Acute and chronic effects of sildenafil in patients with pulmonary arterial hypertension

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Summary
Sildenafil and inhaled nitric oxide (iNO) relax smooth muscle by inhibiting the degradation and stimulating the production of cyclic guanosine monophosphate, respectively. We compared the acute pulmonary vasodilator effects of sildenafil, iNO, and epoprostenol and asked whether the combination of iNO with sildenafil had additive pulmonary vasodilator effects. We assessed the effects of extended use of sildenafil in a small cohort of patients. Twenty patients with pulmonary arterial hypertension underwent an acute vasodilator trial with sildenafil (all patients), iNO and iNO plus sildenafil (11), and epoprostenol (19). We also provided sildenafil to patients who were ineligible for, or had clinical deterioration on, epoprostenol, treprostinil, or bosentan. Mean pulmonary artery pressure dropped by 13 ± 3%, 19 ± 4%, 14 ± 3%, and 26 ± 4% with epoprostenol, iNO, sildenafil, and iNO+sildenafil, respectively. Cardiac index increased with epoprostenol and sildenafil. A correlation was found between the effects of iNO and epoprostenol. Nine out of ten patients who were started on long-term sildenafil treatment alone or in combination with other vasodilators had symptomatic improvement. Three died of right heart failure. In conclusion, sildenafil is a potent acute pulmonary vasodilator, an effect that is potentiated by combination with iNO. Long-term therapy of pulmonary hypertension with sildenafil alone or in combination with other agents appears to be safe and well tolerated.

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Introduction
Pulmonary arterial hypertension (PAH) increases morbidity and shortens survival, both in its primary form, and when associated with other conditions such as connective tissue diseases (CTD) or human
immunodeficiency virus. The pathogenesis is not well understood, but involves altered vascular function characterized by vasoconstriction, smooth muscle cell proliferation and vascular remodeling. Major therapeutic advances have occurred in recent years, with the introduction of intravenous epoprostenol, the subcutaneous prostanoid analog, treprostinil, and the oral endothelin antagonist, bosentan. Current treatment options have limited efficacy, however, often leaving patients with persisting pulmonary hypertension and functional impairment. Consequently, there is a need for new, more effective, less expensive, and safer therapies.

Cyclic guanosine monophosphate (cGMP) is an intracellular second messenger that has been implicated in maintaining the low tone of the normal pulmonary vascular bed. In experimental forms of pulmonary hypertension, agents that increase cGMP levels produce pulmonary vasodilation. Such agents include phosphodiesterase 5 (PDE5) inhibitors, that block the action of PDE5, an enzyme found abundantly in lung parenchyma that metabolizes cGMP, and nitric oxide (NO), the endothelium-derived vasodilator molecule that stimulates soluble guanylate cyclase to produce cGMP.

In the current study, we hypothesized that sildenafil (Pfizer Laboratories, New York, NY), a selective PDE5 inhibitor that inhibits the degradation of cGMP and vasodilates pulmonary vessels in various forms of experimental and clinical pulmonary hypertension, has synergistic vasodilatory effects with inhaled NO (iNO), that stimulates cGMP production. In this prospective observational study, we compared the pulmonary vasodilator effects of sildenafil to those of iNO, epoprostenol, and the addition of iNO to sildenafil in patients with various forms of PAH. In addition, we tested the hypothesis that sildenafil would have longer-term beneficial actions when administered to 10 patients with PAH as a single vasodilator agent or in combination with different agents and monitored symptoms of exertional dyspnea, 6 min walk distance, cardiac echocardiograms and the occurrence of side effects.

Methods

We screened all patients referred between April 2001 and May 2002 to the Pulmonary Hypertension Centers at Rhode Island Hospital in Providence, RI and Boston Medical Center in Boston, MA, who underwent right-heart catheterization for PAH and progressive symptoms of dyspnea. Patients were included in the study if they had a resting mean pulmonary artery pressure (mPAP) > 25 mm Hg, a pulmonary artery wedge pressure (PAWP) < 15 mm Hg, and no evidence of active ischemic heart disease based on symptoms and echocardiography, and if indicated, cardiac stress test, or left heart catheterization. Patients were excluded if they had resting hypotension (systemic systolic blood pressure < 90 mm Hg), a cardiac index (CI) < 2.0 L/min/m², were using nitrates, or had end-stage liver or renal disease.

The study protocol was approved by the Institutional Review Boards at Rhode Island Hospital and Boston Medical Center, and each patient gave written informed consent before entering the study.

Hemodynamic measurements

A Swan-Ganz catheter was inserted through an internal jugular or subclavian vein under pressure, or fluoroscopic guidance. The electrocardiogram, pulmonary arterial pressure, right atrial pressure and oxygen saturation were monitored continuously. Systemic blood pressure was recorded with a noninvasive blood pressure cuff every 5 min. Cardiac output (CO) was measured in triplicate by the thermodilution technique (Cardiac Output Computer, Baxter Edwards). Cardiac index (CI) was calculated as CO divided by the body surface area. Pulmonary and systemic vascular resistances (PVR and SVR, respectively) were calculated using standard hemodynamic formulas.

Acute vasodilator testing

After baseline hemodynamics were measured, patients underwent acute vasodilator testing. Patients at Rhode Island Hospital received the following vasodilators: iNO, epoprostenol, sildenafil, and sildenafil combined with iNO. Patients at Boston Medical Center received epoprostenol and sildenafil. iNO was delivered through a tight fitting mask in sequential concentrations of 5, 10 and 20 ppm, every 5 min, as previously described. Owing to a risk of acute pulmonary edema associated with iNO at concentrations > 10 ppm, patients with CTD received iNO only at 5 and 10 ppm. Epoprostenol infusion was started at 1–2 ng/kg/min and the dose was increased by 1–2 ng/kg every 10–15 min, until limiting side effects (headache, nausea, vomiting, or systemic hypotension) occurred. Oral sildenafil was administered after iNO and epoprostenol in 2 doses, 50 and
100 mg 1 h apart. Dosing of sildenafil was based on previous reports.\textsuperscript{11-15} As a precaution, the sildenafil doses were halved in patients \( \geq 65 \) years. The second dose was withheld if the patient developed systemic hypotension with the first dose (SBP < 90 mm Hg). A washout period of 30 min was allowed between iNO and epoprostenol and between epoprostenol and sildenafil testings. In order to assess the acute vasodilator response to combination therapy, patients at Rhode Island Hospital also received iNO 90 min after the last dose of sildenafil, in the lowest concentration that previously produced the maximum vasodilator response. Ninety minutes was chosen to permit development of a maximal hemodynamic response to sildenafil. Hemodynamic measurements were performed at baseline and before each change in vasodilator concentration, once stabilization had occurred. Supplemental oxygen was administered to maintain an oxygen saturation \( \geq 90\% \). The protocol algorithm is presented in Fig. 1.

### Long-term treatment with sildenafil

Patients were offered compassionate administration of sildenafil if they were ineligible for or declined epoprostenol therapy, if they were deteriorating clinically using their current vasodilator therapy and if they were not receiving concurrent nitrate therapy. Sildenafil was added to pre-existing therapy, which was continued in combination. Sildenafil was begun at a dose of 25 mg twice daily, to avoid systemic hypotension that, in our experience, is encountered occasionally with initial doses of \( \geq 50 \) mg. The dose was then advanced every 3–4 days to 50–100 mg three times daily, as tolerated, while we monitored symptoms (dyspnea, chest

![Figure 1](attachment:figure1.png)

**Figure 1** Algorithm for acute vasodilator testing that gives number of patients receiving different doses. Numbers in parentheses represent number of patients in each group. Brackets indicate occurrence of conditions that prescribed lower sildenafil dose; age \( \geq 65 \) years or SBP \( < 90 \) mm Hg. SBP = systolic blood pressure, measured in mm Hg. IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, iNO = inhaled nitric oxide, BMC = Boston Medical Center, RIH = Rhode Island Hospital.
ary functions were within normal limits on average, most had severe pulmonary hypertension. Pulmonary Association (NYHA) functional classification and mostly females, with class II in Table 1. Patients were middle aged on average, tests and hemodynamic parameters are presented patients’ characteristics, baseline pulmonary function tests and hemodynamics of patients receiving serial vasodilator agents we used a one way repeated measures analysis of variance (ANOVA), with a post hoc Tukey test, when F ratios proved to be significantly increased. Correlation between the percent change in mPAP and PVR during administration of various vasodilators was assessed by linear regression analysis. A P-value <0.05 was considered statistically significant.

Results

Of 35 patients screened consecutively at Rhode Island Hospital and Boston Medical Center, 20 patients met the inclusion/exclusion criteria. Patients’ characteristics, baseline pulmonary function tests and hemodynamics are presented in Table 1. Patients were middle aged on average, mostly females, with class II–IV New York Heart Association (NYHA) functional classification and most had severe pulmonary hypertension. Pulmonary functions were within normal limits on average, although the CTD group had mild restriction, as well as a lower diffusing capacity.

During acute vasodilator testing, all patients received sildenafil, 19 received epoprostenol (the patient with sickle cell disease refused), and 11 received iNO and sildenafil+iNO (the latter being patients from Rhode Island Hospital: 7 with idiopathic pulmonary arterial hypertension (IPAH), 3 with CTD and one with sarcoidosis) (Fig. 1).

Acute pulmonary hemodynamic responses

Inhaled NO was the most potent of the agents in reducing mPAP, lowering it by 19 ± 4% (P < 0.001, Fig. 2a), whereas epoprostenol and sildenafil had smaller effects on mPAP (−13 ± 3%, P = 0.004 and −14 ± 3%, P = 0.005, respectively). The addition of iNO 90 min after the last dose of sildenafil, while the hemodynamic response to sildenafil remained maximal, further decreased mPAP by 13 ± 3%. When compared with the baseline value, combination therapy lowered mPAP by 26 ± 4% (P < 0.001, by paired analysis), a reduction that was greater than either epoprostenol or sildenafil alone.

Epoprostenol had the greatest augmenting effect on Cl (increase of 41 ± 5%, P < 0.001, Fig. 2b), followed by sildenafil (24 ± 5%, P = 0.005). This suggests that sildenafil, similar to epoprostenol, has vasodilatory effects on both the pulmonary and systemic circulations and, possibly, a positive inotropic effect, contributing to a greater increase in blood flow. Inhaled NO did not alter Cl, either alone or when it was added to sildenafil.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristic, baseline pulmonary function tests and hemodynamics.*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>No. of patients</td>
<td>20</td>
</tr>
<tr>
<td>Age, years</td>
<td>55 ± 3</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>NYHA classification</td>
<td>2:17:1</td>
</tr>
<tr>
<td>TLC (% predicted)</td>
<td>85 ± 4</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>DLCO (%) predicted</td>
<td>48 ± 5</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>PVR (dyne/s/cm5)</td>
<td>707 ± 62</td>
</tr>
<tr>
<td>CI (L/min/m2)</td>
<td>2.60 ± 0.15</td>
</tr>
<tr>
<td>PAWP (mm Hg)</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>SVR (dyne/s/cm5)</td>
<td>1445 ± 697</td>
</tr>
</tbody>
</table>

*IPAH = idiopathic pulmonary arterial hypertension; CTD = connective tissue disease; NYHA = New York Heart Association; TLC = total lung capacity; FEV1/FVC = forced expiratory volume in one second/forced vital capacity; DLCO = diffusion capacity for carbon monoxide; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; CI = cardiac index; PAWP = pulmonary arterial wedge pressure; SVR = systemic vascular resistance.
†Other includes 2 patients with sarcoidosis and one patient with sickle cell disease.
‡P = 0.004 compared with the IPAH group by 2 way ANOVA.
Pulmonary and systemic vascular resistances

Epoprostenol decreased PVR by 39 ± 4% (P < 0.001, Fig. 3a), significantly more than iNO or sildenafil alone (24 ± 6% decrease with iNO, P = 0.011 and 29 ± 2% decrease with sildenafil, P < 0.001 from baseline). INO added to sildenafil lowered PVR by an additional 15 ± 4% (total 43%). This combination was more potent than either agent alone (P = 0.033, by repeated measures analysis), but not different from epoprostenol.

Epoprostenol and sildenafil each lowered mean systemic blood pressure, from 91 ± 3 to 82 ± 2 mm Hg (P = 0.023) and from 89 ± 4 to 80 ± 3 mm Hg (P = 0.048), respectively. INO did not affect mean systemic blood pressure, either alone (from 90 ± 3 to 88 ± 3 mm Hg, P = ns), or when added to sildenafil (from 75 ± 3 to 77 ± 4 mm Hg, P = ns). Furthermore, as indicated by changes in the PVR/SVR ratio (Fig. 3b), INO was a specific pulmonary vasodilator both alone (−3 ± 8%, P < 0.001), and when added to sildenafil (−25 ± 4%, P < 0.001), whereas PVR/SVR did not change significantly with either epoprostenol or sildenafil, indicating that their vasodilator effects were nonspecific.
Comparison of acute vasodilator responses

As previously reported,\(^{17}\) the vasodilator responses of iNO and epoprostenol were strongly correlated, both with regard to mPAP (Fig. 4a) and PVR (Fig. 4b). Correlations were weaker for mPAP and PVR between sildenafil and iNO (Fig. 4c,d) and epoprostenol and sildenafil (Fig. 4e,f); for abbreviations, see legend for Table 1.

Long-term treatment

Table 2 shows ages (mean 58 ± 15 years), genders, pulmonary hypertension diagnoses, concurrent pulmonary hypertension medications, and functional
and symptomatic responses of 10 patients receiving long-term sildenafil therapy.

Patients #1, 3, 5, 7 and 9 were tested acutely with sildenafil which lowered their mPAP and PVR by an average of 22 ± 4% and 30 ± 2%, respectively. Four of the five had a significant acute response to sildenafil (a 20% or more decrease in both mean PAP and PVR). The remaining patients did not undergo acute testing with sildenafil because the protocol was not available at the time of the right heart catheterization. Sildenafil therapy was initiated for a deteriorating status despite increasing doses of epoprostenol (patients #2 and 5), bosentan (patients #1 and 8), or a combination of treprostinil and bosentan (patients #6 and 7). Patients #3, 4, 9 and 10 refused prostacyclin therapy and bosentan was not available at the time of initiation of therapy.

The average length of sildenafil follow-up was 12 ± 1.6 months. Six of the 10 patients improved NYHA functional score by at least one class (Table 2) and nine reported improvement in exertional

Figure 5 Serial hemodynamic measurements in the 11 patients that had all four vasodilator challenges. BS = baseline. For rest of abbreviations see Fig. 1. Analysis by one way repeated measures of variance demonstrates statistically significant differences (P < 0.05) between baseline vs. treatment. There was also a statistically significant difference between sildenafil and sildenafil+iNO (P < 0.05).

Table 2 Characteristics of patients who received long-term sildenafil treatment.*

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>NYHA class</th>
<th>Concurrent medication</th>
<th>Sildenafil dose/day length of treatment</th>
<th>NYHA class on sildenafil</th>
<th>Symptoms improved†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57/M</td>
<td>IPAH</td>
<td>III</td>
<td>Bosentan</td>
<td>150 mg/14 months</td>
<td>III</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>48/M</td>
<td>IPAH</td>
<td>IV</td>
<td>Epoprostenol</td>
<td>150 mg/12 months</td>
<td>III</td>
<td>Yes†</td>
</tr>
<tr>
<td>3</td>
<td>77/F</td>
<td>IPAH</td>
<td>III</td>
<td>—</td>
<td>50 mg/7 months</td>
<td>III</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>38/M</td>
<td>IPAH</td>
<td>III</td>
<td>—</td>
<td>400 mg/12 months</td>
<td>II</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>47/M</td>
<td>CTD</td>
<td>IV</td>
<td>Epoprostenol</td>
<td>150 mg/16 months</td>
<td>III</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>69/F</td>
<td>CTD</td>
<td>IV</td>
<td>Treprostinil/Bosentan</td>
<td>150 mg/8 months</td>
<td>III</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>59/F</td>
<td>CTD</td>
<td>IV</td>
<td>Treprostinil/Bosentan</td>
<td>150 mg/7 months</td>
<td>II</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>74/F</td>
<td>CTD</td>
<td>IV</td>
<td>Bosentan</td>
<td>150 mg/8 months</td>
<td>III</td>
<td>Yes†</td>
</tr>
<tr>
<td>9</td>
<td>72/M</td>
<td>Sarcoid</td>
<td>III</td>
<td>—</td>
<td>200 mg/24 months</td>
<td>III</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>38/M</td>
<td>HHT</td>
<td>III</td>
<td>—</td>
<td>200 mg/12 months</td>
<td>III</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*IPAH = idiopathic pulmonary arterial hypertension; DM = dermatomyositis; HHT = hereditary hemorrhagic telangiectasia; CAD = coronary artery disease.
†Symptomatic response was considered an improvement in exercise tolerance as perceived by the patient in daily activities, exertional chest pain, or lightheadness.
‡Both patients improved for a 12 and 8 months, respectively, after that they decompensated and died of right heart failure.
dyspnea. Patient 3 deteriorated despite sildenafil treatment and died. Patient 2 and 8 improved for the first 12 and 8 months, respectively, after which they slowly decompensated and died of right-sided heart failure. The remaining 7 patients have remained symptomatically improved, with an average follow-up time of 12.5 ± 2 months. Interestingly, out of the five patients tested acutely with sildenafil, one acute responder deteriorated with long-term treatment, while the nonresponder improved rapidly and steadily with long-term treatment. Echocardiograms were obtained before sildenafil was started and after 2–8 months of treatment in 7 patients, with no change in estimated peak systolic pulmonary artery pressures or right ventricular function (initial mean systolic PAP was 75 ± 12 and follow-up 73 ± 19 mm Hg, P = ns). Six minute walk tests declined from 267 ± 72 m while on treatment with vasodilators to 191 ± 46 m before sildenafil was started and improved to a mean of 250 ± 50 m with long-term sildenafil (P < 0.05 with one way repeated measures ANOVA, Fig. 6).

Adverse effects

One patient developed substernal chest pain without EKG changes during epoprostenol infusion at 1 ng/kg/min that resolved upon discontinuation of the infusion. The average total dose of sildenafil given acutely was 122.5 ± 44 mg (mean ± so), starting with doses of 25–50 mg, depending on age (see the section “Methods”). During acute vasodilator testing, 3 patients developed asymptomatic hypotension after 50 mg of sildenafil (systolic systemic blood pressures of 80–85 mm Hg) that spontaneously resolved within 1–2 h. Although it did not reach statistical significance, these 3 patients had lower mPAPs and PVRs at baseline than the seven who did not have a decrease in systemic pressures (mPAP 46 ± 7 vs. 54 ± 5 mm Hg and PVR 532 ± 119 vs. 787 ± 114 dyne/s/cm², respectively). Long-term sildenafil was well tolerated except in patient #3, who developed lightheadedness when sildenafil was increased from 50 to 75 mg three times a day. This symptom resolved after the dose was lowered to 25 mg twice a day, but her exertional dyspnea continued to worsen. Patient #9 had increased dyspnea on exertion after 6 months of therapy that improved after the sildenafil dose was increased from 75 to 100 mg twice daily. None of the 10 patients receiving long-term sildenafil experienced symptomatic systemic hypotension.

Discussion

Our findings confirm that the PDE5 inhibitor sildenafil is an effective acute pulmonary vasodilator and that the addition of iNO, a stimulator of cGMP production, potentiates the vasodilator action of sildenafil. The combination of sildenafil and iNO lowered PVR more than either agent alone and was as potent as epoprostenol, but with more pulmonary selectivity. As previously reported, maximal vasodilator responses to epoprostenol and iNO correlated well, but those of sildenafil and either epoprostenol or iNO correlated less well. Finally, in a small cohort of patients, long-term therapy with sildenafil was well tolerated and brought about a sustained symptomatic improvement in most patients.

Maclean et al.20 provided the pathophysiologic rationale for using PDE5 inhibitors as pulmonary vasodilators by demonstrating the presence of PDE5 activity in pulmonary arteries from normoxic rats and an increased activity in response to chronic hypoxia. PDE5 inhibitors have been shown to dilate pulmonary vessels in pulmonary hypertension models,21,22 as well as in normal human subjects with acute hypoxia-induced pulmonary hypertension.11 Subsequently, two studies12,15 reported the effect of PDE5 inhibition in combination with the inhaled prostacyclin, iloprost, in patients with PAH. They demonstrated that oral sildenafil and inhaled iloprost had similar vasodilator effects, and that the combination of these two drugs was more effective than either agent alone. Lastly, in patients with pulmonary hypertension secondary
to pulmonary fibrosis, sildenafil produced acute pulmonary vasodilation similar to that of epoprostenol, but unlike epoprostenol, sildenafil also improved gas exchange by maintaining ventilation/perfusion matching. In the current study, iNO potentiated the pulmonary vasodilator effects of sildenafil. This has previously been shown in an animal model of acute pulmonary hypertension, in which nebulized sildenafil potentiated the vasodilator effects of iNO. In addition, two case reports have observed a prolongation of iNO vasodilatory effects by sildenafil, facilitating weaning from iNO following cardiac surgery and after iNO therapy of a newborn with persistent pulmonary hypertension.

Our study results are also similar to those of Michelakis et al., who found that in patients with severe pulmonary hypertension, the combination of sildenafil and iNO brought about more vasodilation than iNO alone, but not significantly more than 75 mg of sildenafil alone, and that cGMP levels increased synergistically with combined therapy. In our study, combination therapy was more potent than either vasodilator alone in decreasing PVR. This difference between our results and those of Michelakis et al. may reside in the different populations studied (IPAH, PAH associated with left ventricular dysfunction, atrial septal defect, or cirrhosis in Michelakis study), and in differing dosing regimens between the studies, with our patients receiving higher doses of sildenafil, on average.

As previously reported by Sitbon et al., we found that acute pulmonary vasodilator responses to iNO and epoprostenol were highly correlated. In contrast to their utility in predicting calcium channel blocker responsiveness, however, vasodilator responsiveness to iNO and epoprostenol in our study correlated relatively poorly with that to sildenafil, indicating that they are of limited usefulness in predicting acute vasoresponsiveness to sildenafil and raising questions about their ability to predict long-term responsiveness to sildenafil. Of course, whether acute vasodilator responses even to sildenafil predict long-term success with the drug is currently unknown. In addition, the patterns of vasoresponsiveness differed between the agents, with iNO acting as a selective pulmonary vasodilator, lowering mPAP but not affecting cardiac output or systemic blood pressure. Sildenafil and epoprostenol, on the other hand, acted as nonselective vasodilators, with significant effects not only on mPAP, but also on cardiac output and systemic blood pressure. Adding iNO to sildenafil restored pulmonary selectivity and effected greater pulmonary vasodilation than with either agent alone.

Based on our experience, long-term treatment with sildenafil holds promise. Nine of our 10 patients treated long-term tolerated the therapy well and experienced symptomatic and functional improvement, as evidenced by increases in the 6 min walk distance. In addition, NYHA functional class improved in 6 patients. The combination of sildenafil and a prostacyclin (2 patients), or the nonselective endothelin receptor blocker, bosentan (2 patients), or all 3 drugs together (2 patients) was also well tolerated. Whether tolerance develops to sildenafil as it does to infused prostacyclins is unclear, but the worsening of symptoms experienced by patient #9 after 6 months of therapy was promptly reversed after the sildenafil dose was increased raises this possibility. A report on patients using sildenafil regularly for erectile dysfunction, who had to increase their doses after the first few months to maintain a therapeutic response is consistent with this view.

Whether the progressive deterioration and deaths of 3 of our patients, two after initial improvement, are related to tolerance or recalcitrant disease in some patients is unclear from our results, but this experience does indicate that sustained responsiveness to sildenafil is not universal. On the other hand, sildenafil effected sustained symptomatic improvement in 7 of our patients for an average follow-up period exceeding one year, the longest yet reported, and suggesting that the drug achieves durable benefit in the majority of patients. The lack of improvement on follow-up echocardiograms despite symptomatic improvement may be explained by an increase in cardiac output without a corresponding drop in PA pressure, phenomenon that is not detected by echocardiogram.

Our demonstration that sildenafil and iNO have synergistic and pulmonary selective vasodilator effects, along with the previous reports on combinations of sildenafil and other agents, raises the distinct possibility that combination vasodilator therapy may be more effective for the management of pulmonary hypertension than single agent therapy. Whether it is better to combine agents that act via a single second messenger pathway, such as is the case with sildenafil and iNO via cGMP, or via different signaling pathways, such as sildenafil in combination with prostacyclins or endothelin receptor antagonists, remains to be seen. Also, whether the additive effects of iNO and sildenafil are related only to potentiation of increases in intracellular cGMP levels, or whether PDE5 inhibition produces vasodilation by increasing...
cAMP levels as well, a phenomenon referred to as “cross-talking”,27 awaits further study.

We conclude that sildenafil is a potent acute pulmonary vasodilator for patients with different forms of PAH, with acute hemodynamic effects similar to those of epoprostenol. The combination of iNO and sildenafil has more potent acute vasodilatory effects than either agent alone. Because acute vasodilator testing with sildenafil may cause transient systemic hypotension in some patients with PAH, use of lower doses (i.e. 25 mg) and careful monitoring of systemic blood pressure is recommended during initiation. For long-term use, sildenafil is well tolerated both singly and in combination and improves symptoms in most patients, but further study is needed to determine its long-term effects on pulmonary hemodynamics and functional capacity and how long beneficial effects are sustained.

References


