

CASE REPORT

Sudden Sensorineural Hearing Loss Associated with Vardenafil

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The phosphodiesterase type 5 (PDE-5) inhibitors—sildenafil, vardenafil, and tadalafil—are used primarily in erectile dysfunction, but sildenafil is also indicated for pulmonary hypertension. Common adverse effects of vardenafil include headache, flushing, nasal congestion, dyspepsia, and nausea. Recently, PDE-5 inhibitors have been associated with adverse vision effects, and emerging evidence now indicates that they may also be responsible for hearing changes and hearing loss. We describe a patient who developed unilateral sudden sensorineural hearing loss possibly related to the use of vardenafil for erectile dysfunction. To our knowledge, only one other case of hearing loss related to this drug class has been published. Our patient was a 57-year-old man who came to the emergency department with right-sided mild-to-moderate hearing loss in the 500–3000-Hz range, confirmed by audiogram, that occurred after ingestion of vardenafil. The patient was hospitalized 2 days later for administration of intravenous dexamethasone, followed by oral prednisone. He reported that his hearing had improved on the fourth hospital day and was discharged 3 days later, continuing to taper the prednisone on an outpatient basis. A repeat audiogram after 10 days of corticosteroid therapy confirmed that his hearing in the 500–3000-Hz range was within normal limits. Use of the Naranjo adverse drug reaction probability scale indicated a possible (score of 3) adverse reaction of sudden sensorineural hearing loss associated with vardenafil consumption. We also performed an analysis of hearing loss cases related to PDE-5 inhibitors in the United States Food and Drug Administration's Adverse Event Reporting System database to compare the characteristics of our patient with those of other reported adverse event cases. Based on the temporal relation of the sudden sensorineural hearing loss to this patient's drug consumption, we propose that the vardenafil is a likely cause of the hearing loss. This case provides further evidence that PDE-5 inhibitor consumption should be considered as a possible cause in patients presenting with sudden sensorineural hearing loss.

Key Words: vardenafil, phosphodiesterase type 5 inhibitors, PDE-5, sudden sensorineural hearing loss, SSHL, adverse drug reactions, drug safety.

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Sudden sensorineural hearing loss is a symptom of cochlear injury, presumed to be a disturbance of the circulation of the inner ear. Known causes of sudden sensorineural hearing loss include viral or bacterial infection and inflammation, trauma to the ear, vascular

occlusive disease, cochlear membrane rupture, immune-mediated inner ear disease, systemic autoimmune disease, metabolic disease, ototoxic drugs, and primary and metastatic neoplasm.¹ In fact, more than 100 possible causes for sudden deafness have been identified in the literature.²

The most common drugs implicated as being ototoxic include aminoglycoside antibiotics, platinum-based antineoplastic drugs, salicylates, and loop diuretics.³

Sudden sensorineural hearing loss can occur suddenly or gradually over a number of years and is usually defined as hearing loss occurring in a short period of time, from 12 hours–3 days. Tinnitus and the sensation of “fullness” in the ears is common in sudden sensorineural hearing loss, whereas vertigo is reported in less than half of cases. In the general population, estimates of the incidence of sudden sensorineural hearing loss range from 5–20 cases/100,000 persons/year.¹ Between 10% and 33% of sudden sensorineural hearing loss cases remain idiopathic after a detailed history and competent differential diagnosis. Most cases are described in adults and are typically unilateral. Recovery of most of the hearing loss occurs without specific treatment in about 50% of idiopathic sudden sensorineural hearing loss cases within the first month.

The phosphodiesterase type 5 (PDE-5) inhibitors—sildenafil, vardenafil, and tadalafil—are approved by the United States Food and Drug Administration (FDA) and prescribed widely for use in erectile dysfunction. The PDE-5 inhibitors treat erectile dysfunction by preventing the breakdown of cyclic guanosine monophosphate (cGMP). The increase in cGMP augments the effects of nitric oxide, leading to increased smooth muscle relaxation and penile erection.⁴ Vardenafil is well tolerated in most patients, and the most common adverse effects include headache, flushing, nasal congestion, dyspepsia, and nausea.⁵ In July 2005, the FDA announced label changes in response to reports of non-arteritic ischemic optic neuropathy in patients taking PDE-5 inhibitors.⁶ In premarketing trials, sudden sensorineural hearing loss was rarely reported with the use of PDE-5 inhibitors. Of approximately 60,000 patients in premarketing trials, 10 cases of sudden sensorineural hearing loss were reported with sildenafil (five each for

treatment of erectile dysfunction and pulmonary hypertension), and three cases were reported with vardenafil and four with tadalafil in patients receiving treatment for erectile dysfunction.⁷

To our knowledge, only one published case of sudden sensorineural hearing loss after sildenafil ingestion has been published.⁸ However, in October 2007, after this case was reported, the FDA reviewed its Adverse Events Reporting System (AERS) and found 29 cases of sudden sensorineural hearing loss occurring within 3 days of the last PDE-5 inhibitor dose.⁹ These 29 cases include five cases each related to vardenafil and tadalafil and 19 cases related to sildenafil (four patients were receiving treatment for pulmonary artery hypertension and 15 for erectile dysfunction). Of these, one third reported temporary hearing loss and some reports mentioned tinnitus and/or dizziness in conjunction with the hearing loss. This discovery prompted labeling changes in November 2007 to reflect the risk of hearing loss.⁷ After the sildenafil case report⁸ and the FDA’s investigation of the AERS data,⁹ a group of authors assessed high-dose sildenafil’s effects on hearing impairment in mice.⁴ They found a significant dose-related impairment of hearing over time in mice treated with sildenafil.

In this report, we describe a patient with temporary unilateral sudden sensorineural hearing loss after ingestion of vardenafil for erectile dysfunction. In addition, we reviewed the cases in the AERS database and discuss the possible causes and contributing factors in our patient.

Case Report

A 57-year-old man came to the Veterans Affairs Palo Alto Health Care System emergency department with right-sided hearing loss that began 5 days earlier. No visible signs of infection, cerumen impaction, or discharge in the right ear were noted. The patient reported a feeling of fullness in the right ear, accompanied by a hissing, crackling sound. The symptoms began within hours after his first dose of vardenafil 2.5 mg. Before taking his dose of vardenafil, the patient reported also taking a sublingual, nonprescription drug for erectile dysfunction, with a name “something like Primum or Primus.” He had taken sildenafil in the past without incident.

The patient’s concomitant diseases included human immunodeficiency virus (HIV) infection,

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poorly controlled type 2 diabetes mellitus, hyperlipidemia, chronic kidney disease, and hypertension. In addition to vardenafil, his drug therapy included abacavir-lamivudine-zidovudine, lopinavir-ritonavir, tenofovir, lisinopril, atenolol, trimethoprim-sulfamethoxazole, gemfibrozil, and glipizide. His antiretroviral regimen was a result of documented resistance to three antiretroviral classes. Three months before this episode of sudden sensorineural hearing loss, his HIV-1 viral load was less than 50 copies/ml, and his CD4⁺ lymphocyte count and percentage were 268 cells/mm³ and 14%.

As a U.S. Army veteran who spent 2 years in the infantry from 1970–1971, the patient was repeatedly subjected to loud noises such as helicopters, ground transport vehicles, and gunfire. Just over a year was spent in Vietnam, during which he was exposed to Agent Orange. He denied any hearing loss or problems at that time. His occupational history included working as a cook in a retirement home from 1990–2003 and as a security guard from 2003–2005. He reported wearing earplugs when working in buildings with loud noises and denied any hearing loss during those periods.

An audiogram completed the day after presenting to the emergency department confirmed right-sided high-frequency sensorineural hearing loss at 3000–8000 Hz. The audiogram demonstrated mild-to-moderate sensorineural hearing loss in the right ear in the 500–3000-Hz range. Hearing in the left ear was within normal limits in the 125–3000-Hz range. Moderate-to-severe, symmetric, bilateral, high-frequency sensorineural hearing loss at 4000–8000 Hz was noted.

The day after the audiogram confirmed his hearing loss, he was admitted to the hospital for monitoring, rather than for administering corticosteroid therapy on an outpatient basis, due to his poorly controlled diabetes, substantiated with blood glucose levels routinely above 400 mg/dl (normal range 70–100 mg/dl) and hemoglobin A_{1c} of 11.3% (normal 4.0–6.0%, goal < 7.0%). He was given an initial dose of intravenous dexamethasone 20 mg followed by intravenous dexamethasone 10 mg every 8 hours for 3 days. He was then prescribed an oral prednisone taper over a period of 3 weeks, starting at 60 mg/day.

The patient reported that his hearing returned to normal on the fourth hospital day (6 days after presentation), and he was discharged 3 days later. After 10 days of corticosteroid treatment,

repeat audiogram demonstrated normal hearing at 500–3000 Hz in the right ear, with no change in the left ear. However, bilateral, symmetric high-frequency sensorineural hearing loss at 4000–8000 Hz remained. One month after hospital discharge, no further hearing problems were reported. At that time, his HIV-1 viral load was 99 copies/ml and CD4⁺ lymphocyte count and percentage were 283 cells/mm³ and 13%. Another audiogram obtained 4 months after discharge confirmed that his right-sided sensorineural hearing loss at 500–3000 Hz had resolved.

Discussion

Based on the information reported by the patient and the information in his medical record, the vardenafil or the nonprescription erectile dysfunction sublingual tablet is the most temporally relevant source of his hearing loss. As previously mentioned, the patient could not identify the nonprescription agent he took before his dose of vardenafil. For this reason, we cannot rule it out as the cause of his sudden sensorineural hearing loss. In addition, the patient also had other possible confounders associated with hearing loss, including Agent Orange exposure, HIV infection, and HIV drug therapy. Use of the Naranjo adverse drug reaction probability scale indicated that the relation of the hearing loss to the vardenafil consumption was possible (score of 3).¹⁰

Possible Confounders Associated with Hearing Loss

Although the patient could not identify the nonprescription erectile dysfunction agent he took before the dose of vardenafil, a search of the terms “erectile dysfunction treatment” and “sublingual tablet” did return a possible candidate. A sublingual apomorphine hydrochloride tablet is marketed under the brand name Uprima (TAP Pharmaceuticals; now Takeda Pharmaceuticals North America, Deerfield, IL). Uprima is available in the United Kingdom and parts of Europe, but is not currently available in the United States.¹¹ It is useful to note, if our patient’s unknown agent was Uprima, there are no reports in the FDA AERS database linking apomorphine to any hearing loss or related terminology. Further, a PubMed search using the Medical Subject Headings terms “apomorphine” and “hearing loss” returned no

results.

There is evidence that Agent Orange exposure may be correlated with hearing loss. The Veterans Health Administration (VHA) reports hearing loss in 3% of the registered Vietnam veterans in the Agent Orange Registry (5540 cases/186,495 registrants).¹² The VHA has also reported on the Vietnam Experience Study conducted by the Centers for Disease Control and Prevention.¹³ The study evaluated hundreds of physical health items including blood pressure, vision and hearing examinations, electrocardiograms, and immunologic and pulmonary parameters. No statistically significant differences were found for most of these items between the Vietnam veteran group and the non-Vietnam veteran group. However, hearing loss was reported as being one of the most “noteworthy” differences between the two groups. We were unable to find a timeline regarding Agent Orange-related hearing loss and cannot assess whether the timing in our patient is similar to that of other cases.

With regard to our patient’s other drugs, ototoxicity and hearing loss have been reported in conjunction with both nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors.^{14, 15} The cases of three veterans with previous noise trauma who experienced worsening of hearing when treated with NRTIs have been described.¹⁴ The NRTIs involved included zidovudine, stavudine-lamivudine, and stavudine-lamivudine-didanosine, with onset at 6 months, approximately 1 year, and 4 months, respectively. Our patient was treated with lamivudine, abacavir, and zidovudine for over 3 years. In response to the above-mentioned cases, another author reported a case of hearing loss 4 weeks into therapy in a patient taking lopinavir-ritonavir in addition to lamivudine, abacavir, and zidovudine.¹⁵ Ritonavir inhibits cytochrome P450 (CYP) 3A4, which is the major enzyme responsible for vardenafil metabolism. Inhibition of CYP3A4 by ritonavir has been shown to increase the half-life and plasma levels of vardenafil.¹⁶ It has also been reported that combining vardenafil with a total daily dose of 1200 mg of ritonavir can increase plasma concentrations up to 49-fold.¹⁷ Our patient had been treated with lopinavir-ritonavir in addition to his NRTI therapy for more than 3 years, and his total daily dose of ritonavir at the time of the event was 200 mg. Doses of ritonavir 100–200 mg/day, used for boosting plasma concentrations of other HIV-1 protease inhibitors when given in

Table 1. Comparison of Our Patient’s Characteristics and Those of 62 Cases of PDE-5 Inhibitor–Related Adverse Events Reported in the Adverse Event Reporting System Database

Characteristic	Our Patient	AERS Cases (n=62)
Age, mean (range) (yrs)	57	58.2 (36–75) ^a
Vardenafil dose (mg)	2.5	2.5–10
		No. (%) of Cases
Male	Yes	55/61 (90)
Hearing loss		
Unilateral	Yes	16 (26)
Associated with tinnitus	Yes	13 (21)
Associated with dizziness	No	12 (19)
Erectile dysfunction was indication for therapy	Yes	55 (89)
Hearing returned on drug dechallenge	Yes	7/28 (25)
Event occurred on first day of therapy	Yes	6/13 (46)
Concomitant drugs		
β-Blockers	Yes	9 (15)
Sulfonylureas	Yes	3 (5)
ACE inhibitors	Yes	3 (5)
Comorbidities		
Hypertension	Yes	23 (37)
Diabetes mellitus	Yes	7 (11)
Hyperlipidemia	Yes	5 (8)
HIV positive or AIDS	Yes	1 (2)

PDE-5 = phosphodiesterase type 5; AERS = U.S. Food and Drug Administration Adverse Event Reporting System; ACE = angiotensin-converting enzyme; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

^aData were reported for only 49 cases.

combination, are more than sufficient to inhibit CYP3A4-metabolized drugs.

There is evidence that HIV infection or a complication of the infection may lead to hearing loss. Opportunistic infections such as *Pneumocystis jiroveci*, toxoplasmosis, or various causes of meningitis have been found to involve hearing loss.¹⁸ Viral infections in general are widely implicated in cases of sudden sensorineural hearing loss, with some postulating one third of such cases having a recent viral infection. In addition to being lymphotropic, the HIV virus has been shown to be neurotropic and may invade neural tissue to cause hearing loss directly.¹⁹ Our patient did not have any of these secondary or opportunistic infection complications, nor did he have evidence of current or recent infection of the ear.

Review of Adverse Event Reporting System Data

We analyzed the AERS database through the first quarter of 2007 for adverse events after administration of a PDE-5 inhibitor (sildenafil,

tadalafil, or vardenafil). Search terms were sudden hearing loss, sudden hearing loss not otherwise specified, deafness, deafness not otherwise specified, deafness unilateral, deafness neurosensory, deafness bilateral, hearing impairment aggravated, hearing impaired, hard of hearing, hearing aid user, hearing disability, inner ear disorder, ear disorder, ear discomfort, ear pain, and ear injury.

Within the 62 cases found in our search (Table 1), 16 (26%) specifically mentioned the fact that the hearing loss was unilateral in nature, 13 (21%) reported tinnitus accompanied with the hearing loss, and 12 (19%) reported experiencing dizziness or vertigo with the hearing loss (not including an additional three cases reporting orthostatic hypotension or positional dizziness). Of the 49 cases that reported age, the mean age was 58.2 years (range 36–75 yrs). In the 61 cases reporting sex, 55 (90%) were male.

Within the AERS cases, doses up to 10 mg/day for vardenafil, 20 mg/day for tadalafil, and 150 mg/day (for pulmonary arterial hypertension) for sildenafil were reported. Seven (11%) of the 62 patients were taking the PDE-5 inhibitor for pulmonary hypertension; therefore, most patients were prescribed the PDE-5 inhibitor for erectile dysfunction, the same indication as that of our patient. Of the 28 cases reporting dechallenge information, 7 (25%) reported return of hearing when the drug was discontinued, whereas 6 (21%) reported that hearing loss did not abate when the drug was stopped. We could not determine from our review how many patients may have received corticosteroids. The other cases reporting dechallenge information stated that it did not apply or it was unknown if the adverse event terminated. None of the cases reported rechallenge information. Among the 13 cases reporting duration of therapy before hearing loss, the range was from day 0–2 years. Six of these cases stated it was the first day of therapy, another three reported the adverse event within the first 2 months of drug therapy, one reported hearing loss at 6 months, two reported hearing loss at approximately 1 year of drug therapy, and one reported hearing loss 2 years into therapy.

In an effort to look at our patient's characteristics and generalize them to those of the patients in the 62 cases reporting a similar adverse event (Table 1), we found that concomitant drugs at the onset of hearing loss were β -blockers in 9 (15%), sulfonyleureas in 3 (5%), and angiotensin-converting enzyme

inhibitors in 3 (5%); 16 (26%) did not report use of any drug other than the PDE-5 inhibitor. As previously mentioned, our patient had several comorbidities. As comorbidities were not available for analysis in the AERS dataset, we used the drugs reported in the cases as proxies for disease states in the 62 cases. This method has limitations because the drugs used as proxies may have multiple indications, just as using sildenafil as a proxy for erectile dysfunction might be confounded by patients who received the drug for pulmonary hypertension. Comparing our patient's comorbidities with those derived from the proxy drugs in the 62 cases, 7 (11%) had diabetes, 23 (37%) had hypertension, 1 (2%) had HIV-acquired immunodeficiency syndrome, and 5 (8%) had hyperlipidemia.

Conclusion

Our patient experienced temporary, right-sided, sudden sensorineural hearing loss. Several factors may have contributed to this event, including previous noise trauma, Agent Orange exposure, his prescription or nonprescription erectile dysfunction drugs, or HIV infection. We propose that the hearing loss that occurred immediately after his first dose of the non-prescription erectile dysfunction sublingual tablet and vardenafil indicates a possible relationship to the drugs. Furthermore, our patient shares characteristics with the cases of hearing loss reported as a result of pharmacovigilance efforts in patients who ingested PDE-5 inhibitors. Shared characteristics include unilateral hearing loss, return of hearing on dechallenge, hyper-tension, and consistent age and duration of therapy. Therefore, we present this as a case of hearing loss possibly related to vardenafil consumption and as further evidence that clinicians should consider PDE-5 consumption in patients with sudden sensorineural hearing loss on presentation.

References

1. Byl F. Sudden hearing loss: eight years experience and suggested prognostic table. *Laryngoscope* 1984;94:647–61.
2. Leong AC, Fairley JW, Padgham ND. Sudden hearing loss. *Clin Otolaryngol* 2007;32:391–4.
3. Mattox D, Simmons F. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol* 1977;86:463–80.
4. Hong BN, Yi TH, Kim SY, Kang TH. High-dosage sildenafil induces hearing impairment in mice. *Biol Pharm Bull* 2008;31:1981–4.
5. Kamel A, Khaouli R, Sabha M, Al Mitwally K, Fouad W, Landen H. The real life safety and efficacy of vardenafil. *Clin Drug Invest* 2007;27:339–46.

6. **U.S. Food and Drug Administration.** FDA updates labeling for Viagra, Cialis, and Levitra for rare post-marketing reports of eye problems. July 8, 2005. Available from <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01201.html>. Accessed December 19, 2007.
7. **U.S. Food and Drug Administration.** Information for healthcare professionals: sildenafil (marketed as Viagra and Revatio), vardenafil (marketed as Levitra), tadalafil (marketed as Cialis). November 14, 2007. Available from http://www.fda.gov/cder/drug/InfoSheets/HCP/ED_HCP.htm. Accessed December 19, 2007.
8. **Mukherjee B, Shivakumar T.** A case of sensorineural deafness following ingestion of sildenafil. *J Laryngol Otol* 2007;121:395–7.
9. **U.S. Food and Drug Administration.** FDA announces revisions to labels for Cialis, Levitra, and Viagra. October 18, 2007. Available from <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html>. Accessed December 19, 2007.
10. **Naranjo CA, Busto U, Sellers EM, et al.** A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.
11. **Impotence-Guide.com.** A comprehensive guide to Uprima. Available from <http://www.impotence-guide.com/uprima.html>. Accessed February 15, 2008.
12. **Department of Veterans Affairs Employee Education System.** Vietnam veterans and Agent Orange exposure. March 2002. Available from <http://www1.va.gov/agentorange/docs/VHI-agentorange.pdf>. Accessed January 15, 2008.
13. **Department of Veterans Affairs.** Agent Orange review, vol 6, no. 1. October 1988. Available from <http://www1.va.gov/agentorange/docs/Oct88v6-1.PDF>. Accessed February 28, 2008.
14. **Simdon J, Watter D, Bartlett S, Connick E.** Ototoxicity associated with use of nucleoside analog reverse transcriptase inhibitors: a report of 3 possible cases and review of the literature. *Clin Infect Dis* 2001;32:1623–7.
15. **Williams B.** Ototoxicity may be associated with protease inhibitor therapy. *Clin Infect Dis* 2001;33:2100–2.
16. **Reffellmann T, Kloner R.** Vardenafil: a selective inhibitor of phosphodiesterase-5 for the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2007;8:965–74.
17. **McNicholl IR.** Drug interactions among the antiretrovirals. *Curr Inf Dis Rep* 2004;6:159–62.
18. **Morris MS, Prasad S.** Otologic disease in the acquired immunodeficiency syndrome. *Ear Nose Throat J* 1990;69: 451–3.
19. **Real R, Thomas M, Gerwin J.** Sudden hearing loss and acquired immunodeficiency syndrome. *Otolaryngol Head Neck Surg* 1987;97:409–12.