

LEADING ARTICLE

Sildenafil in the Management of Pulmonary Hypertension in Newborn

Mohammad Abdullah Al Mamun

Introduction

Pulmonary hypertension in the newborn is a complicated, often a life threatening disease. It has been a difficult condition to treat for a long time and characterized by an increased pulmonary vascular resistance, right-to-left shunt at atrial and ductal level with severe hypoxemia.¹ The incidence of Persistent Pulmonary Hypertension of Newborn (PPHN) in term or near-term infants is reported to reach around 2-6.8 per 1000 live births with a mortality of 10% to 20%.^{2,3} It occurs when the high pulmonary vascular resistance characteristic of fetal circulation fails to decrease at birth, resulting in right to left shunting of blood through fetal channels, diminished pulmonary blood flow and profound hypoxaemia.

For the majority of PPHN cases aggressive support of cardiac function and perfusion, with volume and inotropic agents to enhance cardiac output and systemic O₂ transport is essential.^{4,5} The principal goal of PPHN treatment is selective pulmonary vasodilatation. Pulmonary vasodilators such as magnesium sulfate, sildenafil, bosentan, prostacyclin and specific agents like inhaled nitric oxide (iNO) is effective. Although iNO and extracorporeal membrane oxygenation (ECMO) are the gold standards of the PPHN therapy, they are expensive therapeutic modalities associated with technical difficulties in developing countries, making it necessary to search for cheaper therapies, assuring quick effectiveness and stabilization of the patient going through a very high-risk situation.^{6,7} However, any single therapy can not be labelled as a magic bullet for PPHN, more clinical trials are required to demonstrate the efficacy and safety of available therapeutic options as well as to develop newer strategies targeted to the underlying pathophysiology.⁸

Sildenafil has been used for the treatment of pulmonary hypertension in adult.⁹ It is recommended in children by European Society of Cardiology (ESC) for pulmonary hypertension, for those aged 1-17 years.¹⁰ But its use in neonate is controversial.¹¹ Role of sildenafil in the treatment of PPHN was first reported in 2002.¹² Initially there was criticism regarding its use. But it was justified by others at that time as there was no option for the attending neonatologist in face of non-availability of iNO and ECMO.¹³ Recent studies also concluded that sildenafil can offer a less expensive but effective alternative treatment.^{14,15}

Sildenafil has been shown to selectively reduce pulmonary vascular resistance in humans. Several controlled studies document improved oxygenation measured by pulse oximetry, significant improvement in oxygenation index (OI) as well as echocardiographic evidence of reduced pulmonary arterial pressures and significant decrease in mortality following the administration of sildenafil in newborns with PPHN.^{16,17} Meta-analysis including randomized trials of sildenafil compared with placebo in PPHN also found significant reduction in mortality.¹⁸ Fatema et al¹⁹, Mamun et al²⁰ and Wadud et al²¹ found that sildenafil is very effective in the treatment of PPHN among Bangladeshi neonate. This review of the recent literature focuses on effectiveness of sildenafil in newborns with pulmonary hypertension.

Mechanism of action of sildenafil

Sildenafil is a selective phosphodiesterase type 5 (PDE-5) inhibitor which potentiates the downstream effects of Nitric oxide (NO). NO induces smooth muscle relaxation and vasodilation through its effects on the cyclic guanosine monophosphate

Correspondence to: Dr. Mohammad Abdullah Al Mamun, Associate Professor, Division of Neonatal Cardiology, Department of Pediatric Cardiology, Bangladesh Institute of Child Health (BICH) and Dhaka Shishu (Children) Hospital. Cell: 01913475529, E-mail: mamundsh@gmail.com

Received: 05 November 2019; **Accepted:** 25 November 2019

(cGMP) pathway. In pulmonary vascular smooth muscle NO is synthesized by nitric oxide synthase (NOS) from the terminal nitrogen of L-arginine. NO stimulates soluble guanylatecyclase (sGC) to increase intracellular cGMP and mediate pulmonary vasodilatation. cGMP breakdown into GMP by PDE-5 enzyme. Sildenafil inhibit the hydrolytic breakdown of cGMP to GMP and thus prolongs the activity of endogenous NO and potentiate cGMP mediated pulmonary vasodilation (Fig 1).

NO pathway

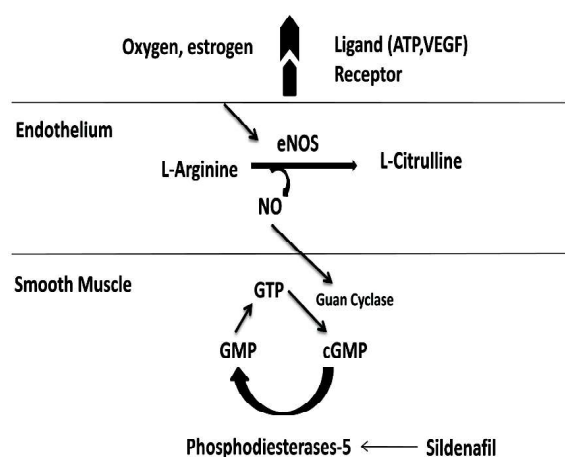


Fig 1 NO signaling pathways in the regulation of pulmonary vascular tone.

Dosage, administration, safety, response and duration of therapy of sildenafil

Time of maximum action and duration of the effect varies depending on the dose, the route of administration and the clinical situation in which sildenafil has been used. The most used route is oral, can be used IV and the duration of the effect goes from 20 minutes to 6 hours afterward.^{22,23} Oral sildenafil is fairly well tolerated, although absorption can be erratic at times. If intravenous preparation is not available, it can be given orally.²⁴ It can also be administered intratracheally at a dose of 0.75 or 1.5 mg/kg per dose which can induce a rapid decrease in mean pulmonary arterial pressure, occurred as soon as 2 minutes and lasted for 120 minutes.²⁵

The optimal dose of oral sildenafil in neonates and children is still not entirely clear. The British

National Formulary for Children advises starting doses of 0.5 mg/kg/dose up to a maximum of 2 mg/kg/dose every 6 hours.^{26,27} In neonate dose of sildenafil is 0.5 mg/kg/dose 6 hourly and considering, if there is no response, increase the dose up to a maximum of 2 mg/kg/dose.¹⁶ Because of a relatively short half-life, sildenafil may be given 4 hourly although it is usually administered 6 hourly.²⁸

Clinical indicators of a successful response would be improved oxygenation indices, a >10% increase in SaO₂ with a reduced differential between pre and post ductal values, a 3 kPa increase in PaO₂, ability to wean FiO₂, an increase in the a/APO₂ ratio and a decrease in OI. Duration of treatment is not yet well defined and one approach is to observe the individual response and stop the medication after a clear response and improvement. The treatment should also be discontinued after 6-8 doses if there is no improvement and reduction in dose or cessation of treatment is necessary if hypotension develops despite inotropic support.²⁸

Side effects and complications

As for safety profile, systemic reviews of 49 studies concerning the safety of sildenafil administration revealed no evidence of serious adverse events in infants.²⁹ Considering sildenafil's mechanism of action, which decreases pulmonary arterial pressure, concerns have been raised that sildenafil could cause serious systemic hypotension and severe haemodynamic instability. Sildenafil was first considered as an anti-hypertensive agent. So one must watch the systemic blood pressure closely, although this has been rarely a problem.¹⁴ There have been reports of hypotension when it is used in conjunction with nitric oxide.³⁰ Common side effects of sildenafil treatment are usually non-life-threatening including vomiting, pyrexia, cough, diarrhoea and nasopharyngitis (nasal stuffiness).^{27,31,32} Severe adverse effects like stridor, raised intra-ocular pressure and ventricular arrhythmias may also occur.³² Additionally, the vasodilatation induced by the blockage of PDE-5 inhibitors can lead to nasal congestion, dyspepsia as well as flushing and can also lead to headaches.³³

Another controversial aspect of sildenafil is its activity on the PDE-6 receptors localized in the rod and cone cells of the eye and whether or not the drug affects the normal development of the visual function of preterm neonates. There has been no

proven evidence of a direct link between sildenafil therapy and ocular complications but visual disturbances and photophobia has been observed in some subjects.^{30,34}

Antenatal sildenafil in experimental congenital diaphragmatic hernia (CDH)

Congenital diaphragmatic hernia is an orphan disease with high neonatal mortality and significant morbidity. An important cause for this is pulmonary hypertension. Prenatal sildenafil administration to expectant mothers prevented fetal and neonatal vascular changes leading to pulmonary hypertension in several animal models, and is, therefore, a promising approach.³⁵ Antenatal sildenafil improved lung structure, increased pulmonary vessel density, reduced right ventricular hypertrophy, and improved postnatal NO which induced pulmonary artery relaxation. Antenatal sildenafil was not associated with adverse effect on retinal structure/function and brain development. Antenatal sildenafil improves pathological features of persistent pulmonary hypertension of the newborn in experimental CDH and does not alter the development of other PDE-5-expressing organs.³⁶

Is preterm neonate are at risk of retinopathy of prematurity after using sildenafil?

Sildenafil is 10 times more selective for PDE-5 as compared to PDE-6. PDE-6 is found in the retina. If used in extremely preterm neonates, sildenafil may increase the risk of severe retinopathy of prematurity. Fang et al³⁷ in a retrospective, case-controlled study in neonates born before 30 weeks gestation showed sildenafil use did not increase the risk of retinopathy of prematurity.

Is sildenafil effective in BPD associated pulmonary hypertension

Sildenafil has been shown to enhance the lung alveolarization and vascularization in newborn animal models after lung injury and has possible therapeutic potential for the prevention of BPD. Systematic review shows that in the treatment of BPD-associated pulmonary hypertension in preterm infants, sildenafil may be associated with improvement in pulmonary artery pressure and respiratory scores.³⁸ Abounahia et al³⁹ found oral sildenafil did not benefits in the prevention of BPD or death in the extreme and very preterm infants. A retrospective series of 25 patients with BPD aged <2 years showed hemodynamic improvement in

pulmonary hypertension in majority cases, with minimal adverse events.⁴⁰

Is sildenafil more effective with iNO in management of PPHN?

Early use of oral sildenafil as an adjunctive therapy together with iNO in cases of PPHN was well tolerated and found to be more effective. Sildenafil may serve as a useful adjunct for infants with poor iNO responsiveness.^{3,41} Combination therapy with iNO and sildenafil leads to a synergistic effect for pulmonary vasodilation, because under conditions of elevated cGMP concentration, sildenafil acts as a more powerful vasodilator by preventing breakdown of the high concentration of cGMP.⁴²

Is sildenafil more effective than MgSO₄ in management of PPHN?

Uslu et al⁴³ in a prospective, randomized and controlled study, found that sildenafil was more effective than MgSO₄ in the treatment of PPHN with regard to time to adequate clinical response, duration of mechanical ventilation with fewer requirements for inotropic support. Shaltout et al⁴⁴ found sildenafil is a more effective therapeutic option in the treatment of PPHN as compared to MgSO₄. Mamun et al²⁰ found magnesium sulphate and sildenafil both are effective in improvement of oxygenation and reduction of pulmonary vascular resistance. Sildenafil was more effective than magnesium sulphate with regard to improvement of oxygenation among Bangladeshi neonate.

Is sildenafil more effective than Bosentan in management of PPHN?

Bosentan is a non-selective endothelin-1 (ET-1) receptor antagonist acting on both ET-A and ET-B receptors. Wadud et al²¹ found sildenafil and bosentan both are effective in improvement of oxygenation and reduction of pulmonary vascular resistance. But sildenafil was found more effective than bosentan in improvement of oxygenation among Bangladeshi neonate with PPHN.

Is sildenafil alone is more effective than sildenafil plus bosentan in management of PPHN?

One study was performed by Nazia et al⁴⁵ to compare the effect of sildenafil alone and sildenafil with bosentan on severity of tricuspid regurgitation and duration of hospitalization in new-borns with PPHN. The combined use of sildenafil and bosentan is more effective than sildenafil alone for control of

pulmonary hypertension in resource limited centres. Goissen et al⁴⁶ reported a successful use of sildenafil as an adjunct therapy to iNO and bosentan in newborns with PPHN complicating transposition of the great arteries.

Is sildenafil more effective than inhaled iloprost in management of PPHN?

A study was performed to examine the effectiveness and safety of oral sildenafil and inhaled iloprost delivered by jet nebulizer in mechanically ventilated term newborns with PPHN. Iloprost appeared to be more effective than sildenafil in the treatment of PPHN with regard to time to adequate clinical response, ventilatory parameters, duration of drug administration, duration of mechanical ventilation, duration of return to normal values of respiratory failure indices, use of MgSO₄ as a second vasodilator and requirement for support with inotropic agents. No side effects on blood pressure or homeostasis was observed. These suggested that inhaled iloprost may be a safe and effective treatment choice in newborn infants with PPHN.¹⁴

Is sildenafil more effective than tadalafil in management of PPHN?

Tadalafil and sildenafil can similarly reduce severity of tricuspid regurgitation (TR), main pulmonary artery (MPA) diameter, mean pulmonary artery pressure (MPAP), and right ventricular end-diastolic diameter (RVEDD).⁴⁷

Use of sildenafil in Pulmonary hypertension after use of ibuprofen

Pulmonary hypertension after prophylactic and therapeutic use of ibuprofen for ductal closure have been reported in some cases.⁴⁸ In such cases, Sildenafil as pulmonary vasodilators is found effective.⁴⁹

Conclusion

Sildenafil is an effective treatment in neonate with a significant increase in the oxygenation, decrease pulmonary vascular resistance and a reduction in mortality with no clinically important side effects in PPHN. At this stage, sildenafil may be considered as a first-line treatment in settings where iNO, HFOV and ECMO are unavailable. More controlled multicenter study is needed to evaluate the safety, efficacy and long term outcome of treatment.

References

1. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;**53**:1573-1619.
2. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics* 2000;**105**:14-20.
3. Perez KM, Laughon M. Sildenafil in Term and Premature Infants: A Systematic Review. *Clinical Therapeutic* 2015;**37**: 2598-2607.
4. Kinsella JP, Abman SH. Inhaled nitric oxide therapy in children. *Paediatr Respir Rev* 2005;**6**:190-98.
5. Gao Y, Raj JU. Regulation of the pulmonary circulation in the fetus and newborn. *Physiol Rev* 2010;**90**:1291-35.
6. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Cochrane Systematic Review - Intervention Version published: 10 August 2011.
7. Yaseen H, Darwich M, Hamdy H. Is Sildenafil an Effective Therapy in the Management of Persistent Pulmonary Hypertension? *J Clin Neonatol* 2012;**1**: 171-75.
8. Amit A, Rashmi A. Persistent Pulmonary Hypertension of the Newborn: Recent Advances in the Management. *International Journal of Clinical Pediatrics* 2014;**2**:1-11.
9. Ikeda D, Tsujino I, Ohira H, Itoh N, Kamigaki M, Ishimaru S, et al. Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005;**45**:286-89.
10. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by:

- Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT) Eur. *Heart J* 2016;**37**:67-119.
11. Simonca L, Tulloh R. Sildenafil in Infants and Children. *Children (Basel)* 2017;**4**:60.
 12. Kumar S. Indian doctor in protest after using Viagra in blue babies. *BMJ* 2002;**325**:181.
 13. Oliver J, Webb DJ, Patole S, Travadi J. Sildenafil for blue babies. *BMJ* 2002;**325**:1174.
 14. Kahveci H, Yilmaz O, Avsar UZ, Ciftel M, Kilic O, Laloglu F, et al. Oral sildenafil and inhaled iloprost in the treatment of pulmonary hypertension of the newborn. *Pediatr Pulmonol* 2014;**49**:1205-13.
 15. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: A pilot randomized blinded study. *Pediatrics* 2006;**117**:1077-83.
 16. Buck ML. Sildenafil for the treatment of pulmonary hypertension in children. *Pediatr Pharm* 2004;**10**:2.
 17. Herrera TR, Concha GP, Holberto CJ, Loera GR, Rodríguez BI. Oralsildenafil as an alternative treatment in the persistent pulmonary hypertension in newborns. *Rev Mex Pediatr* 2006;**73**:107-11.
 18. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. *Cochrane Database Syst Rev* 2011;**8**:CD005494.
 19. Fatema NN. Persistent Pulmonary Hypertension of Newborn: Analysis of 181 cases over one year. *Cardiovascular Journal* 2018;**11**:17-22.
 20. Mamun MAA, Hussain M, Jabbar A. Magnesium Sulphate Versus Sildenafil in the Treatment of Persistent Pulmonary Hypertension of Newborn: A Randomized Clinical Trial. *Journal of Science and Technology Research 2016-2017* 2018;**1**:80-85.
 21. Wadud A. Sildenafil Versus Bosantan in the Treatment of Persistent Pulmonary Hypertension of Newborn. MD Thesis. Bangladesh Institute of Child Health. University of Dhaka 2017.
 22. Ahsman MJ, Witjes BC, Wildschut ED, Sluiter I, Vulto AG, Tibboel D, et al. Sildenafil exposure in neonates with pulmonary hypertension after administration via a nasogastric tube. *Arch Dis Child Fetal Neonatal Ed* 2010;**95**:F109-F114.
 23. Steinhorn R, Kinsella J, Pierce C, Butrous G, Dilleen M, Oakes M, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. *J Pediatr* 2009;**155**:841-47.
 24. Malik M, Nagpal R. Emerging Role of Sildenafil in Neonatology. *Indian Pediatr* 2011;**48**:11-13.
 25. Martell M, Blasina F, Silvera F, Tellechea S, Godoy C, Vaamonde L, et al. Intratracheal sildenafil in the newborn with pulmonary hypertension. *Pediatrics* 2007;**119**:215-16.
 26. Joint Formulary Committee. 2010-2011 ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2010. British National Formulary.
 27. Paediatric Formulary Committee. BNF for Children: 2018-19. Pharmaceutical Press; 2019.
 28. Dhillon R. The management of neonatal pulmonary hypertension. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F223-F228.
 29. Samiee-Zafarghandy S, Smith PB, van den Anker JN. Safety of sildenafil in infants. *Pediatr Crit Care Med* 2014;**15**:362-68.
 30. Shekerdemian LS, Ravn HB, Penny DJ. Interaction between inhaled nitric oxide and intravenous sildenafil in a porcine model of meconium aspiration syndrome. *Pediatr Res* 2004;**55**:413-18.
 31. Barst RJ, Beghetti M, Pulido T, Layton G, Konourina I, Zhang M, et al. Starts-investigators STARTS-2: Long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. *Circulation* 2014;**129**:1914-23.
 32. Siehr SL, McCarthy EK, Ogawa MT, Feinstein JA. Reported Sildenafil Side Effects in Pediatric Pulmonary Hypertension Patients. *Front Pediatr* 2015;**3**:12.
 33. Wardle AJ, Tulloh RM. Paediatric pulmonary hypertension and sildenafil: Current practice and controversies. *Arch Dis Child Educ Pract Ed* 2013;**98**:141-47.
 34. Samiee-Zafarghandy S, Van Den Anker JN, Laughon MM, Clark RH, Smith PB, Hornik CP. Sildenafil and retinopathy of prematurity risk in very low birth weight infants. *J Perinatol* 2016;**36**:137-40.
 35. Russo FM, Benachi A, Mieghem TV, De Hoon J, Calsteren K, Annaert P, et al. Antenatal sildenafil administration to prevent pulmonary hypertension in congenital diaphragmatic hernia (SToP-PH): study protocol for a phase I/IIb placenta transfer and safety study. *Trials* 2018;**19**:524.
 36. Luong C, Rey-Perra J, Vadivel A, Gilmour G, Sauve Y, Koonen D, et al. Antenatal sildenafil treatment attenuates pulmonary hypertension in experimental congenital diaphragmatic hernia. *Circulation* 2011;**123**:2120-31.

37. Fang AY, Guy KJ, König K. The effect of sildenafil on retinopathy of prematurity in very preterm infants. *J Perinatol* 2013;**33**:218-21.
38. van der Graaf M, Rojer LA, Helbing W, Reiss I, Etnel JRG, Bartelds B. Sildenafil for bronchopulmonary dysplasia and pulmonary hypertension: A meta-analysis. *Pulmonary Circulation* 2019;**9**. doi: 10.1177/2045894019837875.
39. Abounahia FF, Abu-Jarir R, Abounahia MF, Al-Badriyeh D, Abushanab D, Abu-Ghalwa M, et al. Prophylactic Sildenafil in Preterm Infants at Risk of Bronchopulmonary Dysplasia: A Pilot Randomized, Double-Blinded, Placebo-Controlled Trial. *Clinical Drug Investigation* 2019;**39**:1093-1107.
40. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009;**154**:379-84.
41. Al Omar S, Salama H, Al Hail M, Al Rifai H, Bunahia M, El Kasem W, et al. Effect of early adjunctive use of oral sildenafil and inhaled nitric oxide on the outcome of pulmonary hypertension in newborn infants. A feasibility study. *J Neonatal Perinatal Med* 2016;**16**:251-59.
42. Webb DJ, Muirhead GJ, Wulff M, Sutton JA, Levi R, Dinsmore WW. Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000;**36**:25-31.
43. Uslu S, Kumtepe S, Bulbul A, Comert S, Bolat F, Nuhoglu A. A comparison of magnesium sulphate and sildenafil in the treatment of the newborns with persistent pulmonary hypertension: A randomized controlled trial. *J Trop Pediatr* 2011;**57**:245-50.
44. Shaltout F, Hegazy R, Aboulghar H, Motelb LA. Magnesium Sulphate Versus Sildenafil in the Treatment of Persistent Pulmonary Hypertension of the Newborn. *International Journal of Clinical Pediatrics* 2012;**1**:19-24.
45. Nazia F, Sohail A, Ahmed Q, Abdur R, Aashee N, Imran I. Comparison Of The Efficacy Of Sildenafil Alone Versus Sildenafil Plus Bosentan In Newborns With Persistent Pulmonary Hypertension. *JAMC* 2018;**30**:333-36.
46. Goissen C, Ghyselen L, Tourneux P, Krim G, Storme L, Bou P, et al. Persistent pulmonary hypertension of the newborn with transposition of the great arteries: successful treatment with bosentan. *Eur J Pediatr* 2008;**167**:437-40.
47. Alipour MR, Lookzadeh MH, Namayandeh SM, Pezeshkpour Z, Sarebanhassanabadi M. Comparison of Tadalafil and Sildenafil in Controlling Neonatal Persistent Pulmonary Hypertension. *Iranian J Pediatr* 2017;**27**:e6385.
48. Bravo MC, Cordeiro M, Deiros L, Pérez-Rodríguez J. Lethal pulmonary hypertension associated with ibuprofen treatment in a very low birth weight infant. *J Paediatr Child Health* 2014;**50**:85-86.
49. Rodriguez-Castano MJ, Aleo E, Arruza L. Oral Sildenafil for Severe Pulmonary Hypertension Developing after Ibuprofen Use in a Neonate. *Indian Pediatr* 2016;**53**:349-50.