Emerging Role of Sildenafil in Neonatology

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Over the last few years, sildenafil is increasingly being used in the neonatal ICU for a variety of indications. The use is even more so in the developing world due to the limited availability of nitric oxide and extracorporeal membrane oxygenation (ECMO). There are still no clear cut guidelines for its use. At present the drug appears relatively safe and effective when other treatment options have been optimized. However, the use of sildenafil must be monitored and reported. Due to its easy availability and ease of administration we must guard against its inappropriate use.

Key words: *Neonate, Management, Persistent Pulmonary Hypertension of Newborn (PPHN), Sildenafil.*

The role of sildenafil in the treatment of persistent pulmonary hypertension in the newborn (PPHN) was first reported in the lay press way back in 2002 [1]. There was much criticism about its use then. However, there were a few who felt that the use was justified [2], as there were no other options for the attending neonatologist in face of non-availability of inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO). There have been published reports of its usefulness in adult cardiac patients as well as in animal models, prior to its use in newborns [3,4]. Since then there have been many more case reports and some small randomized studies regarding the use of sildenafil in babies with severe PPHN. The drug is now frequently being used in many centers in India and other developing countries where the availability of high frequency ventilation, nitric oxide and ECMO is extremely limited.

The reported incidence of PPHN is 0.43-6.8 per thousand newborns [5]. It is likely to be much more in developing countries, where little data is available. The mortality for the condition has remained static at 10% to 20% over the last decade. Nitric oxide alone does not appear to be a solution to the problem. Upto 30% infants fail to improve despite nitric oxide [6]. The cost of its use is prohibitive. Also inhaled nitric oxide has the ability to displace oxygen and bind to hemoglobin forming methemoglobin, thereby further reducing the oxygen carrying capacity of blood. The availability of ECMO, even in developed countries, is limited to few specialist centers and almost always involves transport of a very sick baby to the nearest available centre. ECMO as an option is almost non-existent in developing countries.

The management strategies for PPHN must include optimization of ventilation, fluid, electrolyte and acid base balance along with the maintenance of blood pressure. Oral sildenafil can be a useful adjunct to the treatment if nitric oxide is not available. It can also be used in conjunction with nitric oxide to facilitate quicker weaning off nitric oxide [7].

The pulmonary vascular resistance (PVR) at birth is very high. With the onset of breathing, PVR falls and pulmonary blood flow increases. The failure of this process in the transitional circulation results in PPHN. The various mechanisms regulating the PVR are complex. Nitric oxide (NO)-guanylate cyclase-3'5' cyclic guanosine monophosphate (cGMP) system plays an important role in regulating PVR in the perinatal as well as mature pulmonary

vasculature. Nitric oxide activates soluble guanylate cyclase in vascular smooth muscle cells, resulting in an increase in cGMP levels. Increased cGMP in the vascular smooth muscle results in vasodilation through the activation of cGMP dependent protein kinases. Intracellular cGMP levels are determined by a balance between the synthesis of cGMP and its degradation. Phosphodiesterases (PDEs) are the enzymes responsible for the degradation of all cyclic nucleotides. The lung contains many PDEs but the major component is a cGMP specific PDE called PDE5. There is high PDE5 activity in the fetal pulmonary arteries. Sildenafil acts specifically by inhibiting PDE 5 thus producing pulmonary vasodilation by increasing cGMP levels [8].

The dose of sildenafil was initially chosen empirically, starting at 0.5mg/kg and increasing up to 2mg/kg per dose to achieve required response. It is given every 6 hours. A recent study of the pharmacokinetics of sildenafil shows that an oral dose of 4.2 mg/kg/day is comparable to recommended adult dose of 20 mg three times a day [9]. In this study, there was a high inter-patient variability probably related to variable gut absorption of the drug. Also co- administration of fluconazole resulted in 47% delayed clearance of sildenafil. The dose recommended by Working Group on Management of Congenital Heart Diseases in India [10] is 0.5-5 mg/kg/day in 3-4 divided doses with dose reduction in renal and hepatic impairment. A commonly used dose is 1 mg/kg/dose given 6 hourly. The duration of treatment is usually for 2-3 days. However the drug can be stopped earlier if the oxygenation index (OI) improves to being below 20. There are also a few reports of long term use of the drug, without significant side effects [11].

Oral sildenafil is fairly well tolerated, although absorption can be erratic at times. Since no intravenous preparation is available, it can only be given orally. A 50 mg tablet of sildenafil is crushed and dissolved in water in a concentration of 1 mg/mL and then given via nasogastric tube. Side-effects reported in adult literature are secondary to vasodilatation and include flushing headaches, dizziness, hypotension, blurred vision and painful erection [12]. There have been few reports of side effects in infants. One must watch the systemic blood pressure closely, although this has been rarely a problem. There have been reports of hypotension when it is used in conjunction with nitric oxide [13]. There has been a report of severe retinopathy of prematurity (ROP) in a preterm baby who received Sildenafil [14]. However, this baby had multiple risk factors for developing ROP other than Sildenafil use. There is also a report of severe bleeding in a newborn following circumcision [15]. Thrombocytopenia is a relative contraindication for the use of sildenafil.

A small randomised study of sildenafil versus placebo [5] showed improvement in OI within 6- 30 hours with steady improvement in pulse oxygen saturation over time. Six of seven babies survived in the study group versus one of six in the placebo group. All studied infants were extremely sick with high ventilator parameters, OI >25 and FiO2 of 100%. A Cochrane review of the role of sildenafil in PPHN has also been published [16]. As there were few studies, it still recommends the use of the drug on an experimental basis only.

Apart from PPHN, sildenafil has also been used in the management of congenital diaphragmatic hernia to improve oxygenation and bring down venti-lator requirements [17]. Although this has been on a case to case basis, the results have been encouraging.

Sildenafil has also been used to treat pulmonary hypertension (PH) associated with congenital heart disease, both in newborns and in older children [18]. A recent meta-analysis showed its effectiveness in treating pulmonary hypertension following paediatric cardiac surgery [19].

Sildenafil has been used in the management of PH in association with chronic lung disease in children less than 2 years of age [11]. It was used in 25 children, with 22 (88%) achieving hemodynamic improvement after a median duration of 40 days. Their data suggested that chronic Sildenafil therapy is well-tolerated, safe and effective for infants with PH and chronic lung deseases.

Emerging data continues to show the safety and effectiveness of oral sildenafil therapy. However the published studies are on small number of patients and caution must be exercised in the interpretation of their outcomes. Since the drug is easily available and

convenient to administer, it has the potential for inappropriate use.

We could not find any Indian data or case report on use of sildenafil in PPHN. There is a feeling that the drug is being used by many neonatal intensivists. Although we discourage the use of Sildenafil except on an experimental basis, we urge that experience of use of the drug be shared in a peer reviewed journal.

A controlled multicenter study with adequate sample size is needed to evaluate the safety, efficacy, and long term outcome of treatment with sildenafil of neonates with PPHN. Research is also needed to determine differences in drug efficacy between adults and children, age dependent patterns of pharmacokinetics, and dose optimisation for the individual patient. An intravenous preparation of Sildenafil should also be made available as this would probably provide more predictable plasma concentrations. All experiences with sildenafil, whether it is used in conjunction with other established modalities or by itself, must continue to be monitored and reported. It must be remembered that current published research with sildenafil is limited to term or near term babies and it must be used in them with extreme caution on a case to case basis.

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