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Main Article

Effect of phosphodiesterase-5 inhibitor on hearing

S Okuyucu, O E Guven*, E Akoglu, E Uçar†, S Dagli

Abstract

Objective: Following a report of sudden hearing loss in a patient taking phosphodiesterase type 5 inhibitor, and a Food and Drug Administration announcement concerning this class of drugs, a study was planned to investigate if ototoxicity occurs in patients using phosphodiesterase 5 inhibitor for erectile dysfunction.

Methods: Eighteen patients with erectile dysfunction who had been using phosphodiesterase 5 inhibitor were included in the study. Audiometric tests were performed on all patients, between the frequencies 250 and 16 000 Hz, before and 1, 5 and 72 hours after drug ingestion.

Results: Four patients showed a unilateral threshold decrease compatible with ototoxicity criteria; this change was reversible. A statistically significant difference in pre- versus post-drug hearing thresholds was observed in the right ear at 10 000 Hz ($p = 0.008$). There were no statistically significant hearing threshold differences at any other frequencies ($p > 0.05$).

Conclusion: Although temporary ototoxicity was noted in four patients, we could not find any permanent, deleterious effect of phosphodiesterase type 5 inhibitor on hearing thresholds.

Key words: Vardenafil; Sensorineural Deafness; Drug Toxicity

Introduction

Since the phosphodiesterase 5 inhibitors sildenafil, vardenafil and tadalafil were approved by the US Food and Drug Administration for the treatment of erectile dysfunction, the effectiveness and safety of these drugs has been much studied.[1,2] Although these well tolerated drugs are usually safely used, some adverse events have been reported in the literature, such as headache, flushing, abnormal vision and nasal obstruction.[3–8]

Recently, phosphodiesterase 5 inhibitors have been suspected of causing sudden sensorineural deafness.[9,10] FDA has announced 29 postmarketing reports of sudden hearing loss (defined as new hearing loss occurring over a period of three days or less) occurring after phosphodiesterase 5 inhibitor use, both with and without tinnitus and dizziness.[10] Clinical trials of these drugs have also reported sudden hearing loss in a few patients. One such trial reported sudden hearing loss, either unilateral or bilateral, occurring after the first dose in 10 of 25 cases; hearing loss was temporary in nine patients and permanent in one.[10]

It is well known that nasal physiology can affect eustachian tube function. It has also been shown that specific phosphodiesterase 5 inhibitors affect the erectile tissue in the nasal cavity and cause nasal congestion.[6–8] Therefore, it can be hypothesised that phosphodiesterase 5 inhibitors may change eustachian tube function and thus alter middle-ear pressure.

The aim of this study was to investigate the probable side effects of vardenafil on hearing and middle-ear pressure in patients with erectile dysfunction.

Materials and methods

The study was performed according to the Declaration of Helsinki and Good Clinical Practice Guidelines and approved by the ethics committee of Mustafa Kemal University School of Medicine.

After informed consent was obtained, a medical history was taken and otorhinolaryngological and general physical examinations were performed. Subjects who have received the drug for at least three weeks and who had any unusual findings such as stroke, cardiovascular disease or myocardial infarction in the previous six months were excluded from the study, as were any subjects with myringosclerosis, acute or chronic otitis media, or a history of ear surgery.

Audiometric tests were performed, including pure tone and high frequency air threshold testing between 125 and 16 000 Hz and additional bone threshold testing between 125 and 4000 Hz. These tests were conducted in a noise-insulated cabin, with Madsen Orbiter 922 equipment (Taastrup, Denmark), by an audiometrist unaware of patients' clinical details. Each subject completed the pre-drug audiometric assessment in

From the Departments of Otolaryngology, *Urology and †Internal Medicine, Mustafa Kemal University School of Medicine, Antakya, Hatay, Turkey.
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two consecutive days. After it was ensured that threshold differences were less than 5 dB between two measurements, baseline thresholds were set. Following the second baseline audiometric test, thresholds were assessed at 1–5 and 72 hours after 10 mg vardenafil had been ingested. Inter-test threshold changes were compared with baseline measures; thus, each subject served as their own control.

The study also evaluated the effect of phosphodiesterase 5 inhibitor on middle-ear pressure. For this reason, aural acoustic emission tests at the baseline session and at 1, 5 and 72 hours after vardenafil ingestion were performed with an AZ26 impedance audiometer (Interacoustics A/S, Assens, Denmark).

Ototoxicity was diagnosed according to the ototoxicity criteria of the American Speech Language Hearing Association, i.e.: (1) an alteration of at least 20 dB in any frequency; (2) an alteration of 10 dB or more in two consecutive frequencies; or, (3) loss of responsiveness in consecutive frequencies which was present in prior audiological evaluations.[11,12] These criteria imply significant clinical hearing loss.[13] Sudden deafness was defined as hearing loss greater than 30 dB in at least three consecutive frequencies developing within a maximum of 72 hours.[14]

As far as we are aware, this is the first study to use hearing loss as the primary outcome measure. Actual power was calculated with a post hoc power analysis. Using a sample size calculator (DSS Research, Fort Worth, Texas, USA), we calculated that a hearing loss incidence of 22 per cent and 18 cases gave a power of 0.81 with a 95 per cent confidence interval.

All data were tested for normal distribution using the Kolmogorov–Smirnov test. A repeated-measures analysis of variance was used to compare baseline hearing and middle-ear pressure with subsequent measurements longitudinally. Data were presented as mean $\pm$ standard deviation. Non-parametric data were tested with the Friedman test for several related samples (two-tailed). For all statistical tests used, values of $p < 0.05$ were considered statistically significant.

Results and analysis

Twenty-one patients were included in the study. Two patients with upper respiratory tract infections and one with a tympanic membrane perforation were excluded during the study. The remaining 18 patients were included. Patients' ages ranged between 45 and 65 years (mean 56.3 $\pm$ 6.6).

Four out of the 18 patients (22 per cent) demonstrated unilateral hearing loss which was clinically significant one hour after drug ingestion. As per the ototoxicity criteria cited above, a 20 dB decrease in any frequency was identified in two patients (at 6000 Hz in one and at 8000 Hz in the other) (Figure 1). Two patients showed a 10 dB or more threshold alteration in two consecutive frequencies (2000–4000 Hz and 8000–10 000 Hz) (Figure 2). All four patients' hearing thresholds returned to normal, within 5 hours in three patients and within 72 hours in one patient. A statistically significant difference in pre- *vs* post-drug hearing thresholds

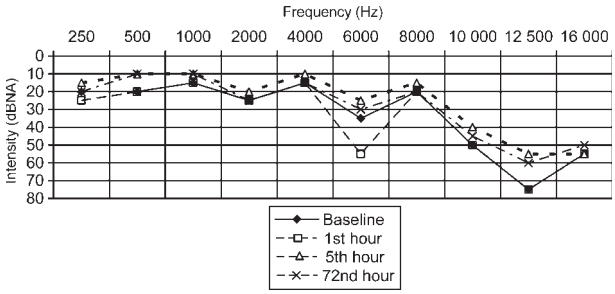

FIG. 1

Pure tone thresholds for the left ear of the patient showing a 20 dB alteration at 6000 Hz, one hour after drug ingestion. This threshold change returned to normal 5 hours after drug ingestion.

was observed in the right ear of all patients at 10 000 Hz ($p = 0.008$, Pillai's trace). Apart from this, there were no statistically significant hearing threshold differences ($p > 0.05$) at any frequency of all patients at comparing audiograms at baseline and at 1, 5 and 72 hours after drug ingestion (Table I). Inter-test middle-ear pressure change assessment revealed no significant differences on the right ($p = 0.30$, Pillai's trace) or left ($p = 0.07$, Pillai's trace) sides when compared with baseline measures (Table II). No patient complained of sudden deafness after taking the drug.

Discussion

Phosphodiesterase 5 is found in the corpus cavernosum, platelets and skeletal muscle and in vascular and visceral smooth muscle. Phosphodiesterase 5 inhibits penile erection and smooth muscle relaxation and promotes platelet aggregation. Therefore, adverse reactions to vardenafil may be related to its effects on phosphodiesterase 5 concentrations in these locations.[3] Vardenafil is a specific phosphodiesterase 5 inhibitor and is rapidly absorbed, with maximal plasma concentrations occurring within one hour of oral administration and a mean terminal half-life of four to five hours.[1] Thus, pure tone and high frequency audiograms were obtained before

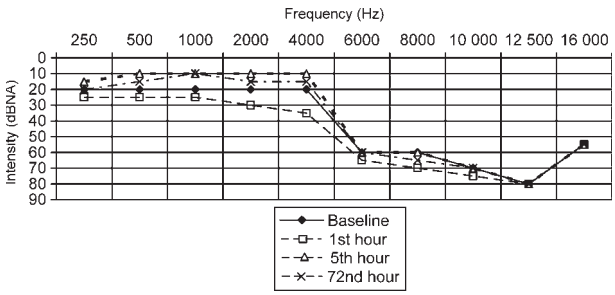

FIG. 2

Pure tone thresholds for the left ear of one of the two patients showing a 10 dB or more alteration in two consecutive frequencies (2000–4000 Hz in this patient) on conventional and high-frequency audiometry. The patient's hearing thresholds returned to normal five hours after drug ingestion.

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TABLE I

SUBJECTS* HEARING THRESHOLDS AFTER PHOSPHODIESTERASE 5 INHIBITOR INGESTION

Test frequency (Hz)	Time post-Rx (hr)	Right ear		Left ear	
		Threshold (dB)	$p^{\dagger}$	Threshold (dB)	$p^{\dagger}$
250	0	18.8 ± 15.8	0.72	16.6 ± 12.8	0.20
	1	18.0 ± 13.9		17.5 ± 10.0	
	5	16.9 ± 14.6		15.8 ± 9.5	
	72	18.3 ± 14.8		17.5 ± 10.6	
500	0	17.5 ± 14.1	0.08	15.8 ± 11.5	0.06
	1	16.1 ± 13.2		14.4 ± 10.5	
	5	14.4 ± 13.1		13.0 ± 11.1	
	72	17.7 ± 13.4		15.2 ± 11.6	
1000	0	12.7 ± 10.8	0.06	12.7 ± 9.1	0.07
	1	11.9 ± 9.4		10.5 ± 9.0	
	5	10.8 ± 8.2		9.7 ± 6.9	
	72	13.6 ± 9.6		11.6 ± 8.0	
2000	0	14.7 ± 12.1	0.16	13.8 ± 9.6	0.71
	1	13.0 ± 11.7		13.3 ± 10.1	
	5	14.1 ± 12.7		12.7 ± 8.4	
	72	12.0 ± 12.0		13.0 ± 9.5	
4000	0	30.0 ± 19.0	0.14	29.4 ± 18.0	0.53
	1	26.6 ± 17.9		29.1 ± 14.5	
	5	27.2 ± 18.9		26.9 ± 15.7	
	72	29.4 ± 18.4		28.0 ± 16.4	
6000	0	37.5 ± 21.9	0.53	43.8 ± 21.7	0.36
	1	36.1 ± 20.3		43.6 ± 22.1	
	5	37.5 ± 22.3		41.1 ± 21.8	
	72	36.9 ± 21.9		42.7 ± 20.9	
8000	0	41.1 ± 28.9	0.58	42.7 ± 27.7	0.40
	1	40.8 ± 29.1		43.6 ± 27.4	
	5	40.5 ± 29.1		42.2 ± 27.1	
	72	41.6 ± 28.9		43.8 ± 26.5	
10 000	0	58.3 ± 24.6	0.008‡	65.2 ± 20.8	0.24
	1	56.6 ± 25.3		65.0 ± 20.2	
	5	56.6 ± 25.8		63.6 ± 20.4	
	72	59.4 ± 24.9		65.2 ± 20.0	
12 500	0	70.5 ± 16.3	0.28	70.5 ± 13.7	0.92
	1	68.8 ± 17.9		70.8 ± 13.5	
	5	69.1 ± 17.2		70.0 ± 12.7	
	72	70.8 ± 14.9		70.5 ± 12.9	
16 000	0	46.9 ± 10.5	0.18**	52.5 ± 6.4	0.20**
	1	45.2 ± 11.4		52.2 ± 5.4	
	5	45.5 ± 10.9		52.7 ± 5.2	
	72	45.8 ± 10.6		51.6 ± 6.4	

Data shown as mean ± standard deviation, following repeated-measures analysis of variance. *$n = 18$. †Comparing hearing threshold results for one test frequency over the 72-hour test period. ‡Statistical significance compared with baseline value. **Friedman test. Post-Rx = after drug ingestion; hr = hours

drug ingestion and 1, 5 and 72 hours afterwards, in order to observe the acute effect of the drug on hearing.

The three drugs most widely prescribed for erectile dysfunction (sildenafil, vardenafil and tadalafil) share many pharmacological and clinical characteristics. These drugs affect smooth muscles by affecting the action of nitric oxide (NO). The relaxant effect of NO on the smooth muscle of the corpus cavernosum is mediated by activation of guanylate cyclase. With guanylate cyclase activation, the tissue concentration of cyclic guanosine monophosphate (cGMP) is

TABLE II

SUBJECTS* MIDDLE-EAR PRESSURE RESULTS FOLLOWING PHOSPHODIESTERASE 5 INHIBITOR INGESTION

Time post-Rx (hr)	Right ear		Left ear	
	Pressure (daPa)	$p^{\dagger}$	Pressure (daPa)	$p^{\dagger}$
0	−50.6 ± 23.8	0.30	−58.0 ± 25.0	0.07
1	−53.2 ± 20.2		−53.7 ± 19.1	
5	−45.0 ± 18.2		−48.0 ± 13.9	
72	−50.7 ± 20.1		−52.3 ± 17.6	

Data are shown as mean ± standard deviation after repeated-measures analysis of variance. *$n = 18$. †Comparing middle-ear pressure results over the 72-hour test period. Post-Rx = after drug ingestion; hr = hours

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elevated. cGMP reduces intracellular calcium, thus leading to smooth muscle relaxation. The degradation of cGMP into its inactive form guanosine monophosphate (GMP) is catalysed by cyclic nucleotide phosphodiesterase. Phosphodiesterase 5 is the predominant isoform of this enzyme in the corpus cavernosum. Inhibitors of this enzyme prevent the breakdown of cGMP, resulting in enhanced penile erection (i.e. phosphodiesterase 5 inhibitor acts by extending the action of cGMP).[7] Phosphodiesterase 5 inhibitor has also been shown to induce vasodilatation in several vascular beds by inhibiting cGMP breakdown.[3–8]

It has been suggested that the NO/cGMP system is more active in the cochlear microcirculation.[15] The existence of NO has been demonstrated in the endothelial cells of blood vessels of the spiral ligament, the stria vascularis, and the spiral blood vessels of the basilar membrane.[15] Following the discovery of all the components of the NO/cGMP pathway in the cochlea, it has been supposed that this signalling pathway is involved in inner-ear physiology, particularly in auditory transmission, endolymphatic fluid homeostasis and blood flow regulation.[16] However, the exact role of the NO–GMP–cGMP-dependent protein kinase (PKG) pathway in auditory neurotransmission remains to be clarified.[17]

The NO–GMP–cGMP–PKG signalling pathway is thought to regulate Ca^{2+} in the sensory systems controlling olfaction[18] and vision.[19] It is well known that phosphodiesterase 5 inhibitor may produce visual disturbances[5] and decreased olfactory sensitivity.[20] Morphological studies have demonstrated that the NO–GMP–cGMP–PKG signalling pathway exists in the cochlea;[21,22] it could therefore be hypothesised that vardenafil may cause hearing alterations.

It has been shown that ototoxic side effects of drugs are dose-related such as quinine, salicylates and aminoglycosides.[23] In patients with pulmonary arterial hypertension, phosphodiesterase 5 inhibitors are used in both continuous and high doses, compared with the doses used to treat erectile dysfunction. In a study of 660 pulmonary arterial hypertension patients receiving phosphodiesterase 5 inhibitor treatment, five cases of phosphodiesterase 5 inhibitor related hearing disturbance have been reported, including cases of sudden hearing loss due to phosphodiesterase 5 inhibitor treatment.[10] Sildenafil therapy was continued in all cases. The sudden hearing loss resolved in two cases (2 months in one case, 1 day in the other), however, the hearing impairment was still present at the end of the study in three cases. However, because of a lack of prospective clinical studies undertaking hearing threshold screening in this group of patients, it is difficult to determine the effect of phosphodiesterase 5 inhibitors on hearing, and the exact incidence of hearing loss, at such continuous and higher doses.

The results of the current study did not demonstrate any permanent hearing loss in patients receiving phosphodiesterase 5 inhibitor. It is interesting to note that, although statistically insignificant, an increase in hearing acuity was observed in some subjects, especially in the first and fifth hours; however, none of these patients reported an improvement in their hearing. It is possible that subjects became accustomed to the audiometric investigations, as they underwent testing three times in the one day (at 0, 1 and 5 hours). There was a statistically significant difference only at 10 000 Hz, compared with baseline audiometric results. This result, although statistically significant, does not appear to be clinically significant.[24] Early detection of hearing loss due to potentially ototoxic drugs requires a baseline audiogram and serial monitoring of a patient's thresholds. High frequency audiometry is highly sensitive for early detection of the ototoxic effects of drugs.[23]

- **Phosphodiesterase 5 inhibitors (sildenafil, vardenafil and tadalafil) have been approved for the treatment of erectile dysfunction**
- **There has been recent speculation on the possibility of these drugs causing sensorineural deafness**
- **This study investigated the possible ototoxic effects of vardenafil**
- **Temporary ototoxicity was seen in four out of 18 patients. There were no permanent effects**
- **Further study is needed regarding the possibility of ototoxicity as a side effect of this group of drugs**

Eustachian tube obstruction and dysfunction may occur due to retrograde spread of an inflammatory process, which may cause nasal mucosal congestion and oedema, impaired mucociliary activity of the nasal pharyngeal mucosa, or obstruction of the lumen due to seromucous gland hypersecretion.[25] Therefore, nasal obstruction can alter eustachian tube function and may influence middle-ear pressures.[26,27] The penile corpus cavernosum and the nasal erectile tissue are very similar structures, and both are specifically affected by phosphodiesterase 5 inhibitors. In the nasal cavities, erectile tissue is located in three sites: the inferior turbinate, the middle turbinate and the nasal septum.[7] It has been shown that specific PDE-5i effects the erectile tissues in the nasal cavity and causes congestion of the mentioned parts of the nose.[6–8] According to the results of present study, this may not spread an inflammatory process towards the eustachian tube in a retrograde fashion that may result in alterations of middle ear pressure.

Conclusion

The present study findings appear to indicate that vardenafil does not affect middle-ear pressure or cause sudden deafness, at a dose of 10 mg. However, clinically significant hearing loss was detected in four patients, which appeared at the time of maximum drug plasma concentration and persisted beyond the mean terminal half-life of the

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drug. Therefore, it could be suggested that phosphodiesterase 5 inhibitor may cause reversible biochemical and metabolic changes in the cochlea, rather than morphological abnormalities. Because such ototoxic side effects are dose-related, further studies using higher doses are needed, in order to determine the exact effects of phosphodiesterase 5 inhibitor on hearing. It may be prudent to inform patients taking phosphodiesterase 5 inhibitors for erectile dysfunction about the possible effects of the drug on hearing.

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Address for correspondence:
Dr Semsettin Okuyucu,
Mustafa Kemal Universitesi Tıp Fakultesi,
Arastirma Hastanesi, KBB AD,
31100 Antakya, Hatay, Turkey.

E-mail: semsettinokuyucu@yahoo.com

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