

Sildenafil for Pulmonary Hypertension associated with Congenital Heart Defect

S Daga, C Valvi, S Janwale, M Manivachagan

Citation

S Daga, C Valvi, S Janwale, M Manivachagan. *Sildenafil for Pulmonary Hypertension associated with Congenital Heart Defect*. The Internet Journal of Pediatrics and Neonatology. 2006 Volume 7 Number 2.

Abstract

Background: Pulmonary hypertension (PH) when associated with congenital heart defects (CHD) carries high post-operative mortality. Various pulmonary vasodilators have been used in such a situation. Our experience of using sildenafil, an affordable option in resource – limited setting, is described in this study.

Objective: To study pulmonary artery pressure (PAP) before and after sildenafil in cases of CHD.

Study design: A case series observational in nature.

Methods: The subjects were 12 neonates and 11 infants. Their mode of presentation was studied. Echocardiography was performed before and after treatment.

Results: Sixteen patients presented with respiratory distress, three with oxygen dependence, three had hypoxaemia disproportionate to pulmonary or cardiac problem and one was asymptomatic. In seven cases, PH was detected during echo performed for suspected CHD. After sildenafil, PAP normalized in six cases, substantially declined in eight, and remained unchanged in nine. The response was better among babies less than two months old.

Conclusion: Sildenafil is effective in the treatment of PH associated with CHD. Oral availability and low cost are valuable considerations in resource-limited setting.

INTRODUCTION

Approximately one third patients with uncorrected congenital heart disease will die from pulmonary vascular disease (1). When surgical repair is performed in presence of high PVR and hypoxemia, it is associated with high post-operative mortality. Selective pulmonary vasodilators such as inhaled nitric oxide and epoprostenol are available for treatment of PH. These are expensive options for resource – limited setting. We narrate our experience of using an inexpensive pulmonary vasodilator, sildenafil, a phosphodiesterase inhibitor, in pulmonary hypertension associated with CHD in children.

MATERIAL AND METHODS

This study was performed at B.J. Medical College and Sassoon General Hospital, Pune during March 2006 and March 2007. The subjects were 12 newborns and 11 infants with CHD. PH was suspected when 1) respiratory distress or

hypoxemia was disproportionate to the pulmonary and / or cardiac problem, or 2) oxygen saturation and/ or colour of the child showed frequent fluctuations or 3) oxygen dependence lasted beyond 3-4 days of apparent resolution of respiratory distress. In seven subjects PH was detected during echocardiography done for diagnosis of CHD. Age at presentation and mode of presentation (respiratory distress, oxygen dependence, disproportionate hypoxemia) and findings on echo were recorded. Repeat echo studies were performed at least once, after 2 weeks, or earlier if visible improvement was noted. Full blood count, chest X ray and venous blood gas analysis were performed. Management included oxygen by head box, antibiotics, minimal handling and sedation. Circulatory support was done with adrenaline-0.1 mcg/kg/min, dobutamine 10mcg/kg/min and milrinone 0.1 mcg/kg/min for everyone for one week. Sildenafil was administered in a dose of 0.5 mg / kg / dose / 6h, through an orogastric tube. Facilities for mechanical ventilation were

not available. The patients were grouped according to age less than two months (Group 1) or > 2 months (Group 2), to study the age – related pattern of response.

RESULTS

Nine neonates presented in first week of life, three between two to four weeks and 11 between one month to one year. Respiratory distress was a presenting feature in 16 cases, oxygen dependence in three , hypoxemia was disproportionate to the pulmonary and / or cardiac problem in three cases. In seven cases PH was detected during echocardiography performed for suspected CHD. Blood counts suggested sepsis in eleven subjects (four newborn and seven infants). Venous blood gas showed metabolic acidosis (pH < 7.3) in eleven cases. Chest Xray showed cardiomegaly in five subjects, hypaeremic lung fields in two subjects . Echocardiography before sildenafil revealed following findings: Pulmonary artery pressure (PAP) was in the range of (92-45 mm of Hg) in 23 cases, (Table 1). Bi-directional shunt was observed in one case. The frequency of CHD among patients was as follows. Ventricular septal defect (VSD): 14, Atrial septal defect (ASD): 13, Patent ducturs arteriosus (PDA) : 5, Co-arcation of aorta, cardiomyopathy, restrictive and hypertrophic, and tricuspid atresia : 1 each. Two cases of VSD had evidence of left ventricular hypertrophy, which later regressed. After sildenafil treatment, PAP normalized in 6 cases, substantially declined in 8 cases (40-20 mm of Hg) and in 9 cases it remained unchanged. Other observations were closure of ASD in 6 cases, PDA in 3 cases and VSD in 3 cases (Table 1). The newborn with co-arcation underwent successful surgery. Two patients had severe growth failure. Three patients expired. In two of them, the PAP was unchanged. In the third case (birth weight 1.3 kg), PAP had normalized, death occurred due to severe respiratory tract infection. Of the 12 cases in the first group, PAP normalized in 5, substantially declined in 5, and in 2 it was unchanged. Of the 2 subjects, whom the PAP was unchanged, 1died and 1 was lost for follow up. In all except 1, left-to-right shunt closed. In the second group, 2 months and above, of the 11 cases, PAP normalized in 1, substantially regressed in 3 and was unchanged in seven.

Figure 1

Table 1: Echocardiographic findings before and after sildenafil administration

| Sr.No. | Heart defect | Pulmonary Artery pressure (mm. Hg) | | Follow-up Echo findings | Follow up and outcome |
|--------|--------------------------------------|-------------------------------------|---------------------------------|--|---------------------------------|
| | | Pre Sildenafil | Post Sildenafil (After 2 weeks) | | |
| 1. | Severe LVH, PFO, Multiple small VSDs | 75 (D-8) | 57 (D-15) | PFO Closed only one VSD | Discharged |
| 2. | VSD, LVH | 50 (D7) | 26 (D-35) | VSD Closed LVH regressed | Discharged |
| 3. | ASD, PDA | 65 (D-18) | 36 (D-48) | 59 (D27) PDA Closed | Discharged |
| 4. | ASD, VSD | 64 (D-30) | 54 (D-40) | ASD Closed | Discharged |
| 5. | ASD, PDA | 77 (D-9) | 16 (D-26) | 25 (4 months) ASD Closed 25 (5 months-PDA closed) | Discharged. |
| 6. | ASD, PDA , VSD | 70 (D-8) | 40 (D-28) | 40 (D-50) 50 (D-90) PDA Closed | Discharged FTT |
| 7. | 2 VSDs | 45 (D-7) | 26 (D-20) | 1 VSD Closed Normal PAP | Discharged |
| 8. | VSD | 65 (D-7) | 60 (D-20) | 26 (D-60) | Discharged |
| 9. | ASD, VSD | 80 (D-6) | 60 (D-21) | 42 (D-75) Closing ASD | Discharged , FTT |
| 10. | ASD, VSD, PDA | 70 (D-18) | 70 (D-31) | Same findings | Expired |
| 11. | Coarctation of aorta, severe LVH | 55 (D-19) | 37 (D-31) | Not done | Operated |
| 12. | 2 ASD , Mild RPA Stenosis | 45 (D-30) | 38 (D-41) | 21 (D-62) Both ASD Closed | Discharged |
| 13. | TA, VSD, ASD, PDA | 90 (D-60) | 95 (D-75) | ASD Closed | Discharged |
| 14. | VSD | 70 (D-60) | 70 (D-64) | | Discharged |
| 15. | VSD | 70 (D-60) | 60 (D-72) | | Discharged |
| 16. | ASD, VSD | 60 (D-60) | 45 (D-65) | | Discharged. |
| 17. | ASD | 45 (D-45) | 32 (D-6) | 25 (D-75) | Expired on readmission for LRTI |
| 18. | ASD | 50 (D-20) | 33 (D-60) | 36 (6 months) | FTT |
| 19. | ASD Restrictive Cardiomyopathy | 44 (5months) | 30 (8 months) | 48 (9 months) | Discharged |
| 20. | Hypertropic Cardiomyopathy | 70 (5months) | 40 (5 ½ months) | | Discharged |
| 21. | VSD | 65 (5 months) | 50 (5 months 12 days) | 70 (7 months) | Expired |
| 22. | ASD | 52 (7 months) | 53 (7 months 7 days) | 55 (7 months 2 weeks) 53 (9 months) | Discharged |
| 23. | VSD | 92 (6months) | 80 (12months) | 50 (12 months 20 days) | Discharged |

ASD- Atrial Septal Defect
VSD- Ventricular Septal Defect
PDA- Patent Ductus Arteriosus
LVH- Left Ventricular Hypertrophy
D- Day
TA- Tricuspid Atresia
FTT- Failure to Thrive
PAP- Pulmonary Artery Pressure

DISCUSSION

PH is a disease of “pre-disposed” individuals. Imbalance between vasodilators as well as substances involving control of pulmonary vascular tone is presumed to be responsible for pathobiology. These include increase in thromboxane and endothelin and decrease in prostacycline and nitric oxide. Post-mortem studies suggest that pulmonary vasoconstriction, leading to medial hypertrophy, may occur early in course of the disease and may precede development of plexiform lesions and other fixed pulmonary vascular changes in some children. It is possible that the non-responders in our study had irreversible vascular changes.

The patients with CHD with PH are at increased risk of post-operative pulmonary hypertensive crisis (2), which is characterized by a sudden increase in pulmonary vascular

resistance (PVR) that results in low cardiac output from right ventricular failure. Pre and peri-operative inhaled nitric oxide and epoprostenol have been proven to be useful in preventing such complications by releasing cGMP or cAMP, respectively. Therefore, pulmonary vascular reactivity is tested pre-operatively by administering inhaled nitric oxide or prostacycline. The responders are most likely to be benefited by surgery (3).

Over the past decade, there has been a significant advance in the treatment of PH. Intravenous and inhaled prostanoids, nitric oxide and endothelin inhibition show promise. Inhaled nitric oxide is the most selective pulmonary vasodilator and has been used successfully in PH of varied origin. Prostaglandin therapy has been instituted by using epoprostenol as a continuous infusion. Aerosolised formulation like iloprost has been used successfully in patients with PH after repair of the CHD. Bosentan – a non-selective endothelin inhibitor – is available for oral administration. Follow up data over three years have shown few deteriorations, with majority of patients maintaining their response on bosentan alone (4). However, bosentan therapy is costly, US \$ 10,000 per year for an adult. Sildenafil, a phosphodiesterase type-5 inhibitor, is a

selective pulmonary vasodilator. It is well tolerated and is available as an oral preparation (5). Affordability is of particular importance to developing countries. Sildenafil therapy for a baby weighing 5 kg costs US \$ 7.5 per month.

To conclude, PH in children with CHD can be reduced in a sizable proportion of newborns and infants by using sildenafil.

References

1. Mcgoon M, Barst R, Badesch DB. Proceedings of Scientific Leadership Council of the Pulmonary Hypertension Association . file://\comp12\My Disc (E)\Pathogenesis in PH\Adv in PH.htm. Accessed on 18/1/2007.
2. Hopkins RA, Bull C, Haworth SG, de Leval MR, Stark J. Pulmonary hypertensive crises following surgery for congenital heart defects in young children. *Eur J Cardiothorac Surg* 1991; 5 : 628 - 634.
3. Rimensberger PC, Spahr-Schopfer, Berner M, Jaeggi E, Kalangos A, Friedli B, Beghetti M. Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease. <http://ahajournals.org/cgi / content / abstract / circulationaha ; 103/4/544> accessed on 1/2/2007.
4. Widlitz A, Barst RJ. Pulmonary arterial hypertension in children. *Eur Respir J* 2003, 21 : 155-176.
5. Travadi JN, Patole SK. Phosphodiesterase inhibitors for persistent pulmonary hypertension of the newborn : A review. *Pediatr Pulmonol* 2003 , 36 : 529-535.

Author Information

S.R. Daga

Department of Pediatrics, B.J. Medical College and Sassoon General Hospital

Chhaya Valvi

Department of Pediatrics, B.J. Medical College and Sassoon General Hospital

Sanjay Janwale

Department of Pediatrics, B.J. Medical College and Sassoon General Hospital

M.N. Manivachagan

Department of Pediatrics, B.J. Medical College and Sassoon General Hospital