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Chronic Outpatient Sildenafil Therapy for Pulmonary Hypertension in a Child After Cardiac Surgery

Chad A. Knoderer
Butler University, cknodere@butler.edu

E. S. Ebenroth

J. W. Brown

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C.A. Knoderer , E.S. Ebenroth, and J.W. Brown

Abstract

We report the case of a 14-month-old male with d-transposition of the great arteries, ventricular septal defect, and pulmonary hypertension successfully treated with long-term sildenafil following cardiac surgery. To our knowledge, this is the first published report of long-term sildenafil treatment in a child after corrective cardiac surgery.

Pulmonary hypertension associated with congenital heart disease in children remains a significant cause of morbidity and mortality postoperatively [*4*, *8*]. Despite many advances in the treatment of adults with pulmonary hypertension, limited therapeutic options are available for infants and children. Inhaled nitric oxide, which is a selective pulmonary vasodilator, has been shown to be safe and effective in reducing pulmonary hypertension when used postoperatively in pediatric cardiac surgery cases [*6*, *7*]. Pharmacologic agents such as intravenous prostacyclin and endothelin antagonists are options for the treatment of pulmonary hypertension; however, inhaled nitric oxide remains the standard drug therapy at our institution. Intravenous chlorpromazine has commonly been used as adjunctive therapy for pulmonary hypertension at our institution due to its alpha-blocking and sedating effects. Sildenafil citrate is an oral phosphodiesterase inhibitor that causes pulmonary vasodilation with minimal systemic vasodilator effects [*9*]. Results from a number of small studies and case reports indicate that sildenafil is safe and effective for pulmonary hypertension in the pediatric population. [*1–3*, *5*, *10*].

Case Report

A 14-month-old boy from the Phillipines arrived in the United States for adoption and was admitted to the hospital with cyanosis and failure to thrive. Echocardiographic evaluation revealed d-transposition of the great arteries, a large muscular ventricular septal defect (VSD), a small secundum atrial septal defect (ASD), and evidence of elevated pulmonary artery pressures. The patient underwent a preoperative cardiac catheterization to better assess pulmonary artery pressures. Catheterization results (Table 1) indicated pulmonary hypertension and mildly reactive pulmonary artery pressures. Despite these discouraging numbers, the patient underwent an arterial switch procedure with a VSD closure and primary closure of the ASD. The patient was mechanically ventilated and maintained on inhaled nitric oxide, intravenous fentanyl, nitroglycerin, and cisatracurium infusions and intermittent intravenous chlorpromazine postoperatively for management of pulmonary hypertension. He was weaned off the nitroglycerin infusion on postoperative day 1. On postoperative day 2 he had a drop in heart rate along with a decline in systemic blood pressures. Pulmonary artery pressures remained elevated at approximately one-half systemic blood pressures, despite treatment with nitric oxide at 30 ppm. Nitric oxide was subsequently weaned off by postoperative day 5, at which time sildenafil was initiated at 1 mg via the nasogastric tube every 6 hours (~0.25 mg/kg/dose). The pulmonary artery catheter was removed on postoperative day 6. Available hemodynamic data before and after the initiation of sildenafil are summarized in Table 2.

Table 1
Preoperative cardiac catheterization results

	Baseline	90% FiO_2	90% FiO_2 +NO 20 ppm
Q_p/Q_s	2	2.64	2.71
R_p	2.9	2.9	2.8
R_s	10.8	14.1	12.4
R_p/R_s	0.27	0.21	0.23

NO, nitric oxide; ppm, parts per million; Q_p/Q_s, pulmonary-to-systemic blood flow ratio; R_p, pulmonary vascular resistance; R_s, systemic vascular resistance; R_p/R_s, ratio of pulmonary to systemic vascular resistance.

Table 2
Hemodynamic data before and after sildenafil dosing

	Pulmonary artery pressures				Systemic blood pressures			
Dose No.	**1-hr predose**	**0.5-hr postdose**	**1-hr postdose**	**2-hr postdose**	**1-hr predose**	**0.5-hr postdose**	**1-hr postdose**	**2-hr postdose**
1	36/6	28/7	27/7	29/8	75/52	72/47	66/39	72/52
2	30/8	24/6	28/7	35/9	73/52	69/46	74/47	74/47
3	44/11	35/13	31/9	38/11	76/49	82/53	73/51	76/49

The patient was extubated on postoperative day 7 and discharged 13 days after surgery on a 2-day weaning course of sildenafil. The sildenafil was initially weaned from 1 mg every 6 hours to 1 mg every 8 hours for 1 day while the patient remained in the hospital. The patient was then discharged home on 1 mg every 12 hours for 1 day and then 1 mg every 24 hours for 1 day. Additional medications upon discharge included furosemide and spironolactone. A follow-up echocardiogram performed 2 days postdischarge revealed elevated pulmonary pressures with pulmonary artery diastolic pressures estimated to be 30–40 mmHg. Sildenafil was restarted at 1 mg orally every 6 hours. Echocardiogram findings 2 months after surgery demonstrated persistently elevated pulmonary pressures, with pulmonary artery diastolic pressures estimated to be 25–30 mmHg. Sildenafil dosing was increased to 1 mg alternating with 2 mg every 6 hours (~0.25 mg/kg/dose alternating with ~0.5 mg/kg/dose). A follow-up echocardiogram at 4 months after surgery indicated normal pulmonary systolic and diastolic pressures, and no dosage adjustments were made to the sildenafil. Sildenafil was increased to 2 mg orally every 6 hours (~0.25 mg/kg/dose) at a follow-up visit 7 months after surgery due to echocardiogram findings suggestive of elevated right-sided pressures. Echocardiogram findings 9 months following surgery demonstrated normal pulmonary pressures. Sildenafil was subsequently weaned off after having completed 323 days of treatment. Sildenafil was weaned by changing to 2 mg every 12 hours for 2 weeks and then 2 mg every 24 hours for 2 weeks, after which the drug was discontinued. A follow-up echocardiogram approximately 4 months after discontinuation of sildenafil showed normal pulmonary artery pressures. No adverse effects were observed by the cardiologist or reported by the parents during treatment course. For this patient, the compounding pharmacy at our institution made 1-mg sildenafil capsules from the 25-mg

sildenafil tablets. The contents of the capsule were mixed with approximately 5–10 ml of water immediately prior to the scheduled dose and administered to the child. The child remains healthy at 3 years of age and does not require any cardiac medications.

Discussion

Sildenafil is a phosphodiesterase (PDE) inhibitor with high selectivity against isoform 5 [*9*]. Phosphodiesterase-5 (PDE-5) is predominantly found in smooth muscle cells of the corpora cavernosa and in high concentrations in the pulmonary vasculature. The phosphodiesterase enzymes catalyze the breakdown of cyclic nucleoside monophosphates. Isoform 5 is a cGMP-specific PDE [*9*]. Inhibition of PDE-5 results in an increased cellular level of cGMP, which increases vascular smooth muscle relaxation [*1*, *9*]. Due to the high concentration of PDE-5 in the pulmonary vasculature, sildenafil use causes significant pulmonary blood pressure reduction and may benefit certain patients with pulmonary hypertension [*1*, *9*].

Randomized, placebo-controlled clinical trials evaluating the use of sildenafil in children with pulmonary hypertension after cardiac surgery have not been published. However, there are many case reports that illustrate its effectiveness as a pulmonary vasodilator and benefit for patients with pulmonary hypertension. These reports all evaluate short-term treatment with sildenafil. In a case series of 16 patients, oral sildenafil significantly reduced mean pulmonary artery pressure from 50 ± 8 to 38 ± 12 mmHg during cardiac catheterization [*5*]. In 5 of the patients in this series, sildenafil allowed for discontinuation of inhaled nitric oxide 4–6 hours after an oral sildenafil dose [*5*]. Similar results were observed in a study evaluating intravenous sildenafil. In children undergoing cardiac catheterization and following cardiac surgery, intravenous sildenafil was found to be an effective pulmonary vasodilator [*10*]. Intravenous sildenafil caused a significant decrease in pulmonary artery pressures in both study groups. It is important to note that this was a European and Canadian study and that intravenous sildenafil is not yet available in the United States.

Other reports have shown that oral sildenafil may aid in the successful withdrawal of nitric oxide [*2*, *3*]. Sildenafil initiation in a 9-month-old with congenital heart disease allowed the weaning of nitric oxide while inducing no further pulmonary hypertensive episodes [*2*]. No rebound pulmonary hypertension was observed in the 36 hours after the nitric oxide was discontinued. Atz and Wessel [*3*] observed similar findings in three patients with pulmonary hypertension. Sildenafil administration facilitated withdrawal of nitric oxide in these patients with no rebound pulmonary hypertension observed. cGMP sampling in these patients showed increases in cGMP plasma levels after sildenafil dosing.

Outpatient oral sildenafil therapy is described in a 4-year-old girl with pulmonary hypertension [*1*]. Treatment was initiated in this patient with intravenous prostacyclin, which produced a 10% decrease in pulmonary artery pressure but no increase in cardiac output. Oral sildenafil was initiated, resulting in an average 10% increase in mixed venous oxygen saturation after drug administration. An increase in exercise capacity was observed in a 3 -month follow-up visit in this patient [*1*].

Sildenafil was initiated in our patient in the immediate postoperative period to facilitate withdrawal of inhaled nitric oxide and prevent rebound pulmonary hypertension. Nitric oxide was chosen initially after surgery due to the preoperative cardiac catheterization results along with postoperative elevations in pulmonary artery pressures and echocardiogram findings consistent with pulmonary hypertension. Outpatient therapy with sildenafil was continued primarily due to echocardiogram findings suggestive of pulmonary hypertension. There are no reports detailing the use of sildenafil for this duration in a child after corrective cardiac surgery.

A dose–time relationship was observed for the pulmonary artery pressure in our patient immediately after sildenafil dosing. As seen in Table 2, the initial decreases in pulmonary arterial pressures were seen in the first 30–60 minutes after dosing. The average decrease in systolic pulmonary artery pressures from baseline to that observed 30 and 60 minutes after a sildenafil dose were 21% and 27%, respectively (Table 2). Pulmonary pressures then began to rise approximately 2 hours after dosing. Systemic blood pressures remained stable after sildenafil dosing. Average decreases in systolic blood pressure were 4% and 8% 30 and 60 minutes after dosing, respectively. The pulmonary artery catheter was removed soon after initiation of sildenafil and a sustained effect on pulmonary artery pressures could not be observed in this patient. An attempt to discontinue sildenafil therapy was made prior to patient discharge after surgery. However, echocardiogram findings at the immediate follow-up visit were suggestive of recurrent pulmonary hypertension. A series of echocardiogram results showed persistent pulmonary hypertension. Of note was the 4-month postoperative echocardiogram that suggested normal pulmonary pressures, whereas the 7-month postoperative echocardiogram revealed elevated pressures. This result may be due to the 1.4-kg weight increase of the patient in this time period and the overall decrease in the dose. Dosing was increased to 2 mg every 6 hours (~ 0.25 mg/kg/dose) and was similar to the dosing used initially after surgery. After dosing was increased, pulmonary pressures gradually returned to normal.

This case illustrates the beneficial effects of sildenafil for patients with pulmonary hypertension after cardiac surgery. In this patient, the resolution of pulmonary hypertension is thought to be due to the combination of long-term sildenafil therapy and time after surgical repair of his congenital heart defect. Although it is difficult to determine the extent of the effect of sildenafil, echocardiogram findings corroborate that sildenafil was an effective treatment for pulmonary hypertension in this patient. Sildenafil appears to be an effective pulmonary vasodilator, and in clinical situations similar to the one presented in this report it should be considered as an option for pulmonary hypertension. Randomized, placebo-controlled clinical studies are needed to determine the effectiveness of long-term sildenafil therapy for patients with pulmonary hypertension.

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