Sildenafil for Pulmonary Hypertension

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OBJECTIVE: To evaluate the efficacy of sildenafil for treatment of pulmonary hypertension.

DATA SOURCES: Literature retrieval was accessed through MEDLINE (1977–March 2005), Cochrane Library, and *International Pharmaceutical Abstracts* (1977–March 2005) using the terms sildenafil and pulmonary hypertension. In addition, reference citations from publications identified were reviewed.

STUDY SELECTION AND DATA EXTRACTION: All articles in English identified from the data sources were evaluated. Studies including >5 patients with primarily adult populations were included in the review.

DATA SYNTHESIS: The treatment of pulmonary hypertension is challenging. Sildenafil has recently been studied as monotherapy and in combination with other vasodilators in the management of pulmonary hypertension. Eight hemodynamic studies and 12 clinical trials were reviewed (1 retrospective, 3 double-blind, 8 open-label). Sildenafil reduced pulmonary arterial hypertension and pulmonary vascular resistance/peripheral vascular resistance index and tended to increase cardiac output/cardiac index compared with baseline. Sildenafil was comparable to nitric oxide and at least as effective as iloprost or epoprostenol in terms of its pulmonary vasoreactivity. Combination therapy with iloprost, nitric oxide, or epoprostenol resulted in enhanced and prolonged pulmonary vascular effects. Clinical trials suggest that sildenafil improves exercise tolerance and New York Heart Association functional class, but large, randomized controlled trials are needed to confirm these findings. Overall, sildenafil was well tolerated.

CONCLUSIONS: Overall, sildenafil is a promising and well-tolerated agent for management of pulmonary hypertension. Further well-designed trials are warranted to establish its place in the treatment of pulmonary hypertension.

KEY WORDS: pulmonary hypertension, sildenafil.

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Pulmonary hypertension, characterized by a mean pulmonary arterial pressure (PAP) >20 mm Hg at rest, may result in progressive right ventricular heart failure and early mortality, depending on the etiology.[1,2] As a result, early diagnosis and prompt management are imperative to treat the underlying cause of pulmonary hypertension.[1-4] Pulmonary hypertension may result from increased pulmonary blood flow, increased pulmonary vascular resistance, or both. Although the incidence of pulmonary hypertension of all causes has not been reported, the annual incidence of a rare form, idiopathic pulmonary hypertension (IPAH), is estimated to be 1–2 per million of the population.[5]

A variety of commercially available vasodilators have been used as monotherapy or in combination to treat pulmonary hypertension.[2,4-9] Since many of these agents are costly, toxic, inconvenient to administer, or partially effective or ineffective in certain patients, other agents have been investigated for pulmonary hypertension.[2,4,6-9] Recently, sildenafil, a phosphodiesterase inhibitor approved for the treatment of erectile dysfunction, has been investigated for the treatment of pulmonary hypertension in both pediatric and adult patients.[4,6,8,10-16] The purpose of this review is to evaluate the efficacy and safety of sildenafil in predominantly adult patients with pulmonary hypertension.

Etiology

One of the most common classes of pulmonary hypertension is pulmonary arterial hypertension (PAH), which can be idiopathic (IPAH) or the result of other etiologies such as collagen vascular disease, portal hypertension, cer-

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tain drugs/toxins (eg, fenfluramine, dexfenfluramine, amphetamines, cocaine, L-tryptophan, inhaled rapseed oil), or vascular/cardiac shunts.[5,17,18] Other major classes of pulmonary hypertension include pulmonary venous hypertension, pulmonary hypertension associated with respiratory system diseases and/or hypoxemia (eg, chronic obstructive pulmonary disease (COPD), alveolar–capillary dysplasia, interstitial lung disease), chronic thrombotic and/or embolic diseases, and inflammatory disorders affecting the pulmonary vasculature (eg, sarcoidosis).

Diagnosis

Pulmonary hypertension is defined by the presence of a mean PAP >20 mm Hg at rest or >30 mm Hg with exercise.[5] In particular, the definition of PAH is a mean PAP >25 mm Hg with a pulmonary capillary pressure <15 mm Hg.[3] Depending on the etiology of pulmonary hypertension, pulmonary vascular resistance (PVR) may be elevated, as exemplified by patients with PAH who have PVR >160 dynes•sec/cm^{-5}.[19] Diagnosis and determination of the etiology and severity of pulmonary hypertension are established by right cardiac catheterization.[1,3,5] Doppler echocardiography can also be used to provide evidence for the etiology and diagnosis of pulmonary hypertension.[3] Many patients do not present with symptoms until their PAP exceeds 3–5 times baseline.[1] Thus, diagnosis is often delayed because patients may present with either no symptoms or nonspecific symptoms.[1,3]

Severity of pulmonary hypertension is based upon the World Health Organization (WHO) functional classification, which integrates symptoms of dyspnea, fatigue, chest pain, or syncope with the New York Heart Association (NYHA) functional classification of physical activity (Table 1).[3] The most common early symptom of pulmonary hypertension is exertional dyspnea,[3,5] which can be measured using the Borg dyspnea index (scale of 1–10; 1 = non-exertion, 10 = maximal exertion).[20] Disease progression and response to treatment are frequently based upon NYHA/WHO functional assessment and the 6-minute walk test.[3]

Table 1. WHO Functional Classification of Pulmonary Hypertension[a]

Class	Population
I	no limitation in physical activity; ordinary physical activity does not cause dyspnea or fatigue
II	slight limitation in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest
III	marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near syncope; no symptoms at rest
IV	unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity

WHO = World Health Organization.
[a]Uses the New York Heart Association functional classification to categorize the level of physical activity.

Treatment

Initial treatment of pulmonary hypertension should be directed at the underlying etiology so that it may result in clinical improvement or resolution.[1,5,7,9] Complete remission of pulmonary hypertension is rare, but has been observed in patients receiving appetite suppressants that were discontinued[7] and in patients receiving certain surgical interventions (eg, thromboendarterectomy for acute pulmonary emboli or mitral valve surgery).[4] Most patients receive medical management to ameliorate symptoms, as surgical options such as lung transplants are not readily available and some patients are not appropriate transplant candidates.

MEDICAL MANAGEMENT

Most patients receive medical management to ameliorate their symptoms.[4-6,8,9] Patients can receive treatment with supplemental oxygen, diuretics, digoxin, and warfarin depending on the etiology and severity of their disease.[4,5,9] In addition, vasodilators, such as calcium-channel blockers, are considered the mainstay of therapy for certain patients with pulmonary hypertension, particularly those with PAH.[4] Since PAH is one of the more common causes of pulmonary hypertension, various drug treatments targeting its management are discussed in greater detail.

Recently, the American College of Chest Physicians (ACCP) published evidence-based clinical practice guidelines for PAH (Figure 1).[4] The ACCP recommends acute vasodilator testing for patients with PAH for evaluation of their response to therapy prior to administering chronic vasodilator therapy. The ACCP defines a positive response to these vasodilators as a reduction in PAP of at least 10 mm Hg to ≤40 mm Hg, with an increased or unchanged cardiac output (CO). Others have defined a positive response as a mean reduction in PVR and PAP >20% with an increase in cardiac index (CI), but with minimal changes in mean arterial pressure and oxygen saturation.[9,21] Short-acting vasodilators, including intravenous epoprostenol, adenosine, and nitric oxide, have been used for vasodilator testing.[4,22] Nitric oxide is frequently used in research and clinical practice as the standard screening agent for vasoactivity because, in contrast to adenosine and epoprostenol, it usually does not cause hypotension and other systemic effects. However, nitric oxide is rarely used as long-term treatment because it requires continuous nebulization due to its short half-life and is not approved for pulmonary hypertension.[19,22]

Table 2 describes the commercially available vasodilators in the US and selective investigational agents used for long-term treatment of pulmonary hypertension including their mechanism of action, usual dosing regimens, toxicities, advantages, and limitations.[4,6,8,23,24] In prospective long-term trials (3 mo–5 y), these agents have demonstrat-

ed significant improvements or improved trends (beraprost) in cardiopulmonary hemodynamic endpoints, including mean decreases in right atrial pressure, PVR, and PAP combined with mean increases in CI.[25-33] In addition, these agents have significantly increased exercise capacity, decreased dyspnea, and improved NYHA or WHO functional class. To date, epoprostenol and calcium-channel blockers are the only agents that have increased survival, predominantly in patients with IPAH.[4,21,29] Because of the many limitations of these vasodilators, other agents have been investigated for the management of pulmonary hypertension, including sildenafil.

Pharmacology of Sildenafil

High concentrations of cyclic nucleotide phosphodiesterase-5 (PDE-5) isoenzymes are found in the lung tissue.[4] This enzyme rapidly degrades cyclic guanosine-monophosphate (cGMP), a secondary intracellular messenger that mediates the activity of nitric oxide (or endothelial-derived relaxing factor).[4,34] Sildenafil inhibits PDE-5, causing decreased hydrolytic breakdown of cGMP. As a result, sustained and increased cGMP concentrations accumulate in the pulmonary smooth muscle vasculature. Activation of cGMP kinase then occurs, leading to the opening of potassium channels, resulting in pulmonary vasodilation.[4,16] In support of the pharmacologic effects of sildenafil, data in humans have shown that nitric oxide plus sildenafil treatment results in synergistic increases in arterial cGMP levels compared with nitric oxide or sildenafil monotherapy.[19]

Clinical Trials

In healthy volunteers, a randomized double-blind study demonstrated that oral sildenafil 100 mg almost completely reversed the pulmonary arterial vasoconstriction induced by hypoxic conditions.[35] A number of case reports have also documented the potential benefits of sildenafil in patients with pulmonary hypertension.[11,36,37] Many of these cases are summarized in detail in one review.[11] Short- and long-term studies evaluating the hemodynamic and clinical

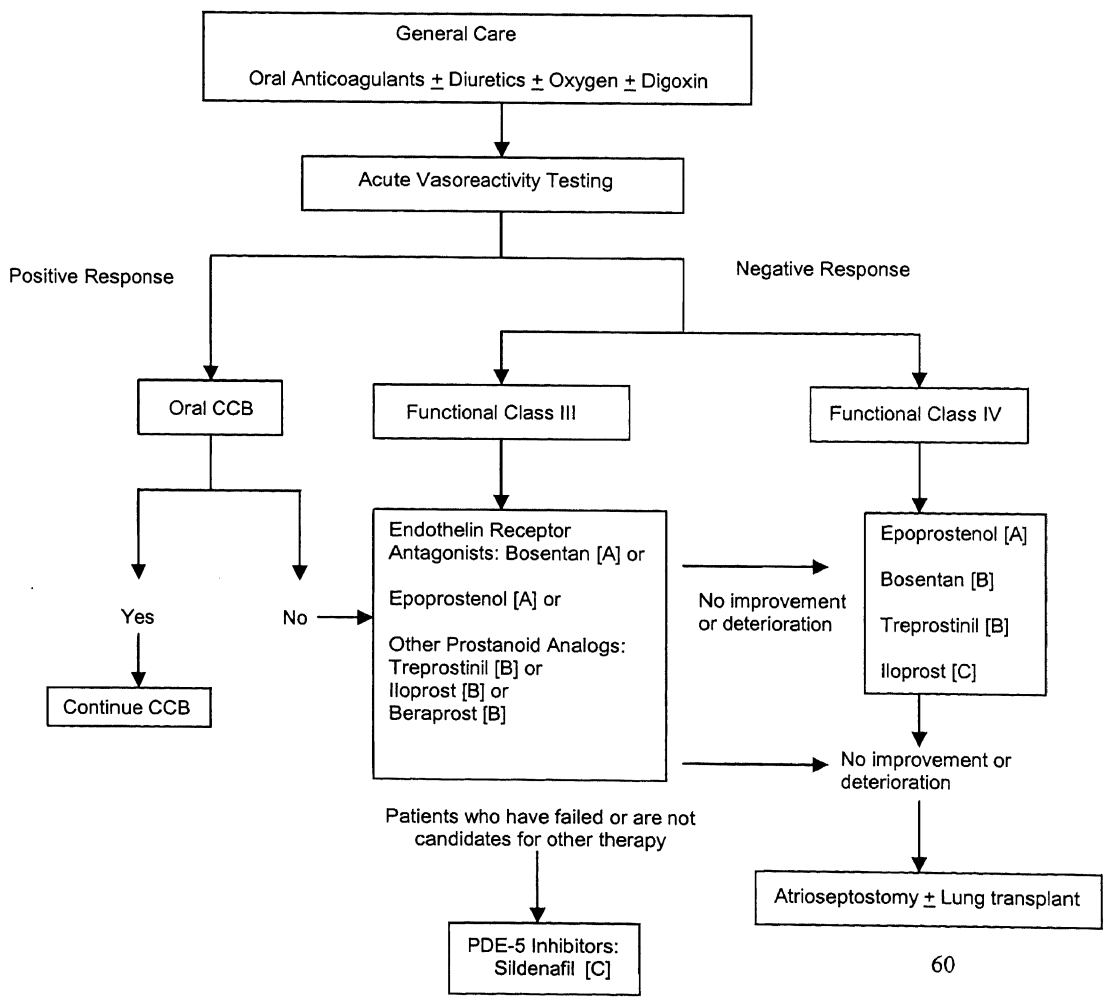

Figure 1. Therapy for PAH for Functional NYHA Class II–IV.[4] A = Grade of recommendation. Level of evidence good, benefit substantial; B = Grade of recommendation. Level of evidence fair, benefit intermediate; C = Grade of recommendation. Level of evidence low, benefit intermediate.
CCB = calcium-channel blocker; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase-5.

effects of sildenafil as monotherapy and in combination with other agents in ≥5 patients with pulmonary hypertension are discussed here. Specific dosing regimens used for all evaluated therapies are described in Tables 3 and 4.

SINGLE-DOSE HEMODYNAMICS

As shown in Table 3, 8 open-label trials compared the hemodynamic effects of sildenafil with those of other vasodilator drugs in patients with pulmonary hypertension.[19,38-44] These studies included between 5 and 60 patients with a mean age range of 18–81 years. The predominant diagnosis was IPAH in 6 of the studies,[19,38,40-42,44] whereas the remaining 2 trials had a heterogeneous patient population.[39,43] Sildenafil was administered orally in these studies, with single doses ranging from 12.5 to 75 mg.

Noncomparative

Sildenafil had decreased trends[38,39] or significant decreases in PAP[19,40,43] and PVR or PVR index[19,38,40] compared with baseline.[19,38,40,43] Sildenafil also demonstrated significant improvements[19,38,43] or trends[39,40] in CO/CI com-

Table 2. Comparison of Commercially Available Agents in the US and Selected Investigational Drugs for Pulmonary Hypertension

Drug	Mechanism of Action	Regimen	Toxicity	Long-Term Clinical Studies		Mortality Benefit	Advantages	Limitations
				IPAH	Other[a]			
Calcium-channel blockers[b]								
nifedipine	blocks vascular smooth muscle calcium channels	titrate dose gradually as tolerated[c]	edema, headache, hypoxia, hypotension	yes	no	yes[d]	inexpensive, available po, regression in LVH, survival benefits	useful in only 25–30% of pts. with IPAH; no randomized controlled trials; high doses may be required; may cause clinical deterioration in pts. with COPD or parenchymal lung disease (worsening oxygen desaturation; V/Q mismatch)
diltiazem	blocks vascular smooth muscle calcium channels	titrate dose gradually as tolerated[c]	bradycardia, heart block, edema, headache, hypotension, hypoxia	yes	no	yes[c]	inexpensive, available iv and po, survival benefits	useful in only 25–30% of pts. with IPAH; no randomized controlled trials; high doses may be required; may cause clinical deterioration in pts. with COPD or parenchymal lung disease (worsening oxygen desaturation; V/Q mismatch)
Endothelin receptor antagonist								
bosentan	inhibits the vasoconstricting action of endothelin, inhibits proliferation of vascular smooth muscle cells, reverses pulmonary vascular remodeling, RVH	weight ≤40 kg: 62.5 mg bid weight >40 kg: 62.5 mg bid for 4 wk, then 125 mg bid	dose-related hepatotoxicity dose-related anemia (usually mild), nasopharyngitis, edema, syncope, flushing, headache, teratogenic effects	yes	yes	not shown	available po, approved for pts. with NYHA class II–IV PAH	high cost; hepatotoxic and teratogenic CYP3A4 and 2C9 inducer, concurrent use of glyburide and cyclosporine contraindicated, not available iv

ACCP = American College of Chest Physicians; COPD = chronic obstructive pulmonary disease; IPAH = idiopathic pulmonary arterial hypertension; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; PAH = pulmonary arterial hypotension; RVH = right ventricular hypertrophy; V/Q = ventilation/perfusion.

[a]Other indications include pulmonary hypertension due to non-primary pulmonary hypertension, appetite suppressants, collagen vascular disease or connective tissue disease (eg, scleroderma), chronic thromboembolic pulmonary hypertension, congenital heart disease (left-to-right shunts).

[b]Calcium-channel blockers are mainly studied in patients with IPAH. Verapamil should usually be avoided because of its negative inotropic effects. Hemodynamic effects of amlodipine and felodipine have been studied in patients with pulmonary hypertension, but no long-term clinical trials have been conducted.

[c]Based upon the ACCP guidelines for pulmonary arterial hypertension.

[d]Only with IPAH.

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pared with baseline. Ghofrani et al.[43] demonstrated that sildenafil produced dose-dependent changes in CI, PAP, and PVR index, although significant differences were not reported between the 12.5- and 50-mg doses. Several studies[39,43] reported that sildenafil decreased the ratio of pulmonary to systemic vascular resistance, suggesting pulmonary vascular selectivity; however, the results of one of these trials suggested that sildenafil may be less pulmonary selective at higher doses.[43] Sildenafil had either no effect on arterial saturation or increased partial pressure of arterial oxygen.[19,39,40,43]

Table 2. Comparison of Commercially Available Agents in the US and Selected Investigational Drugs for Pulmonary Hypertension (continued)

Drug	Mechanism of Action	Regimen	Toxicity	Long-Term Clinical Studies		Mortality Benefit	Advantages	Limitations
				IPAH	Other[a]			
Prostaglandin analogs								
epoprostenol	acts as a non-selective vasodilator, inhibits platelets, inhibits smooth muscle proliferation	1–2 ng/kg/min iv, then 1–2 ng/kg/min as tolerated or until relief of dyspnea (average 2–40 ng/kg/min)	jaw pain, myalgias, leg/feet pain, headache, flushing, rash, hypotension, arrhythmias, nausea, anorexia, edema, iv line-related complications (eg, thrombosis, sepsis, cellulitis, pneumothorax, hemothorax)	yes	yes	yes	approved for pts. with NYHA class III–IV PAH, sustained survival benefits in pts. with IPAH with NYHA Class III, IV	high cost, short half-life (3–5 min), requires indwelling central venous catheter/pump, most pts. require warfarin to prevent catheter-induced thrombosis, drug instability (requires storage on ice after preparation and unstable at acidic pH), tolerance occurs, rebound pulmonary hypertension after discontinuation, may cause oxygen desaturation V/Q mismatch in pts. with lung parenchymal disease or fibrosis
treprostinil	acts as a non-selective vasodilator, inhibits platelets, inhibits smooth muscle proliferation	1.25 ng/kg/min sc and ↑ by 1.25 ng/kg/min over 4 wk, usual minimal effective dose 13.8 ng/kg/min, maximum studied dose 40 ng/min	jaw pain, myalgias, headache, flushing, diarrhea, nausea/vomiting, edema, rash, infusion site reactions (eg, pain, erythema, induration)	yes	yes	not shown	no indwelling central venous iv line, no line-related complications, stable at room temperature, longer half-life than epoprostenol (3–4 h)	high cost, administered sc via an abdominal wall catheter by a small infusion pump, rebound pulmonary hypertension after discontinuation, has potential for causing oxygen desaturation in pts. with lung parenchymal disease,[e] pain/erythema at infusion site
iloprost	acts as a non-selective vasodilator, inhibits platelets, inhibits smooth muscle proliferation	2.5–5 µg inhaled over 5 min (jet nebulizers) or 15 min (ultrasound nebulizers) 6–9 times/day	jaw pain, headache, coughing, flushing, syncope on exertion (not associated with clinical deterioration)	yes	yes	not shown	well tolerated, no line-related complications, no indwelling central venous line, longer half-life than epoprostenol (20–25 min)	inconvenient administration, hemodynamic effects resolve within 30–90 min after inhalation
beraprost	acts as a non-selective vasodilator, inhibits platelets, inhibits smooth muscle proliferation	20 µg po qid, increase by 20 µg po qid each wk if tolerated (maximum 120 µg qid), median 80 µg qid	jaw pain, headache, dizziness, flushing, leg pain, nausea, diarrhea	yes	yes	not shown	po formulation, no line-related complications, no indwelling central venous line, longer half-life than epoprostenol (35–40 min)	orphan drug, hemodynamic effects may decrease with time

ACCP = American College of Chest Physicians; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PAH = pulmonary arterial hypotension; V/Q = ventilation/perfusion.
[a]Other indications include pulmonary hypertension due to non-primary pulmonary hypertension, appetite suppressants, collagen vascular disease or connective tissue disease (eg, scleroderma), chronic thromboembolic pulmonary hypertension, congenital heart disease (left-to-right shunts).
[e]Similar to epoprostenol; therefore, it may cause clinical deterioration in patients with lung parenchymal disease, although, as of March 14, 2005, this has not been documented in the literature.

Table 3. Single-Dose Hemodynamic Studies Involving Sildenafil

Reference	Design	Age (y)	Gender (n)	Diagnosis (n)	NYHA Class (n)	Other Therapy (n)	Treatment Regimen[a] (n)	PAP (mean % change)	PVR/PVRI (mean % change)	CO/CI (mean % change)	Sildenafil ADRs (n)
Michelakis et al. (2002)[19]	OL, non-R N = 13	35–56, mean 44	F (9) M (4)	IPAH (9), PAH (2), LVD (2)	IV (9), III (3), II (1)	warfarin (9), diuretics (11), CCBs (6), E (1), oxygen (5)	NO 80 ppm (12) or 60 ppm (1) S 75 mg S + NO	NO –8[b] S –13[b] S + NO –13.1[b]	PVRI NO –19 S –27 S + NO –32	CI NO +0.2 S + 17 S + NO +17	transient headache (1)
Lepore et al. (2002)[38]	OL, non-R N = 9	28–75, mean 47	F (7) M (2)	IPAH (9)	NR	previously on vasodilators (not specified), oxygen (9)	NO 80 ppm S 50 mg S + NO	NO –9.3 S –3.7 S + NO –11.1	PVR NO –23.1 S –19.7 S + NO –30.5	CI NO +16 S +16 S + NO +24	NR
Ghofrani et al. (2002)[39]	OL, R N = 16	27–79, median 56.5	F (10) M (6)	LF (16) (IPF [7], CREST [3], other [6])	IV (10), III (6)	long-term nasal oxygen (16), other NR	NO with maximum response requiring 10–20 ppm E infusion ↑ every 15 min by 2 ng/kg/min until intolerance (eg, flushing, headache, or MAP <70 mm Hg) (8) S 50 mg (8)	NO –22[b] E –12[b] S –25[b]	PVRI NO –21.9 E –38[b] S –32[b]	CO NO +2.9 E +42.0 S +9.1	none
Leuchte et al. (2004)[40]	OL, non-R N = 10	33–59, mean 46.1	F (7) M (3)	IPAH (10)	IV (1), III (5), II (4)	CCBs (3), I (6)	NO 40 ppm I 15–20 µg S 50 mg initially, then 50 mg after 30 min	NO –13.4 I –17.2 S –11.2	PVR NO –12.7 I –33.2 S –15	CO NO +2.19 I +6.41 S +3.56	NR

ADRs = adverse drug reactions; CCBs = calcium-channel blockers; CI = cardiac index; CO = cardiac output; CREST = calcinosis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia syndrome; E = epoprostenol; I = iloprost; IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LF = lung fibrosis; LVD = left ventricular dysfunction; MAP = mean arterial pressure; NO = nitric oxide; NR = not reported; NYHA = New York Heart Association; OL = open-label; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = peripheral vascular resistance; PVRI = peripheral vascular resistance index; R = randomized; S = sildenafill.

[a]Sildenafil given orally, NO and iloprost by inhalation, and epoprostenol by intravenous infusion.

[b]Estimated from figure since not reported in the text.

[c]Percent change calculated using formula based upon absolute hemodynamic values: (baseline–treatment)/baseline × 100.

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Table 3. Single-Dose Hemodynamic Studies Involving Sildenafil (continued)

Reference	Design	Age (y)	Gender (n)	Diagnosis (n)	NYHA Class (n)	Other Therapy (n)	Treatment Regimen[a] (n)	PAP (mean % change)	PVR/PVRI (mean % change)	CO/CI (mean % change)	Sildenafil ADRs (n)
Kuhn et al. (2004)[41]	OL N = 8	32–63, mean 42.8	F (6) M (2)	IPAH (8)	III (6), II (2)	warfarin (7), diuretics (5), CCBs (1)	E mean dose 25.7 ng/kg/min for average of 2.9 y E + NO 40 ppm E + S 50 mg	E + NO –10 E + S –10 E + S + NO –12	PVR E + NO –13 E + S –24 E + S + NO –23	CO E + NO 0 E + S –8 E + S + NO –13	nausea (1)
Wilkens et al. (2001)[42]	OL N = 5	49–62, mean 56.4	F (4) M (1)	IPAH (5)	IV (3), III (2)	warfarin (5), diuretics (3), I (4), CCBs (1), oxygen (4)	I 8.4–10.5 μg S 25 mg, then 25 mg 30 min later if tolerated, then 50 mg 30 min later if tolerated S 75–100 mg + I 8.4–10.5 μg	I –16.3 S –12.6 I + S –24.7	PVR I –43.8 S –21.8 I + S –43	CO I +43.6 S +9.4[c] I + S +22.5	headache (2), nausea (1), BP drop (1)
Ghofrani et al. (2002)[43]	OL, R, C N = 30	NR	F (23) M (6)	IPAH (10), TE (13), CREST (6), aplasia of left pulmonary artery (1)	III, IV (number NR)	I (11)	NO 20–40 ppm I 2.8 μg low-dose S 12.5 mg (7) high-dose S 50 mg (8) S 12.5 mg + I 2.8 μg (7) (low dose) S 50 mg + I 2.8 μg (8) (high dose)	NO –7.0 I –10[b] low-dose S –8.5 high-dose S –13.5 low-dose S + I –11.5[b] high-dose S + I –17[b]	PVR NO –14.1 I –27.1 low-dose S –14.7 high-dose S –24.3 low-dose S + I –35[b] low-dose S + I –11.5[b] high-dose S + I –17[b] high-dose S + I –44.2	CI NO +7.9 I +22.8 low-dose S +5 high-dose S +13.2 low-dose S + I +35[b] high-dose S + I +45[b]	none
Ghofrani et al. (2004)[44]	OL, R N = 60	18–81, mean 51	F (39) M (21)	IPAH (46), Eisenmenger's disease (7), CREST (4), other (3)	IV (16), III (35), II (9)	CCBs (14)	NO 20–40 ppm (baseline) S 50 mg (19) V 10 mg (7) V 20 mg (9) T 20 mg (9) T 40 mg (8) T 60 mg (8)	S –16.2 V_{10} –14.3 V_{20} –12.1 T_{20} –12.6 T_{40} –18.3 T_{60} –10	PVRI S –28 V_{10} –21.6 V_{20} –26.3 T_{20} –18.6 T_{40} –27.1 T_{60} –26.7	CI S +13.2 V_{10} +9.3 V_{20} +18.4 T_{20} +9.3 T_{40} +7.5 T_{60} +18.8	NR

ADRs = adverse drug reactions; C = controlled; CCBs = calcium-channel blockers; CI = cardiac index; CO = cardiac output; CREST = calcinosis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia syndrome; I = iloprost; IPAH = idiopathic pulmonary arterial hypertension; NO = nitric oxide; NR = not reported; NYHA = New York Heart Association; OL = open-label; PAP = pulmonary arterial pressure; PVR = peripheral vascular resistance; PVRI = peripheral vascular resistance index; R = randomized; S = sildenafil; T = tadalafil; TE = chronic thromboembolic pulmonary hypertension; V = vardenafil.

[a]Sildenafil given orally, NO and iloprost by inhalation, and epoprostenol by intravenous infusion.

[b]Estimated from figure since not reported in the text.

[c]Percent change calculated using formula based upon absolute hemodynamic values: (baseline–treatment)/baseline × 100.

Table 4. Short- and Long-Term Clinical Trials Involving Sildenafil

Reference	Design	Age (y)	Gender (n)	Diagnosis (n)	NYHA Class (n)	Other Therapy (n)	Treatment Regimen[a] (n)	Exercise Tolerance	Improvement in NYHA Functional Class (n)	Sildenafil ADRs (n)
Short-term monotherapy										
Bharani et al. (2003)[45]	R, DB, PC, crossover N = 10	18–60, mean 32.11	F (5) M (4)	PAH (IPAH [3], ILD [2], TE [1]; ES [2])	IV (1), III (5), II (3), NR (1)	warfarin (9), nifedipine (4), diuretics (4), digoxin (2)	P or S for 2 wk, then at least 2-wk washout, then crossover for 2 wk S 25 mg every 8 h	6-min walk test (meters) B 163.89 S 266.67 P 170	improved at the end of 2 wk (2)	none, deaths NR
Sastry et al. (2004)[46]	R, DB, PC, crossover N = 22	16–55, mean NR	F (12) M (10)	IPAH (22)	III (4), II (18)	digoxin, diuretics, anticoagulants (NR)	P or S for 6 wk, then cross-over for 6 wk (no washout) S dose <25 kg = 25 mg tid 26–50 kg = 50 mg tid >51kg = 100 mg tid	exercise time (sec) at 6 wk P 475 S 686	NR	ADRs > placebo backache (3), headache (3), numbness of hands and feet (4), constipation (3), no dropouts due to ADRs, death (1) in P group
Sheth et al. (2005)[47]	OL, non-R N = 6	43–79, mean 60.5	F (1) M (5)	TE (6)	IV (6)	warfarin (6)	S 50 mg tid for 6 wk	NR	changes in class IV to III (3) IV to II (2) no change (1)	none
Chockalingam et al. (2005)[48]	OL, non-R N = 15	range NR, mean 27	F (11) M (4)	IPAH (15)	IV (12), III (3)	warfarin (11), nifedi-pine (5), furosemide (15), spironolactone (10), digoxin (15), dobutamine (4)	S 50 mg bid for 4 wk, then ↑ to 100 mg bid for 4 wk	6-min walk test (meters) B 234 S 50 mg 377 S 100 mg 385	improvement in mean B 3.8 S 50 mg 2.4 S 100 mg 2.5	worsening leg edema in 3 of 5 pts. also receiving nifedi-pine; resolved after stopping nifedipine
Long-term monotherapy										
Mikhail et al. (2004)[49]	OL, non-R N = 10	20–60, mean 35.4	F (8) M (2)	sporadic PAH (7), TE (1), CVD (1), toxin (1)	III (5), II (5)	warfarin (10), diuretics (6), CCBs (4)	S 25 mg, titrated to 50 mg tid	6-min walk test at 3 mo (meters) B 283 S 395	improved at 3 mo (4) III to II (3), III to I (1)	transient blurred vision (1) resolved after discontinuation, no deaths
Ghofrani et al. (2003)[50]	OL, non-R N = 12	NR	F (5) M (7)	TE (12)	NR	phenprocumon (12), diuretics (NR), CCBs (NR)	S 50 mg tid, dosage ↑ over the first 4–5 days	6-min walk test (meters) after 6.5 ± 1.1 mo B 312 S 366	NR	↓ systemic arterial pressure, but no ADRs reported; no deaths

ADRs = adverse drug reactions; B = baseline; CCBs = calcium-channel blockers; CVD = collagen vascular disease; DB = double-blind; ES = Eisenmenger syndrome; IILD = interstitial lung disease; IPAH = idiopathic pulmonary arterial hypertension; NR = not reported; NYHA = New York Heart Association; OL = open-label; P = placebo; PAH = pulmonary arterial hypertension; PC = placebo-controlled; R = randomized; S = sildenafil; TE = chronic thromboembolic pulmonary hypertension.

[a]Sildenafil given orally, iloprost by inhalation.

(continued on page 877)

Table 4. Short- and Long-Term Clinical Trials Involving Sildenafil (continued)

Reference	Design	Age (y)	Gender (n)	Diagnosis (n)	NYHA Class (n)	Other Therapy (n)	Treatment Regimen[a] (n)	Exercise Tolerance	Improvement in NYHA Functional Class (n)	Sildenafil ADRs (n)
Long-term monotherapy										
Michelakis et al. (2003)[51]	OL, non-R N = 5	26–57, mean 40.2	F (2) M (3)	PAH (IPAH [4], ES [1])	III (4), II (1)	warfarin (5), diuretics (5), CCBs (2)	S 50 mg every 8 h for 3 mo	6-min walk test at 3 mo (meters) B 376 S 504	improved in all pts. at 3 mo III to II (4) II to I (1)	no visual abnormalities; no change in liver enzymes, creatinine, or bleeding times; deaths NR
Kothari et al. (2002)[52]	OL, non-R N = 14	5–30, mean 15.6	M (6) F (8)	PAH (IPAH [9], congenital heart disease [5])	IV (8), III (5), II (1)	digoxin (14), diuretics (14), CCBs (7), anticoagulants (5)	S initial dose[b] ≤30 kg = 3.125 mg >30 kg = 6.25 mg S median dose ≤30 kg = 87.5 mg/day >30 kg = 150 mg/day S dose range children 75–150 mg/day adults 125–300 mg/day	6-min walk test (meters) B 264.1 S 408.2 at 3 mo S 453.2 at 6 mo	mean change after average 7.3 mo 3.31–2.00 improvement 2 classes (5), 1 class (7), no change (1)	headache, dizziness, and flushing (2); reported deaths (2) (atrial fibrillation [1], unknown [1]; both pts. had subjectively improved)
Sastry et al. (2002)[53]	OL, non-R N = 29	4–62, mean 25.9	M (16) F (13)	IPAH (29)	IV (4), III (15), II (10)	digoxin (NR), diuretics (NR), anticoagulants (NR), CCBs (NR)	S 25 mg tid, dosage ↑ to maximum 100 mg tid as tolerated	6-min walk test at 3 mo (meters) B 297.07 S 427.68	improvement 2 classes (4),[c] 1 class (13), no change (12)	minor headache, mild abdominal discomfort, flushing sensation (3); no dropouts due to ADRs; death (1) in an accident
Long-term combination										
Ghofrani et al. (2003)[54]	OL, non-R N = 14	mean 58	NR	IPAH (9), CVD (5)	IV (10), III (4)	diuretics (NR), I (14)	I dose NR; average frequency 9 doses/day for 18 ± 4 mo S dose titrated over 3–4 days as tolerated to 25 mg tid (9) or 50 mg tid (5)	6-min walk test (meters) I at B 256 I + S 346 at 3 mo I + S 338 at 6 mo I + S 349 at 9–12 mo	I at B, IV (10), III (4) I + S at 3 mo, IV (3), III (9), II (2) I + S at 9–12 mo, IV (1), III (8), II (3)	asymptomatic minor ↓ in MAP (88–80 mm Hg), but no dizziness; no reports of headache, dyspepsia, unwanted erections, abnormal vision; deaths (2) unrelated to drug therapy

ADRs = adverse drug reactions; B = baseline; CCBs = calcium-channel blockers; CVD = collagen vascular disease; I = iloprost; IPAH = idiopathic pulmonary arterial hypertension; MAP = mean arterial pressure; NR = not reported; NYHA = New York Heart Association; OL = open-label; PAH = pulmonary arterial hypertension; R = randomized; S = sildenafil.

[a]Sildenafil given orally, iloprost by inhalation.

[b]If no fall in BP, second dose administered in 1–2 hours, then dosed 3 times daily, titrating up over 4–6 weeks based on response and adverse effects.

[c]All class IV at baseline.

(continued on page 878)

Table 4. Short- and Long-Term Clinical Trials Involving Sildenafil (continued)

Reference	Design	Age (y)	Gender (n)	Diagnosis (n)	NYHA Class (n)	Other Therapy (n)	Treatment Regimen[a] (n)	Exercise Tolerance	Improvement in NYHA Functional Class (n)	Sildenafil ADRs (n)
Long-term combination										
Bhatia et al. (2003)[55]	retrospective N = 13	mean 55.1	F (10) M (3)	IPAH (11), TE (1), porto-pulmonary hypertension (1)	III (7), II (3), I (2)	epoprostenol (6), bosentan (3), CCBs (4), warfarin (NR), other (NR)	S initial dose 25 mg, dosage ↑ to 50, 75, and 100 mg if tolerated (systolic BP >90 mm Hg) at 8-h intervals S discharge dose[d] 300 mg/day (4) 225 mg/day (5) 150 mg/day (1)	6-min walk test (mean follow-up 117 days) no improvement values NR)	changes in class III to II (2), II to I (1), III to IV (1), no change (6)	mild headache and nausea (1), nasal congestion, malaise, lower extremity edema (2) requiring dropout; facial edema, chills, shortness of breath (1), requiring dropout; hypotension (1), requiring dropout deaths NR
Long-term comparative										
Wilkins et al. (2005)[56]	R, DB N = 26	S 28–62 (mean 44.4)	S F (11) M (3)	S IPAH (12), other (2)	NR	S CCBs (1), digoxin (6), diuretics (10), warfarin (13)	S 50 mg bid for 4 wk, then 50 mg tid for 12 wk (14) or	6-min walk test (meters) change from baseline S 114 bosentan 59	NR	sudden death due to PAH during wk 14 (1), palpitations requiring hospital admission (1)[e]
		bosentan 27–55 (mean 41.1)	bosentan F (10) M (2)	bosentan IPAH (11), other (1)		bosentan CCBs (5), digoxin (8), diuretics (6), warfarin (11)	bosentan 62.5 mg bid for 4 wk, then 125 mg bid (+ midday placebo) for 12 wk (12)			

ADRs = adverse drug reactions; CCBs = calcium-channel blockers; IPAH = idiopathic pulmonary arterial hypertension; NR = not reported; NYHA = New York Heart Association; S = sildenafil; TE = chronic thromboembolic pulmonary hypertension.

[a]Sildenafil given orally, iloprost by inhalation

[d]Ten of 13 patients were discharged on a sildenafil 8-hour regimen based on the highest dose tolerated.

[e]Three patients in the bosentan group were hospitalized due to fluid retention (2) and hemoptysis (1).

Sildenafil vs Nitric Oxide vs Combination

Five studies compared the effects of sildenafil versus nitric oxide 20–80 ppm.[19,38-40,43] Sildenafil appeared to have comparable or greater effects in decreasing PAP and PVR/PVR index compared with nitric oxide. Similarly, sildenafil appeared to demonstrate a similar or greater increase in CO/CI compared with nitric oxide. Two studies[39,43] reported that sildenafil had prolonged hemodynamic effects compared with nitric oxide (>120 vs 15 min). Sildenafil appeared to have similar effects on oxygen saturation versus nitric oxide.[19,40] However, in the study by Lepore et al.,[38] nitric oxide produced a greater decrease in the ratio of pulmonary/systemic vascular resistance than sildenafil (0.44 vs 0.5), suggesting a greater pulmonary vasoselectivity.

Michelakis et al.[19] and Lepore et al.[38] also compared the effects of nitric oxide and sildenafil monotherapy with combination therapy. In both studies, combination treatment was more effective at decreasing PAP and PVR/PVR index than monotherapy with either agent and provided an additive effect in increasing CI. Lepore et al.[38] reported that the hemodynamic effects were prolonged with combination therapy compared with monotherapy with nitric oxide (10–15 vs 5–10 min), but no comparison was made with sildenafil monotherapy. Combination therapy appeared to increase arterial oxygen saturation versus nitric oxide (97.6% vs 96%) or sildenafil.[19] In addition, combination therapy had a comparable ratio of pulmonary to systemic vascular resistance compared with nitric oxide monotherapy (0.44 vs 0.44). Combination therapy had a significantly lower ratio than sildenafil monotherapy (0.44 vs 0.5; $p < 0.05$), suggesting greater pulmonary selectivity.

Sildenafil vs Iloprost vs Combination

Three studies evaluated the effects of sildenafil versus inhaled iloprost (2.8–20 μg).[40,42,43] In the studies by Leuchte et al.[40] and Wilkens et al.,[42] iloprost decreased PAP greater than sildenafil, whereas in the trial by Ghofrani et al.,[43] the PAP appeared to be similar for the drugs. One reason for this difference may be that Ghofrani et al. used a much lower dose of iloprost (2.8 μg) than the other researchers (8.4–20 μg). The percent change in PVR/PVR index was lower for iloprost than sildenafil for all studies. In all of the trials, the percent change in CO/CI appeared to be higher with iloprost compared with sildenafil.[40,42]

Combination treatment with iloprost and sildenafil provided enhanced hemodynamic benefits.[42,43] Compared with sildenafil alone, combination treatment provided additive or synergistic reductions in PAP and PVR. Moreover, combination treatment had a greater effect on CO than sildenafil monotherapy. Interestingly, the pulmonary vascular effects[43] of combination treatment were greater with higher doses of sildenafil (12.5 vs 50 mg) and prolonged than with sildenafil monotherapy (180–210 vs 90–120 min).[42,43] Combination therapy was associated with significant or nonsignificant decreases in the pulmonary/systemic vascular resistance ratio (–5% to –12%) and no[43] or increased[42] changes in oxygen saturation.

Sildenafil vs Epoprostenol vs Combination

Only one study compared the effects of monotherapy with epoprostenol versus sildenafil.[39] The percent change in PVR index was not significantly different between the treatment groups; however, epoprostenol appeared to produce the greatest change. Compared with sildenafil, epoprostenol had a greater effect on increasing CI. Sildenafil demonstrated pulmonary selectivity, as evidenced by a greater percent reduction in the ratio of pulmonary to systemic vascular resistance compared with epoprostenol (–24% vs –2%). Furthermore, pulmonary shunt flow was increased with epoprostenol (+17%), but was unchanged from baseline with sildenafil. As a result, epoprostenol reduced partial pressure of oxygen (–15%) due to increased perfusion to low ventilation areas, whereas sildenafil increased PaO_2 (+14%).

Kuhn et al.[41] compared the hemodynamic efficacy of combination therapy with epoprostenol and sildenafil. Combination treatment was more effective at decreasing mean PAP and PVR than epoprostenol alone (defined as baseline in study). Although a statistically significant difference was not reported, epoprostenol plus sildenafil appeared to be more effective at increasing CO compared with epoprostenol alone. Combination therapy increased the ratio of mean arterial pressure to mean PAP compared with epoprostenol alone (2.1 vs 1.9), and no changes were reported with systemic oxygen saturation. These results support the finding by Ghofrani et al.,[39] suggesting that sildenafil demonstrates a preferential vasodilation of the pulmonary vasculature.

Sildenafil vs Other Phosphodiesterase-5 Inhibitors

As of March 12, 2005, only one study has compared the hemodynamic responses of sildenafil among various doses of other PDE-5 inhibitors.[44] This randomized prospective study demonstrated that sildenafil, vardenafil, and tadalafil decreased mean PAP and PVR index and increased CI compared with baseline (with nitric oxide). Overall, sildenafil had the greatest percent decrease in PVR index compared with baseline, but had similar effects on CI and mean PAP versus the other treatment groups. The peak pulmonary vasodilating effects were the most rapid with vardenafil (40–45 min), followed by sildenafil (60 min) and tadalafil (75–90 min). Sildenafil 50 mg (–15.5), tadalafil 40 mg (–16), and tadalafil 60 mg (–11.5) significantly reduced the pulmonary to systemic vascular resistance ratio, suggesting that these agents had pulmonary vasoselectivity, whereas vardenafil 10 (–6.9) and 20 mg (–0.1) had minimal effects. Sildenafil significantly improved arterial oxygenation compared with vardenafil and tadalafil, suggesting that sildenafil may have beneficial effects on ventilation/perfusion matching.

SHORT-TERM TRIALS

Four short-term (<3 mo) clinical trials have been conducted,[45-48] 2 of which were well designed.[45,46] A randomized, double-blind, placebo-controlled crossover trial eval-

uated the efficacy of sildenafil in patients with IPAH.[46] Sildenafil or placebo was administered for 6 weeks, and patients were then crossed over to the alternate therapy with no washout period. No other vasodilators were permitted. One patient in the sildenafil-first group withdrew from the study one week after randomization and one patient in the placebo-first group died one week after randomization. In the placebo-first group, the exercise times were 459.6 seconds at baseline, 452.1 seconds at the end of the placebo phase, and 687 seconds at the end of the sildenafil phase ($p < 0.0001$ for placebo vs sildenafil).

In the sildenafil-first group, the exercise times were 451.6 seconds at baseline, 698.1 seconds at the end of the sildenafil phase ($p < 0.001$ vs baseline), and 527.4 seconds at the end of the placebo phase ($p < 0.005$ vs sildenafil; $p < 0.001$ vs baseline). When results for the 2 groups were combined, the exercise times were 475 seconds for placebo and 686 seconds after 6 weeks of sildenafil ($p < 0.0001$). The CI was 2.80 L/m^2 for placebo compared with 3.45 L/m^2 for sildenafil ($p < 0.0001$). The difference in pulmonary arterial systolic pressure was not significantly different between sildenafil and placebo (98 vs 105 mm Hg; $p = 0.09$). Quality-of-life scores for dyspnea ($p = 0.009$) and fatigue ($p = 0.04$) were significantly higher for sildenafil compared with placebo. The emotional function component of the quality-of-life score was slightly lower with sildenafil, but this was not statistically significant ($p = 0.06$). There was no significant change in systemic blood pressure with sildenafil therapy.[46]

A similarly designed study in which sildenafil was given for 2 weeks demonstrated comparable findings related to exercise tolerance and hemodynamic improvements.[45] In addition, the mean Borg Dyspnea Score was significantly improved with sildenafil (5.22 at baseline, 5.11 for placebo, 3.56 for sildenafil; $p < 0.01$). The NYHA class improved in 2 patients. A 6-week open-label trial also supported the findings of improved PAP, NYHA class, and dyspnea with sildenafil compared with baseline.[47]

An open-label trial was conducted to evaluate optimal dosing of sildenafil in IPAH.[48] Fifteen patients received sildenafil 50 mg twice daily for 4 weeks, with the dose increased to 100 mg twice daily for an additional 4 weeks. Nifedipine was administered to 5 patients who showed an initial response to this vasodilator, and none of the patients had received specific pulmonary vasodilators in the past.

The 6-minute walk test improved significantly compared with baseline one week after starting sildenafil ($p = 0.002$) and after 4 weeks of the 50-mg dose (377 vs 234 meters; $p = 0.001$). Sildenafil 50 mg twice daily also significantly improved the mean Borg dyspnea index (8.1 vs 4.4; $p = 0.0007$) and mean NYHA class (3.8 vs 2.4; $p = 0.002$). The clinical parameters did not significantly improve further when the dose of sildenafil was doubled. Mean pulmonary artery systolic pressure was significantly reduced with sildenafil 50 mg twice daily compared with baseline (113 vs 125 mm Hg; $p = 0.05$). Overall, 12 (80%) patients showed response to sildenafil. Eleven of these patients responded to a dose of 50 mg twice daily, and one patient responded when the dose was doubled.[48]

LONG-TERM TRIALS

Monotherapy

As described in Table 4, 5 open-label, long-term (>3 mo) trials evaluated the clinical effects of sildenafil monotherapy in patients with pulmonary hypertension.[49-53] Three of the studies included only adults and 2 included both children and adults.[52,53] The studies evaluated between 5 and 29 patients, with an average age of 15.6–40.2 years. These trials included a heterogeneous patient population consisting of predominantly thromboembolic pulmonary disease and patients with PAH related to IPAH, collagen vascular disease, and congenital heart disease. Prior to receiving sildenafil, most patients were receiving conventional therapy with anticoagulants, diuretics, and/or other vasodilators.[49-53] Sildenafil was administered orally in these studies, with daily doses ranging from 75 to 300 mg. The trials ranged from 3 to 7.3 months. In all of these studies, sildenafil significantly improved exercise tolerance, as measured by the 6-minute walk test, compared with baseline. Four of the trials reported improvement in NYHA functional class,[49,51-53] whereas one did not evaluate this endpoint.[50] In contrast to the short-term clinical studies, none of these studies evaluated changes in dyspnea. In the study by Mikhail et al.,[49] 7 (78%) patients had improvement in overall health and well-being and 2 patients reported no change. Most investigators reported significant decreases in PAP,[49-51] PVR/PVR index,[49-51,53] and trends toward increased CO/CI.[49-53] No deterioration in arterial, venous, or pulmonary oxygen saturation was observed,[49,50,53] and some noted a significant trend toward improvement in oxygen saturation with sildenafil.[49,50]

Sildenafil Combination

Two long-term trials evaluated the clinical effects of combination therapy with sildenafil and other vasodilators. The best-designed trial was a prospective uncontrolled comparison of addition of sildenafil to iloprost.[54] Combination therapy with iloprost and sildenafil appeared to lower the mean PAP (50.7 vs 47.8 mm Hg) and increase the CI (2.3 vs 2.6 L/min/m^2), although significant differences were not reported. Combination therapy also significantly decreased the PVR index (1640 vs 1309 dynes•cm^{-5}m^2; $p = 0.014$). Compared with iloprost monotherapy, combination therapy significantly increased the 6-minute walking distance at 3 months (346 vs 256; $p = 0.002$) and provided a sustained improvement in exercise tolerance up to 9–12 months (349 vs 256; $p = 0.002$). Combination treatment also improved NYHA functional class.

A retrospective study reported mixed findings.[55] This study evaluated the clinical and hemodynamic effects of adding sildenafil to various vasodilators, including epoprostenol, bosentan, and calcium-channel blockers, in 13 patients with pulmonary hypertension predominantly due to IPAH. Overall, patients did not have a significant im-

provement in the 6-minute walk test; however, 3 patients demonstrated improvement in NYHA functional class. The epoprostenol dosing regimen was decreased over time in 2 patients because of symptomatic improvement. The addition of sildenafil significantly decreased mean PAP (peak 43 vs 48; $p = 0.01$), decreased PVR index (peak 8.6 vs 6.7; $p < 0.001$), and increased CO (peak 6.2 vs 7.2 L/min; $p = 0.04$) compared with baseline.

Sildenafil vs Bosentan

Only one study to date has compared the effects of sildenafil with those of a specific pulmonary vasodilator.[56] This randomized, double-blind, 16-week trial compared hemodynamic and clinical effects of sildenafil with those of bosentan in patients on conventional therapy. Although 26 WHO functional class III patients were enrolled, one patient in the sildenafil group died during week 14. Both the sildenafil and bosentan groups had a significant improvement in cardiac index compared with baseline, with no difference between treatments (mean change from baseline 0.3 L/min/m^2; $p < 0.01$ for both). In addition, both groups had a significant improvement in the mean 6-minute walk test compared with baseline, with sildenafil producing a 55-meter greater mean change from baseline versus bosentan ($p = 0.044$). The Borg dyspnea index scores did not significantly change from baseline for either treatment. Quality-of-life scores improved significantly with sildenafil (change from baseline 27; $p < 0.01$), but not with bosentan (change from baseline 6), with a significant difference between sildenafil and bosentan ($p = 0.002$).

STUDY LIMITATIONS

Overall, the clinical trials included heterogeneous patient populations, with only 5 having homogeneous populations.[46-48,50,53] There were only 3 randomized, double-blind controlled trials.[45,46,56] Two of these well-designed studies[45,46] were limited by their small size and short treatment duration (2 and 6 wk), preventing adequate assessment of NYHA functional improvement and mortality. Neither study measured adherence or control for concomitant medication use, whereas another lacked a washout period. A third well-designed trial[56] had similar limitations but was longer in duration and did not measure change in NYHA class. The remaining trials were limited by their poor design. All were open-label, nonrandomized, and lacked controls, with the exception of the retrospective study. These studies also had similar limitations as the well-designed trials, but were longer in duration. In addition, only one trial compared the clinical effects of sildenafil monotherapy with those of combination therapy,[54] and no trials compared the clinical effects of sildenafil monotherapy with monotherapy using other vasodilators.

Adverse Effects

Research evaluating the use of sildenafil for pulmonary hypertension has demonstrated that it is well tolerated. One of the best-designed studies had no reports of adverse effects.[45] A similarly designed study reported no serious adverse effects requiring discontinuation of sildenafil.[46] In this trial, the adverse effects that were more frequently reported with sildenafil compared with placebo were backache (3 vs 1), headache (3 vs 1), and numbness of hands and feet (4 vs 1). No or few adverse effects were reported in other clinical trials, as shown in Tables 3 and 4.[19,39,40,42,53,54] Common adverse effects among these and other studies[55] included headache, nausea, mild abdominal discomfort, nasal congestion, flushing, and dizziness.[52,55] Although asymptomatic decreases in blood pressure were reported, there were no significant differences in mean arterial pressure and/or heart rate compared with baseline for the majority of the trials.[19,38-46,49,51,52] Two studies did report significant reductions in mean systemic arterial pressure from baseline, with most patients being asymptomatic.[50,55] Only one patient in one trial required discontinuation of sildenafil due to hypotension.[55] Prospective placebo-controlled studies involving use of sildenafil for erectile dysfunction report similar adverse effects.[57] In those studies, the most commonly reported adverse effects were headache (16%), flushing (10%), dose-related dyspepsia (7%), and nasal congestion (4%).

Serious adverse effects requiring drug discontinuation have occurred infrequently in studies evaluating sildenafil for pulmonary hypertension and have included peripheral edema (combined with malaise and nasal congestion), transient visual disturbance, severe hypotension, facial edema associated with shortness of breath, and chills.[49,55] The manufacturer has reported that priapism, stroke, or cardiovascular events have occurred rarely in patients taking sildenafil for erectile dysfunction[57]; however, these adverse events were not observed in the studies evaluating sildenafil for pulmonary hypertension. Few or no deaths were reported,[46,49,50,52-54] and none was associated with sildenafil therapy.

The manufacturer cautions against the use of sildenafil in patients with retinitis pigmentosa, a visual disorder in which progressive atrophy of the retina results in blindness.[57] In clinical trials of sildenafil for erectile dysfunction, transient dose-related visual changes have been reported (3%; color tinge, increased sensitivity to light, or blurred vision).[57,58] Although the majority of ocular adverse effects are dose-related and reversible, there have been rare reports of retinopathy and long-term visual disturbances. A case of premature retinopathy was reported in an infant after receiving sildenafil for >2 weeks.[59] After sildenafil was discontinued and the patient received laser photocoagulation, the retinopathy regressed. Fourteen cases of nonarteritic ischemic optic neuropathy (NAION) have been reported in adults soon after use of sildenafil for erectile dysfunction. Permanent visual deficits occurred in some of these patients. Patients with preexisting atherosclerotic risk factors (eg, hyperlipidemia, hypertension, diabetes) may be at increased risk for NAION. In patients with NAION in one eye, sildenafil may increase the risk for development of NAION in the other eye. Therefore, sildenafil

should be used cautiously in these patients.[60] In clinical trials with sildenafil in pulmonary hypertension, no irreversible visual disturbances were reported.[46,49-55]

Although no reports of respiratory decompensation have been described in patients with pulmonary hypertension, animal studies involving experimental models of lung injury have shown that sildenafil may worsen gas exchange as a result of impaired ventilation–perfusion matching.[4] As a result, the ACCP recommends that sildenafil should be used cautiously in patients with pulmonary hypertension and severe lung disease.[4]

Place in Therapy

PULMONARY ARTERIAL HYPERTENSION

The ACCP guidelines recommend that all patients with PAH must undergo acute vasoreactivity testing to evaluate their response to vasodilators.[4] For patients who have a favorable response, calcium-channel blockers should be considered first-line therapy (Figure 1). Nifedipine or amlodipine could be considered in patients with bradycardia, and diltiazem is preferred in patients with tachycardia. Verapamil should be avoided because of its negative inotropic effects. If response is inadequate to the calcium-channel blockers, other vasodilator therapy is recommended for patients with NYHA class II, III, or IV heart failure. No specific drug therapy is recommended for patients with NYHA class II heart failure, based on limited data. In comparison, bosentan and epoprostenol are strongly recommended for class III heart failure, and treprostinil and iloprost are considered as alternative therapy. For class IV heart failure, epoprostenol is considered the treatment of choice, whereas the other vasodilators are considered as alternatives. Based on the limited evidence as previously described, sildenafil is recommended for patients with PAH who have failed or who are not candidates for other vasodilator therapies. Although a small trial suggests that sildenafil may provide larger improvements in exercise tolerance and quality of life compared with bosentan,[56] further studies are needed to determine sildenafil's efficacy compared with other pulmonary vasodilators.There is insufficient evidence to recommend sildenafil in combination with other vasodilators.

OTHER PULMONARY HYPERTENSION CLASSES

According to the ACCP, the first-line therapy for patients with thromboembolic pulmonary hypertension is pulmonary thromboendarterectomy if they are appropriate candidates (NYHA functional class III or IV heart failure, PVR >300 dynes•cm^{-5}, surgically assessable thrombus, and no severe comorbidities).[3,61] However, patients who are not surgical candidates may be considered for vasodilator therapy (eg, epoprostenol) combined with other conventional medical therapies, such as warfarin.[4,6,9] Although data are limited, sildenafil may be considered an option in these patients due to lack of response, intolerance, or contraindications to conventional vasodilators.[43,50] No specific recommendations can be made for the other classes of pulmonary hypertension due to lack of adequate evidence.

Future Studies

Overall, sildenafil reduced PAP and PVR/PVR index and tended to increase CO/CI in hemodynamic studies involving predominantly patients with PAH compared with baseline (eg, receiving conventional therapy with diuretics, calcium-channel blockers, warfarin, digoxin, and/or oxygen). Several of these studies suggested that sildenafil and nitric oxide were comparable in efficacy. Sildenafil was at least as effective as iloprost or epoprostenol in terms of its pulmonary vasoreactivity, but more data are needed to confirm these findings. Studies have demonstrated that the addition of sildenafil to iloprost, nitric oxide, or epoprostenol resulted in enhanced and prolonged pulmonary vascular effects. One possible disadvantage of epoprostenol compared with sildenafil may be its lack of pulmonary vasoselectivity, particularly in patients with pulmonary disease, although sildenafil may lose its pulmonary vasoselectivity at higher doses. In one study, sildenafil, vardenafil, and tadalafil decreased mean PAP and PVR index while increasing CI.[44] Although vardenafil had the most rapid pulmonary vasodilating response, sildenafil was the only agent that improved arterial oxygenation, suggesting its pulmonary vasoselectivity and possible beneficial effects on ventilation–perfusion matching. More studies are needed to confirm these findings.

Despite their limitations, well-designed, short-term clinical trials have demonstrated that sildenafil improves exercise tolerance in patients with pulmonary hypertension. Long-term uncontrolled trials have supported these findings and suggest that sildenafil alone or in combination with iloprost may also improve NYHA functional class. One small comparative trial suggests that sildenafil monotherapy may improve exercise tolerance and quality of life greater than bosentan monotherapy. Large, randomized, controlled clinical trials evaluating sildenafil as monotherapy and in combination with other vasodilators, including PDE-5 inhibitors, are needed to substantiate these findings and, more importantly, determine the long-term survival effects in patients with PAH and other etiologies. A Cochrane database system analysis that evaluated sildenafil for pulmonary hypertension supports these conclusions.[62]

Sildenafil was associated with minimal toxicities in all of the studies. However, clinical trials extending a year or longer are needed to confirm the long-term safety of sildenafil in patients with pulmonary hypertension, especially to detect any possible irreversible visual defects. Studies are also needed to determine whether sildenafil can be used safely in patients with severe lung disease.

Summary

Overall, sildenafil is a promising and well-tolerated agent for management of pulmonary hypertension, but fur-

ther well-designed trials are warranted to establish its place in the treatment of pulmonary hypertension and its long-term safety profile. The optimal dose of sildenafil for pulmonary hypertension is unknown. However, based on available data, a dose of 50 mg orally twice daily or 25 mg 3 times daily may be initiated and increased as tolerated if the patient does not respond.

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EXTRACTO

OBJETIVO: Evaluar la eficacia de sildenafil en el tratamiento de la hipertensión pulmonar.

FUENTES DE INFORMACIÓN: MEDLINE (1966–noviembre de 2004), Cochrane Library, International Abstracts (1977–noviembre de 2004), usando las palabras clave: sildenafil y hipertensión pulmonar. Además, referencias citadas en las publicaciones obtenidas de la literatura.

SELECCIÓN Y OBTENCIÓN DE FUENTES DE INFORMACIÓN: Se valoraron todas las publicaciones en inglés relevantes para el tema en cuestión. Se incluyeron todos aquellos estudios realizados en más de 5 pacientes y preferentemente en adultos.

SÍNTESIS: El tratamiento de la hipertensión pulmonar es una tarea difícil. Estudios recientes han evaluado el sildenafil como tratamiento único y en combinación con otros vasodilatadores para el tratamiento de la hipertensión pulmonar. Se revisaron 8 estudios hemodinámicos y 9 clínicos (1 retrospectivo, 2 a doble ciego, y 6 abiertos al tratamiento). Estos estudios mostraron que sildenafil reduce la hipertensión arterial pulmonar, la relación de resistencia vascular pulmonar/índice de resistencia vascular periférica, y tiende a incrementar la relación de gasto cardíaco/índice cardíaco comparado con los valores basales. Sildenafil demostró ser tan eficaz como el óxido nitroso y al menos tan eficaz como iloprost o epoprostenol en lo referente a su vasoreactividad pulmonar. El tratamiento combinado con iloprost, óxido nitroso, o epoprotenol resultó en un aumento y prolongación de los efectos vasculares pulmonares. Los estudios clínicos sugieren que sildenafil mejora la tolerancia al ejercicio y la clase funcional cardíaca tal como la define la New York Heart Association. Sin embargo, se requieren estudios a gran escala y de asignación aleatoria del paciente al tratamiento que confirmen este hallazgo. Por lo general, sildenafil mostró buena tolerancia en los estudios evaluados.

CONCLUSIONES: Sildenafil es un fármaco bien tolerado y prometedor para el manejo de la hipertensión pulmonar. Sin embargo, se necesitan estudios bien diseñados que establezcan su papel en el tratamiento de la hipertensión pulmonar.

Encarnación C Suárez

RÉSUMÉ

OBJECTIF: Évaluer l'efficacité du sildénafil dans le traitement de l'hypertension pulmonaire (HP).

SOURCE DES DONNÉES: Revue de littérature dans MEDLINE (1977–novembre 2004), Cochrane, IPA (1977–novembre 2004) avec les mots-clés sildénafil et hypertension pulmonaire. De plus, les références des articles identifiés ont été revues.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les articles publiés en langue anglaise ont été évalués. Les études portant sur plus de 5 patients chez une population adulte en premier lieu ont été incluses dans la revue.

SYNTHÈSE DES DONNÉES: Le traitement de l'HP est difficile. Le sildénafil a récemment été étudié en monothérapie et en combinaison avec des vasodilatateurs dans le traitement de l'HP. Huit études hémodynamiques et 9 essais cliniques ont été évalués (1 rétrospectif, 2 à double-insu, et 6 essais ouverts). Le sildénafil a réduit l'HP artérielle, la résistance vasculaire pulmonaire/index de résistance vasculaire périphérique et tend à augmenter le débit cardiaque/index cardiaque par rapport aux valeurs initiales. Le sildénafil était comparable à l'oxyde nitrique et au moins aussi efficace que l'iloprost et l'époprosténol en termes de vasoréactivité pulmonaire. La combinaison avec l'iloprost, l'époprosténol, ou l'oxyde nitrique a donné des effets vasculaires pulmonaires augmentés et prolongés. Des essais cliniques suggèrent que le sildénafil augmente la tolérance à l'exercice et la classification de la NYHA, mais des essais randomisés et contrôlés sont requis pour confirmer ces résultats. En général, le sildénafil a été bien toléré.

CONCLUSIONS: Le sildénafil est un agent prometteur et bien toléré pour le traitement de l'HP mais des essais cliniques bien menés sont requis afin d'établir sa place dans le traitement de l'HP.

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