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CASE REPORT

Sildenafil induced seizures in a patient treated for pulmonary hypertension: A case report.

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ABSTRACT

Sildenafil is one of the common drugs used to treat pulmonary hypertension. We report a rare case of a life-threatening adverse effect of Sildenafil. The patient was admitted to our intensive care unit for the management of urosepsis with obesity hypoventilation syndrome with pulmonary hypertension. After administration of the first dosage of Sildenafil, the patient developed generalized tonic-clonic seizure. She had no previous history of seizure disorder. She was investigated for the possible cause of seizure, but none were conclusive. Sildenafil was discontinued and she remained seizure free after discontinuation of it. Sildenafil can increase the effects mediated by nitric oxide and can thus affect the seizure threshold. Though rare, seizure as an adverse effect of Sildenafil should be considered before initiating this drug.

Keywords: *generalized tonic-clonic seizures, pulmonary hypertension, Sildenafil.*

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INTRODUCTION

Pulmonary Hypertension (PH) is classified into five main categories, one of which is a sequelae of sleep disordered breathing.[1] Hypoxia induced pulmonary vasoconstriction is reversible when acute whereas chronic hypoxia cause structural remodeling, proliferation and migration of vascular smooth muscle and an increase in deposition of vascular matrix.[2]

The availability of drugs to treat PH has resulted in improvement in quality of life and mortality. Amongst the different Food and Drug Administration (FDA) approved drugs, Sildenafil is the most widely used agent in our part of the world. Although extremely rare, we report a life-threatening adverse effect of Sildenafil in a patient treated for severe PH.

CASE REPORT

A 49-year-old lady with BMI of 37.10 (weight 88 kilograms, height 1.54 meters) was brought to our intensive care unit with complaints of burning micturition, fever and chills. She was on inotropic support with noradrenaline and vasopressin. She was managed in the line of urosepsis and pyelonephritis. The patient had a history of hypertension and episodic shortness of breath for the past 10 years and was being treated with antihypertensives, inhalers and domiciliary oxygen. In addition, she had symptoms of sleep apnea, suggested by snoring during the sleep followed by frequent awakenings and associated with drop in SpO_2.

During the treatment, her symptoms of urinary tract infection subsided, but she still had high oxygen requirements. Initially, oxygenation and ventilation were maintained with BiPAP and later continued with High Flow Nasal Cannula. Vasopressor support was gradually tapered and then stopped. High Resolution Computed Tomography of chest showed bilateral calcified nodules with mild ground glass appearance and some emphysematous changes. Her blood gas panels slowly corrected and she was shifted to a high care unit. An echocardiography was done, which showed mild concentric left ventricular hypertrophy, minimal pericardial effusion and grade I left ventricular diastolic dysfunction with severe pulmonary hypertension (pulmonary artery systolic pressure of 121 mm of Hg), so she was started on Sildenafil 50 mg once daily, considering PH being contributory cause for her high oxygen demand. She was not hypercapnic. Patient was improving and shifted to the ward.

On the next day in ward (also the next day of initiation of Sildenafil), she had the first episode of generalized tonic-clonic seizure (GTCS). Immediate management was done with injection midazolam and the patient was transferred to the ICU. After a few hours, the patient developed another episode of tonic-clonic seizure lasting 15-20 seconds. She was started on Levetiracetam. All possible causes of seizures were explored, including dyselectrolytemia, dysglycemia, metabolic derangements, organic brain lesion, etc., all of which were within normal range. There were no signs and symptoms of meningitis. Sildenafil was suspected as a possible offending agent and was stopped. The patient did not have any seizures then after. Levetiracetam was stopped after five days and she has been seizure-free for the subsequent 9 months. Neurology opinion was also sought for evaluation of possible cause. After excluding all the causes and seizure cessation after stopping Sildenafil, it was concluded that the seizures were drug induced.

DISCUSSION

PH is defined as mean pulmonary artery pressure>25 mmHg at rest or >30 mmHg with exercise. Patients present with symptoms of breathlessness, weakness, fatigue, chest pain or syncope. The most common cause of death in these patients is due to decompensated right heart failure. The propensity to diagnose patients with PH is frequent, as it is often associated with common disorders like asthma or chronic obstructive pulmonary disease. Although only a screening test, with the advent of wide availability and frequency of performing echocardiography, more patients have been diagnosed and managed early, with significant improvement in quality of life and longevity.[3]

PH was previously classified as primary or secondary, but with increased understanding about the disease pathophysiology, now it has been classified according to similarities in pathophysiologic mechanisms and clinical presentation. The fifth world symposium on PH classified it into five categories: Pulmonary artery hypertension, PH owing to left heart disease, PH owing to lung disease, chronic thromboembolic pulmonary hypertension and PH with unclear multifactorial mechanisms. The symptoms of PH are non-specific and overlap or co-exist considerably with many common conditions, including asthma, other lung diseases and cardiac disease.

Although PH associated with sleep disorder is known to be of milder form, severe PH in this patient might be due to sleep related cause and underlying lung pathology. Several pharmacologic treatments for PH has been approved including direct acting drugs (Hydralazine, Nitroglycerin), α-adrenoceptor antagonists (Tolazoline, Phentolamine), β-adrenoceptor agonists (Isoproterenol), calcium channel blocker (Nifedipine, Diltiazem), prostaglandins (PGE1, Prostacyclin), adenosine, endothelin receptor antagonists, indirect acting vasodilators (Acetylcholine) and phosphodiesterase 5 (PDE5) inhibitors (Sildenafil and Tadalafil). Among these drugs, PDE5 inhibitor Sildenafil is commonly used in our part of the world. By inhibiting PDE5 enzyme, this drug inhibits cyclic GMP metabolism, leading to prolonged vasodilatory effect of nitric oxide, especially within the pulmonary arterial bed where high concentrations of cGMP are found.

The onset time of Sildenafil is 15 minutes and peaks at 2 hours with a half-life of 4 hours. The most commonly reported adverse events of Sildenafil are headache (16%), flushing (10%) and dizziness (2%). Incidence of severe adverse events like life-threatening hypotension, orthostatic hypotension and syncope is below 2%.[4] Seizure has recently been ascribed to as one of the rarest yet serious adverse events of Sildenafil. Various case reports have been published where patients, without any prior seizure disorder, have had an episode of GTCS after a single dose of the drug. In one of the case reports, all investigations were normal and Sildenafil was stopped. On resuming Sildenafil after three months, patient developed another episode of GTCS.[5]

The cause of seizure in our patient was unlikely to be a manifestation of any other disease, as a complete evaluation was done to rule them out. The GTCS occurred immediately (within 24 hours) following intake of the drug and the patient never had another episode of GTCS even after antiepileptic drugs were put on hold once Sildenafil was stopped.

Although the exact mechanism of seizure caused by PDE5 inhibitors is unknown, recent studies have shown that PDE5 inhibitors may increase the effects mediated by nitric oxide. Nitric oxide and cGMP may have effects on the seizure threshold.[6] Sildenafil has also been shown to interact with both exogenously and endogenously released nitric oxide.[7]

To conclude, though uncommon, seizure need to be considered as a possible side effect of Sildenafil in clinical practice.

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