Combined Use of PDE5 Inhibitors and Nitrates in the Treatment of Pulmonary Arterial Hypertension in Patients With Heart Failure

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ABSTRACT

Background: Phosphodiesterase-5 (PDE5) inhibitors, which induce relaxation of smooth muscle with some selectivity for the pulmonary vasculature, are used in the treatment of pulmonary hypertension. In some patients, the use of PDE5 inhibitors does not result in the desired magnitude of pulmonary vasodilation. The use of additional vasodilators to further reduce pulmonary vascular resistance is often accompanied by unacceptable reductions in systemic arterial pressure.

Methods and Results: In 3 patients with heart failure, pulmonary hypertension and low systemic arterial pressures treated with sildenafil, systemic nitrates were added to reduce pulmonary hypertension further. Hemodynamic measurements were made before and after addition of nitrates. Addition of systemic nitrates to sildenafil led to a reduction in mean pulmonary arterial pressure of 11 mm Hg, from 37 mm Hg to 26 mm Hg ($P = .06$), whereas mean systemic arterial pressure decreased by only 4 mm Hg, from 77 mm Hg to 73 mm Hg ($P = .53$). The ratio of pulmonary vascular resistance to systemic vascular resistance was reduced by 45% ($P = .1$). Treatment with sildenafil and nitrates was continued for two to eight months, with no episodes of marked systemic hypotension, syncope, or lightheadedness.

Conclusions: These results suggest that addition of systemic nitrates to sildenafil results in a potentiation of vasodilation that is relatively selective for the pulmonary vasculature, and that this combination may be safe and effective in the treatment of pulmonary hypertension in patients with low systemic arterial pressures. (*J Cardiac Fail 2009;15:31–34*)

Key Words: Pulmonary vasodilation, cyclic GMP.

Pulmonary arterial hypertension in patients with heart failure is usually attributable to some combination of elevated left-ventricular end-diastolic pressure and increased pulmonary vascular resistance. Pulmonary arterial hypertension can be treated with vasodilators, but in patients with severe heart failure, this option is often limited by the presence of low systemic arterial pressures. In this setting, reducing pulmonary arterial pressure without reducing systemic arterial pressure to unacceptable levels can be difficult.

Phosphodiesterase-5 (PDE5) inhibitors are useful in the treatment of pulmonary arterial hypertension. These drugs raise intracellular cyclic guanosine monophosphate (cGMP) content in vascular smooth muscle myocytes by reducing its conversion to GMP; the increase in cGMP content induces relaxation of smooth muscle myocytes through the activation of protein kinase G and the effects of protein kinase G–mediated protein phosphorylation.[1] PDE5 inhibitors have some selectivity for the pulmonary vasculature relative to the systemic vasculature.[2–4] In patients with idiopathic pulmonary arterial hypertension, sildenafil reduces pulmonary vascular resistance, increases cardiac output, and increases functional capacity.[5–7] The effects of PDE5 inhibitors in patients with pulmonary arterial hypertension associated with left ventricular dysfunction are less well known, but several studies have shown that, in this setting as well, treatment with sildenafil reduces pulmonary vascular resistance, increases cardiac output, and increases exercise capacity and is accompanied by an

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improvement in quality of life and a reduction in rates of rehospitalizations.[8–11]

In some patients, however, the use of PDE5 inhibitors does not result in the desired magnitude of pulmonary vasodilation. The addition of nitrates, which raise intracellular cGMP content by stimulating its formation by guanylyl cyclase, would be expected to have a synergistic effect on vascular smooth muscle relaxation. Whether this synergy could be achieved in the pulmonary vasculature without unacceptable reductions in systemic arterial pressures was unknown. In 2 studies, administration of inhaled nitric oxide to patients with pulmonary arterial hypertension taking sildenafil resulted in a relatively selective potentiation of pulmonary vasodilation.[5,12] This selectivity, however, might have been attributable to the administration of nitric oxide directly to the lungs, and might be lost if nitrates were administered systemically. In another study, intravenous nitroglycerin was administered to patients who had been given a single dose of sildenafil to demonstrate the feasibility of using nitrates to treat acute coronary syndromes in patients taking sildenafil.[13] These patients, though, had neither pulmonary arterial hypertension nor heart failure, and effects on pulmonary arterial hemodynamics were not quantified. Other investigators have noted a relatively selective potentiation of pulmonary vasodilation when sildenafil was added to inhaled nitric oxide, intravenous nitroglycerin, or nesiritide.[4] In these patients, sildenafil was used to expedite the discontinuation of inhaled nitric oxide, intravenous nitroglycerin, and nesiritide after cardiac surgery. Whether these agents could have been used together for extended periods in the presence of low systemic arterial pressures was not examined.

Here we report our experience in adding oral nitrates to sildenafil in the treatment of pulmonary arterial hypertension in 3 patients with advanced heart failure and low systemic arterial pressures.

Methods

Patients in our heart failure/transplant program are frequently treated with sildenafil for pulmonary arterial hypertension. In 3 such patients, pulmonary arterial pressures remained elevated, whereas systemic arterial pressures were in the lower range of normal. In these 3 patients, oral nitrates were added to sildenafil. All patients were hospitalized and monitored closely in medical intensive care or telemetry units for the initial administration of nitrates.

Right heart catheterization was performed before initiation of nitrates and after stable medical regimens were achieved. Student *t*-test was used to examine changes in hemodynamic values before and after the use of combined sildenafil and nitrate therapy.

Analysis and reporting of these results was approved by the University of Utah/VA Salt Lake City Health Care System Institutional Review Board.

Results

Patient 1

A 58-year-old man with ischemic cardiomyopathy presented after cardiac arrest with shock and severe pulmonary arterial hypertension despite treatment with intravenous nitroglycerin. Nitroglycerin was stopped and sildenafil was started and increased to 25 mg 3 times daily. Pulmonary arterial pressures decreased, but moderate pulmonary arterial hypertension remained present. Three weeks after sildenafil therapy was initiated, isosorbide dinitrate was added and increased to 20 mg 3 times daily. This led to a further decrease in pulmonary arterial pressures and a small reduction in pulmonary vascular resistance; there was an increase in systemic vascular resistance and a small increase in systemic arterial pressure (Table 1). The patient remained hospitalized on this combination for 2 months. He did not complain of lightheadedness, and no episodes of systemic hypotension were documented. He died from a recurrence of ventricular tachycardia.

Table 1. Effect of Addition of Sildenafil and Nitroglycerin on Parameters of Cardiovascular Function

	Right Atrial Pressure (Mean) mm Hg	Pulmonary Arterial Pressure (s/d/m) mm Hg	Pulmonary Artery Wedge Pressure (Mean) mm Hg	Pulmonary Vascular Resistance (dyn × s × cm^{-5})	Systemic Arterial Pressure (s/d/m) mm Hg	Systemic Vascular Resistance (dyn × s × cm^{-5})	Cardiac Output/ Cardiac Index (L/min / L/min/m^2)
Patient 1							
Baseline	9	82/44/57	20	658	110/6479	1249	4.5/2.5
Sildenafil	7	56/22/34	19	240	111/67/82	1210	5.0/2.4
Sildenafil+ nitrates	5	40/17/25	15	154	97/58/71	1015	5.2/2.5
Patient 2							
Baseline	12	69/30/43	25	351	119/65/83	1385	4.1/2.3
Sildenafil	16	60/37/45	23	391	102/45/64	857	4.5/2.5
Sildenafil+ nitrates	13	42/36/38	20	360	108/68/81	1366	4.0/2.2
Patient 3							
Baseline	11	65/25/38	27	325	112/53/73	1837	2.7/1.4
Sildenafil	5	58/18/31	20	293	117/55/76	1885	3.0/1.6
Sildenafil+ nitrates	1	20/10/15	12	72	102/50/67	1600	3.3/1.8

s/d/m, systolic pressure/diastolic pressure/mean pressure.