Sildenafil treatment of primary pulmonary hypertension

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A 37-year-old woman with primary pulmonary hypertension and worsening symptomatology underwent pulmonary artery (PA) catheterization and vasodilator trials. Oxygen had no effect, but 10 parts/million of nitric oxide reduced mean PA (PAm) pressure by 20%. Prostacyclin infusion at 8 ng/kg/min decreased the PAm pressure by 11%, but further dose increases were limited by systemic hypotension. Sildenafil in doses of 25 mg or higher resulted in an average decrease of 14% in PAm pressure. Sildenafil is a potentially useful treatment option for patients with primary pulmonary hypertension, and further investigation is warranted.

Key Words: *Nitric oxide; Phosphodiesterase inhibitors; Prostacyclin; Pulmonary hypertension; Pulmonary vasodilator; Sildenafil*

Le traitement au sildénafil de l'hypertension artérielle pulmonaire primitive

RÉSUMÉ : Une femme de 37 ans présentant une hypertension artérielle pulmonaire primitive et une symptomatologie défavorable a subi un cathétérisme du tronc pulmonaire (TP) et des essais vasodilatateurs. L'oxygène n'a eu aucun effet, mais 10 parties par million de monoxyde d'azote ont réduit la pression moyenne du TP de 20 %. Une infusion de 8 ng/kg/min de prostacycline a diminué la pression moyenne du TP de 11 %, mais les augmentations supplémentaires de la dose étaient limitées par l'hypotension systémique. Le sildénafil en doses de 25 mg ou plus ont entraîné une diminution moyenne de la pression moyenne du TP de 14 %. Le sildénafil est une possibilité de traitement utile pour les patients souffrant d'hypertension artérielle pulmonaire primitive, et des recherches plus approfondies s'imposent.

Primary pulmonary hypertension (PPH) is a devastating condition that leads to death within three years of diagnosis in approximately one-half of patients. Medical treatment options are limited, and may include oxygen, diuretics, calcium channel blockade, inhaled nitric oxide (NO) and endothelin receptor antagonists, as well as prostacyclin and related compounds. However, these treatments have significant systemic side effects, variable effectiveness, and may be both inconvenient and expensive to administer. Lung or heart-lung transplantation is a treatment option, but it is limited by the availability of donor organs and the complications associated with immune suppression.

Sildenafil (Viagra, Pfizer Laboratories, USA) is a selective phosphodiesterase-5 inhibitor of cyclic guanosine monophosphate (cGMP) degradation that results in vascular smooth muscle vasodilation. Phosphodiesterase-5 is found in high concentrations in the corpus cavernosum, and sildenafil has been proven to be an effective treatment for male impotence. Because pulmonary arteries are also rich in phosphodiesterase-5, sildenafil is also a potential oral therapy for PPH. In the present report, a patient with PPH and her hemodynamic response to sildenafil challenge is described.

CASE PRESENTATION

A 37-year-old, white woman with PPH was electively admitted to the Intensive Care Unit (ICU), Peter Lougheed Centre, Calgary, Alberta, for vasodilator drug challenges for PPH treatment. She had onset of dyspnea on exertion beginning in 1996 and was first referred to the pulmonary medicine service at the Peter Lougheed Centre in 1998, when the diagnosis of PPH was made. At that time, she was described as class II according to the New York Heart Association functional classification of heart failure patients. She had a long-standing history of Raynaud's phenomena, a single episode of iritis in 1989 and a possible diagnosis of pericarditis in 1995. There were no other features to suggest a diagnosis of collagen vascular disease. Results of a physical examination showed signs of pulmonary hypertension, including an increased and palpable P_2 and a grade 1/6 murmur of tricuspid regurgitation, but were otherwise unremarkable. Complete blood count, serum electrolyte, and renal and liver function test results were normal. Tests for antinuclear antibodies were positive to a dilution of 1:160 (homogeneous pattern), and screens for extractable nuclear antigen and rheumatoid factor were negative. A high resolution computed tomography scan of the chest, pulmonary angiogram and transesophageal echocardiogram did not identi-

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TABLE 1
Pulmonary artery hemodynamic responses to sildenafil

Time (h)	0	1	2	3	4	5	6	7	8	9	10	11	12	16
Sildenafil dose (mg)	25				50				100					
Mean pulmonary artery pressure (mmHg)	28	23	24	24	24	23	23	24	27	24	26	23	26	30
Cardiac output (L/min)	6.3	6.7	6.1	5.9	5.9	5.5	5.6	5.5	5.9	6.1	6.8	6.2	6.5	7.2
Pulmonary vascular resistance (mmHg min/L)	3.8	3.1	3.4	3.6	3.7	3.6	3.8	4.0	4.1	3.0	2.9	3.1	3.4	3.3
Mean arterial pressure (mmHg)	69	65	68	71	74	74	70	68	76	70	74	71	73	81
Mixed venous oxygen saturation (%)	76				74				75				75	

fy an underlying secondary etiology for pulmonary hypertension. Spirometry demonstrated mild airflow obstruction. Although her history was suspicious for an underlying connective tissue disease, she was provisionally diagnosed with PPH.

The patient underwent elective ICU admission, pulmonary artery (PA) catheterization and vasodilator challenge in 1998. Baseline PA pressure was 73/30 mmHg, with mean PA (PAm) and pulmonary wedge pressures of 47 mmHg and 6 mmHg, respectively. Her cardiac output (CO) was 6.0 L/min, and her pulmonary vascular resistance (PVR) was 7.2 mmHg min/L. She had a significant response to nifedipine, and was therefore treated with a long acting preparation and systemically anticoagulated with coumadin. Over the subsequent three years, she remained symptomatically well controlled. Results of serial echocardiograms were stable. However, in the summer of 2001, she showed increasing symptoms of dyspnea (New York Heart Association class III), new onset of chest discomfort on exertion and reduction in exercise capacity. Treatment options were discussed with her, including therapy with a continuous prostacyclin infusion and new experimental agents. She raised the possibility of sildenafil treatment based on her research for new therapies using the Internet. After reviewing risks and benefits, repeat right heart catheterization and vasodilator trials were arranged.

She was admitted electively to the ICU, but because of unexpected bed availability, her last dose of nifedipine was administered approximately only 8 h before admission. After written informed consent was obtained, a radial arterial catheter was placed and a PA catheter was inserted through a sheath introducer via the right internal jugular vein. Placement was confirmed by both chest radiography and observation of typical pressure waveforms. All CO determinations were performed using 10 mL of 5% dextrose solution at room temperature. Reported values are the mean value of triplicate determinations.

The following baseline pressures were obtained: mean arterial pressure 84 mmHg, central venous pressure 3 mmHg, PA 48/22 mmHg, PAm 32 mmHg, heart rate 90 beats/min, CO 8.6 L/min, PVR 2.9 mmHg min/L and mixed venous oxygen saturation 78%. Because of the concerns of a residual nifedipine effect, baseline values were repeated before each new drug intervention. No change in PA or PAm pressure was observed with the administration of 100% oxygen. NO challenge was started at 5 parts/million (ppm) and was doubled until a maximum dose of 40 ppm was reached. A 10 ppm dose resulted in a reduction of the PAm by 20%, with no change in PVR. No significant further improvement was observed at higher doses. Prostacyclin infusion was then started at 2 ng/kg/min and increased by 2 ng/kg/min increments every 10 min. Prostacyclin infusion at 8 ng/kg/min resulted in an 11% reduction in PAm pressure and a 19% reduction in PVR, but further dose increases were aborted due to systemic hypotension (mean arterial pressure less than 60 mmHg).

After a 1 h washout period, the patient was given 25 mg oral sildenafil; she was also given 50 mg and 100 mg 4 h and 8 h later, respectively. Repeated assessments at 1 h intervals were performed (Table 1). Sildenafil treatment at doses of 25 mg or greater resulted in an average decrease of 14% in PAm from a baseline value of 28 mmHg to 24 mmHg (mean of 1 to 4 h postdose values [Table 1]). Similarly, a 25 mg or greater dose of sildenafil resulted in an average decrease of 9% in the PVR from the baseline value.

On review of the study results with the patient, including an extensive discussion of the risks and benefits of new treatments, she elected to continue with her current therapy of nifedipine and systemic anticoagulation.

DISCUSSION

Our patient's therapeutic response is consistent with the findings of three other published reports, showing that sildenafil use leads to a significant lowering of PA pressures in PPH (1-3). We observed a good response at a low dose of 25 mg, and its apparent duration of action was at least 3 to 4 h. Wilkens et al (1) evaluated five patients with PPH using PA catheterization and found that a 25 mg dose was optimal and reduced PAm pressure by an average of 13%. However, in the two other published case reports, higher doses of sildenafil were used, based on clinical and echocardiographic response, and were not titrated to direct PA measurements (2,3). We do not have an explanation why the 50 mg dose was not apparently as effective as either the 25 mg or 100 mg doses in our study. There is also a suggestion that the 100 mg dose was more effective than either of the two lower doses based on the degree of reduction of the PVR. Furthermore, although the PAm returned to baseline, the PVR remained lower than baseline 8 h after the administration of the 100 mg dose, potentially suggesting a prolonged effect with this dose. It should be kept in mind, however, that we only observed a single subject in this report, and a further dose response and duration study with a cohort of patients is needed.

Sildenafil appears to be a relatively potent treatment for pulmonary hypertension. We observed that the magnitude of PAm decrease with sildenafil was intermediate between the standard treatments of prostacyclin infusion and NO. There is

some evidence to suggest that these agents may work additively or synergistically in pulmonary hypertension. Case reports and series have demonstrated lower PA pressures with the use of combinations of sildenafil and NO or prostacyclin analogues than with each of these agents alone (1,4,5). An advantage of sildenafil over these other agents is its oral route of administration, although frequent dosing is required. Prospective clinical studies are needed to better define the clinical effect of sildenafil and whether its optimal effect optimized in combination with other therapeutic agents.

Sildenafil is widely used and its safety has been demonstrated in healthy individuals. However, adverse effects associated with the chronic use of sildenafil in patients with PPH have not been systematically studied. Sildenafil selectively inhibits cGMP degradation that relaxes smooth muscle. NO causes vasodilation via a cGMP mechanism; this likely explains why sildenafil potentiates NO activity. A potential benefit of treatment with sildenafil and inhaled NO is that they cause localized vasodilation of the pulmonary, but not the systemic, vasculature, so that complicating hypotension is less likely than with other PPH treatments (1,5,6). Until its efficacy and long term safety have been formally assessed in larger clinical studies, sildenafil should not be adopted as a standard therapy for PPH.

CONCLUSIONS

The present report describes a patient with PPH who demonstrated a significant hemodynamic response to sildenafil treatment. Based on our observations, oral sildenafil 25 mg has a pulmonary vasodilating effect lasting at least 3 to 4 h, and this therapy has, potentially, great promise for PPH. However, until large clinical trials demonstrate the efficacy and long term safety of this treatment, sildenafil cannot be recommended as a standard therapy for PPH.

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