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Sildenafil as an Appropriate Monotherapy Option in the Treatment of Pulmonary Arterial Hypertension (PAH)

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Abstract
Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by constriction in the diameter of the pulmonary arterial lumen. This leads to increased pressure and stress on the right ventricle of the heart, which may lead to heart failure and death. Currently there are only a few treatment options for patients with PAH. Sildenafil, a phosphodiesterase type 5 (PDE-5) inhibitor, can be used to treat PAH. Sildenafil inhibits the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation. Current clinical trials have indicated that sildenafil can significantly improve many of the symptoms of PAH. The trials have also shown that when used appropriately, sildenafil can be used with minimal side effects. It is important for pharmacists and other health care professionals to understand PAH as a disease state and its treatment options, such as sildenafil.

Introduction
Pulmonary arterial hypertension (PAH) is a debilitating disease that, if left untreated, will lead to death. Pulmonary arterial hypertension is characterized by constriction in the diameter of the pulmonary arterial lumen. Since there is less space for blood to pass through, pressure begins to build up in the pulmonary artery. As a result, stress is exerted on the right side of the heart which can lead to heart failure and death. Due to its low prevalence, health care practitioners only have a few options for treating PAH: prostacyclins and prostacyclin analogues which cause dilation of blood vessels and a decrease in platelet adhesion, endothelin receptor antagonists which prevent endothelin from constricting blood vessels or PDE-5 inhibitors which lead to vasodilation. Other medications are typically used in conjunction with these options, such as diuretics, digoxin, calcium channel blockers and anticoagulants.

In their more widely advertised role, PDE-5 inhibitors are indicated to treat erectile dysfunction through their vasodilation activity. Sildenafil, under the brand name of Viagra®, is a PDE-5 inhibitor currently indicated to treat erectile dysfunction. Under the brand name Revatio®, sildenafil is indicated for PAH as well. It is important to note that in November 2012, generic versions of sildenafil became available to the public. The intent of using sildenafil in PAH patients is to dilate the pulmonary artery and ultimately relieve some of the stress on the heart. Current studies have indicated that sildenafil is an effective treatment for PAH. Through a review of current literature, the writers hope to review the presentation and dangers of PAH and describe when sildenafil monotherapy is an appropriate treatment.

Pulmonary Arterial Hypertension
Pulmonary arterial hypertension is classified into three categories based on etiology: idiopathic, familial or associated. Both familial and idiopathic PAH can be present at birth or develop later in life. Associated PAH occurs when the disease is secondary to other pre-existing conditions such as autoimmune disease, congenital heart and lung disease, portal hypertension, the use of drugs similar in structure to amphetamines and Human Immunodeficiency Virus (HIV) infection among other conditions.

While the pathophysiology of PAH is not fully understood, its basic mechanisms have been identified. In patients with PAH, there is evidence of irregular expression of potassium channels in the endothelium and smooth muscle cells in the pulmonary artery. This irregular function can lead to an inhibited expression of the vasodilators nitric oxide and prostacyclin. Conversely, it can also lead to the overproduction of vasoconstrictors, thromboxane A2 and endothelin-1. These changes result in increased vasoconstriction, inflammation and thrombosis.

In PAH patients, high cellular proliferation is present in the vascular wall of the pulmonary artery. This leads to increased pressure and stress on the right ventricle of the heart; stress which, in time, can lead to heart failure and death.

Family history is an effective tool in identifying patients who have a higher risk of acquiring PAH. While no age, ethnic or racial group is categorized as high risk, PAH does on average affect more women than men. Additionally, PAH is more prevalent in patients with associated conditions such as autoimmune disease, congenital heart and lung disease, portal hypertension, HIV infection and the use of some drugs such as fenfluramine, cocaine or amphetamines. Patients with PAH may present with side effects similar to other heart and lung conditions such as chest pain, dizziness, fainting, fatigue, swelling, and shortness of breath and light-headedness while exercising. Since signs and symptoms are not specific to PAH, the disease may be advanced at time of diagnosis. Perfusion lung scan, echocardiogram, right heart catheterization, electrocardiogram and chest x-rays are all indicative in the diagnosis of PAH.

Sildenafil and General Prescribing Information
Sildenafil inhibits PDE-5 in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation. This occurs when PDE-5 breaks down cGMP that forms in response to increased nitric oxide. Increased intracellular...
cGMP inhibits calcium entry into the cell, which results in smooth muscle relaxation. Sildenafil is available as both an intravenous injection (IV) and an oral medication. If administering as an IV, the dose of sildenafil is 10 mg IV bolus three times per day; if taking the oral formulation, the dose is 20 mg by mouth three times per day (four to six hours apart) without regard to meals. The onset of action is about 60 minutes, and its duration of action is two to four hours. Sudden cessation of sildenafil could result in an exacerbation of PAH. There is no dose adjustment needed in renal impairment or in hepatic impairment with Child-Pugh class A or B. This drug is a major substrate of CYP3A4 and a minor substrate of CYP1A2, CYP2C19, CYP2D6, and CYP2E1. It is also a weak inhibitor of CYP2C9 and CYP3A4. Therefore, dose adjustments are required when using potent CYP3A4 inhibitors, except with erythromycin. Concomitant use of sildenafil and itraconazole/ketoconazole is not recommended; concurrent use with protease inhibitors and organic nitrates is contraindicated. Sildenafil should be used with caution in patients over 65 years of age, and this drug is Pregnancy Category B. Chronic use in children is not recommended. Patients should avoid drinking grapefruit juice while taking this drug.

Additionally, blood pressure and heart rate should be monitored as hypotension may develop while taking sildenafil. Patients at increased risk of hypotension are those taking an antihypertensive medication or those with aortic stenosis, hypertrophic obstructive cardiomyopathy or fluid depletion. If the patient develops pulmonary edema when taking this drug, sildenafil should be discontinued as this could be pulmonary veno-occlusive disease. Sildenafil should be used with caution in people taking alpha-blockers, bosentan, nitrates and other erectile dysfunction drugs. Adverse effects such as flushing, diarrhea, myalgia and visual disturbances may be increased with adult doses >100 mg/24 hours. Over 10 percent of patients experience a headache and dyspepsia. Other common adverse effects are erythema, dizziness, insomnia, increased liver function tests (LFTs), urinary tract infection and dyspepsia.

Selected Clinical Trials
Impact of First-line Sildenafil Monotreatment for Pulmonary Arterial Hypertension, a study conducted by the Keio and Kyorin University Hospitals, analyzed the efficacy of sildenafil as a monotherapy for PAH. Fifty-seven patients with New York Heart Association functional class (NYHA FC) ratings of I, II, or III were enrolled; four patients dropped out of the study due to high cost of off-label use, and seven patients with Eisenmenger Syndrome were dismissed because of their differing clinical characteristics from other patients with PAH. The remaining patients were given 20 mg sildenafil three times daily as a monotherapy from January 2003 to December 2010. A 6-minute walk distance (6MWD; an independent predictor of death in patients with PAH) and B-type natriuretic peptide (BNP) levels were evaluated before treatment began and again during follow-up.

It was found that the BNP tended to be lower after sildenafil treatment, but the results were not significant. Hemodynamic parameters, however, such as the pulmonary vascular resistance (14.6±8.7 versus 11.6±8.6 Wood units, P<0.05), mean pulmonary arterial pressure (PAP: 52.1±14.0 versus 45.7±15.7 mmHg, P<0.01), mean right atrial pressure (RA: 8.0±5.5 versus 6.4±4.4 mmHg, P<0.05), and cardiac output (CO: 3.7±1.6 versus 4.2±1.9 L/min, P<0.05), improved significantly following sildenafil treatment in the enrolled patients as a whole. These results are indicative of sildenafil's positive cardiovascular effects, which result in improved cardiac function. NYHA FC either improved (n=12, 26.1 percent) or was maintained (n=30, 65.2 percent) in 42 of 46 patients; NYHA FC worsened in four patients (8.7 percent). Due to the NYHA FC maintenance or improvement rate of 91.3 percent, the study concluded that sildenafil demonstrated superior efficacy as a monotherapy for PAH. Critics of this study included its lack of control group and small study population.

Clinical Efficacy of Sildenafil in Primary Pulmonary Hypertension, a randomized, double-blind crossover study, compared the efficacy of sildenafil with placebo in patients with primary pulmonary hypertension. Change in exercise time on a treadmill was used as a primary endpoint. Patients were randomized into a placebo group or sildenafil group with doses ranging from 25 to 100 mg three times daily based on body weight. A baseline evaluation was done before treatment began, and again after six weeks of treatment. After the six-week evaluation, patients were crossed over to the therapy alternative to their current treatment (i.e. the sildenafil group ceased sildenafil treatment and began the placebo regimen, and vice versa). A final evaluation was performed after another six weeks of treatment.

Twenty-two patients completed the study. Exercise time increased by 44 percent from 475 ± 168 seconds at the end of placebo phase to 686 ± 224 seconds at the end of sildenafil phase (p < 0.0001). It was also noted that cardiac index improved from 2.80 ± 0.9 l/m² to 3.45 ± 1.1 l/m² (p < 0.0001). Pulmonary artery systolic pressure decreased from 105.23 ± 17.82 mm Hg to 98.50 ± 24.38 mmHg, but these results were found to be insignificant. Patients also reported significant improvements in dyspnea and fatigue in a Quality of Life questionnaire. From these results it was concluded that sildenafil significantly improves exercise tolerance, cardiac index, and quality of life in patients with primary pulmonary hypertension. No serious side effects were noted. While these results reflect those of other studies, the authors acknowledged that a larger study population, longer treatment duration, and a washout period between crossover treatment would help lend credibility to these findings.

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension, a double-blind, placebo-controlled study conducted by the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group, used the 6MWD test indicating a change in exercise capacity as a primary end point of sildenafil efficacy. Placebo or sildenafil treatment (20, 40, or 80 mg) orally three times daily for 12 weeks was randomly assigned to 278 patients with PAH class II or III. Among the 265 patients who completed the study, an increase in the 6MWD was observed in all groups receiving sildenafil in comparison to the placebo. Improvement was noted at week
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four and maintained at weeks eight and twelve. The observed treatment-related increases of 45 to 50 meters is similar to the increases observed with other PAH medications such as intravenous epoprostenol (47 m), inhaled iloprost (36 m), and oral bosentan (44 m), and is higher than the increase seen with the use of subcutaneous treprostinil (16 m). There was no evidence of a dose-response relationship associated with exercise capacity. It is possible that this is due to complete 5-PDE inhibition at the lowest dose.

Patients receiving sildenafil treatment also experienced improvements in functional class. After twelve weeks of treatment, seven percent of patients receiving placebo noted an improvement of at least one functional class. The proportions of FC improvements for those receiving treatment were 28 percent for those receiving 20 mg of sildenafil (P=0.003), 36 percent for those receiving 40 mg (P<0.001), and 42 percent for those receiving 80 mg (P<0.001). A significant decrease from baseline in mean pulmonary-artery pressure and pulmonary vascular resistance was also noted in those taking sildenafil from the placebo group. The proportion of hospitalizations for worsening PAH was greater in the placebo group than in the combined sildenafil treatment groups (P=0.02).

Adverse events experienced (such as headache, dyspepsia and back pain) were mild to moderate in intensity for all treatment groups.

Two hundred seventy-seven patients were enrolled in a 12-week, double-blind, randomized, placebo-controlled trial (SUPER-1), a continuation of the original SUPER study. Two hundred fifty-nine patients completed the study and entered into an open-label, uncontrolled extension study (SUPER-2) that continued until the last patient had completed three years of sildenafil treatment. The median duration of sildenafil treatment was 1,242 days. Patients were titrated to a dose of 80 mg of sildenafil three times daily for treatment of PAH. As in previous studies, the 6MWD test was used as a primary endpoint. At three years post-baseline, 127 patients (49 percent) had an increased 6MWD. Sixty-four percent of patients either improved or maintained their functional class; 81 patients noted improvement, while 86 patients maintained their current level of functioning. Treatment with sildenafil was generally well-tolerated, and noted adverse events were of mild to moderate severity. The study authors acknowledged that an increased treatment duration would be necessary to support these findings of efficacy.

While more thorough and lengthy studies would further validate recent findings, all current evidence suggests that sildenafil is an effective treatment for PAH. It has been shown to significantly improve pulmonary vascular resistance, mean pulmonary arterial pressure, mean right atrial pressure, cardiac output, exercise capacity, FC and quality of life. Sildenafil was found to be generally well-tolerated among all patients studied, with mild to moderate side effects.

Because most studies were aimed at assessing sildenafil’s efficacy as a monotherapy compared to placebo, more studies regarding specific dosing effectiveness would be helpful in determining the optimal dosage for PAH treatment. Given current findings, however, the recommended daily dose for PAH treatment remains at 20 mg three times daily.

There is no evidence suggesting that sildenafil treatment has a decreased efficacy or increased adverse effects in comparison to other PAH therapies.

Pharmaceutical Application

It is important for health care professionals, especially pharmacists, to be knowledgeable about sildenafil and PAH. Because sildenafil has many drug interactions and possible adverse events associated with its use, pharmacists can play a vital role in therapy by counseling patients when they receive this medication. Although PAH is not a common condition, pharmacists need to be aware of PAH and to know the signs and symptoms of PAH as well as how to treat it in order to improve the patient’s quality of life. Sildenafil can significantly improve the quality of life of a patient with PAH and should be considered as an option for treatment in a PAH patient. Specifically, sildenafil is one of two treatment options indicated for functional class II patients with PAH, and one of five treatment options indicated for functional class III patients.

Conclusion

Pulmonary arterial hypertension is the constriction of the pulmonary arterial lumen that can result in stress on the right side of the heart which ultimately leads to heart failure and death. There are only a few treatment options for PAH, and sildenafil, a PDE-5 inhibitor, is one of the options due to its ability to dilate the pulmonary artery. Through various studies, sildenafil has been proven to be effective in treating PAH as monotherapy with mild to moderate adverse events while improving dyspnea, fatigue and quality of life. It is important for pharmacists and other health care professionals to understand PAH as a disease state and to counsel patients on appropriate treatment options, including sildenafil.

References