both TEOAE and DPOAE were significantly higher than the pretreatment values at 1.0 kHz. There were no significant differences between pre- and post-treatment TEOAE and DPOAE amplitudes in the tadalafil group. In the vardenafil group, the post-treatment DPOAE amplitudes were significantly lower at 3.0 kHz, while there were no differences in TEOAE amplitudes.

Sildenafil. It is known that in both humans and animals, ototoxic effects (e.g., sensorineural hearing loss [SNHL]) commence at high frequencies, corresponding anatomically to the basal turn of the cochlea. Later, these effects extend toward the lower frequencies. The lower frequencies are associated with the T2 and T3 areas and the apical turn of the cochlea.[27]

We found that sildenafil affected hearing at 1.0 kHz and vardenafil affected hearing at 3.0 kHz. Therefore, we speculate that PDE5 inhibitors principally affect the T2 and T3 areas and the apical turn of the cochlea. We also found that hearing improved with sildenafil treatment, as reflected in the increased TEOAE and DPOAE amplitudes at 1.0 kHz. This may be attributable to an increase in cochlear blood flow caused by the release of NO in the endothelium and the resultant increase in cGMP level, which triggers vasodilation.

Side effects of sildenafil include flushes, headache, nasal congestion, heartburn, and nonarteritic anterior ischemic optic neuropathy.[13,28-31] Mukherjee and Shivakumar reported that sildenafil also induced profound bilateral SNHL in a 44-year-old man after ingestion of 50 mg/day for 15 days.[32]

Hong et al ran electrophysical auditory brainstem response tests on days 0, 5, 10, 15, 25, 35, 105, and 135 of sildenafil treatment in a 7-week-old male rat and

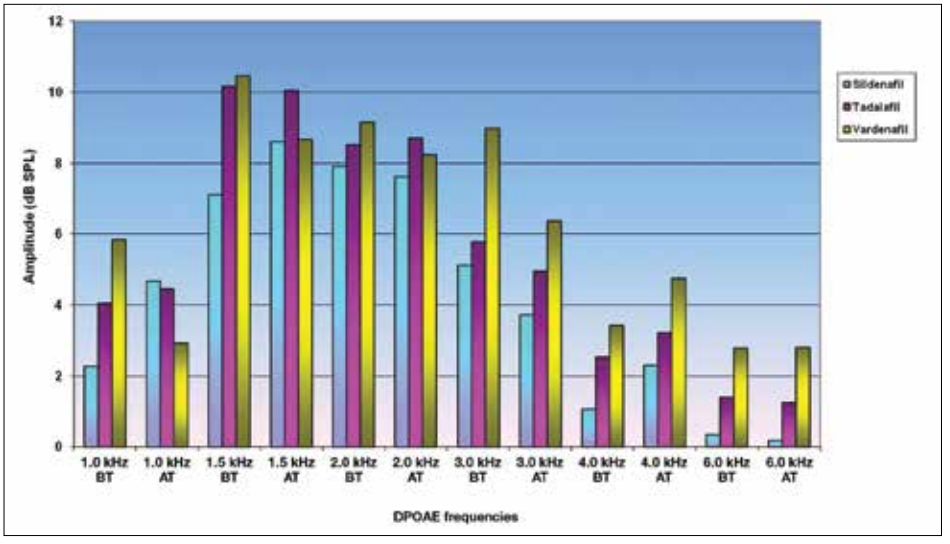

Figure 2. Graph shows comparison of DPOAEs in the three drug groups (BT = before treatment; AT = after treatment).

found that sildenafil increased hearing thresholds to clicks at 4.0 and 8.0 kHz in a time-dependent manner.[33] To assess the cochlear response of sildenafil-treated mice, they measured TEOAE amplitudes on day 105. Signal-to-noise ratios in the 2.0- and 3.0-kHz TEOAE test range in the sildenafil-treated animals fell into the stimulus range of 60 to 90 dB by day 105. Hong et al concluded that the outer hair cells of the organ of Corti were impaired.

Our findings differed from those of both Mukherjee and Shivakumar[32] and Hong et al.[33] Our TEOAE and DPOAE data showed that the 1.0-kHz thresholds increased after sildenafil treatment.

Hamzavi et al described the case of a 79-year-old man who developed severe vestibular neuritis-like symptoms (horizontal nystagmus with rotatory components and vomiting) 2 hours after taking a 50-mg dose of sildenafil.[34] The patient also complained of tinnitus in both ears. No pathologic findings were evident, and the patient had no history of cardiovascular disease. His symptoms lasted for 24 hours and then resolved completely. These symptoms were suggestive of a drug-related reaction, and they should be included in the (long) list of potential sildenafil side effects, although none of our patients reported any such effects.

McGwin evaluated a population-based sample of 11,525 men aged 40 years and older with and without self-reported hearing loss.[35] They found that the overall prevalence of hearing impairment and PDE5 inhibitor use in the two groups was 17.9 and 2%, respectively.[35] Men who reported hearing impairment were more likely to have used sildenafil. No significant association between hearing impairment and drug use was observed among men who took tadalafil or vardenafil.

Tadalafil. Tadalafil is generally well tolerated. When adverse events have occurred, they have included back pain, headache, dyspepsia,[36] and facial flushing.[37]

No report on the effects of tadalafil on TEOAE or DPOAE amplitudes has yet appeared. In our study, there were no differences in pre- and post-treatment amplitudes.

Vardenafil. The common adverse effects of vardenafil include flushes, headache, nasal congestion, dyspepsia, and nausea.[38] Okuyucu et al evaluated 18 patients with erectile dysfunction, including several who were taking vardenafil.[12] Audiometric testing using tones from 0.25 to 16.0 kHz was performed in all patients before ingestion and 1, 5, and 72 hours thereafter. Four patients exhibited unilateral decreases in hearing thresholds consistent with ototoxicity; these impairments were reversible. Okuyucu et al reported a statistically significant difference in pre- and post-treatment hearing thresholds at 10.0 kHz in right-sided ears ($p = 0.008$). They concluded that although temporary hearing losses occurred in 4 patients, no permanent deleterious effects were evident.

Snodgrass et al described the case of a 57-year-old man with erectile dysfunction who developed sudden deafness that was possibly associated with the use of vardenafil.[38] Audiometry confirmed a mild to moderate right-sided SNHL in the 0.5- to 3.0-kHz range. The patient was hospitalized 2 days later for administration of intravenous dexamethasone followed by oral prednisone. On hospital day 4, he reported that his hearing had improved, and he was discharged 3 days later with continued tapering of prednisone on an outpatient basis. Repeat audiometry performed after 10 days of steroid therapy confirmed that hearing in the 0.5- to 3.0-Hz range had returned to normal. Snodgrass et al concluded that vardenafil was a likely cause of hearing loss. Therefore, PDE5 inhibitor ingestion should be considered as a possible etiology in patients who present with sudden SNHL.

The findings of our study were consistent with those of Okuyucu et al[12] and Snodgrass et al[38] in that the DPOAE threshold at 3.0 kHz decreased after treatment with vardenafil, possibly secondary to an accumulation of an NO/cGMP complex that was toxic to the cochlea. The TEOAE amplitudes in these studies did not change. Since the DPOAE amplitude fell at only 3.0 kHz in our study, vardenafil's effects on hearing can be regarded as minimal.

In our study, a decrease in DPOAE amplitude at 3.0 kHz in the vardenafil group was evident only in the post-treatment data. Therefore, we recommend that vardenafil not be taken by patients with any hearing loss or known ear pathology. Patient noncompliance with vardenafil dosing or timing, very narrow intervals between drug ingestions, or simultaneous acoustic trauma may cause the DPOAE amplitude to decrease at 3.0 kHz. However, no patient in our study complained of tinnitus or vertigo, so the extent of NO/cGMP accumulation is likely to have been minimal.

In conclusion, our findings suggest that sildenafil-induced increases in OAE amplitudes at 1.0 kHz might have been associated with enhanced cochlear blood flow. The NO/cGMP system actively modulates cochlear microcirculation. An increase in cGMP level reduces intracellular calcium levels, triggering relaxation of the smooth muscles in the endothelial cells of blood vessels, the stria vascularis, and the basilar membrane. PDE5 inhibitors block cGMP degradation and induce vasodilation of vascular structures within the cochlear microcirculation, thus increasing cochlear blood flow.[12,14,39]

Further work is required to comprehensively assess the effects of the PDE5 inhibitors on hearing, particularly when higher doses are taken over prolonged periods.

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