JPPT | Single Center Retrospective Study

Tadalafil in Neonates and Infants With Pulmonary Hypertension Secondary to Bronchopulmonary Dysplasia

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OBJECTIVES The primary outcome of this study was to describe the dosing regimen of tadalafil in neonates and infants diagnosed with pulmonary hypertension (PH) secondary to bronchopulmonary dysplasia (BPD). Secondary outcomes included tolerability, efficacy, adverse events, discontinuation of therapy, and changes in echocardiography.

METHODS This was a single-center, retrospective review of neonates and infants <1 year of age at initiation of tadalafil for PH secondary to BPD from January 2010 to November 2021. Data collected from the electronic medical record included patient demographics, tadalafil dosing, oxygen support, mechanical ventilation, concomitant PH medications, adverse events, and echocardiography information.

RESULTS Forty-two patients—4 neonates and 38 infants—met the inclusion criteria. The postnatal and postmenstrual age (median, IQR) at diagnosis were 121 (35.5–153.5) days and 42.6 (40.6–47.6) weeks, respectively. The initial and highest tadalafil doses (median, range) were 1 (0.25–2) and 1 (0.5–2) mg/kg/day. Only 1 patient experienced pulmonary overcirculation and required tadalafil to be discontinued. Over half (57.1%) of the patients in this study discontinued tadalafil therapy owing to improvements in pulmonary artery pressures.

CONCLUSIONS Tadalafil 1 mg/kg/day was the most commonly used dose regimen in neonates and infants. Tadalafil at this dose of 1 mg/kg/day appears well tolerated in neonates and infants with PH secondary to BPD and correlates with improvements in pulmonary artery pressures. Further studies evaluating tadalafil in comparison to other phosphodiesterase-5 inhibitors in neonates with PH secondary to BPD are warranted.

ABBREVIATIONS BPD, bronchopulmonary dysplasia; iNO, inhaled nitric oxide; PDE5, phosphodiesterase-5; PH, pulmonary hypertension; RVSP; right ventricular systolic pressure

KEYWORDS bronchopulmonary dysplasia; infant; neonate; phosphodiesterase 5 inhibitor; pulmonary hypertension

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Introduction

Bronchopulmonary dysplasia (BPD) is a cardiopulmonary complication that leads to impaired proximal airway and bronchoalveolar development.[1] Approximately 28% of premature infants in the United States have BPD and it is often associated with pulmonary vascular disease and pulmonary hypertension (PH).[1,2] PH secondary to BPD is characterized by alveolar diffusion impairment, abnormal vascular remodeling, and pulmonary vascular growth arrest, leading to increased pulmonary vascular resistance and right-sided heart failure.[1] Risk factors of BPD include extreme prematurity, very low birth weight, intrauterine growth restrictions, and mechanical ventilation; about 25% of infants with moderate to severe BPD develop PH.[1] Therapies include inhaled nitric oxide (iNO), prostacyclin analogs, soluble guanylate cyclase stimulators, endothelin receptor antagonists, phosphodiesterase-3 inhibitor, and phosphodiesterase-5 (PDE-5) inhibitors.[3,4] In pediatric patients with PH, PDE-5 inhibitors have been shown to improve echocardiography measurements, cardiac catheterization parameters, and oxygenation when compared with baseline or placebo.[4] Sildenafil is often a first-line medication in the treatment of PH secondary to BPD in pediatric patients.[1] Alternatively, tadalafil, another PDE-5 inhibitor, has gained interest given its long half-life and once-daily dosing regimen. Given the concerns with sildenafil (e.g., black box warning) and the frequent dosing requirements of sildenafil, tadalafil gained interest for use in this patient population. Potential adverse effects of both agents include hearing loss, visual disturbances, hypotension, priapism, flushing, dyspepsia, nausea, headache, myalgia, and respiratory tract infections.[5] Given the limited data and gap in translation into clinical practice for the use of tadalafil in PH secondary to BPD, the primary outcome of this study was to describe the dosing and frequency of tadalafil in neonates and infants. Secondary outcomes included

tolerability, efficacy, adverse events, discontinuation of therapy, and changes in echocardiography.

Materials and Methods

This was a single-center, retrospective review at John Hopkins All Children's Hospital between January 2010 and November 2021. Patients were included if they were <1 year of age at initiation of tadalafil and received ≥1 dose of tadalafil for PH secondary to BPD (diagnostic criteria for BPD at our institution includes those premature infants requiring oxygen after 36 weeks post-conceptual age). Pulmonary hypertension was typically diagnosed from echocardiogram findings of increased tricuspid regurgitation jet velocity and/or systolic flattening of the interventricular septum. All other patients not meeting the inclusion criteria were excluded. Patients were identified from a pharmacy report of all medication administration records of tadalafil use in infants and neonates, and data were collected from the electronic medical record. Patient characteristics collected included sex, race, ethnicity, age at diagnosis of PH, oxygen support, iNO use, mechanical ventilation, age, and weight at initiation of tadalafil. Initial dosing of tadalafil and the highest doses were collected. The use of iNO and dose at initiation of tadalafil therapy were recorded, as well as other PH medications (i.e., sildenafil, treprostinil, bosentan) being used prior to or in addition to tadalafil. Other medication use was defined as any PH medication being administered to the patient before tadalafil was initiated or added to the regimen after tadalafil initiation. Adverse events and tolerability were assessed by documented adverse drug events, changes in therapy, or discontinuation of therapy. Evaluation for adverse events was based on a review of the medical record. Reasons for discontinuation of therapy were recorded and included: no improvement in PH, adverse events, or improvement in PH no longer requiring therapy. For those patients whose initial tadalafil dose required up-titration, the medication was typically increased by 25% to 50% from the starting dose every 4 to 5 days until the target dose was achieved. All PH diagnoses and subsequent evaluations were conducted by pediatric cardiology. The efficacy of tadalafil was assessed by reviewing quantitative changes in right ventricular systolic pressure (RVSP) by tricuspid regurgitation jet on echocardiogram or cardiac catheterization and/or qualitatively by assessing intraventricular septal positioning on echocardiography. Patients received a compounded tadalafil suspension prepared in our pharmacy department, which was prepared with tadalafil tablets and OraBlend (Perrigo, United States) to make a 5-mg/mL suspension with standard expiration dating of no more than 91 days when stored at room temperature.[6] Descriptive statistics for nonparametric data, specifically medians and IQR or numbers and percentages, were used to analyze data.

Results

Forty-two neonates and infants met the inclusion criteria and were included in the data analysis. Patient characteristics are described in the Table. The postnatal and post-menstrual age (median, IQR) at diagnosis was 121 (35.5–153.5) days and 42.6 (40.6–47.6) weeks, respectively. Of note, 3 (9.5%) patients were neonates at the time of tadalafil initiation. Patients had a median weight (median, IQR) of 3.95 (3.2–5.4) kg at the time of tadalafil initiation. Most patients were on oxygen support (95.2%), iNO (76.2%), or receiving mechanical ventilation (64.3%) at the initiation of tadalafil. After tadalafil was initiated, 30 patients (71.4%) did not require other

Table. Patient Characteristics

Baseline Characteristics	N = 42
Sex, n (%)	
Male	27 (64.3)
Race, n (%)	
White or Caucasian	19 (45.2)
Black or African American	13 (31)
Other	5 (11.9)
Not reported	5 (11.9)
Postnatal age at diagnosis, median (IQR), days	121 (35.5–153.5)
Post-menstrual age at diagnosis, median (IQR), wk	42.6 (40.6–47.6)
Postnatal age at initiation of tadalafil, median (IQR), days	134 (96–174)
Weight at initiation of tadalafil, median (IQR), kg	3.95 (3.2–5.4)
Time between PH diagnosis and tadalafil initiation, median (IQR), days	6 (2–16.8)
Oxygen support at the time of tadalafil initiation, n (%)	40 (95.2)
iNO at initiation of tadalafil, n (%)	32 (76.2)
iNO dose at tadalafil initiation, median (range), ppm	20 (0–40)
Mechanical ventilation, n (%)	26 (64.3)
Medications prior to tadalafil therapy, n (%) sildenafil	1 (2.4)
Concomitant medications after tadalafil initiation*, n (%)	
None	30 (71.4)
Bosentan and treprostinil (IV)	8 (19)
Bosentan	3 (7.1)
Treprostinil (IV)	1 (2.4)

iNO, inhaled nitric oxide; IV, intravenous; PH, pulmonary hypertension; ppm, parts per million

* Patients started and stopped medications during tadalafil therapy.

concomitant PH medication, while 3 (7.14%) patients were on bosentan, 1 (2.4%) patient was on treprostinil, and 8 (19%) patients were on both bosentan and treprostinil. iNO was weaned on the basis of clinical tolerability, typically when Fio2 requirements were below 45%.

The initial tadalafil dose (median, range) was 1 (0.25–2) mg/kg/day (Figure 1). One patient was started on 0.25 mg/kg/day dosing and the medication titrated to 1 mg/kg/day. Nine patients were started on 0.5 mg/kg/day; for 7 of these patients, the medication was titrated to 1 mg/kg/day and 2 patients had no changes. Two patients received 2 mg/kg/day as an initial dose. Of the 2 patients receiving 2 mg/kg/day as an initial dose, 1 patient was on an oscillator and the other patient was previously on sildenafil 0.9 mg/kg 3 times a day and switched to tadalafil. Of all 42 patients in this study, 17 (40%) required a dose increase, 23 (55%) had no dose change, and 2 (5%) had a dose decrease. The highest dose (median, range) was 1 (0.5–2) mg/kg/day (Figure 1). Of note, all patients received tadalafil once daily for a median (IQR) duration of 265 (148–634) days. Figure 2 describes the baseline and final RVSP in an echocardiogram. Of note, most data were obtained via echocardiogram, because cardiac catheterization data were limited. A total of 24 (57.1%) patients discontinued tadalafil owing to improvement of PH based on echocardiogram. For patients with a suprasystemic RVSP prior to tadalafil initiation, all but 1 patient had subsystemic RVSP at the time of tadalafil discontinuation (Figure 2). Other reasons for discontinuation of tadalafil were for pulmonary overcirculation on a dose of 1 mg/kg/day (n = 1), nothing by mouth status (n = 1), noncompliance in the outpatient setting (n = 1), and transfer of care to a different hospital on a dose of 2 mg/kg/day (n = 1). No adverse events were identified in this study. Mortality was collected through the most recent follow-up and was reported in 9 (21.4%) patients. Reasons for mortality were difficult to capture given the retrospective nature of this study.

Discussion

This study reports the use of tadalafil in neonates and infants for PH secondary to BPD. The dosing regimen of tadalafil in pediatric patients has been described in limited studies.[7–9] In a prospective study of pediatric patients with pulmonary arterial hypertension, oral tadalafil was shown to be well tolerated and improved mean pulmonary artery pressure at a dose of 1 mg/kg/day.[7] Yamazaki et al[8] describe a similar dosing regimen of tadalafil with weight-adjusted doses (mean ±SD) of 0.991±0.5403 mg/kg in patients <18 years of age. Another study investigated a fixed-dose regimen of tadalafil based on weight categories.[9] Patients received tadalafil 20 mg/day if they weighed between 25 and 39 kg, or tadalafil 40 mg/day if they weighed ≥40 kg.[9] While tadalafil-dosing regimens have been described in pediatric pulmonary arterial hypertension, our study is the first to describe tadalafil dosing in neonates and infants with PH secondary to BPD. In our study, the median (range) initial dose of tadalafil was 1 (0.25–2) mg/kg/day, and most patients did not require a dose change, and of those who did, it was an increase from 0.5 to 1 mg/kg/day. The time (median, IQR) of 6 (2–16.8) days between the age of PH diagnosis and initiation of tadalafil reflects both those patients who were medication naïve and those who had tadalafil added to their pulmonary vasodilatory regimen. Medication dose adjustments were based on the patient's clinical status and response. Although titration varied depending on the patient, 88.2% of the patients had the dose doubled from 0.5 to 1 mg/kg/day. Those with a starting dose of 1 mg/kg appeared to tolerate it and did not require as many dose increases. The median duration of therapy was 265 days, with most patients stopping therapy owing to improvement in PH, which may have been attributed to medication or normal growth processes. The age at discontinuation varied from 6 months to 2 years of age. The therapy was not typically weaned off. In the studies previously described, the median age of patients was ≥1 year, whereas our study only focused on neonates and infants.[7–9] Additionally, our patients had lower weights with a median (IQR) of 3.95 (3.2–5.4) kg compared with other studies.[9]

A prospective study demonstrated the effectiveness of tadalafil in patients with PH with statistically significant improvement in mean 6-minute walk test, cardiac catheterization, and echocardiogram measurements.[8] Tricuspid regurgitation pressure gradient was significantly

Figure 1. Tadalafil dosing.

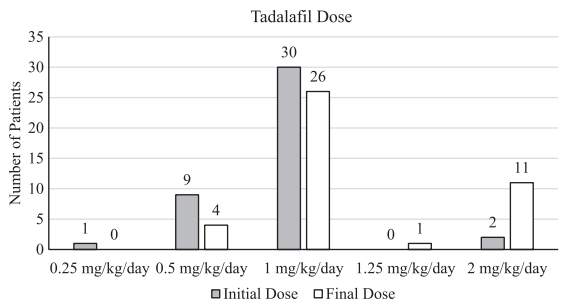
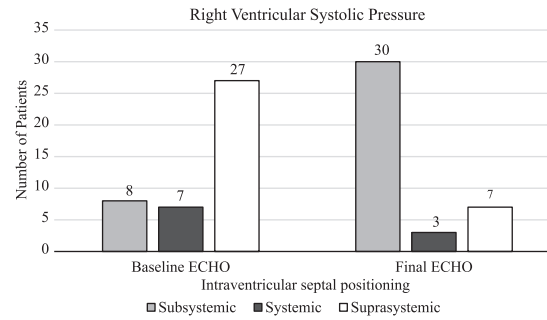


Figure 2. Baseline and final echocardiogram.



ECHO, Echocardiogram

decreased from baseline at all observation points in this study.[8] In our study, we observed that most patients (n = 27) had a suprasystemic RVSP prior to tadalafil use and most patients (n = 30) had subsystemic RVSP in the final echocardiogram. Prospective studies are warranted to confirm echocardiographic improvement with tadalafil use.

In this study, tadalafil appeared to be well tolerated with only 1 patient experiencing reported overcirculation in the setting of a patent ductus arteriosus, resulting in the discontinuation of tadalafil. Other studies have reported side effects including nausea, headache, diarrhea, and flushing, which are usually transient and mild to moderate in intensity.[8] Mortality in our cohort was similar to what has been previously noted in other studies (26%–36%), highlighting the high risk of PH in patients with BPD.[10,11] The specific causes of death in this study were difficult to determine.

Limitations to this study include the retrospective study design, the lack of a comparator group, and potential variations in practice between providers. Owing to the retrospective nature of the study, all adverse events were collected through chart review, therefore limiting the number of reported adverse events. Additionally, there was a change in the electronic health record system that could have affected the ability to obtain data. Although there has been growth in the PH team at the study institution, there has not been a change in providers during the study period. To our knowledge, this was the first study describing tadalafil dosing in neonates and infants diagnosed with PH secondary to BPD. Future studies comparing tadalafil and sildenafil in this population would be valuable in determining optimal therapy for pediatric patients.

Conclusion

This study reports that tadalafil 1 mg/kg/day was the most used dose regimen in neonates and infants. Tadalafil at a dose of 1 mg/kg/day appears to be well tolerated in neonates and infants with PH secondary to BPD and correlates with improvements in pulmonary artery pressures. Further studies evaluating tadalafil in comparison to other PDE5 inhibitors in neonates with PH secondary to BPD are warranted.

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Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required.

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