

CLINICAL THERAPEUTICS

Phosphodiesterase Type 5 Inhibitors for Pulmonary Arterial Hypertension

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

A 46-year-old woman presents with progressive exertional dyspnea and recurrent exertional syncope. Her jugular venous pressure is 16 cm of water, and moderate peripheral edema is noted. Auscultation reveals a pronounced pulmonic component of the second heart sound and a grade 2/6 holosystolic murmur of tricuspid regurgitation. Echocardiography shows moderate right ventricular and right atrial enlargement, right ventricular systolic dysfunction, and an estimated right ventricular systolic pressure of 100 mm Hg. Cardiac catheterization reveals a mean right atrial pressure of 13 mm Hg, a pulmonary-artery pressure of 80/40 mm Hg (mean, 58), a mean pulmonary-capillary wedge pressure of 10 mm Hg, and a cardiac output of 5 liters per minute. The results of additional studies to detect causes of secondary pulmonary hypertension or associated conditions are unremarkable, and she receives a diagnosis of idiopathic pulmonary arterial hypertension. Her pulmonary-artery pressure does not decrease in response to inhaled nitric oxide. Therapy with sildenafil is recommended.

THE CLINICAL PROBLEM

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Pulmonary arterial hypertension, a disease of the pulmonary vasculature, is diagnosed when there is both an increased mean pulmonary-artery pressure (>25 mm Hg at rest or 30 mm Hg with exercise) and a pulmonary-capillary wedge pressure of less than 15 mm Hg. The diagnosis also requires that secondary pulmonary hypertension due to lung disease, hypoxia, thromboembolism, and left ventricular muscle or valve disease be ruled out.¹ Pulmonary arterial hypertension occurs in a rare idiopathic form (in which 10% of cases are familial) but is more commonly associated with other conditions, including connective-tissue diseases, congenital heart disease, portopulmonary disease, and human immunodeficiency virus (HIV) infection¹ or the use of anorexigens (see the Table in the Supplementary Appendix, available with the full text of this article at NEJM.org). The functional classification system of the New York Heart Association has been adapted by the World Health Organization (WHO) for use in classifying symptoms in patients with pulmonary hypertension (Table 1).

Although idiopathic pulmonary arterial hypertension is rare, this syndrome in association with other conditions is increasingly recognized, particularly with the common use of echocardiography. National databases in France³ and Scotland⁴ report incidences of 2.4 cases and 7.1 to 7.6 cases per 1 million persons per year, respectively, and prevalences of 15 cases and 26 to 52 cases per 1 million, respectively. The prevalence of pulmonary arterial hypertension is expected to increase

further as cases resulting from schistosomiasis (probably a common cause of pulmonary hypertension globally⁵) and hemoglobinopathies are recognized and early diagnosis is improved. The prognosis for patients with pulmonary arterial hypertension has improved in recent years; the 1-year survival rate is now approximately 85%,⁶ as compared with a rate of approximately 68% in the 1980s.⁷

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The cause of pulmonary arterial hypertension is unclear, although pulmonary-artery endothelial dysfunction is an early feature of the disease.⁸ Pulmonary arterial hypertension may reflect a “double hit” from genetic abnormalities, such as loss-of-function mutations of the bone morphogenetic protein receptor type 2, and environmental factors, such as drugs, viruses, or toxins.^{9,10} Endothelial dysfunction is associated with vasoconstriction due to an imbalance between endothelium-derived vasodilators (e.g., nitric oxide and prostacyclin) and vasoconstrictors (e.g., endothelin-1 and thromboxane). As pulmonary arterial hypertension progresses, vascular remodeling occurs, characterized by a proliferative and anti-apoptotic state of cells within the vascular wall (smooth-muscle cells, fibroblasts, and endothelial cells), resembling neoplasia.¹⁰⁻¹² Clones of endothelial cells proliferate and give rise to plexiform lesions, the pathologic hallmark of this condition, while smooth-muscle cells and myofibroblasts proliferate and lead to medial hypertrophy and adventitial hyperplasia.¹⁰⁻¹³ Disruption of the extracellular matrix with elastase activation, infiltration of inflammatory cells, and thrombosis in situ combine to reduce the cross-sectional area of the small pulmonary arteries and stiffen the large pulmonary arteries,^{1,10} increasing the right ventricular afterload and leading to right heart failure.^{1,10}

Two important pathologic features of pulmonary arterial hypertension (Fig. 1) are decreased endothelial nitric oxide production¹⁴ and increased phosphodiesterase type 5 expression and activity in pulmonary-artery smooth-muscle cells¹⁵⁻¹⁷ and the right ventricular myocardium.¹⁸ Nitric oxide activates soluble guanylate cyclase, stimulating the production of cyclic guanosine monophosphate, and phosphodiesterase type 5 hydrolyzes

Table 1. WHO Functional Classification of Pulmonary Arterial Hypertension.*

Class	Description
I	No limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope
II	Mild limitation of physical activity; no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope
III	Marked limitation of physical activity; no discomfort at rest, but minimal ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope
IV	Inability to perform any physical activity at rest and possible signs of right ventricular failure; dyspnea, fatigue, or both may be present at rest, and symptoms are increased by almost any physical activity

* The class descriptions are from McLaughlin and McGoon.² WHO denotes World Health Organization.

cyclic guanosine monophosphate. The decrease in nitric oxide production and increase in phosphodiesterase type 5 activity both act to decrease levels of cyclic guanosine monophosphate, which in turn increases intracellular calcium¹⁹ and potassium,²⁰ promoting vasoconstriction, proliferation of smooth-muscle cells, and resistance to apoptosis.^{10,17,21}

The goals of therapy for pulmonary arterial hypertension include promoting vasorelaxation, suppressing cellular proliferation, and inducing apoptosis within the pulmonary-artery wall. Furthermore, because pulmonary arterial hypertension is associated with right heart failure, another goal of therapy, as in patients with left ventricular failure, is to increase cardiac output by decreasing afterload (pulmonary vascular resistance) and by enhancing ventricular inotropy. The combination of a relatively fixed pulmonary vascular resistance and a normal systemic vasculature presents a unique challenge in the treatment of pulmonary arterial hypertension, because nonselective vasodilator therapy increases the risk of hypotension due to systemic vasodilatation that cannot be compensated for by an increase in right ventricular output, which can cause cardiovascular collapse. Ideal therapies for pulmonary arterial hypertension decrease pulmonary vascular resistance, spare the systemic circulation, and increase right ventricular inotropy. Although molecular abnormalities have been identified that may have potential as future therapeutic targets,¹⁰ phosphodiesterase type 5 inhibition meets many requirements for an ideal therapy now.

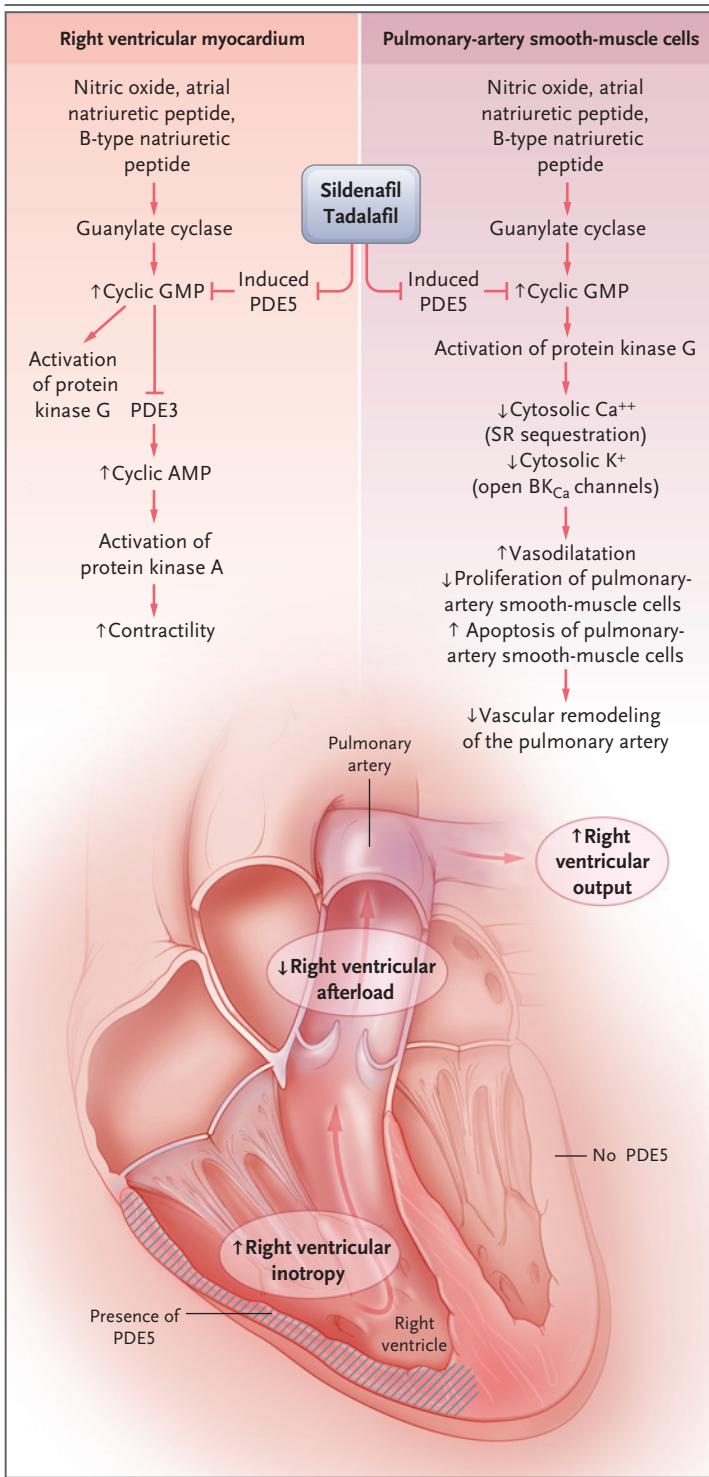


Figure 1. Effects of Phosphodiesterase Type 5 Inhibitors in Pulmonary Arterial Hypertension.

The combined effect of phosphodiesterase type 5 inhibitors on both the right ventricle and the pulmonary artery (i.e., increasing right ventricular inotropy and decreasing right ventricular afterload) may be more advantageous than drugs that affect only the pulmonary artery. Because PKG is much less abundant in the myocardium than in the vasculature, and because PKG activity is further decreased in right ventricular hypertrophy, the main effect of phosphodiesterase type 5 inhibitors is cyclic guanosine monophosphate–mediated inhibition of protein kinase A (a milrinone-like effect that increases right ventricular contractility). In contrast, in pulmonary-artery smooth-muscle cells, the effects of phosphodiesterase type 5 inhibitors are mediated by PKG and its multiple targets, leading to vasodilatation, reduced cell proliferation, and increased apoptosis. These combined effects lower the pulmonary vascular resistance. BK_{Ca} denotes the large conductance calcium-sensitive potassium channel, GMP guanosine monophosphate, PDE3 phosphodiesterase type 3, PDE5 phosphodiesterase type 5, and SR sarcoplasmic reticulum.

drolysis of cyclic guanosine monophosphate, agents in this class increase its levels, with consequent vasodilatory, antiproliferative, and proapoptotic effects that may reverse pulmonary-artery remodeling.¹⁷ Phosphodiesterase type 5 is expressed at minimal levels in the systemic vessels, other than the penile circulation, allowing for the relative selectivity of phosphodiesterase type 5 inhibitors for the pulmonary circulation. In addition, there is evidence that phosphodiesterase type 5 inhibitors may directly enhance right ventricular contractility through cyclic guanosine monophosphate–mediated inhibition of phosphodiesterase type 3¹⁸ (Fig. 1).

The phosphodiesterase type 5 inhibitor sildenafil (Revatio) was approved for the treatment of pulmonary arterial hypertension by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in 2005. Tadalafil (Adcirca) received FDA approval for this indication in 2009. A third agent in this class, vardenafil, has not yet been approved for the treatment of pulmonary arterial hypertension.

Sildenafil is a preferential inhibitor of phosphodiesterase type 5 with a 50% inhibitory concentration of 3.5 nmol per liter for phosphodiesterase type 5, as compared with 50% inhibitory concentrations of 37 and 280 nmol per liter for phosphodiesterase type 6 and phosphodiesterase type 1, respectively.²² A single dose of

The rationale for the use of phosphodiesterase type 5 inhibitors in pulmonary arterial hypertension is augmentation of the cyclic guanosine monophosphate pathway. By inhibiting the hy-

sildenafil (100 mg) in patients with pulmonary arterial hypertension results in a plasma level of $1.2 \mu\text{mol}$ per liter,²³ a level that inhibits phosphodiesterase type 1, which is also up-regulated in pulmonary arterial hypertension.²⁴ Some of sildenafil's beneficial effects may be mediated by inhibition of phosphodiesterase type 1 and the resulting antiproliferative effects of increasing cyclic AMP.²⁴

The expression of phosphodiesterase type 5 in the right ventricle and lungs of adults is repressed.²⁵ However, in patients with pulmonary hypertension, there is induction of phosphodiesterase type 5 in the small pulmonary arteries and right ventricular myocytes, perhaps representing reactivation of a fetal gene package.¹⁸ In a small study comparing oral sildenafil (75 mg) with inhaled nitric oxide (80 ppm), the two interventions caused similar reductions in mean pulmonary-artery pressure; however, only sildenafil increased cardiac output,²⁶ suggesting increased right ventricular contractility. This finding was subsequently confirmed in humans in whom right ventricular contractility was directly measured.²⁷ Indeed, phosphodiesterase type 5 inhibitors elicited a dose-dependent increase in right ventricular contractility and lusitropy in rats.¹⁸ Sildenafil-induced increases in cyclic guanosine monophosphate in the hypertrophied right ventricular myocardium (but not in the normal left ventricle, where phosphodiesterase type 5 is not up-regulated) inhibit phosphodiesterase type 3 and increase contractility in a manner that mimics milrinone¹⁸ (Fig. 1).

CLINICAL EVIDENCE

The benefit of sildenafil in pulmonary arterial hypertension was shown in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) study, a Pfizer-sponsored randomized trial.²⁸ In this trial, 278 patients (39% with WHO class II pulmonary arterial hypertension and 58% with class III) received placebo or sildenafil (20, 40, or 80 mg administered orally three times a day) for 12 weeks. The mean placebo-corrected increase in the 6-minute walking distance (the primary end point) for the three doses of sildenafil was 45, 46, and 50 m, respectively. The baseline 6-minute walking distance at enrollment was 339 to 347 m. The mean decrease in pulmonary vascular resistance was 171, 192, and 310 $\text{dyn} \cdot \text{sec} \cdot \text{cm}^{-5}$, re-

spectively. In a 1-year extension trial in which sildenafil was given at a dose of 80 mg three times a day, there was a sustained increase in the mean 6-minute walking distance (by 51 m).

Tadalafil was evaluated in the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study, a 16-week, randomized trial sponsored by Eli Lilly.²⁹ The trial enrolled 405 patients (who either had not received bosentan or were receiving bosentan, and almost all of whom had WHO class II or III pulmonary arterial hypertension). Doses of 2.5, 10, 20, and 40 mg were compared with placebo. Only patients receiving the 40-mg dose had a significant improvement in the primary end point, the placebo-corrected 6-minute walking distance, which was increased by 33 m. In the patients who had not received bosentan, the increase was greater than in patients who were receiving bosentan (44 vs. 23 m). Tadalafil did not alter the WHO functional class but slightly prolonged the time to clinical worsening.

CLINICAL USE

Patients who are candidates for therapy with a phosphodiesterase type 5 inhibitor should undergo a careful clinical assessment by a specialist with expertise in pulmonary hypertension. Cardiac catheterization is an important part of this evaluation. A trial of a short-lived, selective pulmonary vasodilator such as inhaled nitric oxide during the diagnostic catheterization is useful in assessing the patient for the presence of reversible pulmonary vasoconstriction, which portends a good prognosis and indicates that the patient may benefit from calcium-channel blockers. Patients with pulmonary hypertension should also undergo extensive evaluation for secondary causes of the disorder (see the Table in the Supplementary Appendix). Although some studies have suggested that phosphodiesterase type 5 inhibitors may be useful in patients with secondary pulmonary hypertension, the FDA approval did not include such use, and the evidence supporting it is limited.

Sildenafil and tadalafil are both indicated for use in patients with pulmonary arterial hypertension who have symptoms that are mild to moderately severe (WHO class II or III). On the basis of the exclusion criteria used in the SUPER and PHIRST trials, there is no evidence support-

ing the use of these drugs in patients who have severe symptoms (WHO class IV; 6-minute walking distance, <100 m) or who are relatively asymptomatic (WHO class I; 6-minute walking distance, >450 m).

Several alternatives to phosphodiesterase type 5 inhibitors are in clinical use for pulmonary arterial hypertension. Patients who have a clinically significant response to acute vasodilator challenge may have a response to calcium-channel-blocker therapy. Other agents for patients with mild-to-moderate symptoms include the orally active endothelin-receptor antagonists bosentan, sitaxsentan, and ambrisentan, the inhaled prostacyclin analogue iloprost, and the subcutaneous prostacyclin analogue treprostinil. For patients with severe (class IV) symptoms, intravenous epoprostenol or treprostinil is preferred. Although the optimal agent for monotherapy remains unclear,¹ it is unlikely that head-to-head comparisons among approved therapies will be funded by the pharmaceutical industry.

Of the two currently approved phosphodiesterase type 5 inhibitors, there is longer experience with the use of sildenafil than with the use of tadalafil in patients with pulmonary arterial hypertension, and data from the SUPER and PHIRST trials suggest that sildenafil may be slightly more efficacious. However, tadalafil has the advantage of once-daily administration.

Both the FDA and the EMEA have recommended that sildenafil be used at a dose of 20 mg given orally three times a day. This recommendation was based on the results of the SUPER trial, in which the benefit of sildenafil with respect to the 6-minute walking distance was not dose-dependent.²⁸ However, the effect on hemodynamic variables was dose-dependent, with an increasing benefit at 40 and 80 mg. Furthermore, dose-titration studies have suggested incremental improvement in functional capacity with doses up to at least 225 mg daily.³⁰ It is therefore our practice to begin at a dose of 20 mg given orally three times a day and to increase the dose every 2 weeks to a maximum of 80 mg given orally three times a day or until dose-limiting side effects (usually headache, nasal congestion, or dyspepsia) occur. In the PHIRST trial, the highest dose of tadalafil (40 mg daily) was the only effective dose,²⁹ and this is the dose approved by the FDA. There are no substantial data on higher doses of tadalafil.

Dose adjustments for sildenafil are not required in patients with mild-to-moderate renal or hepatic dysfunction. In contrast, it is recommended that the dose of tadalafil be reduced to 20 mg daily in such patients. Studies of the use of sildenafil in patients with more severe renal or liver disease are limited. Both drugs are metabolized predominantly by the hepatic enzyme cytochrome P-450 3A4 isoform (CYP3A4), and their clearance is affected by inhibitors or inducers of this isozyme. For example, the protease inhibitors ritonavir and saquinavir and the antibiotic erythromycin markedly increase sildenafil exposure,³⁰ which is of concern in patients with pulmonary arterial hypertension associated with HIV infection. Sildenafil is also partially metabolized by the cytochrome P-450 2C9 enzyme (CYP2C9). Bosentan (a CYP2C9 and CYP3A4 inducer) decreases sildenafil plasma levels by more than 50%²³ (an interaction that appears to be less pronounced with tadalafil).

Patients who are treated with a phosphodiesterase type 5 inhibitor should receive regular follow-up care in a clinic with expertise in treating pulmonary arterial hypertension. Although no specific tests are required to monitor phosphodiesterase type 5-inhibitor therapy (i.e., no liver-enzyme tests are required, as is the case for bosentan), it is our practice to repeat the hemodynamic assessment on a yearly basis and to assess functional capacity with the use of the 6-minute walking test and exercise treadmill testing yearly or with changes in symptoms or medications.

The average wholesale cost in the United States for 1 year of treatment with sildenafil (20 mg given orally three times a day) is approximately \$13,000; this compares favorably with bosentan (annual cost, >\$40,000).

ADVERSE EFFECTS

The pivotal randomized clinical trials of sildenafil and tadalafil provided some estimates of adverse-event rates associated with the two agents. In the SUPER trial, the most common adverse effects at the 20-mg dose of sildenafil were headache (46%, vs. 39% with placebo), dyspepsia (13% vs. 7%), flushing (10% vs. 4%), and epistaxis (9% vs. 1%).³⁰ In the PHIRST trial, the most common adverse effects at the 40-mg dose of tadalafil were similar to those with sildenafil at a dose of 20 mg (Fig. 2).

One of the most frequent concerns in the use of phosphodiesterase type 5 inhibitors is the risk of hypotension. This risk is clinically significant primarily when these agents are used together with nitrates, since the nitrate-induced increase in cyclic guanosine monophosphate is potentiated and sustained by phosphodiesterase type 5 inhibition. This combination can lead to severe refractory hypotension. Consequently, nitrates should not be used in combination with sildenafil or tadalafil. For both agents, a lower initial dose may be prudent in patients with low systemic blood pressure or presyncope.

In patients treated with sildenafil for erectile dysfunction, visual problems (altered color vision, increased light sensitivity, and blurred vision) have been reported; these problems are probably due to retinal inhibition of phosphodiesterase type 6.³⁰ In patients treated with 80 mg of sildenafil daily, the incidence of such effects is up to 7%. Sudden loss of vision after the use of sildenafil has been reported in postmarketing studies of erectile dysfunction.³⁰ The patients in these studies had a diagnosis of nonarteritic anterior ischemic optic neuropathy. A causal relationship between this condition and sildenafil has not been established. However, previous nonarteritic anterior ischemic optic neuropathy or the presence of vascular risk factors such as diabetes may increase the risk of this condition in response to sildenafil or tadalafil. Whether this risk is also increased among patients with pulmonary arterial hypertension, who are typically younger than those with erectile dysfunction, is not known.

As a measure of the severity of side effects, approximately 86% of enrolled patients completed the 1-year, open-label trial of 80 mg of sildenafil, and 83% completed the extension trial of tadalafil. This profile is better than the profiles for intravenous epoprostenol (which is associated with such adverse events as catheter-related infections, sepsis, and pump malfunctions), subcutaneous treprostinil (which is associated with infusion-site pain), inhaled iloprost (which involves an inconvenient regimen of multiple daily inhalations), or even bosentan (which requires indefinite monitoring for hepatic dysfunction and interaction with several drugs, including sildenafil and warfarin). In addition, the potentially serious fluid retention, requiring an increase in the use of diuretics, that can occur with am-

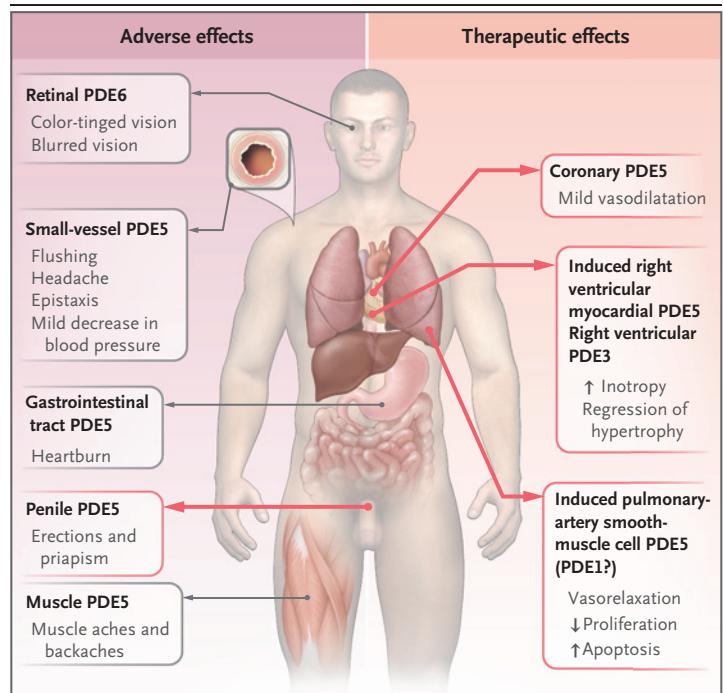


Figure 2. Therapeutic and Adverse Effects of Sildenafil in Pulmonary Arterial Hypertension.

The beneficial and harmful effects of sildenafil can be predicted on the basis of the tissue distribution of its target enzyme, phosphodiesterase type 5, and its off-target effects on some other phosphodiesterases. The preferential activity of sildenafil on penile cavernosal muscle and arteries and the pulmonary circulation is high, reflecting the high basal expression of phosphodiesterase type 5 in these tissues. In pulmonary arterial hypertension, phosphodiesterase type 5 expression is induced in the pulmonary vasculature, with new expression of phosphodiesterase type 5 in the hypertrophied right ventricular myocyte, allowing sildenafil to selectively target the right ventricle and pulmonary circulation in a beneficial and relatively selective manner. Sildenafil can directly inhibit retinal phosphodiesterase type 6, altering color vision, and it can indirectly inhibit right ventricular phosphodiesterase type 3, enhancing contractility. The adverse effects listed on the left, which are those most commonly reported in clinical trials and postmarketing studies, reflect cyclic guanosine monophosphate-mediated effects on systemic vascular and other types of muscle. PDE1 denotes phosphodiesterase type 1, PDE3 phosphodiesterase type 3, PDE5 phosphodiesterase type 5, and PDE6 phosphodiesterase type 6.

brisentan or bosentan does not occur with phosphodiesterase type 5 inhibitors. Finally, in contrast to endothelin antagonists, sildenafil is not teratogenic, which is relevant for a disease that is common among women in their reproductive years.

AREAS OF UNCERTAINTY

The SUPER and PHIRST trials examined the use of sildenafil and tadalafil almost exclusively in

patients with WHO class II or III disease. It has not yet been determined whether these agents are beneficial in patients with class I or class IV disease. The EMEA approved sildenafil only for use in patients with class III disease, whereas the FDA did not restrict approval according to the WHO class.

In patients who do not have an adequate response to a phosphodiesterase type 5 inhibitor, the options are to switch to another agent or try combination therapy. The available data on combination therapy are limited. In trials of brief duration, the combination of sildenafil plus inhaled iloprost has additive pulmonary vasodilatory effects.³¹ In small, unblinded studies, sildenafil (50 mg administered orally three times a day) combined with treprostinil, epoprostenol, or inhaled iloprost was safe and appeared to have additive beneficial effects.³²⁻³⁴ The combination of sildenafil with endothelin-receptor antagonists is not yet supported by data.

The most common mimic of idiopathic pulmonary arterial hypertension is secondary pulmonary hypertension due to left ventricular diastolic dysfunction.³⁵ In some patients, secondary pulmonary hypertension is misdiagnosed as pulmonary arterial hypertension and is treated accordingly. In two clinical trials, the exposure of patients with heart failure to endothelin-receptor antagonists was associated with clinical worsening early after the initiation of treatment.^{36,37} These findings underscore the need for caution regarding the use of agents that have been tested in patients with pulmonary arterial hypertension in the broader spectrum of patients with secondary pulmonary hypertension in whom occult left ventricular dysfunction may be exacerbated by certain therapies. However, preliminary data on sildenafil suggest that its use may be safe and even beneficial in patients with left ventricular dysfunction.^{27,38} The use of sildenafil in practice must await proper evaluation in randomized clinical trials.

GUIDELINES

“Evidence-based” guidelines for the treatment of patients with pulmonary arterial hypertension should be interpreted with caution because the clinical trials thus far have been brief (<4 months)

and, unlike studies of left ventricular failure, most have not included survival as an end point. The comparison of survival in unblinded extension studies with survival in archived historical data (e.g., from the registry of the National Institutes of Health⁷) is not a substitute for true survival studies. A recent meta-analysis concluded that none of the existing oral therapies for pulmonary arterial hypertension have any effect on survival.³⁹

A 2009 joint expert-opinion consensus document¹ from the American Heart Association and the American College of Cardiology recommended either sildenafil or endothelin-receptor antagonists as first-line therapy in patients with pulmonary arterial hypertension, WHO category 1 (see the Table in the Supplementary Appendix), with functional class II or early class III disease. Parenteral prostanoids should be initiated in patients with WHO class IV disease because these drugs improve the otherwise poor short-term prognosis.

RECOMMENDATIONS

We would avoid using a calcium-channel blocker in the patient in the vignette, who has WHO class II idiopathic pulmonary arterial hypertension, since pulmonary hypertension in this patient did not respond to inhaled nitric oxide. Our first choice of specific therapy is sildenafil at a dose of 20 mg given orally three times a day (with an increase in the dose every 2 weeks, to a maximum of 80 mg given orally three times a day, depending on side effects, to achieve relief of symptoms). We would add warfarin (despite the lack of data from randomized studies) and diuretics. If this patient's condition deteriorates with the use of sildenafil, we would add inhaled iloprost or intravenous epoprostenol.

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