

Sildenafil Treatment of Infants With Bronchopulmonary Dysplasia–Associated Pulmonary Hypertension

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ABSTRACT

OBJECTIVE: This study had 2 goals: (1) to identify clinical and demographic characteristics associated with sildenafil exposure for infants with bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension (PH); and (2) to characterize hospital-specific treatment frequency, age at first administration, and length of sildenafil treatment.

METHODS: This retrospective cohort study used data from the Pediatric Health Information System to determine variables associated with sildenafil exposure and between-hospital variations in sildenafil utilization patterns. The study included infants with BPD-PH who were discharged between January 1, 2006, and December 31, 2013.

RESULTS: Within 36 US pediatric hospitals, 3720 infants were diagnosed with BPD, of whom 598 (16%) also had a diagnosis of PH (BPD-PH). Among infants with BPD-PH, 104 infants (17%) received sildenafil. The odds for sildenafil treatment among infants born between 25 and 26 weeks' gestational age (GA) and <24 weeks' GA, respectively, were 2.26 (95% confidence interval [CI]: 1.20–4.24) and 3.21 (95% CI: 1.66–6.21) times those of infants born at 27 to 28 weeks' GA. Severity of BPD correlated with sildenafil exposure, with adjusted odds ratios (ORs) for moderate BPD (OR: 3.03 [95% CI: 1.03–8.93]) and severe BPD (OR: 7.56 [95% CI: 2.50–22.88]), compared with mild BPD. Greater rates of sildenafil exposure were observed among small for GA neonates (OR: 2.32 [95% CI: 1.21–4.46]). The proportion of infants with BPD-PH exposed to sildenafil varied according to hospital (median: 15%; 25th–75th percentile: 0%–25%), as did the median duration of therapy (52 days; 25th–75th percentile: 28–109 days).

CONCLUSIONS: The odds of sildenafil treatment were greatest among the most premature infants with severe forms of BPD. The frequency and duration of sildenafil exposure varied markedly according to institution. Patient-centered trials for infants with BPD-PH are needed to develop evidence-based practices.

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Bronchopulmonary dysplasia (BPD) is associated with pulmonary hypertension (PH),^{1–3} with BPD-PH occurring in 30% to 45% of infants with moderate to severe BPD.^{1,3,4} Mortality rates in infants with BPD-PH are 4-fold greater than in infants without PH, with the majority of deaths linked directly to PH.^{3,5} Supplemental oxygen is the mainstay of therapy for patients with BPD-PH.^{6–8} However, survival rates of infants with BPD-PH treated by using supplemental oxygen are 61% and 52% at 1 and 2 years of age, respectively.⁴ Inhaled nitric oxide (iNO) improves pulmonary artery pressures acutely during cardiac catheterization,⁹ but the economic burden and cumbersome mode of administration of iNO limit its use in chronic treatment.¹⁰

A pragmatic therapeutic option for patients with BPD-PH is oral sildenafil, a selective type 5 phosphodiesterase inhibitor.^{11,12} In adults with PH, sildenafil has improved survival rates, exhibited low toxicity, and is available as an enteral preparation that is more practical for long-term, outpatient therapy.^{13–20} Early clinical experience indicates that sildenafil treatment may be efficacious for infants with BPD-PH, with evidence suggesting that sildenafil normalizes lung development and may improve outcomes.^{21–25} However, practice patterns for sildenafil treatment in infants with BPD-PH have not been fully reported; these patterns include variables associated with exposure, timing of initiation, length of treatment, and interhospital variation in use. Current sildenafil exposure among infants with BPD-PH remains influenced largely by the personal preferences of individual physicians and single-center experiences of safety and efficacy. A better understanding of current sildenafil utilization patterns, including interinstitutional differences in sildenafil exposure for BPD-PH, will be important in designing patient-centered trials to examine the comparative effectiveness of sildenafil treatment for improving BPD-PH outcomes.

The objectives of the present study were: (1) to determine clinical characteristics associated with sildenafil exposure in infants with BPD-PH; and (2) to characterize hospital-

specific treatment frequency, age at first administration, and length of treatment.

METHODS

Study Design and Data Source

Data from the Children's Hospital Association Pediatric Health Information System (PHIS) database (Shawnee Mission, KS) were used to perform a retrospective cohort study (infants discharged January 1, 2006–December 31, 2013) to evaluate sildenafil exposure among infants with BPD-PH. The PHIS database contains administrative, billing, and record review data, including patient demographic characteristics (eg, gender, birth weight, gestational age) as recorded in the patient chart, diagnoses, medications, and procedures, from 43 freestanding US children's hospitals; these hospitals account for 85% of all national freestanding children's hospitals (Children's Hospitals Association, Shawnee Mission, KS). To certify comparability of charge-level data among institutions, including medications and procedures, Thompson-Reuters Healthcare (Ann Arbor, MI), the PHIS data-processing partner, mapped each hospital's daily charge codes to a common classification system (ie, the Clinical Transaction Classification [CTC]). Seven of the hospitals had no patients who satisfied our inclusion criteria, thus leaving 36 hospitals in the study. The Nationwide Children's Hospital institutional review board determined the study to be non-human subjects research because it was an analysis of a preexisting, de-identified data set with no patient contact.

Study Population

Inclusion Criteria

Patients admitted to the NICU in the first 7 days of life who were <29 weeks' gestational age (GA), were diagnosed with PH (*International Classification of Diseases, Ninth Revision* [ICD-9], codes 416.0, 416.8, and 747.83), and had BPD according to the National Institutes of Health Consensus Definition²⁶ modified by Ehrenkranz et al²⁷ were included in the study. GA at delivery was defined by using a multistep process (described in the following discussion). GA was classified into groups based on ICD-

9 codes: ≤24 weeks, 765.22; 25 to 26 weeks, 765.23; and 27 to 28 weeks, 765.24. The GA ICD-9 codes were then compared for consistency versus chart data on GA as reported in the file regarding basic demographic characteristics. Infants with BPD were hospitalized at 36 weeks' corrected GA and had received respiratory support via mechanical ventilation (CTC code 521166), continuous positive airway pressure (CPAP) (CTC code 521162), and/or supplemental oxygen (CTC code 521171) from the date of admission through day 28 of life. We used respiratory charge data (mechanical ventilation, CPAP, and supplemental oxygen) at 36 weeks' postmenstrual age (PMA) to assign each infant a BPD severity stage: mild (room air), moderate (supplemental oxygen), or severe (CPAP or mechanical ventilation).

Exclusion Criteria

Patients were excluded from the sample if they had congenital heart disease (other than patent ductus arteriosus [PDA] or ostium secundum defects) with 1 of the following ICD-9 codes: 429.0 to 429.9, 745.0 to 745.4, 745.6 to 745.9, 746.1 to 746.9, 747.10 to 747.29, 747.31 to 747.39, 747.40 to 747.49, and 747.89. Patients with a diagnosis of chromosomal anomalies (ICD-9 code 758.0) or diaphragmatic hernia (ICD-9 code 756.6) were also excluded.

Outcome Measures

Three primary outcome measures were determined: (1) whether a patient received at least 1 dose of sildenafil (pharmacy CTC code 191321) and the impact of measured covariates on the odds of receiving sildenafil (as described in the Statistical Analysis section); (2) the duration of sildenafil exposure, defined as the total number of days on sildenafil; and (3) the proportion of patients with BPD-PH who received at least 1 dose of sildenafil at each hospital.

Additional Patient-Level Covariates

A treatment course of sildenafil was defined as consecutive days of sildenafil exposure. We created an indicator for small for gestational age (SGA) by combining information on birth weight from ICD-9 codes and demographic data (gender and

GA) to determine whether the patient was below the gender-specific 10th percentile of weight-for-GA. ICD-9 codes were used to identify diagnoses that might affect the decision to use sildenafil, including PDA (747.0), severe (grade 3 or 4) intraventricular hemorrhage (IVH; 772.13 or 772.14), necrotizing enterocolitis (NEC; 777.5), and retinopathy of prematurity (ROP; 1424).

Data on the timing of administration of iNO (CTC code 521173) were examined relative to the initiation of sildenafil to determine whether sildenafil was administered before or after administration of iNO. Length of stay, which is a measure of morbidity, was calculated by the difference between the discharge date and the admit date plus 1.

Hospital-Level Covariates

The following hospital-level characteristics were evaluated within our cohort: NICU volume (the total number of discharges for each NICU during the study period), BPD volume (the total number of patients per NICU satisfying criteria for BPD during the study period), and BPD-PH volume (the total number of patients per NICU with BPD who had a concurrent ICD-9 diagnosis of PH).

Statistical Analysis

Descriptive statistics were used to describe the overall sample (BPD-PH) and the subsample that received sildenafil. Logistic regressions were performed to identify patient and hospital factors, including NICU volume, BPD volume, and BPD-PH volume associated with the odds of sildenafil exposure. Simple logistic regression models were used to determine unadjusted odds ratios (ORs) for associations between sildenafil use and neonatal demographic/clinical risk factors. Multivariate logistic regression modeling with a random intercept for hospitals was used to adjust the ORs for multiple predictor variables and to evaluate the contribution of within-hospital clustering to variation in sildenafil exposure. The model was created by purposeful, forward selection and included GA, BPD staging, SGA, NEC, PDA, IVH, ROP, gender, race, and study year. Variables related to length of time on CPAP or mechanical ventilation were excluded

because they were collinear with our definition of BPD staging. An α level $<.05$ was considered statistically significant. Analyses were conducted by using Stata version 12.1 (StataCorp, College Station, TX).

RESULTS

Over the study period, 224 200 neonates were admitted to 36 US children's hospitals, and 3720 of these infants met the criteria for BPD. Our cohort was composed of 598 (16%) infants with BPD who also had a diagnosis of PH (BPD-PH). Among infants with BPD-PH, 104 (17%) were treated with at least 1 dose of sildenafil. The majority of neonates (72 of 104 [69%]) were treated with 1 course of sildenafil, and 32 (31%) of 104 received ≥ 2 treatment courses. At discharge, 41% (43 of 104) of infants continued on sildenafil.

Characteristics of Sildenafil-Treated Patients

In the unadjusted analysis, lower GA, greater BPD severity, and SGA status were associated with greater odds of sildenafil treatment. Gender, race, and study year

were also examined but did not correlate with the odds of sildenafil treatment. When all variables were included in a multivariate logistic regression model (Table 1), the odds of receiving sildenafil treatment were associated most strongly with severe BPD (OR: 7.56 [95% confidence interval (CI): 2.50–22.88]). GA at birth and SGA status were also related to sildenafil treatment. The odds for sildenafil treatment among infants born between 25 and 26 weeks' GA and <24 weeks' GA, respectively, were 2.26 and 3.21 times those of infants born at 27 to 28 weeks' GA. Even after adjusting for GA and BPD severity, greater rates of sildenafil exposure were observed among SGA infants (OR: 2.32 [95% CI: 1.21–4.46]). We observed no differences in other measured comorbidities (NEC, PDA, IVH, or ROP) between infants receiving sildenafil and those not receiving sildenafil. The intraclass correlation coefficient, a measure of the correlation in use of sildenafil within hospitals, indicated that clustering by hospital was a component of the overall variation in sildenafil exposure (intraclass correlation coefficient: 0.08 [95% CI: 0.02–0.29]).

TABLE 1 Clinical Characteristics Associated With Sildenafil Use

Variable	BPD-PH Cohort ^a (n = 598)	Received Sildenafil ^b (n = 104 [17%])	Multivariate Logistic OR ^c (95% CI)
Gestation, wk			
27–28	181 (30.3)	18 (17.3)	—
25–26	226 (37.8)	44 (42.3)	2.26* (1.20–4.24)
≤ 24	191 (31.9)	42 (40.4)	3.21*** (1.66–6.21)
BPD severity			
Mild	84 (14.1)	4 (3.9)	—
Moderate	346 (57.9)	53 (51.1)	3.03* (1.03–8.93)
Severe	168 (28.1)	47 (45.2)	7.56*** (2.50–22.88)
SGA status			
No	530 (88.6)	85 (81.7)	—
Yes	68 (11.4)	19 (18.3)	2.32* (1.21–4.46)
Comorbidities			
NEC	96 (16.1)	15 (14.4)	0.66 (0.34–1.29)
PDA	446 (74.6)	79 (75.9)	1.15 (0.66–1.99)
IVH ^d	127 (21.2)	15 (14.4)	0.55 (0.29–1.03)
ROP	330 (55.2)	54 (51.9)	0.68 (0.42–1.10)

* $P < .05$, *** $P < .001$. —, relative to the reference group.

^a Frequency and percentage (in parentheses) of patients with the study characteristic.

^b Frequency and percentage of patients with BPD-PH who received sildenafil.

^c OR (95% CI) from multivariate logistic regression with OR relative to the reference group indicated by (—).

^d Severe IVH defined as grade 3 or 4 hemorrhage on head ultrasound.

Among the 598 patients with BPD-PH, 32% received iNO alone, 15% received iNO and sildenafil, and 3% received sildenafil alone. Cardiac catheterization was performed in 4% (22 of 598) of patients with BPD-PH. Less than 2% of neonates underwent cardiac catheterization before treatment with sildenafil.

Between-Hospital Variation in Sildenafil Treatment of Neonates With BPD-PH

Sildenafil exposure for infants with BPD-PH varied between children's hospitals. Figure 1 illustrates the between-hospital variation in the percentage of BPD-PH neonates who received sildenafil. Seven hospitals (19%) did not use sildenafil. We observed no correlation between the proportion of BPD-PH patients receiving sildenafil at a hospital and NICU volume or BPD volume. We observed no differences in hospital characteristics (NICU volume, BPD volume, or BPD-PH volume) between hospitals with high use of sildenafil (>25% neonates with BPD-PH) and low use (<5% neonates with BPD-PH). Sildenafil was initiated, on average, at 41.4 weeks' PMA (median: 40.2 weeks; 25th–75th percentile: 39–44 weeks).

Duration of Sildenafil Treatment

Figure 2 illustrates the between-hospital variation in percentage of patient-days sildenafil was received during the NICU stay. Infants received sildenafil a median of 52 days (25th–75th percentile: 28–109 days). The variation in sildenafil exposure length between hospitals persisted even after controlling for length of exposure to positive pressure via mechanical ventilation or CPAP, birth weight, GA, NEC, PDA, IVH, and ROP in our multivariate logistic regression model with random intercepts (Table 1). No differences in therapy duration associated with GA or severity of BPD were observed. We observed no correlation between the percentage of BPD-PH neonates receiving sildenafil at a hospital and the average number of days they spent receiving sildenafil ($r = 0.13$; $P = .57$). There was no significant association between the average age when sildenafil was started and either the rate of use of sildenafil ($r = -0.15$; $P = .38$) or the average number of days of

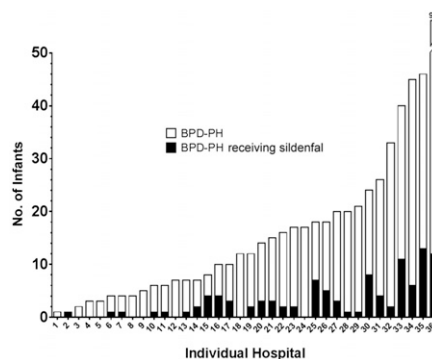


FIGURE 1 Number of neonates with BPD-PH per hospital and the number of neonates per hospital who received sildenafil. Nine hospitals reported no sildenafil use. Hospitals are listed in order of increasing number of BPD-PH neonates. The proportion of BPD-PH infants exposed to sildenafil varied according to hospital (median: 15%; 25th–75th percentile: 0%–25%). One hospital (no. 36) had 96 infants with BPD-PH.

sildenafil use per patient ($r = 0.16$; $P = .35$).

DISCUSSION

Single-center experiences suggesting sildenafil therapy may improve outcomes^{23,28} led us to investigate utilization patterns of this drug at US children's hospitals. The main findings of our study are that patterns of utilization vary markedly between institutions and that infants with BPD-PH treated with sildenafil represent a high-risk subgroup of patients. The marked variability in practice patterns of sildenafil exposure is consistent with other treatments across NICUs^{29–31} and underscores the importance of comparative effectiveness research to develop evidence-based recommendations.

Evidence suggests sildenafil may be an important therapeutic option and potentially alter the natural course of the disease for some infants.^{23,24,28,32,33} However, the absence of long-term safety and efficacy data³⁴ may have contributed to the fact that the majority (83%) of infants with BPD-PH in this study population did not receive sildenafil. Clinicians seem to reserve sildenafil for a “sicker” subgroup of infants with BPD-PH: those receiving sildenafil were born more

prematurely, were more likely to be SGA, had more severe lung disease, and had longer hospitalizations. Use of sildenafil therapy as part of an overall program to aggressively treat lung disease and PH in infants with BPD will require a better understanding of risk/benefit profiles, indications for use, and optimal therapeutic regimens (eg, as monotherapy or in combination with iNO).

Without evidence on the optimal regimens for use, substantial variations have been observed in the average number of days of sildenafil exposure. Steinhorn et al²⁸ described improvements in oxygenation status among infants 4 hours after sildenafil administration. Nyp et al²⁴ showed that, among 21 preterm infants with moderate or severe BPD, sildenafil exposure for a median of 167 days was associated with clinically significant reductions in estimated right ventricular peak systolic pressures. In our cohort, the median duration of sildenafil therapy was 52 days, with marked variation in the duration of treatment. These variations in length of treatment suggest that clinical or echocardiographic parameters associated with treatment efficacy or treatment response are poorly understood. To better characterize the timing and magnitude of responses after administration of sildenafil, more robust pharmacokinetic and pharmacodynamic analyses of this drug are clearly needed.

The substantial interhospital variation in sildenafil administration may be due in part to the recommendation that sildenafil be prescribed only by pediatric cardiologists specialized in the care of pediatric PH, as well as differences in access to subspecialty care among institutions.³³ In addition, lack of an accepted algorithm for PH surveillance likely contributes to considerable heterogeneity in the diagnosis and assessment of PH among infants with BPD.^{10,33} Although some authors suggest that PH should be confirmed with cardiac catheterization before initiating sildenafil therapy, >95% of our cohort did not undergo catheterization, suggesting that clinicians are relying on echocardiography in the diagnosis of PH. Because of the poor correlation between standard

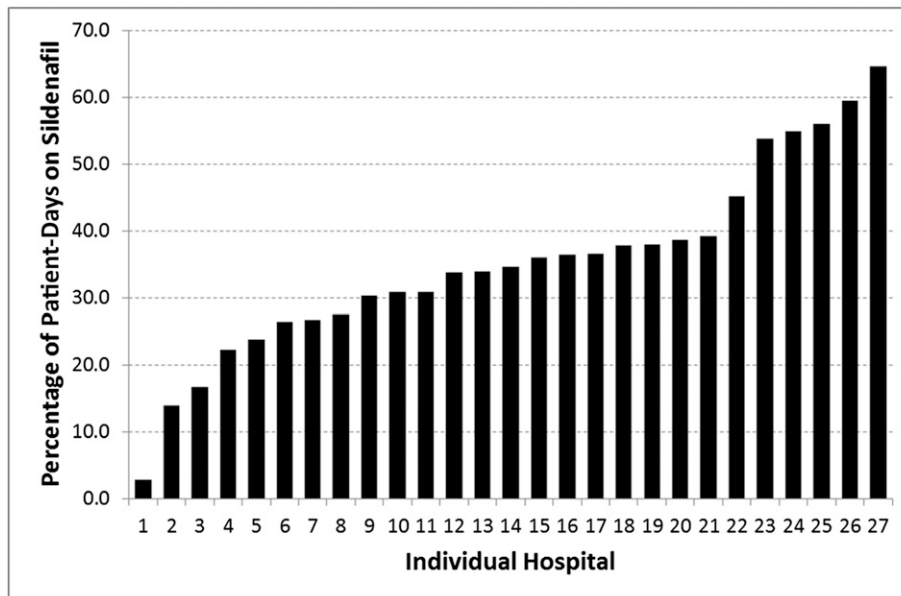


FIGURE 2 Mean proportion of days that neonates received sildenafil during their NICU stay according to hospitals using sildenafil (range: 2%–63%). Patient-days = mean patient-days on sildenafil/mean length of stay.

echocardiography and cardiac catheterization,³⁵ clinicians are left to balance the limitations of echocardiography with the risks associated with cardiac catheterization.³⁶ Given the difficulties in accurately diagnosing PH and the relatively infrequent nature of BPD-PH in the pediatric population, efforts to promote regionalization of care in this unique subgroup of patients will be an important first step in better characterizing disease phenotype, natural history, and response to sildenafil administration.³⁷

The present study had certain limitations. Because of the retrospective nature of the study, the observed associations between sildenafil exposure and adverse outcomes impart no implications of causation. The development of PH is likely affected by a number of modifying influences, including environmental, genetic, and epigenetic factors³⁸ that are not reported in the PHIS database. Although all the infants in our cohort were diagnosed with PH, the database does not provide information on the severity of PH, a factor that likely influenced the decision to use sildenafil. The PHIS data set does not include dates for when patients received a diagnosis. Therefore, data on the age of initiation of

sildenafil exposure cannot be put in the context of when a diagnosis of PH was made. Without knowing timing of diagnosis, our regression model predicting sildenafil use may have included variables that developed after the initiation of therapy.

In addition, our clinical information is primarily from ICD-9 diagnostic codes and pharmaceutical and procedural codes, as defined from billing data; nonbillable data are more likely to be incomplete or omitted. Nevertheless, the data set is screened rigorously for errors, with quality thresholds in place if specified inclusion criteria are not met. The PHIS database was not designed to capture the full spectrum of potential drug effects, nor does it have adequate granularity to describe specific dosing intervals or medication-weaning strategies. Therefore, although we know the duration of sildenafil exposure in days, the doses are unknown. Because previous studies have shown that few patients <40 weeks' PMA receive sildenafil,²³ the likelihood that neonates with mild BPD received sildenafil but were discharged from the hospital before 36 weeks' PMA is low.

Despite these limitations, the present study has a number of strengths. First, the PHIS

database provides a large sample size and a daily record of medication use for each study subject. Second, the data included many children's hospitals. These factors are important because attempts to characterize national variability in sildenafil exposure require a large and diverse sample of children's hospitals.

CONCLUSIONS

To our knowledge, this report is the first among children's hospitals regarding sildenafil exposure for infants with BPD-PH. The frequency of sildenafil treatment, as well as treatment duration, varied greatly among pediatric hospitals. Although sildenafil was not administered to the majority of infants with BPD-PH during their hospitalization, the likelihood of sildenafil exposure was greatest among the most premature infants with severe forms of BPD. Patient-centered trials of infants with BPD-PH are needed to develop evidence-based practices.

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