Sildenafil and an Early Stage of Chronic Hypoxia-Induced Pulmonary Hypertension in Newborn Piglets

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Summary. Devising therapies that might prevent the onset or progression of pulmonary hypertension in newborns has received little attention. Our major objective was to determine whether sildenafil, a selective phosphodiesterase inhibitor, prevents the development of an early stage of chronic hypoxia-induced pulmonary hypertension in newborn pigs. Another objective was to determine whether sildenafil causes pulmonary vasodilation without systemic vasodilation in piglets with chronic pulmonary hypertension. Piglets were raised in room air (control, n = 5) or 10–11% O2 (hypoxic, n = 17) for 3 days. Some piglets (n = 4) received oral sildenafil, 12 mg/kg/day, throughout exposure to hypoxia. All piglets were anesthetized and catheterized, and pulmonary arterial pressure (Ppa), pulmonary wedge pressure (Pw), aortic pressure (Ao), and cardiac output (CO) were measured. Then for some piglets raised in hypoxia for 3 days, a single oral sildenafil dose (3 mg/kg, n = 6) or placebo (n = 5) was given, and hemodynamic measurements were repeated. For piglets raised in hypoxia for 3 days, mean Ppa and calculated PVR were elevated above respective values in control piglets. Mean Ppa and PVR did not differ between piglets that received sildenafil throughout exposure to hypoxia and those that did not. For piglets with chronic hypoxia-induced pulmonary hypertension that received a single oral dose of sildenafil, mean Ppa and PVR decreased, while mean Pw, CO, mean Ao, and systemic vascular resistance remained the same. All hemodynamic measurements were unchanged after placebo. Oral sildenafil did not influence the early stage of chronic hypoxia-induced pulmonary hypertension in newborn piglets. However, a single oral dose of sildenafil caused pulmonary vasodilation, without systemic vasodilation, in piglets with chronic hypoxia-induced pulmonary hypertension, which may have therapeutic implications. Pediatr Pulmonol. 2005; 40:72–80.

Key words: pulmonary circulation; nitric oxide pathway; phosphodiesterase inhibitors; selective pulmonary dilation; cyclic GMP; pulmonary vascular resistance.

INTRODUCTION

Pulmonary hypertension in newborns is a serious disease and is a significant problem in neonatal intensive care units. Due to a variety of causes, including perinatal hypoxia, neonatal pulmonary hypertension sometimes manifests in the first few hours after birth. In addition, ongoing hypoxia from conditions such as chronic lung disease, which many newborns in the intensive care unit experience, can lead to the postnatal development or to the progression of pulmonary hypertension. Once established, pulmonary hypertension can delay the resolution of lung disease and of cardiac function, and may eventually lead to cardiorespiratory failure and death. Current therapies in neonates are limited, and no single therapy is universally effective.1 Moreover, the therapeutic goal of most research has been to acutely decrease pulmonary arterial pressure in infants with pulmonary hypertension presenting in the immediate perinatal period. By comparison, therapies to prevent the development and progression of pulmonary hypertension or to acutely lower pulmonary arterial pressure in neonates with established pulmonary hypertension resultant from chronic cardiorespiratory conditions, including those associated with chronic hypoxia, have received little attention. Therefore, treatment of infants with chronic types of pulmonary hypertension has advanced minimally, remains inadequate, and would benefit from the development of new treatment strategies.2–4

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One therapy for pulmonary hypertension in the perinatal period is inhaled nitric oxide, which acts on soluble guanylate cyclase, which then increases cyclic guanosine 3’,5’-cyclic monophosphate (GMP) levels. cGMP is a potent vasodilator, but its effect is short-lived, since it is rapidly metabolized to GMP by phosphodiesterase.5 Sildenafil is a phosphodiesterase (PDE) inhibitor, and thus prevents the breakdown of GMP. Although relatively selective for type 5 PDE, which is the isoform found predominantly in lung tissue,6,7 other PDE isoforms, such as PDE 6, the subtype which hydrolyzes cGMP in the retina, are also inhibited by sildenafil.6 Phosphodiesterase type 5 is not found in high levels in the systemic vasculature, so that a potential advantage of sildenafil is that its use would not be expected to have significant effects on systemic blood pressure or cardiac output.6 Although there are an increasing number of reports of the clinical use of sildenafil in infants with pulmonary hypertension due to a variety of causes,8–11 whether or not sildenafil lowers pulmonary arterial pressure without adverse effects on the systemic circulation in infants remains uncertain.10,11 Moreover, there is almost no information9 regarding the possibility that sildenafil might be efficacious in preventing the development and progression of pulmonary hypertension in infants suffering from chronic cardiopulmonary conditions associated with chronic hypoxia. We and others previously showed that newborn piglets raised in hypoxic conditions for 3 days develop pulmonary hypertension.12,13 These studies were designed to test the hypothesis that treatment with oral sildenafil given repeatedly throughout 3-day hypoxic exposure would prevent the development of this early stage of pulmonary hypertension. In addition, because concerns about potential deleterious effects on the systemic circulation of newborns persist,10,11 we also evaluated whether a single oral sildenafil dose will acutely lower pulmonary vascular resistance without adversely affecting cardiac output or systemic vascular resistance in newborn piglets with chronic pulmonary hypertension resultant from 3-day exposure to hypoxia.

MATERIALS AND METHODS

Animals

For hypoxic piglets, newborn pigs (2–3 days old) were placed in a normobaric hypoxic environment (chronic hypoxia; n = 17 pigs) for 3–4 days. Normobaric hypoxia was produced by delivering compressed air and N2 to an incubator (Thermocare). The O2 content was regulated at 8–10% (PO2, 60–72 Torr), and CO2 was maintained at 3–6 Torr by absorption with soda lime. The chamber was opened 3–4 times per day to clean, to weigh the animals, and to give medication. The animals were fed ad libitum with an artificial sow milk replacer from a feeding device attached to the chamber. We previously found no difference in hemodynamic measurements and vascular responses between piglets raised in a room-air environment for 3–4 days and piglets raised on a farm.12 For this study, all control piglets were studied on day of arrival from the farm at 5–7 days of age. All protocols were reviewed and approved by the Wake Forest University School of Medicine Animal Care Committee.

Long-Term Sildenafil Treatment

Sildenafil was given orally to some (n = 6) piglets throughout the 3–4 days that they were raised in the hypoxic environment. Four piglets treated with sildenafil received a total daily dose of 12 mg/kg/day (3 piglets received 3 mg/kg/dose given qid; 1 piglet received 4 mg/kg/dose given tid). Because we found no effect from this total daily dose of sildenafil on the development of pulmonary hypertension (see Results), the other 2 piglets received a total daily dose of 18 mg/kg/day (6 mg/kg/dose given tid).

Hemodynamic Measurements in Anesthetized Animals

After 3–4 days in their chamber (n = 11 untreated chronic hypoxic piglets; n = 6 chronic hypoxic piglets treated with sildenafil) or on day of arrival from the farm (n = 5 control piglets), animals were weighed, and anesthetized with acepromazine (2 mg/kg im), ketamine (30 mg/kg im), and pentobarbital (10 mg/kg iv). Note that all piglets were postnatal age 5–7 days on the day of hemodynamic measurements, and that catheters were placed in chronic hypoxic piglets within the first hour after removal from the hypoxic chamber. Additional intravenous sodium pentobarbital was given as needed via an ear vein to maintain anesthesia during the placement of catheters. First, the trachea of the piglet was cannulated so that the animal could be ventilated if necessary. Then a catheter was placed in the right femoral artery for monitoring systemic blood pressure and arterial blood gases. Another catheter was placed through the right external jugular vein into the pulmonary artery to monitor pulmonary artery pressure. To obtain pulmonary wedge pressure, the pulmonary arterial catheter was advanced into a distal vessel. In some animals, wedge pressure could not be obtained, and left ventricular end diastolic pressure was then measured. We previously found no difference between measurements of pulmonary wedge pressure and left ventricular end diastolic pressure in anesthetized piglets.12 The zero reference for vascular pressures was the midthorax. To measure cardiac output by the thermodilution technique (model 9520 thermodilution cardiac output computer, Edwards Laboratory), a thermistor was placed in the aortic arch via the left femoral artery, and a catheter that served as an injection port was placed in the left ventricle via the left carotid artery. Cardiac output was
measured at end-expiration as the mean of three injections of 3 ml of 0.9% saline (0°C). All animals were breathing room air during in vivo measurements. Due to apnea induced by anesthesia, some animals (n = 5, untreated chronic hypoxic; n = 1, chronic hypoxic piglet treated with sildenafil) were ventilated with a piston-type ventilator at a tidal volume of 15 ml/kg, end-expiratory pressure of 2 mm Hg, and respiratory rate of 16 breaths per minute during in vivo hemodynamic measurements.

**Acute Sildenafil Treatment**

After placement of catheters as described above, hemodynamic measurements were obtained. Then some chronically hypoxic animals were given a single dose of sildenafil (3 mg/kg via an orogastric tube, acute sildenafil group; n = 6) or placebo (1 ml 0.9% saline via an orogastric tube, placebo group; n = 5). Pulmonary arterial pressure and aortic pressure were continually monitored for 1 hr after administration of either sildenafil or placebo, at which time, measurements of cardiac output and pulmonary wedge pressure were repeated. All animals were breathing room air during in vivo measurements, and some animals (acute sildenafil treated, n = 2; placebo treated, n = 3) were ventilated with a piston-type ventilator at a tidal volume of 15 ml/kg, end-expiratory pressure of 2 mm Hg, and respiratory rate of 16 breaths per minute during in vivo hemodynamic measurements.

**Drug Preparation**

The enteric coating of sildenafil (Pfizer Pharmaceuticals) tablets (25 mg) was removed with a 1:1 solution of acetone and methanol. Two tablets were then crushed with mortar and pestle. The powder was then mixed with 0.5 ml glycerin to form a paste, which was suspended with 2.5 ml Karo syrup and 2.0 ml distilled water for a final concentration of 10 mg/ml. Sildenafil was refrigerated (20°C) up to 6 months.

**Cyclic GMP Determinations in Small Pulmonary Arteries**

Some animals (n = 5 control piglets used for in vivo hemodynamic measurements, plus 3 control piglets not used for hemodynamic measurements; n = 7 untreated chronic hypoxic piglets; n = 3 chronically hypoxic piglets treated with long-term sildenafil, 12 mg/kg/day) were anesthetized, euthanized, and their lungs excised for dissection of small pulmonary arteries, 50–600 μm in diameter. During dissection of the small pulmonary arteries, tissue was maintained in Krebs with 3-isobutyl-1-methylxanthine (IBMX), a nonspecific phosphodiesterase inhibitor, to prevent the metabolism of cGMP present. The small pulmonary arteries were immediately frozen in liquid N₂, pulverized with mortar and pestle, and sonicated in 1-ml phosphate buffer with 7.5% trichloroacetic acid. Then the vessel samples were centrifuged at 1,500 g for 10 min, and the supernatant was used for determination of cGMP by enzyme immunoassay, using standard techniques and kits from Cayman Chemical. The vessel pellet was dried and weighed. The concentration of cGMP for each sample was normalized to the vessel dry weight.

**Statistics**

Data are presented as means ± SEM. One-way ANOVA with Fisher’s protected least significant difference (PLSD) post hoc comparison test was used to compare data between control, untreated chronic hypoxic, and sildenafil-treated chronic hypoxic animals. Paired t-tests were used to compare data of chronic hypoxic animals before and after a single acute dose of sildenafil or placebo during in vivo measurements. Data were analyzed using Statview (version 4.0) software. P < 0.05 indicated statistical significance.

**RESULTS**

**In Vivo Hemodynamics and Long-Term Sildenafil Treatment**

After 3–4 days of hypoxia, there was no significant difference in weight between control, untreated chronic hypoxic, and long-term sildenafil-treated chronic hypoxic piglets (Table 1). During in vivo hemodynamic measurements, the measured values of pH, PO₂, and PCO₂ did not differ significantly between any groups of piglets (Table 1).

Mean pulmonary arterial pressure and calculated pulmonary vascular resistance [(mean pulmonary arterial pressure – mean wedge pressure or mean left ventricular end diastolic pressure) ÷ by cardiac output] did not differ between untreated chronic hypoxic piglets and those chronic hypoxic piglets that received 12 mg/kg/day

| TABLE 1—Data for Control, Chronically Hypoxic, and Long-Term Sildenafil-Treated (12 mg/kg/day) Chronically Hypoxic Piglets |
|---|---|---|---|---|
| n | Weight (kg) | pH | pCO₂ (Torr) | pO₂ (Torr) |
| Control | 5 | 2.45 ± 0.08 | 7.44 ± 0.01 | 36 ± 2 | 86 ± 7 |
| Chronic hypoxia | 11 | 2.34 ± 0.12 | 7.44 ± 0.02 | 41 ± 2 | 77 ± 3 |
| Sildenafil-treated chronic hypoxia | 4 | 2.78 ± 0.09 | 7.43 ± 0.02 | 45 ± 2 | 89 ± 9 |
sildenafil throughout exposure to hypoxia (values for untreated chronic hypoxic piglets: mean $P_{\text{pa}} = 29.5 \pm 2.7 \, \text{cm} \, \text{H}_2\text{O}$, $\text{PVR} = 0.09 \pm 0.01 \, \text{cm} \, \text{H}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{kg} \cdot \text{min}$; values for piglets that received 12 mg/kg/day sildenafil: mean $P_{\text{pa}} = 32 \pm 3 \, \text{cm} \, \text{H}_2\text{O}$, $\text{PVR} = 0.09 \pm 0.01 \, \text{cm} \, \text{H}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{kg} \cdot \text{min}$). Mean pulmonary arterial pressure (Fig. 1A) and calculated pulmonary vascular resistance (Fig. 1B) were significantly greater in untreated and sildenafil-treated groups of chronically hypoxic piglets than in control piglets. Mean pulmonary wedge pressure did not differ between any group of piglets (control group, $6.6 \pm 0.8 \, \text{cm} \, \text{H}_2\text{O}$; untreated chronically hypoxic group, $8.9 \pm 0.9 \, \text{cm} \, \text{H}_2\text{O}$; and long-term 12 mg/kg/day sildenafil-treated chronically hypoxic group, $9.5 \pm 2 \, \text{cm} \, \text{H}_2\text{O}$). Cardiac output did not differ significantly between untreated chronically hypoxic piglets or long-term 12 mg/kg/day sildenafil-treated chronically hypoxic piglets (Fig. 1C). Cardiac output was significantly less in both groups of chronically hypoxic piglets compared with controls (Fig. 1C). Neither mean aortic pressure nor calculated systemic vascular resistance (Fig. 1D) differed significantly between the control group, untreated chronically hypoxic group, or long-term 12 mg/kg/day sildenafil-treated chronically hypoxic group (values for mean aortic pressure were $61.8 \pm 1.5 \, \text{cm} \, \text{H}_2\text{O}$, $64.2 \pm 2.9 \, \text{cm} \, \text{H}_2\text{O}$, and $60 \pm 1.8 \, \text{cm} \, \text{H}_2\text{O}$, respectively).

Values for the 2 piglets that received 18 mg/kg/day sildenafil did not differ from those for piglets that received 12 mg/kg/day sildenafil (values for the 2 piglets that received 18 mg/kg/day sildenafil: mean $P_{\text{pa}} = 34.5 \pm 6 \, \text{cm} \, \text{H}_2\text{O}$, mean pulmonary wedge pressure $= 5.8 \pm 0.04 \, \text{cm} \, \text{H}_2\text{O}$, cardiac output $= 284 \pm 58 \, \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, $\text{PVR} = 0.11 \pm 0.04 \, \text{cm} \, \text{H}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{kg} \cdot \text{min}$, mean aortic pressure $= 64 \pm 14 \, \text{cm} \, \text{H}_2\text{O}$, $\text{SVR} = 0.33 \pm 0.13 \, \text{cm} \, \text{H}_2\text{O} \cdot \text{ml}^{-1} \cdot \text{kg} \cdot \text{min}$).

**Acutely Treated Animals**

When a single orogastric dose of sildenafil was given to anesthetized chronically hypoxic piglets, mean pulmon-
ary artery pressure (Fig. 2A) and calculated pulmonary vascular resistance (Fig. 2B) both significantly decreased, whereas cardiac output (Fig. 2C) and calculated systemic vascular resistance (Fig. 2D) were not significantly altered. Moreover, mean aortic pressure and pulmonary wedge pressure did not change significantly with the single dose of sildenafil (mean aortic pressure was 64.0 ± 3.5 cm H₂O before and 62.7 ± 3.5 cm H₂O after sildenafil treatment; mean pulmonary wedge pressure was 9.4 ± 1.5 cm H₂O before and 8.5 ± 1.7 cm H₂O after sildenafil treatment).

When a placebo was given to anesthetized chronically hypoxic piglets, none of the hemodynamic measurements changed significantly. Specifically, neither mean pulmonary arterial pressure (Fig. 3A), mean pulmonary wedge pressure (7.7 ± 0.9 cm H₂O before vs. 7.7 ± 1.0 cm H₂O after placebo), calculated pulmonary vascular resistance (Fig. 3B), cardiac output (Fig. 3C), mean aortic pressure (64.0 ± 3.6 cm H₂O before vs. 65.2 ± 6.6 cm H₂O after placebo), nor calculated systemic vascular resistance (Fig. 3D) changed with placebo treatment.

Measured values of pH, PO₂, and PCO₂ were similar for all anesthetized chronically hypoxic piglets, both before and after treatment with a single dose of sildenafil or placebo (Table 2).

cGMP Determinations in Small Pulmonary Arteries

cGMP levels were the same for small pulmonary arteries from control (2.8 ± 0.2 pmol/mg, n = 8) and chronically hypoxic (2.9 ± 0.5 pmol/mg, n = 7) piglets. Notably, cGMP levels for small pulmonary arteries from piglets treated long-term with 12 mg/kg/day sildenafil (7.8 ± 4.1 pmol/mg, n = 3) were greater (P < 0.05) than those for small pulmonary arteries from both control and chronically hypoxic piglets.

DISCUSSION

Similar to our previous findings, newborn piglets exposed to 3–4-day chronic hypoxia developed pulmonary hypertension. In this study, we found that repeated
doses of sildenafil given throughout the 3–4-day hypoxic exposure did not influence this early stage of pulmonary hypertension. Our findings contrast with those showing that sildenafil inhibited the development of pulmonary hypertension in adult mice\(^7\) and rats\(^{14,15}\) exposed to chronic hypoxia. Sildenafil treatment also attenuated the progressive increase in pulmonary vascular resistance in another rodent model of chronic pulmonary hypertension, monocrotaline-induced pulmonary hypertension.\(^{16}\)

Various reasons could account for the difference in outcomes with our study in newborn piglets and previous studies with adult rodents. Variability between species is one possibility. It is also possible that since various regulators of pulmonary vascular resistance change with postnatal age,\(^{17,18}\) developmental changes in pulmonary vascular regulation could contribute to variability in outcomes between newborn pigs and adult rodents. Differences in doses could also contribute to the disparity in results. In the rodent studies, the dose of sildenafil used was much higher (25–75 mg/kg\(^{14,15}\)), and the effect on the severity of chronic hypoxia-induced pulmonary hypertension was dose-dependent.\(^{15}\) We initially chose a 3 mg/kg dose of sildenafil for repeated, long-term treatment based on other studies in which a single 2–3-mg/kg dose of sildenafil caused an acute decrease in pulmonary arterial pressure in newborn animals.\(^{19,20}\) Notably, our findings confirm that a 3-mg/kg dose of oral sildenafil is sufficient to cause an acute decrease in pulmonary arterial pressure in newborn piglets (Fig. 2).

Dosing intervals should also be considered. In the rodent studies, sildenafil was dissolved in drinking water, to which the animals had constant access, as opposed to our study, where the animals received sildenafil 3–4 times a day. Although the half-life of sildenafil in newborns

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<th>TABLE 2— Data in Chronically Hypoxic Piglets Before and After Acute Oral Dose of Sildenafil, 3 mg/kg (n = 6), or Placebo (n = 5)</th>
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Fig. 3. Acute placebo dosing of chronically hypoxic piglets (n = 5). Hemodynamic measurements before and 1 hour after placebo. A: Mean Ppa (cm H\(_2\)O). B: PVR (cm H\(_2\)O · ml \(^{-1}\) · kg · min). C: CO (ml · kg \(^{-1}\) · min \(^{-1}\)). D: SVR (cm H\(_2\)O · ml \(^{-1}\) · kg · min). Data presented as mean ± SEM.
is not known, the half-life of sildenafil measured in adults is relatively short, approximately 4 hr. More frequent doses of sildenafil might have been more efficacious, but the feasibility of long-term compliance when dosing intervals exceed 3–4 times a day must be taken into account.

Problems with absorption of sildenafil could also contribute to the variability in findings. Notably, we found that cGMP levels were greater in small pulmonary arteries of piglets treated long-term with 12 mg/kg/day sildenafil than cGMP levels measured in small pulmonary arteries from either control or chronically hypoxic piglets. Thus, in our study, absorption of sildenafil was effective enough to increase cGMP levels in the vessels most important for regulation of pulmonary vascular tone. However, our findings indicate that this increase in tissue cGMP levels was not sufficient to prevent the early stage of chronic hypoxia-induced pulmonary hypertension. It is also important to remember that strategies yielding higher serum levels of sildenafil, hence higher tissue levels, will impact not only PDE 5, but will have greater effects on other PDE isoforms inhibited by sildenafil, such as PDE 6, the PDE subtype which hydrolyzes cGMP in the retina. Hence, although higher, more frequent dosing strategies warrant future investigation, adverse effects, especially ophthalmologic considerations in newborns and the potential for decreasing systemic blood pressure, must be considered.

Differences in pathogenesis underlying pulmonary hypertension provide another potential reason why sildenafil ameliorated chronic hypoxia-induced pulmonary hypertension in adult rats and mice, but did not affect the development of pulmonary hypertension in our study with newborn piglets. In this regard, a key difference between the previous studies with rats and mice, and our study with newborn piglets, is the duration of hypoxic exposure. Rats and mice were given sildenafil throughout puberty, toward constrictors, such as thromboxane, in piglets exposed to 3–4-day hypoxic exposure by piglets in this study. Both we and other investigators provide evidence that the mechanisms underlying early and later stages of chronic hypoxia-induced pulmonary hypertension differ. In particular, we found that pulmonary vascular nitric oxide signaling remains intact, but that there is a shift in balance of prostanoid production by resistance pulmonary arteries, away from dilators, such as prostacyclin, toward constrictors, such as thromboxane, in piglets exposed to 3–4-day hypoxia. Pulmonary vascular nitric oxide signaling is impaired in newborn piglets when hypoxic exposure is extended to 10–12 days, and was also shown to be impaired when adult rats were exposed to more than 1 week of hypoxia. Thus, it could be that the beneficial effect of sildenafil treatment occurs during a period of hypoxic exposure extending beyond 3 days when NO signaling is impaired. Yet it also seems reasonable to explore the possibility that even at stages in which the pathway is not impaired, sufficiently overdriving cGMP/NO signaling could ameliorate the development and progression of pulmonary hypertension.

Another important finding in this study is that a single 3-mg/kg oral dose of sildenafil acutely lowered pulmonary vascular resistance without adversely affecting cardiac output or systemic vascular resistance in newborn pigs with chronic pulmonary hypertension resulting from 3–4-day exposure to hypoxia. Consistent with our finding, a number of other studies also showed that sildenafil decreases pulmonary arterial pressure without significant effects on systemic blood pressure or cardiac output. Many previous studies showing the efficacy of sildenafil were performed with adults, i.e., healthy adult humans, adult humans with pulmonary hypertension, or adult animals with experimentally induced pulmonary hypertension, including adult animals with chronic hypoxia-induced pulmonary hypertension.

It is noteworthy that the number of reports describing the acute use of sildenafil in human newborns is increasing. In addition, over the past few years, a number of investigators showed that acute doses of sildenafil cause pulmonary dilation without concomitant systemic decreases in both pulmonary and systemic pressure in lambs with pulmonary hypertension caused by airway administration of meconium or intravenous infusion of vasoconstrictors. As to newborns with chronic pulmonary hypertension, use of oral sildenafil to treat an infant with congenital diaphragmatic hernia and chronic pulmonary hypertension was recently reported. Another phosphodiesterase inhibitor, dipyridamole, was evaluated in a fetal ovine ductal ligation model of pulmonary hypertension. Dipyridamole, a nonselective phosphodiesterase inhibitor, caused significant decreases in both pulmonary and systemic pressure in lambs with pulmonary hypertension. By comparison, our study shows that the more selective PDE 5 inhibitor, sildenafil, causes pulmonary dilation without significant effects on the systemic circulation in a newborn model of hypoxia-induced chronic pulmonary hypertension. That the effect of sildenafil on the systemic circulation must continue to be evaluated in newborns, especially for intravenous use in infants without pulmonary hypertension, is suggested by the recent report that intravenous sildenafil produced systemic hypotension in infants with congenital heart disease who were at risk for, but did not have, pulmonary hypertension when studied shortly after cardiac surgery.

In conclusion, a single 3-mg/kg oral dose of sildenafil causes pulmonary dilation without concomitant systemic vasodilation in newborn piglets with pulmonary hypertension induced by 3–4-day exposure to chronic hypoxia. Although caution must be taken when extrapolating these findings to human newborns, we speculate that oral sildenafil may be a useful short-term, acute therapy for infants...
with pulmonary hypertension associated with chronic hypoxia. Our findings also suggest that neither the 3 mg/kg nor 6 mg/kg oral doses of sildenafil, when given repeatedly throughout a 3–4-day exposure to hypoxia, will influence the early stage of pulmonary hypertension in newborn piglets. These doses of sildenafil are much smaller than doses shown to ameliorate chronic hypoxia-induced pulmonary hypertension in adult rodents. Long-term use of sildenafil to prevent the progressive development of pulmonary hypertension in neonates requires more extensive evaluation, with strong consideration given to optimal dosing and the potential for adverse effects.

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