Sildenafil weaning post-discharge in congenital diaphragmatic hernia

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Abstract:

Introduction: Sildenafil is used to treat pulmonary hypertension (PAH) in infants with congenital diaphragmatic hernia (CDH). However there is limited data to guide sildenafil dosing and weaning. This is of concern in light of a recent report of increased risk associated with high dose sildenafil regimens in non-CDH PAH.

Methods: Retrospective cohort study of sildenafil usage, dosing and weaning in infants with CDH at our institution.

Results: Seventeen percent (19/122) of infants were discharged on sildenafil of median dose 8mg/kg/day (2.91-5.78). Weaning rate was mg /kg/week 0.1 (0.01-0.5). Infants ceased therapy at 343 days median duration. At 1 year of age 29% were receiving a dose of sildenafil >1.5mg/kg/day. One infant died from severe PAH.

Discussion: Sildenafil therapy at discharge is common in severe CDH. Variation in dosing and weaning rates highlights the need for standardised assessment and treatment of PAH after discharge, to optimise benefits and minimise adverse effects of sildenafil.

Introduction

Pulmonary hypertension (PAH) is an important cause of morbidity, and mortality, in congenital diaphragmatic hernia (CDH)[1]. Sildenafil, a phospho-diesterase-5 inhibitor, is employed to treat PAH in CDH, in the acute setting as a synergistic pulmonary vasodilator with inhaled nitric oxide (iNO), or to allow weaning of iNO[2]. Sildenafil therapy may itself subsequently be weaned if it is perceived to no longer be necessary.[3]

In our Unit sildenafil is used in babies with severe PAH. It is commenced either as an adjunct to iNO in those infants with ongoing echocardiographic evidence of severe PAH and right ventricular dysfunction, or to facilitate iNO weaning.

There is minimal data in the literature regarding appropriate dosing of sildenafil at discharge and weaning regimes, and none relating to CDH specifically. More recently, a dose-ranging study in children with non-CDH PAH by Barst et al has observed increased mortality and side effects in children receiving high dose compared to medium dose sildenafil over a 2 year follow-up[5]. For the lowest weight group in this study (8-20kg) high dose regime (20mg three times per day) equated to 3-7.5mg/kg/day, whereas medium dose equated to a dose range of 1.5 – 3.75 mg/kg/day. In response to this study there has been an FDA warning recommending that sildenafil should not be prescribed for children with PAH between 1-17 years of age [6].

In light of these reports, and in the absence of data relating to sildenafil use in CDH, we aimed to determine the proportion of CDH patients discharged on sildenafil, dosing, duration and rate of weaning in our institution.

Methods

We performed a retrospective cohort study. All CDH patients managed in our institution between September 2005 and September 2012 were identified from our departmental database.

Sildenafil dosing and patient weights were obtained from the discharge summary and subsequent outpatient case records, to enable a daily dose calculation (mg/kg/day) using the most recent available weight. Rate of sildenafil weaning and duration of therapy were also obtained. In addition the time taken to wean to a dose < 1.5mg/kg/day was calculated. This threshold was chosen based on recent concerns of higher dosing regimens[5].

In our institution doses of sildenafil used were in accordance with a local formulary[4] (maximum dosing 2-3mg/kg/dose six hourly). Typically sildenafil is commenced at 1mg/kg/dose six-hourly as an inpatient therapy to facilitate weaning of iNO. The decision to commence sildenafil, and any subsequent dose increases were made by the treating neonatal clinical team based on clinical and echocardiographic findings suggestive of ongoing severe PAH (i.e. elevated tricuspid regurgitation velocity and/or bidirectional/right-to-left ductal shunting, indicating pulmonary artery pressures equal to or exceeding systemic arterial pressure). Infants with CDH managed in our Unit receive regular functional echocardiograms to assess PAH and cardiac function. If considered necessary, increases in dose were made by 0.5 mg/kg/day at a minimum of 48 hour intervals, up to maximum recommended dosing. Any variation in timing of dose adjustment between patients may have reflected differences in severity of PAH, concomitant therapies, physician discretion and the absence of formal guidelines. Sildenafil therapy was continued at discharge if PAH persisted at that time, and weaned thereafter. Weaning was performed in the outpatient setting by the Paediatric Cardiologist Team, on the basis of serial clinical evaluation, ECG and echocardiographic findings to assess improvement of PAH.

Results

One Hundred and Twelve eligible infants with CDH were managed in our institution during the study period, of which 19 (17%) infants were discharged on sildenafil. Details of sildenafil weaning were available for 17 infants. CDH was right-sided in 4 infants, and left-sided in 13 infants.

All infants commenced on sildenafil as inpatients survived to discharge and remained on sildenafil at the time of discharge.

Group demographic and sildenafil weaning data are shown in Table 1. At discharge median (range) weight was 4.56Kg (2.91 – 5.78Kg), median dose of sildenafil 7.9 mg/Kg (1.2 – 18.9mg/kg/day).

Sildenafil dose was weaned in all infants after discharge, at a median rate of 0.1mg /kg/week (0.01-0.5). Sixteen infants were receiving maximal sildenafil dose at discharge, and weaned thereafter. One infant had their dose increased after discharge and achieved a maximal dose of sildenafil on day 257. (Discharge dose 3mg/kg/day, maximal dose of 9.4mg/kg/day, subsequently weaned to stop at 562 days).

Ten infants ceased sildenafil during the study period. The median time to stopping was 343 (105 – 671) days, and median time to achieve a dose of <1.5mg/kg/day was 226 days (0-562 days). The other 7 infants remained at a higher dose during the study period; median dose of 5.4mg/kg/day (3.8-8.9mg/kg/day) with median time of follow-up of 186 days (55-644).

Fifteen infants halved their sildenafil dose at a median time of 192 (88-577) days. Only two infants remained on greater than half of starting dose at latest clinic review, (both less than 100 days of age); discharge doses weaned from 9.8 to 8.9mg/kg/day and 7.7 to 5.4mg/kg/day at 92 and 55 days respectively).

One infant died at 192 days from complications of severe PAH. This patient was not atypical of the group: discharged at 90 days on a dose of 3.7mg/kg/day, subsequently had weaned to 2.4mg/kg/day at the time of death at a rate of 0.05 mg/kg/week.

At 1 year of age 5 infants (29%) were still receiving > 1.5 mg/kg/day sildenafil (Figure 1). Seven infants had not yet reached two year follow-up. In the infants for whom complete growth parameters were available (n=9) median growth velocity was 120g/week (39-215g/week).

Five infants (29%) were discharged on low flow oxygen. The median oxygen requirement was 0.5L/minute (0.05-0.8L/minute). Within the study follow-up period 3 infants weaned off oxygen,

within a range of 342-577 days. The median sildenafil dose at discharge for those infants requiring oxygen was 3.7mg/Kg (1.2-18.2mg/Kg).

Discussion

Nearly one-fifth of infants with CDH in our series received sildenafil post-hospital discharge, as treatment of PAH. This usage rate is comparable to other institutions managing infants with CDH³. We provide the first report of sildenafil dosing after discharge; all infants had their sildenafil dose weaned after discharge, but remained on treatment for between 3 to 22 months. The rate of weaning and duration of therapy were comparable in to those infants with BPD-associated PAH reported by Mourani et al[76]. In the latter study dose ranges were 1.5-8mg/kg and median duration of treatment 241 days.

Doses used in our cohort were comparable to prior reports and within current prescribing regimens [2,3]. However, there was significant variation in dose and rate of post-discharge weaning within our cohort. This variation may have reflected variable illness severity, or pre-discharge weaning in some infants, but also highlights the lack of current data to guide uniform sildenafil use and weaning in CDH. Weight-gain also contributes to relative dose weaning. Infants with poor growth may therefore be exposed to higher relative dosing for longer, whilst optimisation of nutrition and growth may indirectly produce faster weaning of relative sildenafil dose.

Our study was in part prompted by a recent report by Barst et al which raised concerns of increased side-effects and mortality associated with high dose, long-term (2 year) sildenafil therapy, in children with non-CDH PAH[5], and the FDA response advising against sildenafil use in children with PAH [6]. Based on these findings the authors recommended using a medium dosage regime, equating to a dose range of 1.5 – 3.75 mg/kg/day in a weight group of 8-20kg.

In our series the majority of infants were discharged on > 1.5 mg/kg/day and took a median of 7.5 months to wean below this level. Nearly one third remained on a dose > 1.5 mg/kg/day at one year of age. This may raise concerns regarding potential adverse effects of current sildenafil use in our population of CDH infants. However, differences between study populations may prevent direct application of Barst et al's findings to our cohort. Barst et al's study was performed in treatment naive individuals, whereas in our series sildenafil was commenced in infants after a period of inhaled nitric oxide (iNO) therapy. Most infants in our study weighed less than 8 kg, whilst in Barst's study all weighed more than 8kg.

Furthermore, Barst et al studied older children with non-CDH PAH which is likely to be chronic, life-limiting and require prolonged therapy with associated sustained side-effect risks. In CDH, however, PAH usually improves and, as our study demonstrates, therapy may be weaned thereby potentially minimising adverse events. The retrospective nature and small sample size of our series prevented full assessment of potential side-effects and adverse events. However, it is notable that no infant had treatment ceased for this reason, and the one infant who died was not receiving the highest sildenafil dosing. To resolve whether the concerns raised by Barst et al apply to a younger, lighter group of infants with CDH requires further study. In the meantime our current practice aims to limit future discharge dosing to 1.5mg/kg/day.

Could sildenafil be weaned more quickly in CDH? Ideally dose would be optimised regularly based on accurate assessment of pulmonary artery pressure (PAP), and the secondary effects on cardiac function, functional status and growth. In current practice, clinical assessment is combined with serial echocardiography. However, PAP may be difficult to quantify accurately using echo, particularly in the absence of a tricuspid regurgitation. Improved non-invasive assessment of PAH and cardiac function would inform understanding of the natural history of PAP in CDH. Plasma biomarkers of PAH and new echocardiographic modalities, such as tissue Doppler imaging, may hold potential for this purpose and merit future study. With improved assessment of PAH post-discharge we would hope for the development of standardised guidelines for dosing, PAH assessment and sildenafil weaning after discharge, to potentially shorten the course of treatment and avoid dose-related side effects.

References

1. Dhillon R. The management of neonatal pulmonary hypertension. *Archives of Disease in Childhood Fetal and Neonatal Edition*. 2012; 97: F223-F228
2. Noori S, Friedlich P, Wong P et al. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. *Neonatology* 2007;91:92-100
3. Hunter L, Richens T, Davis C, Walker G, Simpson JH. Sildenafil use in congenital diaphragmatic hernia. *Arch Dis Child Fetal Neonatal Ed* 2009 Nov;94(6):F467
4. Shann Frank, *Drug doses*, 13th edition, Collective Pty Ltd 2005, ISBN 0958743452
5. Barst R, Ivy D, Gaitin et al. A randomised double blind placebo controlled dose-ranging study of oral sildenafil citrate in treatment naïve children with pulmonary arterial hypertension. *Circulation* 2012. 125(2) 324-34
6. FDA Drug Safety Communication: FDA recommends against use of Revatio (sildenafil) in children with pulmonary hypertension (<http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm>)
7. Mourani P M, Sontag M K, Ivy DD, Aloma SH. Effects of long term sildenafil for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009 Mar; 153(2): 379-84

Table 1: Demographics and sildenafil treatment data for CDH infants discharged on sildenafil

N=17 (9 female, 8 male)	Median	Range
Weight at discharge (Kg)	4.6	2.9 – 5.8
Length of NICU stay (days)	71	32 – 132
Sildenafil dose at discharge (mg/kg/d)	7.9	1.2– 18.9
Time to stopping sildenafil,(days), (N=10)	257	105 – 671
Time to halve sildenafil dose after discharge (days) (N=15)	209	88 – 577
Time to achieve <1.5mg/kg/day dosing (days) (N=10)	226	0 – 562
Duration of sildenafil treatment (days) (N=17, of which 10 stopped therapy)	343	105 – 671
Rate of sildenafil dose reduction (mg/kg/week)	0.1	0.01 – 0.5
Low flow oxygen therapy at discharge (L/minute)(N=5)	0.5	0.05-0.8
Sildenafil dose in those on oxygen at discharge (mg/Kg) (N=5)	3.7	1.2-18.2
Post-discharge growth velocity (g/week) (N=9)	120	3.9-215

Figure 2: Percentage of patients receiving sildenafil dose of >1.5mg/kg/day and time post discharge