Outcome of Oral Sildenafil Therapy on Persistent Pulmonary Hypertension of the Newborn at Queen Sirikit National Institute of Child Health

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Background: *Persistent pulmonary hypertension of the newborn (PPHN) is a common problem in the neonates with a high mortality rate. The prevalence ranges from 0.38-0.99 per 1,000 live births at Queen Sirikit National Institute of Child Health. The survival rate has improved after the advent of high-frequency ventilation and inhaled nitric oxide. However, inhaled nitric oxide is expensive and unavailable in most neonatal centers in Thailand. Sildenafil is a phosphodiesterase inhibitor type 5 that selectively reduces pulmonary vascular resistance and hence may play a role in the treatment of PPHN.*
Objective: *To evaluate effectiveness and short-term side effects of oral sildenafil for infants > 36 weeks gestational age who have PPHN.*
Material and Method: *The present study was conducted between January 2006 and December 2008 in the neonatal intensive care unit (NICU) at Queen Sirikit National Institute of Child Health. All infants ≥ 36 weeks gestational age who were diagnosed as PPHN by echocardiogram and had an oxygenation index ≥ 20 were included in the study. Oral sildenafil was given as per study protocol with a starting dose of 0.25-0.5 mg/kg/dose. Oxygenation index (OI), oxygen saturations (SpO2), alveolar arterial oxygen gradient (A-aDO2) and mean arterial blood pressure (MAP) were monitored serially.*
Results: *A total of 40 infants were diagnosed with PPHN during this period. Eleven infants were included in the present study. The initial median OI was 31.95 (24.25-48.25). All infants received standard therapy with mechanical ventilation, sedation and inotropic drugs. OI decreased 4.6% from base line after the first hour of starting oral sildenafil and progressively decreased by 13%, 27%, 37%, 41% and 90% at 2, 4, 6, 12 and 24 hours respectively. Oral sildenafil was discontinued in one infant. It was combined with inhaled iloprost in 2 infants due to systemic hypotension and with inhaled nitric oxide in one infant due to deterioration. One infant died during the present study.*
Conclusion: *Oral sildenafil may be effective in improving oxygenation in some infants with persistent pulmonary hypertension of the newborn. Systemic hypotension was a cause for concern in the present study. Further studies are needed to assess the pharmacokinetics, efficacy and long term side effects of this drug.*

Keywords: *Persistent pulmonary hypertension, Sildenafil, Oxygenation index*

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Persistent pulmonary hypertension of the newborn (PPHN) is a serious neonatal illness, which in the past was associated with high mortality and morbidity. With the advent of new technology and advanced neonatal care, there has been an improvement in the overall outcome. PPHN is a clinical syndrome caused by a vast number of diseases. It results from failure of the neonate to make a postnatal transition from a high resistance fetal pulmonary circulatory state to a low resistance pulmonary circulation. This increased pulmonary vascular resistance and decreased pulmonary blood flow prevents adequate gas exchange in the lungs resulting in severe respiratory distress and hypoxemia in the neonate.

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The pathophysiologies underlying PPHN are underdevelopment (pulmonary hypoplasia, congenital diaphragmatic hernia), maldevelopment (chronic hypoxia, placental insufficiency, elevated pulmonary pressure), or maladaptation (triggered by acidosis, hypoxemia and hypercarbia) of pulmonary vasculature[1,2]. PPHN is associated with meconium aspiration syndrome (50%), pneumonia/sepsis (20%), idiopathic (20%), RDS (5%) and other causes (5%) such as asphyxia, congenital diaphragmatic hernia, alveolar capillary dysplasia and polycythemia[3].

The prevalence of PPHN has been reported to be 1.9/1,000 live births with a wide variation observed amongst centers (0.43-6.82/1,000 live births). The mortality rate also varies ranging from 4 to 33% in various centers in the United States[4]. At Queen Sirikit Nationnal Institute of Child Health (QSNICH), PPHN occurs in 0.38-0.99/1,000 live births with a mortality rate of 24 %[5]. The main goals of treatment of PPHN are to decrease pulmonary vascular resistance and increase pulmonary blood flow. This is done by correcting the underlying disease, good supportive care and selective pulmonary vasodilators. Inhaled nitric oxide (iNO) is a selective vasodilator and large trials have shown it to be the mainstay in the treatment of PPHN[6-9]. However, 30% of neonates do not respond to iNO[10]. It has also been shown that iNO does not reduce the mortality rate in PPHN or decrease the duration of hospital stay[11]. This and the fact that iNO is expensive and not easily available, makes it a less than ideal treatment in resource poor underdeveloped or developing countries. Hence, there has been an increased effort to find alternative treatments for PPHN. Of interest have been therapies that can modulate the pulmonary vasculature targeting the nitric oxide-cyclic guanosine monophosphate (cGMP) pathway. One such therapy has been the phosphodiesterase inhibitors. Inhibition of phosphodiesterase 5 leads to an increase in the cyclic GMP which leads to pulmonary smooth muscle relaxation[12]. Thus, action of phosphodiesteras 5 inhibitors in the lungs, which have a high concentration of phosphodiesterase 5, can potentially result in a significant decrease in pulmonary vascular resistance. The phosphodiesterase 5 inhibitors include sildenafil, dipyridamole and Zaprinast.

Animal studies and anecdotal human reports have shown improvements in pulmonary vascular resistance with sildenafil[13-17]. Baquero et al reported the comparison of the use of oral sildenafil and a placebo in 13 neonates with severe PPHN. The infants in the treatment group showed improvement in oxygenation and survival compared with the placebo group[18]. However, there has been a report of severe retinopathy of prematurity in one study following the use of sildenafil in a neonate with PPHN[19]. It has also been suspected of worsening proliferative diabetic retinopathy in adults[20,21]. An animal study by Shekerdeman et al, showed that even though there was improvement of pulmonary vascular resistance, there was also an associated systemic vasodilatation and deterioration of oxygenation when sildenafil was administered with iNO[22]. Thus, it is important to study the safety of this drug. A systematic review of sildenafil for pulmonary hypertension in 77 adults and children from four eligible studies concluded that more studies of adequate size were necessary[23]. A similar systematic review in neonates also concluded that the safety and effectiveness of PPHN could not be established and further randomized control trials of adequate power were necessary[24].

Objective

The present study was conducted to evaluate the effectiveness and safety of oral sildenafil in treating neonates greater than 36 weeks gestation with PPHN.

Material and Method

The present case series study was conducted in the neonatal intensive care unit of the Queen Sirikit National Institute of Child Health between January 2006 and December 2008 after approval from the institutional review board. A written, informed consent was obtained from the legal guardians of each patient. All neonates greater than 36 weeks of gestation and diagnosed as PPHN were eligible for the present study. PPHN was considered when there was hypoxemia and a preductal to postductal oxygen gradient greater than 20 mmHg. Diagnosis was confirmed by an echocardiogram (GE Vingmed) performed by a single pediatric cardiologist demonstrating a structurally normal heart with increased pulmonary arterial pressure, and or the presence of extrapulmonary right to left shunting at the ductus arteriosus or foramen ovale. Only those infants with PPHN and two oxygenation indices $\geq$ 20 at least 30 minutes apart and a mean arterial blood pressure > 45 mmHg were included in the present study. Patients with major congenital anomalies, congenital diaphragmatic hernia, congenital heart disease and maternal HIV were excluded from the present study.

Study protocol

Once the infants were enrolled in the present

study, complete history and physical examination were performed and blood drawn to obtain baseline laboratory data including a complete blood count, arterial blood gases, and liver function test. All patients had a continuous pulse oximeter and blood pressure monitoring. Patients were ventilated either using the conventional mode or the high frequency oscillatory ventilation (SLE 2000 HFO). Blood pressure and intravascular volume were maintained with fluid boluses (crystalloid or colloidal solution) and or inotropes (dopamine, dobutamine or adrenaline) infusion. Hematocrit was maintained at 45% and higher in all patients. Each patient was started on oral sildenafil at 0.25 to 0.5 mg/kg/dose. Arterial blood gases (ABG) were followed at 30, 60, 90, 120 minutes and at 4, 6, 8, 12, 24 and 48 hours. Oxygenation index (OI) was calculated from the ABGs. If after the first dose of sildenafil, the OI dropped to less than 20 or by more than 5 to 10% from the baseline value, the patient was maintained at the initial dose every 6 hours. If on the other hand, there was no decrease in the OI or it dropped by less than 5% in 1 hour, double of the initial dose was repeated at 1 hour. The dose could be increased by 0.25 to 0.5 mg/kg every hour till the maximum of 2 mg/kg/dose was given or the patient developed hypotension. The dose at which the patient responded was then maintained every 6 hours. Sildenafil was discontinued once the OI had decreased to less than 10, or the oxygen administered had decreased to less than 40% (Fig. 1). The patients who did not experience a drop in the OI as per protocol, had other pulmonary vasodilators added to the treatment regimen, or died within 14 days of treatment, were considered to be non responders.

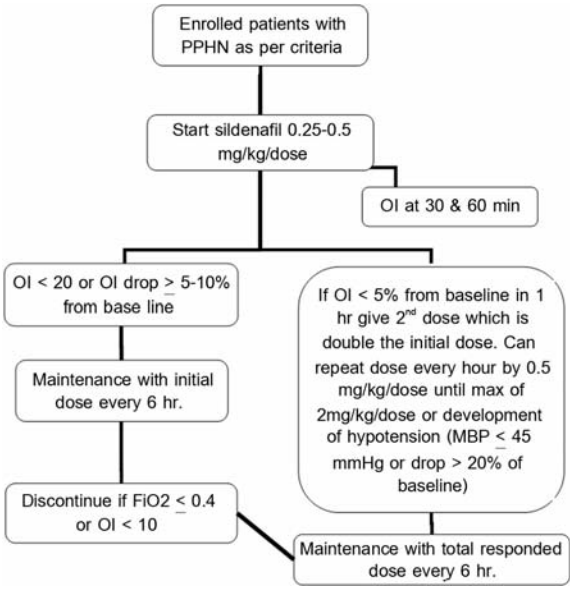

Fig. 1 Study protocol

Sildenafil suspension used for the present study was prepared by the pharmacist using sildenafil (Viagra® by Pfizer) 100 mg/tab dissolved in 50 ml of diluent (Orabase) to make a concentration of 2 mg/ml. This preparation could be refrigerated for a month.

Primary outcomes were to monitor the changes in OI, PaO2, SpO2, and AaDO2 after the first dose and at 2, 6, 12, 24, 36 and 48 hours after sildenafil administration. Secondary outcomes were the detection of any side effects such as hypotension, retinopathy of prematurity, bronchopulmonary dysplasia, length of oxygen administration and hospital stay.

Statistical analysis

The results were analyzed using SPSS (version 16) for Windows. Median values (P 25-P75) were used for continuous data. Differences between values over time were evaluated with analysis of variance for repeated measurement. Mann Whitney U test and Wilcoxon signed rank test were used for paired design. The threshold for significance was $p < 0.05$.

Results

A total of 40 neonates were eligible for the present study; 11 were enrolled. The 29 excluded patients consisted of 11 with congenital diaphragmatic hernia, 5 who had an OI < 20, 2 who were less than 36 weeks gestation, who did not have an echocardiographic confirmation, 8 who was treated initially with inhaled nitric oxide, and one with pulmonary artery sling (Fig. 2). PPHN occurred in 0.74/1000 live births.

Of the 11 patients included in the present study, 6 were male, 6 inborn, median gestation age was 38 (38-40) weeks and the median birth weight was 3,205 (2,800-3,930) grams. The causes of PPHN were meconium aspiration syndrome 7 cases (63.6%), pneumonia 2 cases, birth asphyxia and idiopathic 1 case each. The median age at enrollment was 11.5 (9.25-46.5) hours. Nine neonates were on HFOV at enrollment. The median mean airway pressure was 16 (12.75-19) cm H2O. The median PaO2, PaCO2 and pH at enrollment were 43.55 (34.48-58.18) mmHg, 33.85 (31.28-40.65) mmHg and 7.38 (7.35-7.42) respectively. The median oxygenation index at the time of entry was 31.95 (24.25-48.25) (Table 1). All patients were on vasopressors and 10 were on analgesic and or sedative at the time of enrollment. The starting dose of sildenafil ranged from

0.25-0.5 mg/kg /dose and the total dose ranged from 0.5-19.5 mg/kg with an average of 4.39 ± 5.63 mg/kg.

Primary outcome

Both the mean preductal and postductal SpO2 increased after the initial dose of sildenafil, but this change was not statistically significant over time (p 0.69). The PaO2 also increased after the first dose of sildenafil, but this change was not significant over time and even showed a decrease at 24 and 48 hours (Fig. 3). The AaDO2 decreased after the first dose of sildenafil but it was not statistically significant over time (Fig. 4). The OI decreased after the first dose of sildenafil and when analyzed, it showed as a statistically significant decrease over time (Fig. 5). The decrease from the baseline at enrollment was by 4.6%, 13%, 27%, 37%, 41%, 90% after 1, 2, 4, 6, 12 and 24 hours (Fig. 6).

Secondary outcome

There were a total of 5 neonates who did not respond to the therapy. One died, 3 cases had either inhaled nitric oxide or iloprost combined with sildenafil treatment and 1 was switched to inhaled iloprost. There

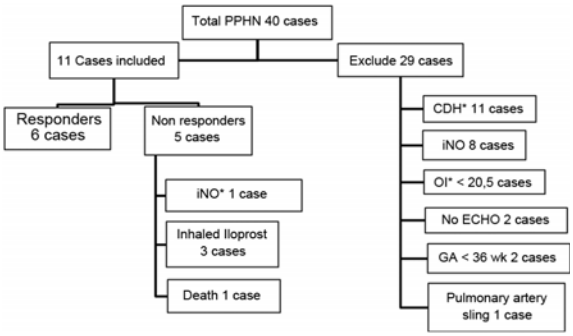

Fig. 2 Study derivation

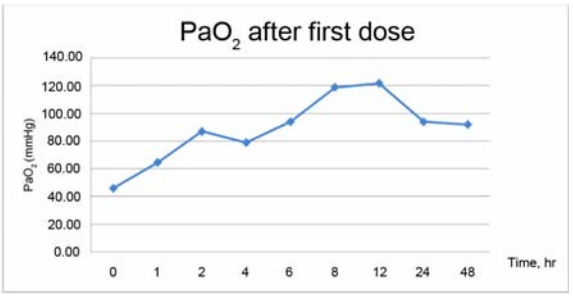

Fig. 3 Mean PaO_2 after first dose of sildenafil (n = 11)

Table 1. Demographic data

Variable	Sildenafil (n = 11)
Gender, female/male	6/5
Gestational age, wk	38 (38-40)
Birth weight, g (range)	3,205 (2,800-3,930)
Apgar score	
1 min	8 (5.75-9.0)
5 min	9 (8.75-9.25)
Cesarean section, n (%)	8 (72.7)
Out-born/Inborn, n (%)	5/6 (45.5/54.50)
Meconium aspiration, n (%)	7 (63.6)
Pneumonia, n (%)	2 (18.1)
Age at enrollment, hr	11.5 (9.25-46.5)
Treatment before enrollment	
Fluid bolus, n (%)	10 (90.9)
Vasopressor support, n (%)	11 (100)
Sedative or analgesia, n (%)	10 (90.9)
Air leaks before enrollment, n (%)	4 (36.4)
High frequency ventilation (HFV), n	9
Mean airway pressure (MAP), cmH_2O	16 (12.75-19.0)
Fraction of inspired oxygen (FiO_2)	1.0
pH	7.38 (7.35-7.42)
$PaCO_2$ (mmHg)	33.85 (31.28-40.65)
PaO2 (mmHg)	43.55 (34.48-58.18)
HCO_3 (mmol/L)	20.7 (19.75-22.75)
Oxygenation index (OI)	31.95 (24.25-48.25)

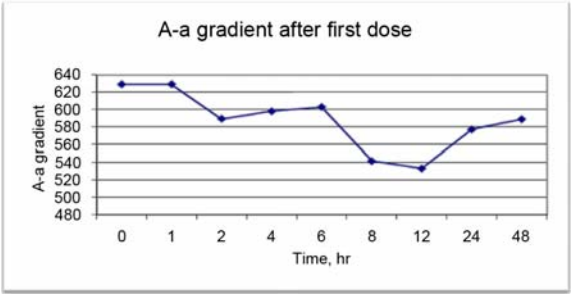

Fig. 4 Change in the A-a gradient ($AaDO_2$) after the first dose sildenafil (n = 11)

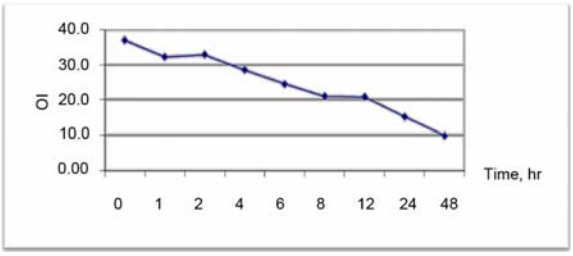

Fig. 5 Mean OI after the first dose of sildenafil (n = 11)

were no statistically significant differences between the responders and the non-responders with regards to demographic data, diagnosis, age at enrollment, treatment before enrollment, ventilator settings and blood gases analysis. There was however, a statistically significant difference between the two groups with regards to OI at enrollment, with the non-responders having a higher median OI 46.12 (30.3-62) compared with that of the responders 29.31 (21.5-36.45) p 0.045 (Table 2).

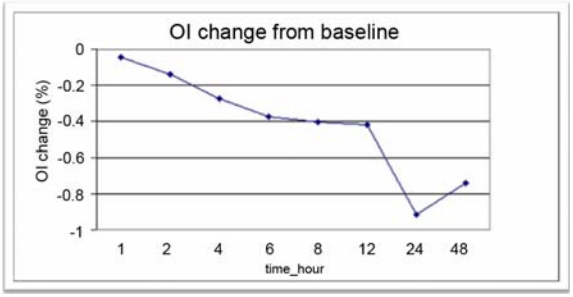

Fig. 6 Change in mean OI from baseline after the first dose of sildenafil

Table 2. Comparison between responders and non responders to sildenafil

Variables	Responders (n = 6)	Non-responders (n = 5)	p-value
Gender, female/male	3/3	2/3	0.60
Gestational age, wk*	39.8 (38-42)	37.2 (35-39)	0.07
Birth weight, g*	3,670 (3,175-4302)	3,031 (2610-3567)	0.1
Apgar score,			
1 min	7.33 (5.75-9.25)	7.5 (5.75-8.75)	1.0
5 min	9.0 (8.5-10)	8.75 (8.25-9.0)	0.4
Cesarean section, n (%)	6 (100)	2 (40)	0.06
Out-born/Inborn, n (%)	3/3 (50,50)	2/3 (40/60)	0.60
Meconium aspiration, n (%)	5 (83.3)	2 (40)	0.57
Pneumonia, n (%)	1 (16.6)	1 (16.6)	1
Age at enrollment, hr*	25.5 (9.25-48)	16.0 (5.5-29.5)	0.31
Treatment before enrollment			
Fluid bolus, n (%)	6 (100)	4 (80)	0.36
Vasopressor support, n (%)	6 (100)	5 (100)	1.0
Sedative or analgesia, n (%)	6 (100)	4 (80)	0.36
Air leaks before enrollment, n	3 (50)	1 (20)	1.0
High-frequency ventilation (HFV), n	5 (83.3)	4 (80)	0.49
Fraction of inspired oxygen, (FiO_2)	1.0	1.0	-
pH*	7.39 (7,31-7.48)	7.37 (7.3-7.42)	0.52
$PaCO_2$* (mmHg)	33.2 (28.4-37.6)	37.08 (31.25-42.3)	0.27
PaO2* (mmHg)	50.15 (39.4-58)	41.34 (29.3-56.5)	0.1
HCO_3* (mmol/L)	19.72 (18.2-20.95)	21.26 (17.05-25.1)	0.17
Oxygenation index (OI)*	29.31 (21.5-36.45)	46.12 (30.3-62)	0.045

*median (P_{25}-P_{75})

One patient developed pneumothorax after starting treatment. The median duration on ventilator and supplemental oxygen were 6 (3-8) and 10.5 (7-12) days respectively. The median length of hospital stay was 17.5 (8.75-23) days. One patient died during the present study. Two patients developed bronchopulmonary dysplasia and none developed retinopathy (Table 3).

Although the mean blood pressure decreased after the first dose of sildenafil, the change was not significant over time (p 0.072) (Fig. 7). Despite a trend of lower mean arterial blood pressure in the non-responders, subgroup analysis did not show any statistically significant differences between the two groups before and after sildenafil (Table 4). However, there was a statistically significant drop in the mean arterial blood pressure in both groups after sildenafil (Table 5).

Description of the non-responders

Case 1 initially responded to sildenafil, but 4 hours after the 3rd dose he developed an unexplained seizure and hypotension which was unresponsive to

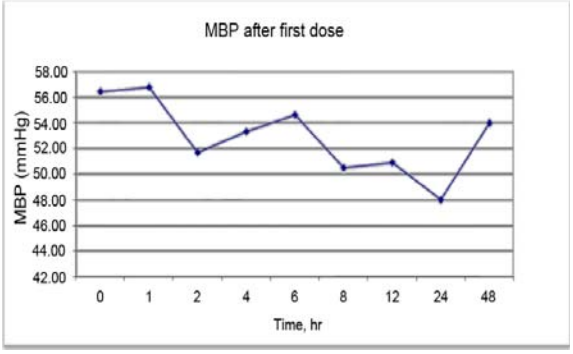

Fig. 7 Change in mean blood pressure after the first dose of Sildenafil over time n = 11

Table 3. Secondary outcome

Variable	Sildenafil (n = 11)
Air leak after enrollment, n (%)	1 (9.1)
Assisted ventilation, days*	6 (3-8)
Supplemental oxygen, days*	10.5 (7-12)
Length of hospital stay, days*	17.5 (8.75-23)
Retinopathy of prematurity (ROP), n (%)	0
Bronchopulmonary dysplasia (BPD), n (%)	2 (18.1)
Seizure, n (%)	1 (9.1)
Death, n (%)	1 (9.1)

*Median (P_{25}-P_{75})

Table 4. Comparison of mean blood pressure between the two groups

	Responders n = 6	Non-responders n = 5	p**
MBP before* (mmHg)	60.0 (50.75-67.5)	50.0 (49.5-53)	0.05
MBP after* (mmHg)	51.0 (46.0-61.25)	45.0 (34.0-48.0)	0.06

*Median (P_{25}-P_{75}), **Mann-Whitney U-test

Table 5. Comparison of blood pressure before and after sildenafil

	Responders n = 6	Non-responders n=5
MBP before* (mmHg)	60.0 (50.75-67.5)	50.0 (49.5-53)
MBP after* (mmHg)	51.0 (46.0-61.25)	45.0 (34.0-48.0)
p**	0.028	0.043

* Median (P_{25}-P_{75}) ****,** Wilcoxon Signed- Ranks test

fluid boluses, dopamine, dobutamine and adrenaline. This baby died at 33 hours of age. Blood tests and head ultrasound did not reveal any abnormalities. Autopsy was refused by the parents. Case 2 showed a drop in the OI after the first dose, but increased after the 2nd dose. The OI increased further after the 3rd dose with a simultaneous drop in blood pressure. The attending neonatologist switched the baby to inhaled iloprost to which the baby responded well. Case 3 did respond to the first dose of sildenafil of 0.25 mg/kg, but since the OI was still over 40, the attending neonatologist increased the 2nd dose to 0.5 mg/kg. The patient developed systemic hypotension within 1 hour of this dose and needed a fluid bolus. The attending neonatologist decided to combine inhaled iloprost and 0.25 mg/kg/dose of sildenafil every 6 hours. Case 4 did not show any response to sildenafil and so was combined with inhaled iloprost. The last patient responded well to 0.5 mg/kg/dose every 6 hours but started to have desaturations after 48 hours with an increase in the OI to 24. The attending neonatologist added inhaled nitric oxide to the therapy. However, a blood culture report from the day of deterioration was positive for Acinetobacter baumanii which explained worsening in this baby.

Discussion

The objective of the present study was to evaluate the effectiveness and short term safety of oral sildenafil for the treatment of PPHN in the term/near term neonate. The present study found that there was an increase in the PaO2 and SpO2 and a decrease in the AaDO2 after the first dose of oral sildenafil. The increase in PaO2 was not sustained over time especially after 24 hours. This could have been caused by the steady decrease in the OI allowing for the lowering of the FiO2 by the attending neonatologist especially at 24 and 48 hours when the percentage drop in the OI from baseline was the maximum.

In this small study, 6 infants responded to sildenafil-whilst 5 did not. Comparison between the groups showed the OI to be significantly higher in the non-responders, with a median of 46.12 versus 29.31 in the responders indicating a greater severity of disease in the former. A study by Finer et al demonstrated that 30% of babies with PPHN and an OI > 40 did not respond to iNO and had to be treated by ECMO[11].

The starting dose of sildenafil in the present study was lower than that of other studies because previous experiences at QSNICH with a higher dose of 0.5-1 mg/kg had frequently resulted in hypotension. Even though the present study, like other studies, did not show a significant decrease in blood pressure over time, the authors did find a significant drop when comparing the blood pressure before a dose and within one hour after sildenafil. Most of the infants in the present study required fluid boluses after sildenafil hence the overall blood pressure did not show any change over time. The hypotension resulted in deterioration of oxygenation in a few patients making it necessary to add other vasodilators to the treatment. This could be explained by the increase in right to left shunt with systemic hypotension. A previous study by Sherkerdemian et al in an animal model, showed, that even though there was pulmonary vasodilatation with sildenafil, it did result in hypotension and worsening of oxygenation when combined with iNO[22]. In the present study there was no change seen in mean arterial blood pressure in the one case where sildenafil was combined with iNO. Recently, Steinhorn et al concluded that intravenous sildenafil was well tolerated at a loading dose of 0.4 mg/kg delivered over 3 hours followed by a maintenance infusion at 1.6 mg/kg/day. The study did not detect any a significant decrease in systemic blood pressure. However, sildenafil had to be discontinued in 2 infants due to drug related hypotension[25].

None of the infants in the present study experienced any retinopathies unlike in a few other reports[19,21]. Death did occur in one of our patients. The infant developed seizures followed by hypotension a few hours after the 3rd dose of sildenafil. The hypotension was unresponsive to fluid boluses or vasopressors and the patient finally succumbed at 33 hours of life. Even though some adult reports have considered sildenafil to be the cause of central nervous disturbances via the NO-cGMPcascade modification, the authors did not find any reports of seizures[26]. Since an autopsy was not authorized in this patient, cause of death could not be identified.

Three of our non-responders showed an improvement in their oxygenation when their treatment was combined with other vasodilators. This conforms to other studies that have shown that oral sildenafil acts synergistically with other vasodilators such as inhaled iloprost or nitric oxide to cause pulmonary vasodilatation in severe PPHN[27-30]. Sildenafil has also been reported to ameliorate the effects of iNO withdrawal[31].

Conclusion

Oral sildenafil may be effective in improving

oxygenation in some infants with persistent pulmonary hypertension of the newborn. Systemic hypotension was a cause for concern in the present study. Further studies are needed to assess the pharmacokinetics, efficacy and long-term side effects of this drug.

Potential conflicts of interest

None.

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การศึกษาผลของการใช้ยา sildenafil รักษาภาวะความดันหลอดเลือดในปอดสูงใน ทารกแรกเกิดในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

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ความเป็นมา: ภาวะความดันหลอดเลือดในปอดสูงในทารกแรกเกิด (Persistent Hypertension of the Newborn, PPHN) เป็นปัญหาที่พบในผู้ป่วยทารกครบกำหนดและเป็นภาวะที่มีอัตราการตายสูง สถาบันสุขภาพเด็กแห่งชาติมหาราชินีพบอุบัติการณ์ ของภาวะความดันหลอดเลือดในปอดสูงในทารกแรกเกิด 0.38-0.99 รายต่อทารกแรกเกิดมีชีพ 1,000 ราย การรักษาด้วยเครื่องช่วยหายใจความถี่สูงใช้ร่วมกับการให้ก๊าซ nitric oxide พบว่าอัตราการรอดชีวิตร้อยละ 85 แต่เนื่องจากก๊าซ nitric oxide มีราคาแพงจึงมีใช้เฉพาะบางสถาบัน ปัจจุบันพบว่า sildenafil เป็น phosphodiesterase inhibitor ออกฤทธิ์ขยายหลอดเลือดในปอดทำให้ออกซิเจนดีขึ้นและเริ่มนำมาใช้รักษาทารกที่มีภาวะ PPHN

วัตถุประสงค์: เพื่อศึกษาผลการให้ sildenafil (Viagra®) ในรูปรับประทานในการรักษาทารกที่มีภาวะความดันหลอดเลือดในปอดสูง และศึกษาผลข้างเคียงในระยะสั้น

วัสดุและวิธีการ: การศึกษารูปแบบ case series ในทารกที่รับไว้ในหอผู้ป่วยเด็กหนักทารกแรกเกิด ระหว่าง มกราคม พ.ศ. 2549 ถึง ธันวาคม พ.ศ. 2551 สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ซึ่งมีอายุครรภ์มากกว่า 36 สัปดาห์ที่ได้รับการวินิจฉัยเป็นภาวะความดันหลอดเลือดในปอดสูงจากการทำ echocardiogram และมีค่า oxygenation index (OI) มากกว่าหรือเท่ากับ 20 ได้รับยา sildenafil (Viagra®) ขนาดเริ่มต้น 0.25-0.5 มก./กก./ครั้ง โดยติดตามค่า OI, SpO_2, MBP และ $AaDO_2$ ที่ชั่วโมงต่าง ๆ หลังได้รับยา

ผลการศึกษา: พบมีทารกที่ได้รับการวินิจฉัยภาวะความดันหลอดเลือดในปอดสูงในทารกแรกเกิดทั้งหมดจำนวน 40 ราย มีทารกเข้าศึกษาจำนวน 11 ราย ได้รับการรักษาด้วย sildenafil ในรูปรับประทานโดยมีค่า OI และค่ามัธยฐานที่ 31.95 (24.25-48.25) ทารกทุกรายได้รับการรักษาเบื้องต้นด้วยเครื่องช่วยหายใจ, และ inotrope หลังจากได้รับยา oral sildenafil พบว่า OI มีค่าลดลงเฉลี่ย 4.6% ที่ชั่วโมงแรก และมีค่าลดลง 13%, 27%, 37%, 41% และ 90% ที่ชั่วโมงที่ 2, 4, 6, 12 และ 24 ชั่วโมง ตามลำดับพบว่ามีผู้ป่วย 1 ราย หยุดยา sildenafil และมีผู้ป่วย 2 ราย ที่ได้รับยา inhaled iloprost ร่วมกับ sildenafil เนื่องจากพบความดันโลหิตต่ำหลังได้รับยาผู้ป่วย 1 ราย ได้รับก๊าซ nitric oxide และ มีผู้ป่วยเสียชีวิต 1 ราย

สรุป: ยา sildenafil ในรูปรับประทานอาจจะมีประโยชน์ในการรักษาผู้ป่วยความดันหลอดเลือดในปอดสูงบางรายในการลด ความดันหลอดเลือดในปอดทำให้ค่าออกซิเจนดีขึ้น แต่ควรใช้ด้วยความระมัดระวังเนื่องจากอาจพบความดันโลหิตต่ำได้ หลังจากได้รับยาเนื่องจาก sildenafil เป็นยาใหม่ทำให้มีข้อจำกัดในข้อมูลทางด้านขนาดยาที่เหมาะสมประสิทธิภาพรวมทั้งภาวะแทรกซ้อน และความปลอดภัยในการใช้ยาในทารกแรกเกิดมีความจำเป็นต้องได้รับการศึกษาเพิ่มเติม