SILDENAFIL AND FUROSEMIDE ASSOCIATED OTOTOXICITY: CONSIDERATION OF DRUG-DRUG INTERACTIONS, SYNERGY, AND BROADER CLINICAL RELEVANCE

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ABSTRACT

Drug-induced ototoxicity, particularly those involving phosphodiesterase type 5 (PDE-5) inhibitors, is considered to be rare and to our knowledge such an adverse effect has not been reported in Canada. Here we present a case of a 77-year old man initiated on a sildenfil regimen for the treatment of pulmonary hypertension, who developed sudden bilateral hearing loss after taking sildenafil, in the setting of high dose furosemide and diltiazem. We outline the likely interplay of patient characteristics, drug synergy and drug-drug interactions in the development of his ototoxicity. Importantly, given the extent and popularity of PDE-5 inhibitors for erectile dysfunction as well as a newer therapeutic option for pulmonary hypertension, clinicians should be aware of the risk for drug-induced ototoxicity, particularly in the setting of concomitant loop diuretics and CYP3A4 inhibiting medications.

Key Words: *Ototoxicity, sildenafil, furosemide*

Case Report

A 77-year old gentleman with advanced interstitial lung disease presented to hospital with increasing dyspnea. Investigations, including an echocardiogram and subsequent right heart catheterization, diagnosed moderately severe pulmonary hypertension. He was treated with high-dose furosemide for his right heart failure and was started on sildenafil (Revatio) after the right heart catheterization demonstrated a positive vasodilator response to inhaled nitric oxide.

On the same day that sildenafil was initiated, the patient developed sudden and profound bilateral hearing loss that was associated with intermittent tinnitus. Prior to his hearing loss, he received ten days of high-dose furosemide for symptomatic right heart failure (Figure 1). He had no fevers, otalgia, otorrhea, skin changes or oral fullness. He had no recent head trauma or infection, and did not complain of any neurological or constitutional symptoms. His only other symptoms were dyspnea and bilateral leg swelling.

The patient's medical history included interstitial pulmonary fibrosis requiring 5 liters of home oxygen. He also had obstructive sleep apnea, type 2 diabetes, hyperlipidemia, hypertension and a recent myocardial infarction. He had multiple myeloma in remission after undergoing chemotherapy in 2009. He was diagnosed with presbycusis, age-related sensorineural hearing loss, three years prior to this presentation.

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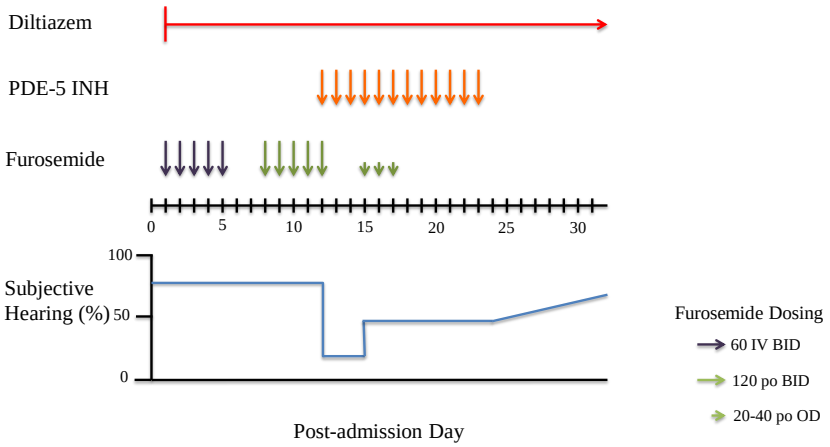
FIG. 1 Timeline of Events



His medications at admission were aspirin 81 mg daily, clopidogrel 75 mg daily, atorvastatin 40 mg daily, fluticasone/salmeterol 250/125 mcg inhaled diskus BID, tiotropium 18 mcg inhaled daily, acetylcysteine 600 mg TID, domperidone 10 mg BID and vitamin B12 supplementation. New medications in hospital were diltiazem 120 mg daily, furosemide 120 mg orally BID (initially 60mg IV BID) and sildenafil 20 mg orally TID. He had been exposed to furosemide in the past with no previous side effects.

On examination he required 50% oxygen (Fi02 0.5), but had otherwise normal vital signs, including temperature. He had no lymphadenopathy and his head and neck examination, including auditory canals, was unremarkable. He had evidence of mild right-sided heart failure, as well as fine inspiratory crackles on respiratory examination. His neurological examination was normal.

Laboratory investigations revealed a normal white blood cell count, hemoglobin, electrolytes, renal and liver function. His blood sugar was well controlled with diet alone (HbAIC 6.3%). An MRI head was normal.

Based on clinical grounds, it was suspected that sildenafil was the most likely etiology of acute hearing loss based on several key risk factors. Diltiazem, a medication that inhibits sildenafil metabolism via cytochrome P450 enzyme inhibition, may have led to increased drug levels of sildenafil. In addition, the daily high dose of sildenafil for the treatment of pulmonary hypertension may have resulted in a sustained level of sildenafil between dosing intervals.We suspect that the patient's baseline hearing deficits may have lowered his threshold for cochlear damage and that high dose furosemide contributed synergistically to the patient's profound hearing loss. In order to confirm this, discontinuation of the furosemide resulted in a self-reported improvement in hearing within days. Furthermore, after discontinuation of sildenafil, this patient's hearing loss self-reportedly returned to baseline.

DISCUSSION

Phosphodiesterase type 5 (PDE-5) inhibitors, such as sildenafil, are commonly used to treat erectile dysfunction (ED) and pulmonary hypertension. Sildenafil inhibits the enzyme PDE-5 that degrades cyclic guanosine monophosphate (cGMP), leading to enhanced vasodilation and decreased vascular resistance. Although rare, ototoxicity has been described in patients taking PDE-5 inhibitors.[1] Indeed, after a case report documented sudden bilateral hearing loss in a patient taking sildenafil for ED, the FDA reviewed post-market research and discovered 29 cases of sudden hearing loss associated with PDE-

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5 inhibitors.[1,2] The hearing loss is sensorineural in origin and may be associated with dizziness, tinnitus or nausea. Retrospective review of available reports found that the majority of hearing loss was unilateral (88-96%), occurred within 24 hours of taking a PDE-5 inhibitor (66.7-88%), and in some patients was at least partially reversible after stopping the medication.[3,4] Unfortunately, none of the case reports adequately addressed whether concurrent medications could have contributed or caused the hearing loss. A cross-sectional study of 11,525 men age 40 or older found that individuals with self-reported hearing impairment were more likely to report using sildenafil, independent of other risk factors.[5] Alterations in the nitric oxide pathway, including cGMP and downstream second messenger molecules, have been previously linked to cochlear pathophysiology in conditions such as aminoglycoside ototoxicity.[6,7,8] PDE-5 inhibitors increase cGMP and may similarly affect cochlear function.

Sildenafil (Revatio) was approved in Canada in 2006 for the treatment of pulmonary hypertension. Individuals taking Revatio may be at increased risk of hearing loss because of prolonged exposure to the drug at relatively high doses. Furthermore, patients taking chronic PDE-5 inhibitors for erectile dysfunction may also be at increased risk. In a mouse model, administration of high-dose long-term sildenafil led to significant hearing impairment when compared to control mice.[9] Physicians must consider the possibility that a high or cumulative dose may magnify the risk of hearing loss.

Role of Drug-Drug Interactions and Synergistic Effects

Drug interactions may contribute to the ototoxicity seen with PDE-5 inhibitors. Although loop diuretics such as furosemide are not widely appreciated for their potential to cause cochlear injury and hearing loss, it has been shown that loop diuretics, particularly in combination of known ototoxic drugs such as aminoglycosides, have been well documented to have synergistic effects in terms of ototoxicity.[10] Indeed, our patient was taking high-dose furosemide prior to starting sildenafil. Furosemide is a commonly prescribed medication for patients with pulmonary hypertension. Furthermore, furosemide is widely used for a variety of indications, and a subset of such patients may also be taking PDE-5 inhibitors for erectile dysfunction. It is possible that when PDE-5 inhibitors are used intermittently, the risk for ototoxicity is much lower than during continuous therapy. We do note that there are daily dosing regimens for the treatment of ED using PDE-5 inhibitors, thus the risk and prevalence of PDE-5 inhibitor-associated ototoxicity may increase in the coming years. Accordingly, caution and close monitoring is needed when prescribing two potentially ototoxic medications such as PDE-5 inhibitors and loop diuretics.

In addition to the pharmacodynamic effect of ototoxic medications, pharmacokinetic drug interactions with sildenafil should be acknowledged. Sildenafil is primarily metabolized by the cytochrome P450 enzyme, CYP3A4. Medications that inhibit the CYP3A4 enzyme will result in increased levels of substrate drugs. Known potent inhibitors of CYP3A4 include azole antifungals such as ketoconazole and itraconazole or the HIV protease inhibitor ritonavir (Table 1).

TABLE 1 Ototoxicity risk factors and CYP 3A4 inhibitors

Sildenafil ototoxicity risk factors	Furosemide ototoxicity risk factors	CYP 3A4 Inhibitors
High peak levels (high dose)	**High peak levels (high dose)**	**Ketoconazole** **Itraconazole**
Renal dysfunction	**Renal dysfunction**	**Ritonavir** **Indinavir**
Concomitant ototoxic medication	**Concomitant ototoxic medication**	**Erythromycin** **Clarithromycin**
Chronic use		**Diltiazem**

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Macrolide antibiotics such as erythromycin and clarithromycin are also potent inhibitors. In addition, certain calcium channel blockers such as diltiazem are also capable of inhibiting this enzyme. Diltiazem may be a concomitant medication that is frequently prescribed with sildenafil because of its indication in patients with pulmonary hypertension, as well as being a non-nitrate option for the treatment of angina. Contraindications or dose adjustments of sildenafil have been recommended for potent CYP3A4 inhibitors. It should be noted that although our case highlights ototoxicity in the setting of sildenafil, other PDE-5 inhibitors such as vardenafil and tadalafil are also CYP3A4 substrates and their product monographs clearly indicate drug interaction risk when using CYP3A4 inhibitors.

Recommendations

To our knowledge, this is the first case report of ototoxicity in a patient taking sildenafil and furosemide. This case report highlights the rare but important side effect of sildenafil associated sudden hearing loss. Counseling patients prior to prescribing PDE-5 inhibitors is recommended, and caution is required when adding other ototoxic medications such as furosemide or drugs that inhibit CYP3A4. The value of monitoring patients clinically or with audiograms has not been validated, but may be beneficial in detecting hearing loss that is potentially reversible.

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