CLINICAL INVESTIGATION

Evaluation of the Tolerability of Intermittent Intravenous Sildenafil in Pediatric Patients With Pulmonary Hypertension

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OBJECTIVES: The primary purpose of this study was to determine the tolerability of intermittent intravenous (IV) sildenafil for the treatment of pulmonary hypertension in pediatric patients. Secondary objectives were to evaluate parameters related to efficacy.

METHODS: This was a retrospective chart review from January 2013 to August 2014 of pediatric patients under age 18 years treated with intermittent doses of IV sildenafil for pulmonary hypertension. Patients were excluded if they were over age 18 years or received sildenafil for other indications. Measures collected to assess tolerability include blood pressure and heart rate before and after the administration of IV sildenafil, as well as adverse events.

RESULTS: Thirty-seven patients (21 females and 16 males) were identified meeting inclusion criteria, and 21 (56.8%) were on oral sildenafil prior to the initial IV dose. The mean decrease in blood pressure after the first dose of IV sildenafil was 7.16/2.74 mmHg. The decrease in systolic blood pressure was statistically significant. During the study period, 5 patients experienced medication related adverse events, primarily hypotension. Despite this, none of the patients had the medication discontinued due to these events. For secondary objectives, a statistically significant difference was not found between other clinical measures before and after intermittent IV sildenafil dosing.

CONCLUSIONS: Sildenafil, when administered as intermittent IV doses, was tolerated by the majority of patients evaluated in this study. For pediatric patients with pulmonary hypertension in whom enteral or continuous IV sildenafil cannot be administered, intermittent IV sildenafil may be considered as an alternative administration option.

INDEX TERMS: intermittent doses, intravenous sildenafil, PDE-5 inhibitor, pulmonary arterial hypertension

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INTRODUCTION

Pulmonary hypertension is a disorder characterized by an increase in pulmonary vascular resistance and pulmonary artery pressures. If left untreated, this may ultimately lead to right sided heart failure and death. Common etiologies of pulmonary hypertension seen in pediatric patients include persistent pulmonary hypertension of the newborn (PPHN), pulmonary hypertension associated with congenital heart disease (PAH-CHD), pulmonary hypertension secondary to chronic lung disease, idiopathic pulmonary hypertension (IPAH), and familial pulmonary hypertension.^{1,2} Treatment options include inhaled nitric oxide (iNO), phosphodi-

esterase type 5 (PDE-5) inhibitors, endothelin receptor antagonists, and prostacyclins.¹

In the acute management of pulmonary hypertension, iNO is commonly utilized. iNO results in pulmonary vasodilation by increasing the levels of cyclic-guanosine 5'-monophosphate (cGMP), a vasodilator, in pulmonary vascular smooth muscle.³ Disadvantages with the use of iNO include failure of some patients to respond to therapy, development of rebound pulmonary hypertension upon withdrawal, and the cost of the medication.^{1,4} For these reasons other medications have been utilized as part of the acute management of pulmonary hypertension.

Sildenafil inhibits PDE-5, an enzyme involved in the breakdown of cGMP, which is the predomi-

nant phosphodiesterase in the lung. Sildenafil is the only PDE-5 inhibitor available as an intravenous (IV) formulation.⁴ It is approved as both an IV and oral dosage form for the treatment of pulmonary hypertension in adults. Sildenafil has been studied as monotherapy for pulmonary hypertension in children, and it may also be useful in the prevention of iNO associated rebound pulmonary hypertension, postoperative pulmonary hypertension, and pulmonary hypertension related to chronic lung disease.¹

Intravenous sildenafil has been studied as a continuous infusion in neonates with PPHN, for the management of pulmonary hypertension associated with congenital diaphragmatic hernia, and for postoperative pulmonary hypertension in children with congenital heart disease.⁵⁻⁷ These studies suggested that a continuous infusion of sildenafil was well tolerated and improved oxygenation. A study in postoperative children with congenital heart disease treated with IV sildenafil also demonstrated a shortened time to extubation and decreased intensive care unit stay.⁷ Recently, a case report was published that described 3 patients who were successfully treated with intermittent IV sildenafil.⁸

Administration of sildenafil via continuous infusion, while efficacious, may not always represent the best option for the patient. Currently, prospective efficacy data on sildenafil is only available for continuous infusion in a 5% dextrose solution. As this is a relatively new formulation, compatibility data are limited, thus requiring a dedicated IV access point for administration.⁸ In the postoperative period for patients with PAH-CHD, many medications may be needed to stabilize the patients, and the dedication of an IV line for sildenafil may not be an option. Placing and maintaining an additional line for infusion of a single medication could increase the patient's risk for adverse outcomes such as clots or line infections. The enteral route may not be acceptable in the setting of postoperative ileus with PAH-CHD, a critically ill patient on vasopressors, poor oral absorption, or an increased risk for aspiration. Thus, an alternative administration option for IV sildenafil is needed. Providing sildenafil as an intermittent bolus would minimize the majority of the concerns listed above. In addition, it would provide an alternative modality for those patients on sildenafil as an outpatient when they are unable to take medications enterally for a procedure

or due to illness. At our institution, IV sildenafil has been administered to pediatric patients as intermittent doses since 2013. The present study was undertaken to evaluate how these patients treated with intermittent IV sildenafil tolerated the administration.

MATERIALS AND METHODS

This was a retrospective chart review conducted at a single center. The study was approved by the Institutional Review Board at the University of Illinois College of Medicine at Peoria with a waiver of informed consent. Patients were included for review if they were < 18 years of age, admitted to the Children's Hospital of Illinois during the study period of January 1, 2013, to August 31, 2014, and had received at least 1 dose of IV sildenafil for the treatment of pulmonary hypertension. Patients were excluded from review if they were ≥ 18 years of age or if they received IV sildenafil for indications other than the treatment of pulmonary hypertension.

The primary objective was to evaluate the tolerability of IV sildenafil when administered as intermittent doses. Systolic blood pressure, diastolic blood pressure, and heart rate before and after the first dose of IV sildenafil, and adverse medication events were collected to evaluate tolerability. The secondary objective was to assess markers of efficacy related to the use of intermittent IV sildenafil. To evaluate the secondary objectives, data on oxygenation index, pH, partial pressure of oxygen (PO₂), partial pressure of carbon dioxide (PCO₂), bicarbonate, and base excess were collected. When available, a single pediatric cardiologist evaluated the patients' echocardiographic data, both before and after IV sildenafil administration. Patients were excluded from the echocardiographic review if they had a single ventricle cardiac physiology or if the echocardiographs before and after IV sildenafil administration were separated by more than 1 month. Data collected to determine patient characteristics included age, sex, prior oral sildenafil administration, presence of congenital heart disease, number of IV sildenafil doses, duration of IV sildenafil administration, time to maximum dose of 1 mg/kg or desired effect, use of iNO at time of IV sildenafil initiation, duration of iNO, duration of concomitant iNO and IV sildenafil administration, duration of ventilator support,

Table 1. Patient Characteristics (n = 37)

Characteristic	Value
Age,* mo	11.7 ± 17.3 (0.2-87.5)
Male sex, n (%)	16 (43.2)
Congenital heart disease, n (%)	28 (75.7)
Previous oral sildenafil, n (%)	21 (56.8)
Number of IV sildenafil doses*	51.8 ± 55.8 (1-235)
Duration of IV sildenafil,* days	12.9 ± 13.7 (0.2-58.4)
Time to 1 mg/kg dose,* days	10.8 ± 23.3 (0.2-92.2)
iNO at initiation of IV sildenafil, n (%)	14 (37.8)
Duration of iNO,* days	17 ± 10.7 (1.5-77)
Duration of concomitant sildenafil and iNO,* days	11.8 ± 17.5 (0.9-74)
Ventilator duration,* days	37.8 ± 29.1 (0.7-102.7)
ICU length of stay,* days	68.4 ± 75.1 (1.3-337.9)
Hospital length of stay,* days	74.8 ± 73.8 (2.0-360.9)

ICU, intensive care unit; iNO, inhaled nitric oxide; IV, intravenous

* Mean ± SD (range)

length of stay in the intensive care unit, and total hospital length of stay.

In sildenafil naïve patients, IV sildenafil was initiated at 0.25 mg/kg every 6 to 8 hours. Doses were increased in 0.25 mg/kg increments as tolerated to a maximum dose of 1 mg/kg or 10 mg. Each dose was infused over 15 minutes. When converting a patient from oral to IV sildenafil, the dose was decreased by 50% at the same frequency due to differences in bioavailability.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc, Cary, NC). Means, standard deviations (SDs), and ranges were presented as continuous variables, and the absolute and percentage values were presented as categorical variables. The paired t-test, or when appropriate Wilcoxon signed-rank test, was used to compare variables from before and after IV sildenafil administration. A p value of less than 0.05 was considered significant. Unless otherwise specified, all data are presented as mean ± SD.

RESULTS

Thirty-seven patients met inclusion criteria for review during the study period; none met exclusion criteria. The mean age of patients was 11.7 months, 43.2% of patients were male, and 75.7% had congenital heart disease. The majority (56.8%) of patients were receiving oral sildenafil

before being switched to the IV formulation. These patients received a mean of 51.8 doses of intermittent IV sildenafil, with a wide range anywhere from 1 to 235 doses. The mean duration of IV sildenafil was 12.9 days, with a large variation, from 0.2 to 92.2 days. Further characteristics of the patients reviewed are summarized in Table 1.

A statistically significant ($p = 0.0045$) decrease in the mean systolic blood pressure after patients were administered IV sildenafil from 86.08 ± 16.27 mmHg to 78.92 ± 15.40 mmHg was observed. A decrease in mean diastolic blood pressure from 47.97 ± 10.35 mmHg to 45.24 ± 13.05 mmHg was also observed; however, it was not statistically significant ($p = 0.09$). The heart rate was unaffected by intermittent IV sildenafil doses ($p = 0.72$).

Adverse events that could be attributed to the medication occurred in 5 patients (13.5%). Of these, 4 patients had 1 or more sildenafil doses held due to hypotension or other reasons. The degree of hypotension was reduced by extending the infusion time. One patient experienced priapism associated with sildenafil administration, which resolved with dose reduction. All these patients continued on intermittent IV sildenafil despite these adverse effects.

The data reviewed to assess the secondary outcomes are listed in Table 2. Statistically significant differences were not found for any of these variables after sildenafil administration.

Table 2. Outcomes for Tolerability and Efficacy of Intermittent IV Sildenafil*

Variable	Before IV Sildenafil	After IV Sildenafil	P Value
Primary objectives			
Systolic blood pressure, mmHg	86.08 ± 16.27	78.92 ± 15.40	0.0045
Diastolic blood pressure, mmHg	47.97 ± 10.35	45.24 ± 13.05	0.09
Heart rate, bpm	130.05 ± 24.90	130.81 ± 24.33	0.72
Secondary objectives			
Oxygenation index, median (IQR)	10.81 (6.54-16.07)	11.11 (5.69-16.07)	0.607
pH	7.39 ± 0.08	7.39 ± 0.09	0.593
pCO ₂ , mmHg	48.77 ± 10.84	47.98 ± 10.67	0.468
pO ₂ , mmHg; median (IQR)	61 (44-104)	65 (46-104)	0.833
Bicarbonate, mmol/L	30.61 ± 6.06	30.52 ± 5.55	0.319
Base excess, mmol/L; median (IQR)	2 (0-9)	3 (0-9)	0.239

bpm, beats per minute; IQR, interquartile range; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; SD, standard deviation

* Unless specified all data are presented as mean ± SD

Twenty-three patients had echocardiographs available for analysis both before and after IV sildenafil initiation. Of these patients, only 7 were deemed appropriate for analysis by the pediatric cardiologist. For those patients analyzed, 1 had worsening of pulmonary hypertension, 2 had improvement, while 4 did not have any appreciable change. The 2 patients who experienced improvement were not on sildenafil prior to the initial echocardiogram. The 5 patients who had no improvement or worsened were on sildenafil prior to both echocardiograms.

DISCUSSION

The primary objective of this study was to evaluate the tolerability of IV sildenafil when administered as intermittent doses to pediatric patients being treated for pulmonary hypertension. Our study showed that despite decreases in blood pressure, the majority of patients tolerated receiving multiple intermittent doses of IV sildenafil. Overall, 86.5% of patients receiving intermittent IV sildenafil doses did not experience a documented adverse event during the course of therapy.

The results of this study suggested that there may be a statistically significant decrease in systolic blood pressure associated with administration of intermittent IV sildenafil. This decrease was often not clinically significant as the majority of patients tolerated the decrease

in blood pressure with a minority having doses held due to hypotension. It is possible that the true decrease in blood pressure associated with IV sildenafil may not have been appreciated in this retrospective study, as suggested by the wide range of blood pressure measurements that were recorded. Reasons for this wide range in values could have been due to differences in the timing of the pre- and postsildenafil blood pressure measurements, variations in protocols for measurement of vital signs between the pediatric and neonatal intensive care units, as well as differences in clinical status of patients included in this study.

The degree of blood pressure reduction observed in this study (i.e., mean systolic blood pressure 7.16 ± 14.39 mmHg and mean diastolic blood pressure 2.73 ± 9.53 mmHg) was similar to those observed in other studies utilizing IV sildenafil. Single dose studies examined the effects of IV sildenafil on hemodynamic parameters after congenital heart surgery and found a decrease in systemic mean pressure by 12% and in diastolic blood pressure by 10% to 11%.^{9,10} There was a trend toward lowered systolic blood pressure, with an average change of 11 ± 2 mmHg. Other studies examined the effects of single IV doses of sildenafil or continuous infusions on mean systemic arterial pressure, systemic systolic blood pressure, and diastolic pressure.^{3,4,7} The studies documented a decrease in mean systemic arterial pressure ranging from 7.3 ± 2.5 mmHg to 12 ± 1.2

mmHg, as well as minor reductions in systemic systolic blood pressure (82 ± 14 mmHg to 79 ± 13 mmHg) and diastolic blood pressure (49.9 ± 9 mmHg to 45 ± 7 mmHg). A pharmacokinetic study of a single 10 mg IV bolus dose of sildenafil in adults resulted in an observed decrease in systolic blood pressure of 8.4 ± 11.7 mmHg and a decrease in diastolic blood pressure of 2.6 ± 7.3 mmHg.¹¹

The dosing scheme used in this study represents a novel approach to dosing IV sildenafil for pediatric patients. To date, the majority of publications investigating the use of IV sildenafil have focused on the use of a continuous infusion. One case report described the experience of a single center utilizing IV sildenafil as intermittent doses with different dosing schemes for each patient described.⁸ In this analysis, sildenafil naïve patients were initiated on an IV dose of 0.25 mg/kg/dose given either every 6 or 8 hours. This dose was titrated as tolerated to the desired effect by 0.25 mg/kg increments to a maximum dose of 1 mg/kg or 10 mg, which is the adult maximum dose. For patients who were receiving oral sildenafil, the dose was reduced by 50% when IV dosing was initiated.

The dosing scheme utilized may raise some concern given the US Food and Drug Administration's drug safety communication stating that sildenafil should not be used in pediatric patients following recent literature regarding high-dose sildenafil for treating pulmonary hypertension in pediatric patients.¹² This statement was subsequently modified to recommend that sildenafil not be used chronically in pediatrics.¹³ These warnings stemmed from the STARTS-1 and STARTS-2 trials.^{14,15} The STARTS-1 trial found that low dose sildenafil was not effective, and that medium and high doses were more effective in improving exercise capacity when compared to placebo in treatment naïve patients.¹⁴ The authors conducted STARTS-2, a follow-up study, which suggested that patients on high dose sildenafil may have an increased risk for mortality.¹⁵ Unfortunately, this observation is plagued by numerous sources of bias. The majority of patients who died had IPAH, a World Health Organization functional class III/IV, and worse baseline values when compared with patients who survived. The authors deemed that the majority of deaths were related to disease progression, but the results could not be wholly explained by patient risk

factors alone. Additionally, the survival rates in all groups was higher compared to 3-year rates for the natural progression of IPAH and pulmonary arterial hypertension prior to utilization of medication therapy.¹⁵ Although information was not collected regarding certain risk factors such as pulmonary vascular resistance index and right atrial pressure, the majority of our patients were receiving sildenafil for PAH-CHD. As the literature for mortality is not as robust in this group, medication therapy may be titrated off over time, and comparison studies with alternative therapies in pediatrics have not been completed, sildenafil doses were titrated to upwards of 1 mg/kg as deemed by the treating physician.

While 13.5% of patients reviewed in the present study experienced adverse effects related to the administration of IV sildenafil as intermittent doses, these adverse effects did not warrant medication discontinuation. The majority of adverse effects experienced were hypotension resulting in doses being held. It is possible that this hypotension was related to the rate at which the sildenafil was infused. The standard infusion time in this study was 15 minutes. Many of the patients who experienced hypotension had their infusion times increased to 30 minutes or 1 hour to lessen this effect. The majority of patients experienced an adverse event during the titration phase of their sildenafil course as suggested by the time taken to attain a dose of 1 mg/kg in some patients. Once the patient was stable on the longer infusion duration, doses were escalated as necessary without incident. Two of the patients had a dose held around the timing of a procedure. It could not be elucidated if the dose was held because of a procedure or because of an adverse drug event. In these cases, a conservative approach was utilized and these doses were considered to be held due to an adverse drug event. It is also possible that the patients who experienced the most significant hypotension related to sildenafil doses might have been more critically ill and therefore less hemodynamically stable prior to receiving the first dose of the medication. This data, however, was not collected and therefore cannot be assessed by the current study. It is possible that other adverse effects related to the medication might not have been identified by this study. As this study was retrospective in nature, it relied heavily on documentation. Adverse effects could have occurred but not been documented by staff.

The secondary objective of this study was to evaluate the efficacy associated with IV sildenafil when administered as intermittent doses. No statistically significant differences were found on any data collected for these objectives. This result is likely due to the fact that the markers evaluated could be affected by multiple factors such as the sample size in the study. Efficacy is also difficult to evaluate when conducting a retrospective analysis as ideal markers may not be present, especially if invasive monitoring was not conducted during the study period.

Limitations of the study include its retrospective design, variations in practice between units, as well as the lack of a comparison group. A comparison group was not utilized for this study due to the low number of patients expected to have received IV sildenafil during the study period. By limiting the patients enrolled to only those patients who were sildenafil naïve, it is likely that only a small number of patients would have been eligible for analysis. Future prospective studies would be necessary to establish the efficacy of intermittent IV sildenafil for pediatric patients.

The results of this study suggested that despite moderate decreases in blood pressure the use of intermittent IV sildenafil was well tolerated by pediatric patients. Intermittent IV sildenafil may potentially be a safe option for pediatric patients with pulmonary hypertension when the enteral route or continuous IV infusion is unavailable or inappropriate. Intermittent sildenafil will improve a practitioner's ability to provide care for patients with pulmonary hypertension when they are unable to tolerate enteral administration.

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Abbreviations cGMP, cyclic-guanosine 5'-monophosphate; iNO, inhaled nitric oxide; IPA, idiopathic pulmonary arterial hypertension; IV, intravenous; PAH-CHD, pulmonary hypertension associated with congenital heart disease; PCO₂, partial pressure of carbon dioxide; PDE-5,

phosphodiesterase type 5; PO₂, partial pressure of oxygen; PPHN, persistent pulmonary hypertension of the newborn; SD, standard deviation.

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