

Oral Sildenafil Reduces Pulmonary Hypertension After Cardiac Surgery

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Background. Treatment of postoperative pulmonary hypertension with intravenous (IV) pulmonary vasodilators is hampered by the lack of selectivity. Inhaled nitric oxide produces selective pulmonary vasodilation; however, it requires a special device, and weaning can cause rebound. Oral sildenafil is a phosphodiesterase type V inhibitor. Sildenafil can produce sustained pulmonary vasodilation in patients with hypoxic or primary pulmonary hypertension; however, experience with postoperative pulmonary hypertension is limited. We report our initial experience with eight patients who received oral sildenafil as adjunctive therapy for postoperative pulmonary hypertension.

Methods. We reviewed the charts of eight adult patients with postoperative pulmonary hypertension who received oral sildenafil (25 to 50 mg) to facilitate weaning of IV (milrinone, nitroglycerine, and sodium nitroprusside) and inhaled (nitric oxide) pulmonary vasodilators.

Hemodynamic data were recorded before and 30 and 60 minutes after the initial dose of sildenafil.

Results. After the initial dose of sildenafil, mean pulmonary artery pressure was reduced by 20% and 22% at 30 and 60 minutes, respectively ($p < 0.05$). Pulmonary vascular resistance index decreased by 49% and 44% at 30 and 60 minutes, respectively ($p < 0.05$). Sildenafil had no clinically significant effects on cardiac index, mean arterial pressure, or systemic vascular resistance. Subsequent doses of sildenafil were administered at regular intervals, allowing successful weaning of concomitant pulmonary vasodilators.

Conclusions. Oral sildenafil is an effective agent for treatment of postoperative pulmonary hypertension and can be used to facilitate weaning of inhaled and IV pulmonary vasodilators.

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Pulmonary hypertension can present a formidable challenge in the management of patients undergoing cardiac surgery. Strategies to reduce pulmonary vascular tone aim to enrich vascular smooth muscle cyclic adenosine monophosphate levels through beta agonists (isoproterenol) or with phosphodiesterase type III inhibitors (milrinone). Alternatively, increasing cyclic guanine monophosphate (cGMP) with nitroso vasodilators (sodium nitroprusside, nitroglycerin, inhaled nitric oxide [NO]) also reduces pulmonary vascular tone. Even though inhaled NO is extremely efficacious in reducing mean pulmonary artery pressure (MPAP) in cardiac patients, its application has been limited because it must be administered through a closed inhalation circuit because of toxic byproducts [1]. In addition, withdrawal of inhaled NO therapy can lead to dangerous rebound pulmonary hypertension.

Oral sildenafil, a phosphodiesterase type V (PDE-V) inhibitor, prevents the degradation of cGMP and has been shown to be as effective as inhaled NO in the setting of primary pulmonary hypertension and pulmonary fibrosis. However, sildenafil does not require an inhaled delivery system and does not cause rebound pulmonary hypertension [2-4]. Furthermore, its effects have been noted to last for at least three hours without affecting systemic arterial pressure [5]. In the laboratory we have demonstrated an intravenous formulation of a sildenafil analogue, UK 343 to 664, shows sustained reduction of pulmonary hypertension in a porcine model of pulmonary hypertension [6]. Increasing evidence has shown that sildenafil is an effective pulmonary vasodilator for both children and adults with primary pulmonary hypertension [7-10]. We report our initial experience with the use of sildenafil as adjunctive therapy for the postoperative pulmonary hypertension following cardiac surgery.

Material and Methods

After Institutional Review Board approval, we conducted a retrospective review of the initial eight consecutive patients that received sildenafil to treat persistent pulmonary hypertension after mitral valve surgery ($n = 6$) or

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Table 1. Patient Demographics

Patient #	Age/Sex	Primary Procedure	Sildenafil (mg)	Concomitant Therapy	Disposition
1	71/M	MVR	25 BID	NTG, Milrinone	D/C Home 18 d
2	50/M	MVR	25 BID	NTG, nesiritide epinephrine, dopamine	D/C Home 21 d
3	47/F	MVR	50 TID	NO, milrinone, NTG	D/C Home 10 d
4	64/M	MVR	50 QD	NO, milrinone, nesiritide	D/C Rehab 90 d
5	46/F	MV Repair	50 TID	milrinone, epinephrine, NTG, isoproterenol	D/C Home 28 d
6	49/F	MVR	50 BID	NTG, milrinone, SNP, nesiritide	D/C Home 28 d
7	58/M	LVAD Thoratec	50 BID	NTG, milrinone, nesiritide	Heart tx 14 d
8	40/M	LVAD Heartmate	50 QID	Nesiritide, dopamine	Heart tx@8 mo

BID = twice daily; D/C = discharge; d = day; LVAD = left ventricular assist device; mo = month; MV repair = mitral valve repair; MVR = mitral valve replacement; NO = nitric oxide; NTG = nitroglycerine; QD = once daily; QID = four times daily; Rehab = rehabilitation center; SNP = sodium nitroprusside; TID = three times daily.

left ventricular assist device (LVAD) placement (n = 2) at our institution. In each case, sildenafil was administered only if the patient had persistently elevated pulmonary artery pressures despite multiple, conventional pulmonary vasodilators (Table 1). Oral sildenafil was initiated in an intensive care setting, hemodynamics were closely monitored, and the dose was readministered based on pulmonary hemodynamics. Once initiated, sildenafil continued through discharge. Conventional agents were typically weaned 24 hours after administration of the first dose of sildenafil. The dose of sildenafil was recorded along with the hemodynamic factors. Pulmonary artery and systemic arterial vascular resistance indices were calculated according to standard formulas: $PVRI = MPAP - LAP/CI$ and $SVRI = MAP - CVP/CI$, where $PVRI$ = Pulmonary vascular resistance index MAP = mean arterial pressure, CVP = central venous pressure, $MPAP$ = mean PAP, LAP = left atrial pressure, CI = cardiac index, and $SVRI$ = systemic vascular resistance index. Hemodynamic measurements were recorded before the administration of the initial dose of sildenafil and 30 and 60 minutes later. Statistical analysis was performed with SAS software (Cary, NC) using analysis of

variance with repeated measures. A p value less than 0.05 was considered significant.

Results

This review includes five males and three females. The mean age was 52 ± 10 years. The initial dose of sildenafil was based on surgeon preference and ranged between 25 and 50 mg. The same individual dose was repeated at regular intervals based on the tendency of pulmonary hemodynamics to return to baseline. Table 1 shows the patients' demographics and the dose regimen for sildenafil.

Following the administration of sildenafil, $MPAP$ decreased by 9 mm Hg at 30 and 60 minutes ($p < 0.05$) (Table 2). A relative high degree of pulmonary selectivity was observed. Although a statistically significant difference in MAP was identified; it was not clinically significant (Fig 1). While systemic vascular index was not significantly different after sildenafil at 60 minutes, a marked decrease in $PVRI$ was observed at both 30 and 60 minutes (Fig 2). Other concomitant pulmonary vasodilators were weaned while sildenafil administration contin-

Table 2. Hemodynamic Measurements

Parameter	Baseline	30 Minutes Post Sildenafil	60 Minutes Post Sildenafil	p value 30 vs Baseline	p value 60 vs Baseline
Heart rate (bpm)	100.8 ± 9.6	100 ± 7.9	99.6 ± 7.9	NS	NS
MAP	68.7 ± 8.6	61.25 ± 9.6	62.3 ± 8.4	0.006	0.016
MPAP	41.2 ± 13.2	32.87 ± 9.1	32.3 ± 7.1	0.01	0.007
CVP	9.1 ± 2.5	8.8 ± 3.3	9.4 ± 5.7	NS	NS
LAP	12.4 ± 2.9	13 ± 5.2	15 ± 5.7	NS	NS
CI	3.8 ± 0.7	4.65 ± 1.4	3.9 ± 0.7	NS	NS
SVRI	1249 ± 295.7	928.9 ± 334.5	1096.5 ± 326.4	0.002	NS
PVRI	556.4 ± 504.1	281.9 ± 233.5	313.6 ± 246.1	0.026	0.042

bpm = beats per minute; CI = cardiac index (liters/minute/body surface area); CVP = central venous pressure (mm Hg); LAP = left atrial pressure (mm Hg); MAP = mean arterial pressure (mm Hg); MPAP = mean pulmonary arterial pressure (mm Hg); SVRI = $(MAP - CVP)/CI \times 80$; PVRI = $(MPAP - LAP)/CI \times 80$.

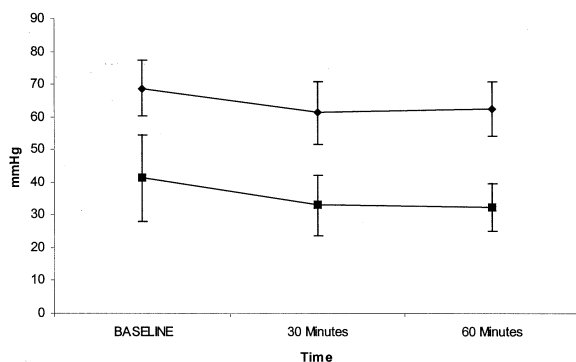


Fig 1. Values of mean arterial pressure (MAP; ◆) and mean pulmonary arterial pressure (MPAP; ■) before and after the administration of a single dose of oral sildenafil. There was a reduction in MPAP without a clinically significant change in MAP.

ued. There were no in-hospital mortalities among the eight patients.

Comment

This retrospective review suggests that sildenafil produces marked pulmonary vasodilation when added to a preexisting regimen of nitrovasodilators in patients with pulmonary hypertension following cardiac surgery. The pulmonary hypertension in this series of patients was refractory to conventional pharmacologic agents and was reduced on average by 20% with sildenafil. Sildenafil not only provided an additive pulmonary vasodilatory effect, but also allowed the successful weaning of inhaled and intravenous pulmonary vasodilators.

Because experience with sildenafil and postoperative pulmonary hypertension is limited, the optimal dose has not been established. Initial doses were similar to that described in previous case reports, with intervals determined by observation of pulmonary hemodynamics.

Preexisting pulmonary hypertension and postopera-

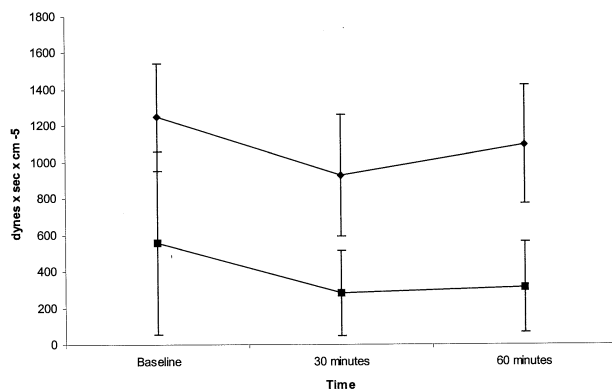


Fig 2. Changes in systemic vascular resistance index (◆) and pulmonary vascular resistance index (PVRI; ■) following the administration of sildenafil. The effect on PVRI is more pronounced, denoting relative pulmonary selectivity.

tive acute pulmonary hypertension complicate the management of patients with mitral valve disease. Our experience showed that in six different patients undergoing mitral valve surgery, PAP and PVR decreased following sildenafil administration. Furthermore, conventional therapies for pulmonary hypertension were successfully weaned with no rebound pulmonary hypertension.

Severe pulmonary hypertension can also lead to right ventricular failure in patients with LVADs. In order to assure delivery of preload to the LVAD, right ventricular function must be preserved. Sildenafil reduced pulmonary hypertension in both our patients with LVADs, improving LVAD filling and obviating the need for RVAD placement. Consequently both LVAD patients progressed to heart transplantation without difficulty.

The ability of PDE-V inhibitors, including sildenafil, zaprinast, and dipyridamole to decrease MPAP and PVR has been previously demonstrated in experimental models of pulmonary hypertension [11-14]. Their effectiveness correlates with the level of PDE-V inhibition and the increase in pulmonary vascular smooth muscle cGMP [15].

This report has significant limitations, as it is a retrospective review of a small number of patients with no controls. However, the findings are consistent with the few isolated case reports describing the use of PDE-V inhibitors as pulmonary vasodilators in patients undergoing cardiac surgery. Intravenous dipyridamole was used successfully in a small series of pediatric heart surgery patients [16]. However, dipyridamole has antiplatelet effects that are undesirable in the perioperative period. Anecdotal reports of oral sildenafil in cardiac surgery patients include both the successful pulmonary vasodilation in a child with mitral stenosis and in an adult patient who underwent placement of a biventricular assist device [17, 18]. While lack of an intravenous formulation for sildenafil may limit its use in the early postoperative period; the availability of an effective, oral selective pulmonary vasodilator facilitates later postoperative management.

In summary, this initial experience suggests that oral sildenafil can be an effective agent as part of a multimodal approach to postoperative pulmonary hypertension. Further studies are necessary to more clearly define the optimal dosing and role of sildenafil in patients following cardiac surgery.

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DISCUSSION

DR JACOB DELAROSA (Atlanta, GA): Thank you for the paper. Great presentation. My question is quick. How did you deal with the tumescence using Viagra on these patients? Was it a blessing or was it a problem?

DR TRACHTE: We did not note tumescence, nor did our nurses examine for that, but we did notice some increased sexual drive in some of our patients as anecdotal reports.

DR ROBERT B. LEE (Jackson, MI): I appreciate your presentation. It was well done. I would assume that at least some of these patients were known to have pulmonary hypertension prior to operation. Have you looked at using it prophylactically to decrease their pulmonary hypertension 24 to 48 hours preoperatively and what would be your recommendation in that regard?

DR TRACHTE: That is an excellent question. Thank you, Dr. Lee. Our anesthesia attendings that are interested in Viagra are especially interested in this concept. We did have patients who did have preoperative pulmonary hypertension. In fact, one of

the eight patients mentioned was on intravenous milrinone prior to reoperation. We have not used it preoperatively, but they have talked of trying to use that and are attempting to study that, and that is a very good question.

DR JOHN H. CALHOON (San Antonio, TX): This is a very nice paper. My question would be what benefit do you think there is in simply affecting the pulmonary artery pressure and the pulmonary vascular resistance when you didn't make any change in the cardiac output?

DR TRACHTE: Thank you, Dr Calhoon. That is a good point. When you look at our patients, we looked at the hemodynamic data and found that there were no changes. Particularly for the left ventricular assist device patients, though it should be noted that these patients did not require return trips to the operating room for right ventricular assist devices, and that is a significant outcome, but we don't have enough numbers or data to make a firm projection on whether or not this really affects the clinical outcomes of the patients.