

Oral Sildenafil Is an Effective and Specific Pulmonary Vasodilator in Patients With Pulmonary Arterial Hypertension

Comparison With Inhaled Nitric Oxide

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Background—The prognosis of patients with severe pulmonary hypertension (PHT) is poor. To determine prognosis and guide therapy, an acute hemodynamic trial of selective pulmonary vasodilators, usually inhaled nitric oxide (iNO), was performed. We hypothesized that oral sildenafil, a phosphodiesterase-5 inhibitor, is a safe and effective alternative to iNO.

Methods and Results—We studied 13 consecutive patients (mean $\pm$ SEM, 44 $\pm$ 2 years of age; 9 women) referred for consideration of heart-lung transplantation or as a guide to medical therapy. All but one were functional class III or IV. Patients had primary PHT (n=9), pulmonary arterial hypertension (n=2), or secondary PHT (n=2). Hemodynamics and serum cyclic guanosine-monophosphate levels (cGMP) were measured at baseline and at peak effects of iNO (80 ppm), sildenafil (75 mg), and their combination. The decrease in pulmonary vascular resistance was similar with iNO ($-19\pm 5\%$) and sildenafil ($-27\pm 3\%$), whereas sildenafil+iNO was more effective than iNO alone ($-32\pm 5\%$, $P<0.003$). Sildenafil and sildenafil+iNO increased cardiac index ($17\pm 5\%$ and $17\pm 4\%$, respectively), whereas iNO did not ($-0.2\pm 2.0\%$, $P<0.003$). iNO increased, whereas sildenafil tended to decrease, pulmonary capillary wedge pressure ($+15\pm 6$ versus $-9\pm 7\%$, $P<0.0007$). Systemic arterial pressure was similar among groups and did not decrease with treatment. cGMP levels increased similarly with iNO and sildenafil, and their combination synergistically elevated cGMP ($P<0.0001$).

Conclusions—A single oral dose of sildenafil is as effective and selective a pulmonary vasodilator as iNO. Sildenafil may be superior to iNO in that it increases cardiac output and does not increase wedge pressure. Future studies are indicated to establish whether sildenafil could be effective over a longer duration. (*Circulation*. 2002;105:2398-2403.)

Key Words: hypertension, pulmonary ■ nitric oxide ■ hemodynamics

The prognosis of patients with severe pulmonary arterial hypertension (PAH) is poor, and treatment options are limited.^{1,2} The goals of long-term therapy are to reduce pulmonary vasoconstriction, cause regression of vascular remodeling, and prevent thrombosis.³ Initiation of long-term therapy usually follows an acute hemodynamic trial to determine prognosis, assess safety of a proposed treatment, and guide future medical therapy.⁴⁻⁷ The acute hemodynamic study uses a selective pulmonary vasodilator, usually inhaled nitric oxide (iNO), to evaluate the responsiveness of the pulmonary vasculature while avoiding systemic hypotension.^{4,6-8} Although NO is a potent and selective pulmonary vasodilator, long-term use is limited by its short half-life. Even its use as an acute vasodilator is cumbersome, requiring an expensive medical form of NO gas, a complicated delivery system, and monitoring equipment. However, iNO is presently considered the gold standard for the

evaluation of patients with PAH.^{4,6-8} A positive response to iNO ($>20\%$ decrease in pulmonary artery pressure or pulmonary vascular resistance) predicts the response to conventional vasodilators, such as calcium channel blockers,^{4,7} and identifies patients with a better long-term prognosis than the nonresponders.⁵ In addition to patients with PAH, iNO also is used in patients with severe pulmonary hypertension attributable to left ventricular dysfunction as part of the preoperative assessment for cardiac transplantation. Because unresponsive and severe pulmonary hypertension is a contraindication to cardiac transplantation, the response to iNO is used to identify patients that require a combined heart-lung transplantation.^{9,10}

iNO causes vasodilatation by increasing the levels of cyclic guanosine-monophosphate (cGMP) in vascular smooth muscle cells.^{11,12} cGMP is short lived because of the rapid degradation by phosphodiesterases.¹³ There are numerous

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TABLE 1. Baseline Characteristics of the Study Population

Patient No.	Sex	Age	Class	Etiology	PAWP	Flolan	CCB	Coumadin	Diuretics	O ₂
1	F	41	4	PPH	20	—	+	+	+	+
2	M	42	3	PPH	24	—	—	—	+	—
3	M	42	4	SPH	13	—	—	+	+	—
4	F	56	4	SPH	26	—	—	+	+	—
5	F	40	4	PPH	9	—	+	+	+	+
6	F	36	3	PPH	14	—	+	+	+	—
7	F	42	2	PPH	7	—	+	—	—	—
8	F	35	4	PPH	17	+	—	+	+	+
9	F	56	4	PAH (ASD)	20	—	—	—	+	+
10	M	35	4	PPH	15	—	—	+	+	—
11	F	56	3	PPH	16	—	+	+	+	—
12	M	38	4	PAH (cirrhosis)	10	—	—	—	—	—
13	F	54	4	PPH	10	—	+	+	+	+

SPH indicates secondary pulmonary hypertension associated with left ventricular dysfunction; CCB, calcium-channel blockers; ASD, atrial septal defect; and PAWP, pulmonary artery wedge pressure.

phosphodiesterases, but the isoform that is active in degrading cGMP in the lung is cyclic nucleotide phosphodiesterase-5.¹⁴ Phosphodiesterase-5 inhibitors cause pulmonary vasodilatation by promoting an enhanced and sustained level of cGMP.¹⁵ There have been recent anecdotal reports and preliminary studies indicating that sildenafil, a specific phosphodiesterase-5 inhibitor widely used in the treatment of erectile dysfunction,¹⁶ decreases pulmonary vascular resistance in humans with primary pulmonary hypertension (PPH),^{17,18} in healthy volunteers with hypoxic pulmonary vasoconstriction,¹⁹ and in animals with experimental PAH.^{20,21} We hypothesized that sildenafil would be as effective in decreasing pulmonary vascular resistance as iNO in the acute assessment of patients with severe pulmonary hypertension. We directly compared the effects of iNO with a single dose of oral sildenafil as well as their combination on pulmonary and systemic hemodynamics in patients with severe pulmonary hypertension.

Methods

We studied 13 consecutive patients with a mean ($\pm$ SEM) age of 44 ± 2 years referred to the University of Alberta Hospital cardiac catheterization laboratory over a period of 1 year for evaluation of suitability for transplantation or medical therapy (Table 1). Nine patients had PPH (a subset of PAH in which no cause can be identified) and 2 had PAH, as defined by World Health Organization criteria.⁶ In addition, 2 patients had pulmonary hypertension, which, although it was associated with left ventricular dysfunction, was disproportionate to their pulmonary wedge pressure (Table 1). In the patients diagnosed with PPH, primary cardiac abnormalities were ruled out with echocardiography or left heart catheterization. Thromboembolic disease was ruled out by ventilation-perfusion scan (negative or low probability for pulmonary embolism) or spiral CT scans. Lung disease and hypoxia were excluded by pulmonary function tests, arterial blood gases, and sleep studies as clinically needed. Rheumatologic diseases were excluded by physical examination and serological markers. Of the patients with PAH, 1 had Eisenmenger's syndrome attributable to an atrial septal defect and

the other had portal-pulmonary hypertension attributable to cryptogenic cirrhosis. Of the patients with secondary pulmonary hypertension, 1 had cardiomyopathy attributable to both coronary and mitral valve disease and the other cardiomyopathy associated with constrictive pericarditis and coronary disease. They were both evaluated for heart versus heart-lung transplantation. All subjects of the study provided written informed consent, and the human research ethics committee of the University of Alberta approved the protocol.

Protocol

All patients continued taking their medications on the day of the study, except for coumadin, which was held to reach an international normalized ratio of <1.5 . One patient was taking continuous epoprostenol (Flolan, Glaxo Wellcome Canada), and this was continued throughout the study. The patients fasted for at least 6 hours, and no patient was premedicated with analgesics or sedatives. Twelve patients were studied in the catheterization laboratory, and 1 patient was studied in the coronary care unit.

A 4F catheter was placed in the right radial artery under local anesthesia for continuous arterial pressure monitoring. A 7F catheter was then placed in the right jugular vein under local anesthesia, and a Swan-Ganz catheter was advanced into the pulmonary artery under fluoroscopy. After lines were placed, patients were allowed to rest for 15 minutes, and then the following hemodynamic measurements were recorded and defined as the baseline measurements: arterial pressure, right atrial pressure, pulmonary arterial pressure and pulmonary capillary pressure, heart rate, and cardiac output, using the thermodilution method. All measurements were performed during end expiration, and the mean pressures were electronically calculated over at least 10 beats.

The response to iNO delivered through a custom-made airtight mask (10, 20, 40, and 80 ppm, each for 10 minutes) was then studied. The pulmonary artery pressure was continuously monitored, and complete hemodynamics were obtained at the most effective dose of iNO, which was 80 ppm in all patients (except in patient No. 7, in whom it was 60 ppm). These were defined as the iNO measurements. NO was discontinued, and after 10 minutes, a single dose of sildenafil (Viagra, Pfizer Canada, 75 mg) was given. The effects of iNO, which has a half-life of ≈ 3 minutes, had completely subsided before giving sildenafil. The patients were monitored for 50 minutes with continuous ECG and arterial and pulmonary artery pressure recordings, and then a complete set of hemodynamics was recorded

TABLE 2. Hemodynamic Variables at Baseline and After Intervention*

Variable	BL	iNO	Sildenafil	iNO + Sildenafil
Mean pulmonary artery pressure, mm Hg	58.2±5	54.3±5	50.9±4	50.6±4
Mean arterial pressure, mm Hg	83.2±3	88.9±4	83.7±3	85.6±3
Cardiac index, L/min per mm ²	3.53±0.3	3.5±0.5	4.03±0.3	4.08±0.2
Pulmonary capillary wedge pressure, mm Hg	15.9±1.7	18.3±2.3	14.8±2.1	16.4±2.1
Pulmonary vascular resistance index, mm Hg · min · mm ² /L	3.9±0.6	3.3±0.6	2.8±0.4	2.6±0.4
Heart rate, bpm	80.4±4	80.8±4	79.6±4	80±3
O ₂ saturation, %	94±2	96±1	96.3±1	97.6±1

*All values are given as means±SEM.

(defined as the sildenafil measurements). Previous studies have shown that the peak hemodynamic effects of sildenafil occur at ≈50 minutes after oral intake²² and that its biological effects last for at least 3 hours.¹⁶ One hour after the sildenafil dose and while its effects were still at peak, patients were re-exposed to iNO, and these were defined as iNO+sildenafil measurements. In addition, 5 mL of pulmonary and systemic blood was obtained for oxygen saturation and cGMP level measurements during each of the 4 periods (baseline, iNO, sildenafil, and iNO+sildenafil). For the cGMP measurements, the blood was placed in tubes containing the nonspecific phosphodiesterase inhibitor isobutylmethylxanthine to avoid ex vivo degradation of cGMP, as previously described.²³ Blood was immediately centrifuged and the serum stored at -80°C for future measurements. cGMP was performed using a commercially available ELISA kit (Biomedical Technologies Inc). After the catheters were removed, the patients were observed for 3 to 4 hours, with vital signs recorded every hour.

Statistical Analysis

The data are expressed as mean±SEM. Because every patient served as his or her own control, interventions were compared using a repeated-measures ANOVA with a post hoc analysis using a Fisher's probable least-significant differences test (Statview, SAS Institute). $P<0.05$ was considered statistically significant. Regression analysis was performed using the same software to determine whether there is a correlation between the levels of cGMP and pulmonary vascular resistance either at baseline or during the 3 interventions. Although the investigators performing the hemodynamic studies were not blinded to the different treatments, the investigators performing the analysis from computerized data spreadsheets were blinded.

Results

Clinical Characteristics

Nine of the patients were female, and all patients were New York Heart Association functional class III or IV (except patient No. 7, who was class II). This patient had had PPH for 3 years and had responded very well to calcium channel blockers but was restudied because she was trying to become pregnant. Seven of the patients with PPH had been diagnosed within the previous 3 months, and this was their first right heart catheterization. Patient No. 8 had had PPH for 3 years and had been taking continuous intravenous epoprostenol for 1 year. Six of the PPH patients were taking calcium channel blockers, and almost all were taking both coumadin and diuretics (Table 1). Five of the study patients were using home oxygen. The group had normal hemoglobin (133 ± 4 mg/dL) and creatinine (104 ± 12 mg/dL) levels. All patients had normal liver function tests, except patient No. 12, who

had cryptogenic cirrhosis and portal hypertension and was being evaluated for combined hepatic and lung transplantation.

Hemodynamics

The mean hemodynamic data at baseline and after interventions are shown in Table 2. The individual responses of the pulmonary vascular resistance index and the cardiac index to iNO, sildenafil, or their combination are shown in Figure 1. The percent changes in all hemodynamic parameters are shown in Figure 2, where probability value for intergroup differences (using repeated-measures ANOVA) as well as probability value for differences between groups (using a Fisher's post hoc analysis) are shown. Sildenafil alone decreased the mean pulmonary artery pressure more than iNO (Figure 2A). Both iNO and sildenafil decreased pulmonary vascular resistance significantly and to a similar extent (Figure 2B). The combination of iNO and sildenafil had greater effects on pulmonary vascular resistance than iNO alone (Figure 2B). Sildenafil significantly increased the

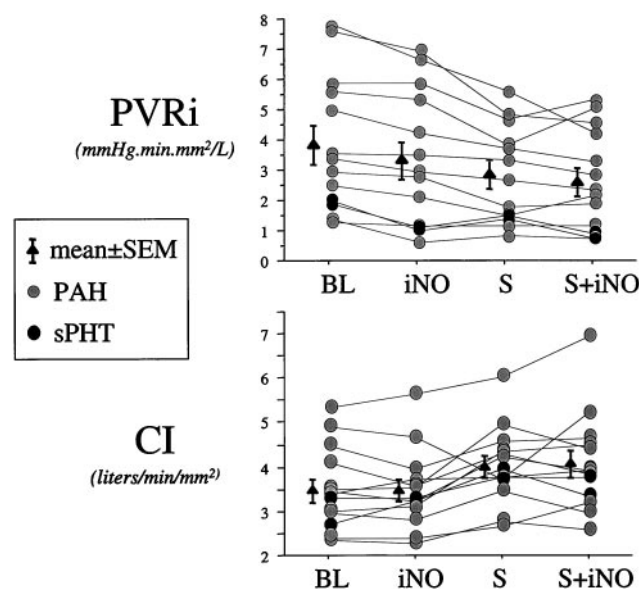


Figure 1. Individual responses of the pulmonary vascular resistance index (PVRi) and cardiac index (CI) to iNO (80 ppm), sildenafil (S) (75 mg), or their combination.

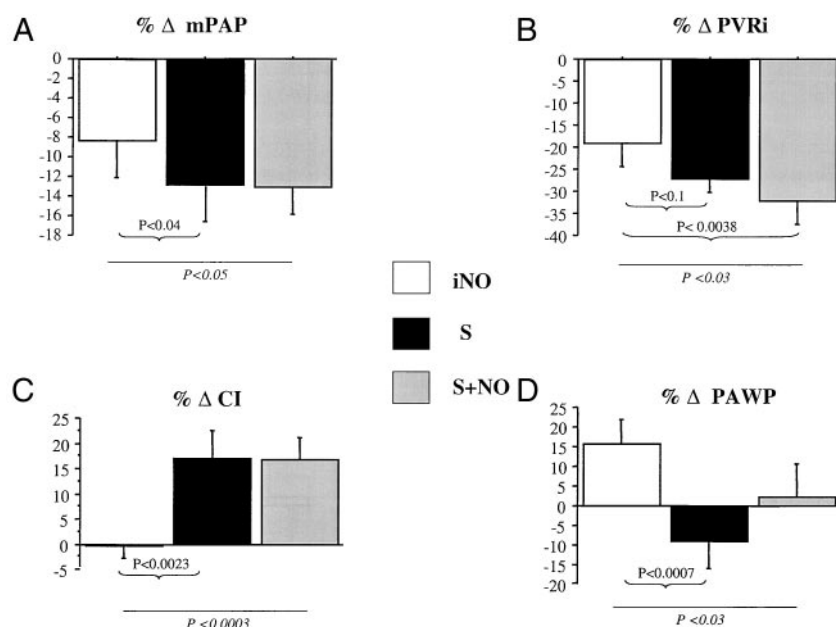


Figure 2. Percent change in hemodynamic parameters from baseline and in response to iNO (80 ppm), sildenafil (S) (75 mg), or their combination (mean $\pm$ SEM). The probability values for differences between specific groups are shown in regular fonts, whereas the overall probability values for differences across all 3 groups (repeated measures ANOVA) are shown in italics. A, Sildenafil is superior to iNO in decreasing mean pulmonary artery pressure (mPAP) and as effective as their combination. B, Sildenafil is as effective as iNO in decreasing pulmonary vascular resistance index (PVRI), and their combination has additive effects. C, Sildenafil increases the cardiac index (CI), whereas iNO does not. D, Sildenafil decreases, whereas iNO increases, the pulmonary artery wedge pressure (PAWP).

cardiac index, in contrast to iNO (Figure 2C). The combination of the 2 treatments on cardiac index was not different from the effect of sildenafil alone (Figure 2C). There was a significant difference in the effects of the 2 treatments on the pulmonary capillary wedge pressure. iNO increased the wedge pressure, whereas sildenafil decreased it (Figure 2D). None of the 3 treatments decreased the mean arterial pressure (Table 2). The heart rate was not altered by any treatment (Table 2). The arterial oxygen saturation was improved by both iNO and sildenafil with a trend for statistical significance in the iNO+sildenafil group ($P=0.06$, Table 2).

cGMP Levels

Both iNO and sildenafil significantly raised cGMP levels in the arterial blood (Figure 3). As expected, their combination had an additive effect (Figure 3). However, there was no correlation between cGMP levels and either baseline pulmonary vascular resistance or the fall in pulmonary vascular resistance achieved by iNO or sildenafil.

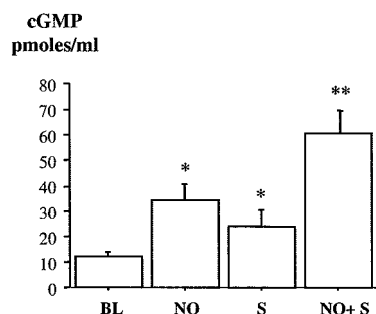


Figure 3. Arterial cGMP levels at baseline (BL) and in response to iNO (80 ppm), sildenafil (S) (75 mg), or their combination (mean $\pm$ SEM). Sildenafil and iNO have synergistic effects on cGMP production. The arterial cGMP levels reflect the pulmonary cGMP output. * $P < 0.05$ compared with the baseline; ** $P < 0.0001$ compared with all other groups.

Adverse Effects

There were no significant hemodynamic or other adverse effects with any of the treatments during the 3 hours of the study or the 3 hours of observation after the study. One patient reported a self-limited headache 2 hours after sildenafil intake.

Discussion

We have shown that a single dose of oral sildenafil is a potent and selective pulmonary vasodilator. Compared with the gold standard, iNO, sildenafil is superior in decreasing the mean pulmonary artery pressure and equally effective and selective in reducing pulmonary vascular resistance, the primary end point of this study. In contrast to iNO, sildenafil causes a significant increase in the cardiac index. Both iNO and oral sildenafil are selective pulmonary vasodilators, inasmuch as neither lowers the mean arterial pressure.

Our study confirms previous reports that iNO causes increase in the pulmonary artery wedge pressure, especially in patients with left ventricular dysfunction,^{24,25} perhaps explaining occasional cases of pulmonary edema with this therapy.²⁶ Our finding that sildenafil tends to decrease the wedge pressure suggests that sildenafil might be superior to iNO in the evaluation of the patients with severe pulmonary hypertension. This might have important safety implications both for the acute study and for eventual long-term use of this drug in patients with left ventricular dysfunction.

The preferential effect of sildenafil on the pulmonary circulation probably reflects the high expression of this isoform in the lung. However, phosphodiesterase-5 also is found in the myocardium, where it maybe downregulated in heart failure.²⁷ The finding that sildenafil decreases the wedge pressure and increases the cardiac index suggests that it does not have negative inotropic effects, at least in the patients studied. Phosphodiesterase-5 has been implicated in modulation of sympathetic tone,²⁷ and sildenafil recently has been shown to cause sympathetic nervous system activation in

normal volunteers.²⁸ However, the fact that the heart rate did not change after sildenafil in our study (Table 2) suggests that sympathetic activation is not the basis for the observed increase in the cardiac index (Figure 2C). The data suggest that sildenafil increases cardiac index because of its selective pulmonary vasodilatory effects and the resulting reduction in right ventricular afterload.

Another important finding of this study is that iNO and sildenafil have additive vasodilatory effects in the pulmonary but not the systemic circulation (Table 2, Figures 1 and 2). The mechanism for this might be related to the synergistic effects of iNO and sildenafil on serum cGMP levels (Figure 3). The data suggest that NO 80 ppm, which presently is usually the maximum dose used in acute vasodilator testing, is not as effective in lowering pulmonary vascular resistance alone as it is in combination with sildenafil. In fact, in patients No. 2 and No. 13, iNO 80 ppm had no effect in pulmonary vascular resistance, whereas sildenafil caused a 21% and a 32% decrease, respectively. Although the standard use of iNO in the assessment of these patients suggested that they were nonresponders, the use of sildenafil suggested that they might indeed be responders to acute pulmonary vasodilators. This finding may have important prognostic and therapeutic implications for patients with pulmonary hypertension.

The dose of sildenafil used in the present study is smaller than the 100 mg that recently has been used in acute hemodynamic studies involving sildenafil,^{19,29} although it is in the range used for erectile dysfunction (50 to 100 mg).¹⁶ Wilkens et al¹⁸ very recently showed that the maximal hemodynamic effects of sildenafil on the human pulmonary circulation were achieved with a 25 mg dose. They also showed that maximal hemodynamic effects were achieved within 30 minutes after intake.¹⁸ Furthermore, newer phosphodiesterase-5 inhibitors that are perhaps more potent and specific than sildenafil are presently under development.^{30,31}

This study has several limitations. First, because the disease is rare, the sample size is relatively small. However, with an estimated incidence of 1 case per 1 000 000, this study reflects one third of all Canadians that will develop PAH in 1 year.⁶ In addition, we did not establish the maximal duration of the pulmonary vasodilatation induced by sildenafil. Pharmacokinetic studies are needed to clarify this important issue in this particular disease state, especially because, on the basis of our findings, sildenafil might be a good candidate for long-term treatment of pulmonary hypertension. More studies are also needed to establish the safety of sildenafil in terms of systemic hemodynamics in patients with severe pulmonary hypertension. Although none of the patients in this study experienced a decrease in the systemic arterial pressure, it is theoretically possible that patients that have fixed pulmonary hypertension and are unable to increase their cardiac output might become hypotensive with sildenafil.

The simplicity and safety of the short-term administration of sildenafil versus iNO and its possible superiority over iNO in terms of its effects on cardiac index and wedge pressure suggest a role for sildenafil in the evaluation and treatment of

patients with pulmonary hypertension and support the need for additional studies of its long-term use.

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