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Use of Sildenafil to Facilitate Weaning From Inhaled Nitric Oxide in Children With Pulmonary Hypertension Following Surgery for Congenital Heart Disease

Jaclyn E. Lee

Simon C. Hillier

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

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Abstract

Pulmonary hypertension frequently complicates the postoperative management of patients after congenital cardiac surgery. Inhaled nitric oxide is an effective treatment option, but rebound pulmonary hypertension can occur upon its withdrawal. Sildenafil may facilitate its withdrawal by restoring cyclic guanosine monophosphate availability via phosphodiesterase-5 inhibition. The purpose of this study was to evaluate the use of sildenafil in facilitating weaning from inhaled nitric oxide after congenital cardiac surgery in patients who had previously failed weaning, and to compare the effects of sildenafil on pulmonary and systemic hemodynamics. Children who received sildenafil after cardiovascular surgery during a 23-month period at Riley Hospital for Children were identified. Medical records were retrospectively reviewed to determine sildenafil and nitric oxide dosing, pulmonary and systemic blood pressures, and adverse effects. Oral sildenafil was administered to 7 children who had failed attempts at inhaled nitric oxide weaning. Inhaled nitric oxide was weaned from 29.8 ± 5.9 ppm prior to sildenafil initiation to 12.2 ± 3.4 ppm (mean ± SE; P = .024) in the 24 hours after sildenafil. Mean pulmonary artery and systemic arterial pressure were unchanged from baseline when measured 1 hour after sildenafil dosing (mean pulmonary artery pressure, 29 ± 1 to 27 ± 0.7 mm Hg, P = .066; mean systemic arterial pressure, 56 ± 1.2 to 54 ± 1.2 mm Hg, P = .202). Sildenafil may facilitate withdrawal of inhaled nitric oxide and prevent rebound pulmonary hypertension in patients previously failing inhaled nitric oxide weaning attempts.

Pulmonary hypertension (PHTN) is an important cause of morbidity and mortality in pediatric patients with congenital heart disease. Congenital heart defects that are associated with significant increases in pulmonary blood flow, pulmonary venous obstruction, and cyanosis are most likely to predispose to postoperative PHTN.[1,2] Surgery for congenital heart disease usually requires cardiopulmonary bypass (CPB), which is associated with temporary pulmonary endothelial dysfunction and suppression of endogenous nitric oxide (NO) production, further predisposing to PHTN. Furthermore, the systemic inflammatory response to CPB is associated with increases in endothelin production, which also contributes to elevations in pulmonary vascular tone.[3-5] Children with PHTN following CPB require significantly longer ventilatory support and intensive care stays.[6] Patients who undergo correction of total anomalous pulmonary venous connection (TAPVC), transposition of the great arteries (TGA), ventricular septal defect (VSD), and atrioventricular canal (AVC) are at particularly increased risk for postoperative pulmonary hypertensive events and subsequent morbidity and mortality.[7]

There are a number of pharmacologic treatment options for PHTN in children after cardiac surgery. In most cases, inhaled NO (iNO) effectively reduces pulmonary artery pressures (PAP) and reduces the incidence of postoperative pulmonary hypertensive crises.[8-10] Inhaled nitric oxide causes selective vasodilation in the pulmonary circulation by increasing smooth muscle intracellular cyclic guanosine monophosphate (cGMP) availability. However, the effect of cGMP is short-lived because it is promptly degraded by local phosphodiesterases. Sildenafil is a phosphodiesterase (PDE) inhibitor with high selectivity against isoform 5, the predominant PDE isoform in the lung responsible for the breakdown of cGMP.[11] Sildenafil would be predicted to enhance and prolong the effects of cGMP in pulmonary circulation, causing significant PAP

reduction with minimal systemic effects.[12] Despite widespread adoption of sildenafil as an adjunct to or in place of iNO, there are limited data regarding dosing and efficacy. Furthermore, the use for PHTN in children remains off-label and is not approved by the Food and Drug Administration (FDA).

The primary objective of this retrospective study was to evaluate the use of sildenafil in facilitating weaning from iNO in patients who had previously failed iNO weaning after congenital cardiac surgery at a single tertiary care pediatric center. A secondary objective was to compare the effect of sildenafil on pulmonary and systemic hemodynamics. We sought to test 2 hypotheses. First, sildenafil administration would be associated with a reduction in iNO requirements as determined by comparing the mean iNO doses in the 24-hour periods before and after sildenafil administration in patients who had previously failed attempts to wean iNO. Second, sildenafil would preferentially reduce PAP versus systemic arterial pressures (SAP).

Methods

This retrospective study was conducted after approval from the institutional human subjects review board. All patients undergoing cardiovascular surgery and receiving sildenafil during a 23-month period between January 2003 and November 2004 at Riley Hospital for Children, Indianapolis, Ind, were eligible for inclusion in the study. This time frame represented the initial period of sildenafil use at our hospital. A pharmacy computer-generated list was used to identify patients meeting these inclusion criteria. Patients older than 18 years were excluded. Patient cases in which the complete medical chart was unavailable for review after 3 requests from the hospital's medical records department were excluded. Examination of all patient charts meeting inclusion criteria was performed to identify those patients who had previously failed iNO weaning and patients who had both PAP and SAP data from before and following sildenafil administration.

Table 1. Inhaled Nitric Oxide Weaning Protocol

iNO Dose Range at Wean Initiation, ppm	Dose Increment Decrease, ppm	Wean Frequency, Hours
20 – 40	5	1-2
10 – 20	2	1-2
2 – 10	1	1-2
0 – 2	0.5	1-2

NOTES: iNO = inhaled nitric oxide; ppm = parts per million.

The iNO weaning protocol used during the study period is described in Table 1. Failure to tolerate weaning was defined as a significant decrease in cardiac output (as reflected by declining blood pressure, declining mixed venous oxygen saturation, increasing base deficit or lactate, or worsening peripheral perfusion) and/or increasing PHTN or pulmonary hypertensive crises (typical clinical manifestations include declining arterial saturation, sustained increased PAP above previous values, and increasing arterial carbon dioxide). It should be noted that transient (<30 minutes) hemodynamically insignificant increases in PAP frequently occur in association with downward adjustments of the iNO doseand do not necessarily reflect weaning failure.

Table 2. Characteristics and iNO Data for Children Who Failed iNO Weaning

Patient Age/Gender	Defect	Initial iNO Dose, ppm	Maximum iNO Dose, ppm	Days of iNO Therapy Prior to Sildenafil Adminsitration	Total iNO Duration, Days
11 mo/F	DORV	20	80	20	23
1 wk /M	DTGV	40	80	6	7
1 mo/F	DTGV	10	60	28	37
4 mo/M	DTGV, VSD	20	20	5	6
21 mo/M	HLHS, s/p Hemi-Fontan	40	40	9	10
4 d/F	PA, ASD	20	40	10	22
3 d/M	TAPVC, ASD	20	40	10	17

NOTES: iNO = inhaled nitric oxide; ppm = parts per million; F = female; DORV = double outlet right ventricle; DTGV = d-transposition of the great vessels; VSD = ventricular septal defect; HLHS = hypoplastic left heart syndrome; s/p = status post; PA = pulmonary atresia; ASD = atrial septal defect; TAPVC = total anomalous pulmonary venous connection.

Demographic data collected included patient age, weight, gender, and underlying congenital heart defect. Additional data included sildenafil and iNO dosing and documentation of adverse effects. Mean iNO doses were calculated for the 24-hour periods preceding and following the first administration of sildenafil. The time to cessation of iNO administration after sildenafil initiation was also determined. Pulmonary and systemic blood pressures were retrieved from the nursing flow sheet and recorded at baseline (prior to sildenafil dosing) and every hour for up to 4 hours after each sildenafil dose. Sildenafil was administered to all patients as a 2 mg/mL liquid formulation compounded by the hospital pharmacy.

Hemodynamic data were compared using analysis of variance (ANOVA) to determine if sildenafil administration was associated with hemodynamic change from control levels. Mean 24-hour iNO dose data were compared using a paired-sample t test to determine if sildenafil administration was associated with significant decreases in iNO dosing. P values of less than .05 were considered to be statistically significant. Statistical analyses were conducted using Statistical Package for Social Sciences version 14.0 (SPSS Inc, Chicago, Ill).

Results

Fifty-four children received oral sildenafil after cardiac surgery during the 23-month study period. Complete medical records were available for review in 35 patients. Nineteen patients received iNO therapy, with 7 patients previously failing iNO weaning. Patient characteristics (including congenital heart defects) of these 7 patients are displayed in Table 2.

Patients (n = 7) ranged in age from 3 days to 21 months (median, 12 months) and weighed from 3.0 kg to 12.7 kg (mean, 5.7 kg). The average initial and maximal doses of sildenafil were 0.3 mg/kg (SD, 0.088 mg/kg; range, 0.22-0.47 mg/kg), and was administered 4 times daily either orally or via nasogastric tube. Sildenafil was continued for an average of 28 days.

In these 7 patients, iNO was weaned from 29.8 +- 5.9 parts per million (ppm) prior to sildenafil initiation to 12.2 +- 3.4 ppm (mean +- SE; P = .024) in the 24 hours after sildenafil initiation.

Rebound PHTN was not observed in these patients. The mean time to discontinuation of iNO after sildenafil initiation was 4.4 days.

Mean pulmonary artery pressure (MPAP) and mean systemic arterial pressure (MSAP) were evaluated in 10 patients (of the initial group of 35) who had both pulmonary artery and arterial hemodynamic cathers placed to determine if sildenafil would preferentially reduce PAP versus SAP. From baseline to 1 hour after sildenafil dosing (mean dose, 0.33 mg/kg; range, 0.1-0.62 mg/kg), the MPAP decreased from 29 +- 1 to 27 +- 0.7 mm Hg (mean +- SE; P = .066), and MSAP decreased from 56 +- 1.2 to 54 +- 1.2 mm Hg (mean +- SE; P = .202). Mean pulmonary artery pressure (P = .272) and MSAP (P = .692) did not differ from control levels (prior to sildenafil initation) when compared to any of the hourly intervals after sildenafil dosing (Figure 1).

One patient out of the group of 35 experienced systemic hypotension requiring sildenafil discontinuation (this patient had not failed iNO weaning and is not represented in the group of 7). No other sildenafil-associated adverse effects were observed.

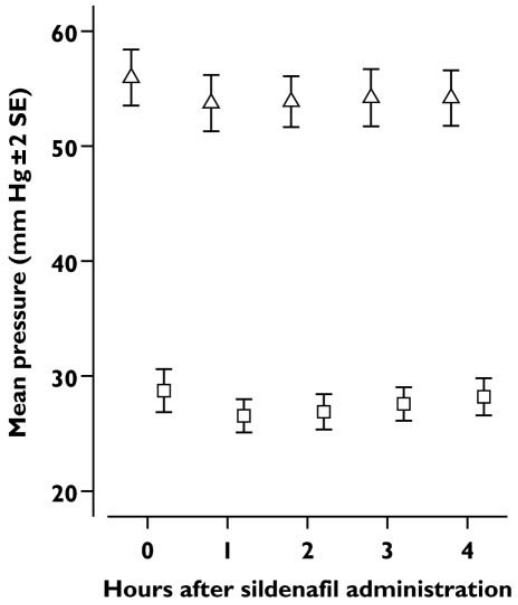

Figure 1 Mean pulmonary artery and mean systemic arterial pressure at baseline and after sildenafil administration (n = 10). Δ, mean systemic arterial pressure (*P* = .692); □, mean pulmonary artery pressure (*P* = .272)

Discussion

Sildenafil appears to be a useful adjunct for the treatment of PHTN after surgery for congenital heart disease. Our data show that sildenafil administration resulted in significantly decreased iNO dose 332 (Figure 1). Mean pulmonary artery and mean systemic arterial pressure at baseline and after sildenafil administration (n = 10). ^, mean systemic arterial pressure (P = .692); #, mean pulmonary artery pressure (P = .272) requirements and facilitated iNO weaning in patients previously failing weaning attempts. Sildenafil administration appears safe in our patient

population. Discontinuation of sildenafil due to systemic hypotension is uncommon in our experience, occurring in 3% (1/35) of cases. However, we continue to be cautious to avoid the administration of sildenafil in patients whom we suspect are hypovolemic.

The oral dosing used in our setting was extrapolated from previous published experiences. Our starting doses of sildenafil were similar to those used in previous reports.[13-16] However, in the immediate postoperative period, drug absorption may be unpredictable because of alterations in gastric motility and perfusion. Sildenafil dosing was not increased in our 7 patients previously failing iNO weaning. Higher doses of sildenafil may be required in the postoperative setting to achieve a decrease in PAP when compared to the dose required to prevent increases in pulmonary pressure during iNO weaning. The intravenous preparation is not yet available in the United States, but it is likely that intravenous dosing of sildenafil will avoid the issues related to erratic oral pharmacokinetics.

Inhaled nitric oxide is the standard pharmacologic therapy for postoperative PHTN at our institution and is generally used in conjunction with controlled moderate hyperventilation, sedation, and paralysis. However, rebound PHTN can complicate the withdrawal of iNO. Exogenous NO is associated with down-regulation of endothelial NO synthase.17-19 Inhaled NO presdisposes patients to rebound PHTN by increasing levels of endothelin-1, a potent pulmonary vasoconstrictor.[20] Sildenafil has a high selectivity for PDE-5, thus increasing endothelial production of cGMP and ultimately facilitating withdrawal of iNO in patients with PHTN.

There are few clinical studies evaluating the efficacy of sildenafil in children with congenital heart disease (Table 3). Erickson and colleagues demonstrated in 5 children that sildenafil administration facilitated discontinuation of iNO 4 to 6 hours after oral administration.15 Namachivayam et al showed that 1 dose of oral sildenafil (0.4 mg/kg, rounded to nearest 1 mg) successfully prevented rebound PHTN in 15 children who were weaned from iNO.16 In this study, rebound PHTN occurred in 10 of 14 placebotreated patients. Namachivayam and colleagues reported success in facilitating withdrawal from iNO but specifically excluded patients who had previously failed iNO weaning attempts.16 However, 4 of the placebo-treated patients subsequently failed to wean from iNO.[16] In contrast, our data demonstrates that the addition of oral sildenafil aids in the withdrawal of iNO and prevents rebound PHTN in children who had previously failed iNO weaning attempts.

There are additional case reports that describe the effectiveness of oral sildenafil to facilitate iNO weaning in children after cardiac surgery.[13,14,21,22] Results of our study are consistent with these previously reported cases. Sildenafil was used in a 9-monthold with congenital mitral stenosis and allowed for the weaning of NO and prevented further pulmonary hypertensive episodes.13 Atz and Wessel also reported that sildenafil administration facilitated withdrawal of NO without rebound PHTN in 3 patients with PHTN after cardiac surgery.[14]

Other clinical investigations demonstrate the effectiveness of sildenafil in children with PHTN. While currently not available in the United States, intravenous sildenafil is associated with a significant decrease in PAP in both children undergoing cardiac catheterization and in those after cardiac surgery.[23]

Table 3. Reports of Sildenafil With Inhaled Nitric Oxide in Children With Pulmonary Hypertension

Reference, Design	N	Age Range	Sildenafil Dose	Outcome
Namachivayam (2006)[16], RCT	29	0.1-1.31 y	0.4 mg/kg PO for one dose	Rebound PHTN: 0/15 vs 10/14 in sildenafil vs placebo groups ($P < .001$). Reinstitution of iNO: 0/14 vs 4/14 in sildenafil vs placebo groups ($P < .001$).
Stocker (2003)[24], RT	15	Mean age[a]: 139 d Mean age[b]: 123 d	0.35 mg/kg IV for one dose (randomized to receive before or after iNO)	Sildenafil reduced PVRI in patients already receiving iNO. SBP decreased significantly in both groups ($P < .05$). Arterial oxygenation and alveolar-arterial gradient worsened after sildenafil administration.
Erickson (2002)[15], PT	16	3 days-18 y (median, 6 y)	0.25-0.5 mg/kg PO for one dose, up to 4 times daily	Mean PAP decreased from 50 ± 8 to 38 ± 12mm Hg ($P < .05$) after sildenafil. Rebound PHTN: 0/5 patients weaned off iNO.
Mychaskiw (2001)[21], CR	1	17 y	50 mg PO for 1 dose	Mean PAP decreased from 37 to 24 mm Hg and patient weaned off iNO 45 min after dosing.
Atz (2002)[13], CR	1	9 mo	0.3 mg/kg/dose NG every 4 h	iNO weaned without further PHTN epidsodes or rebound.
Atz (1999)[14], CR	3	3 d, 6 wk, 4 mo	0.27-0.32 mg/kg/dose	iNO weaned without rebound PHTN in 2/3 cases.
Saygili (2004)[22], CR	1	9 y	0.75 mg/kg/dose NG every 6 h	PAP decreased 60% 24 h after initiation of sildenafil, and iNO weaned within 36 h with no rebound PHTN.

NOTES: RCT = randomized controlled trial; PO = by mouth; PHTN = pulmonary hypertension; iNO = inhaled nitric oxide; RT = randomized trial; IV = intravenous; PVRI = pulmonary vascular resistance index; SBP = systemic blood pressure; PT = prospective trial; PAP = pulmonary artery pressures; CR = case report; NG = nasogastric; a = iNO then sildenafil group; b = sildenafil then iNO group.

Stocker and colleagues demonstrate that intravenous sildenafil enhances the pulmonary vasodilatory effects of iNO, but significantly decreases oxygenation.[24] Our study of oral sildenafil did not reveal similar effects on PAP and did not adequately assess oxygenation changes.

Our study did not demonstrate that that sildenafil would preferentially reduce PAP versus SAP. The lack of significant effect observed on PA pressures in our study may be due to a number of reasons. The most likely reason is the simultaneous attempts to wean iNO. However, our data is similar to those of Namachivayam and colleagues who did not find significant changes in PAP after sildenafil dosing.[16] Additionally, a steady-state serum concentration of sildenafil may not have been achieved when the PAP were evaluated.

Limitations

Limitations of our study include the retrospective design, absence of a control group, and small sample size. These limit the ability of this study to determine if the ability to wean iNO was an effect of sildenafil administration or time after surgery. Sildenafil dosing was extrapolated from previous published experiences, but ultimately was left to the discretion of the primary physician, which may account for the observed variability in initial dosing or upward titra- tion. A larger sampling may allow for subgroup analysis of the effects of sildenafil in patients with

congenital heart defects who are at greatest risk for postoperative PHTN. Although sildenafil was safely used in our population, because of the retrospective design, we were unable to adequately evaluate potential complications of sildenafil administration such as intrapulmonary shunting or worsening of oxygenation that have been reported by other investigators.[16]

Conclusion

Sildenafil may facilitate the withdrawal of iNO therapy while preventing rebound PHTN in pediatric patients after surgery for congenital heart disease 334 who have previously failed to wean from iNO. Only 1 patient in our study required discontinuation of sildenafil because of systemic hypotension. Further con- trolled prospective analyses are warranted to determine if sildenafil, or other PDE-5 antagonists, may be routinely indicated to facilitate weaning from, and thus limiting exposure to, iNO and to test the hypothesis that there is no preferential effect of sildenafil on systemic versus the pulmonary circulation.

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