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Sildenafil: Emerging Pulmonary Vasodilator for Pulmonary Hypertension due to Congenital Heart Disease

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Abstract

Pulmonary arterial hypertension is a life-threatening condition for which therapeutic options are limited. The current expensive gold standard-inhaled nitric oxide-is usually not affordable in developing countries. Moreover, nitric oxide has also not proved to be the single magic bullet for persistent pulmonary hypertension in newborn infants and those with complex congenital heart disorders. Nearly 20-30% of these cases do not respond to nitric oxide. Sildenafil (Viagra™) a selective phosphodiesterase type 5 (PDE-5) inhibitor, primarily used to treat male erectile impotence, is under investigation as a novel therapy for this condition. PDE-5 is abundant in the lung and hydrolyses cyclic GMP, a mediator of vasorelaxation and antitrophic effects in vascular tissue. Chronic PDE5 inhibition has been shown to elevate pulmonary cyclic GMP levels and abrogate hypoxia-induced pulmonary hypertension and vascular remodeling in animal models, and to reduce pulmonary artery pressure in primary pulmonary hypertension. This article reviews the available evidence on the use of sildenafil for treating pulmonary hypertension in children with congenital heart disorders.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive, debilitating disease with a poor prognosis. Progressive obliteration of the pulmonary vasculature eventually leads to right heart failure, severe functional limitations, and death. Treatment options have expanded in recent years, but medications used to induce pulmonary vasodilation and/or cause regression of remodeling within the pulmonary vascular bed have had limited success due to lack of efficacy, nonselectivity, cost, adverse effects, and complications.

AVAILABLE TREATMENT OPTIONS FOR PULMONARY HYPERTENSION

Continuous intravenous administration of epoprostenol (prostacyclin analogue) has improved exercise tolerance and hemodynamics in patients with primary PAH and PAH associated with the scleroderma spectrum of collagen vascular disease.[1,2] Epoprostenol is also associated with improved survival in primary PAH.[3] Unfortunately, parenteral administration of the medication is cumbersome.[4] Frequent adverse effects may occur, including jaw and leg pain, diarrhea, flushing, systemic hypotension due to lack of selectivity for the pulmonary vasculature, drug tolerance, high output states, catheter infection, or rebound hemodynamic deterioration if the infusion is interrupted.[4] Because of vasodilation in underventilated lung segments, epoprostenol may exacerbate preexisting ventilation-perfusion mismatch; also, the enormous costs to treat and manage adverse effects impede long-term use.[4]

Inhalation of aerosolized iloprost, a longer-acting prostacyclin analogue, has been shown to dilate pulmonary vessels preferentially in patients with primary and secondary pulmonary hypertension.[5,6,7] Pulmonary vasodilatation is better matched to ventilated areas of the lung, thereby improving gas exchange. However, the short half-life of the drug means patients must take multiple inhalations daily to experience improvement in symptoms.[4]

Bosentan is an orally administered, nonselective endothelin receptor antagonist that counteracts the vasoconstrictive effect of augmented levels of endothelin in patients with PAH. Clinical studies have shown beneficial effects in terms of improved exercise tolerance and hemodynamics.[8,9] Drawbacks include potential hepatotoxicity and expense.[4]

Inhaled nitric oxide (iNO), a selective pulmonary vasodilator, is used primarily as a screening agent for pulmonary vasoreactivity.[10,11,12,13] Inhaled nitric oxide diffuses into pulmonary vascular smooth muscle cells, activates soluble guanylate cyclase, and stimulates production of cyclic guanosine monophosphate (cGMP), a mediator of vasodilatation.[14] The pulmonary vasodilatory effects of iNO may be incomplete and short-lived because of rapid degradation of cGMP by phosphodiesterases (PDEs). Although iNO has been used successfully for short-term management of acute PAH as well as long-term management of patients with chronic PAH,[15,16,17,18] it is expensive and requires a complicated delivery system, and extensive monitoring equipment.[4]

PHOSPHODIESTERASE INHIBITORS AS EMERGING PULMONARY VASODILATORS

In recent years, strategies have been proposed to augment and improve current treatment options for PAH. The use of phosphodiesterase (PDE) inhibitors alone or combined with other vasodilatory agents offers potential improvement in pulmonary hemodynamics and functional status. The PDEs are a family of multiple isoenzymes that inactivate cyclic adenosine monophosphate and cGMP, the second messengers of prostacyclin and iNO, respectively.[19] Phosphodiesterase-5 is preferentially expressed in penile tissue and lung tissue.[20] The PDE-5 inhibitors, such as sildenafil, enhance and prolong the vasodilatory action of cGMP, and their use in treating erectile dysfunction is well-documented. The effects of sildenafil alone or combined with established vasodilatory agents have not been established firmly in the treatment of PAH, although early reports suggest a potentially beneficial hemodynamic response.[21,22,23,24,25]

PHOSPHODIESTERASE-5 AND MECHANISM OF ACTION OF SILDENAFIL

Several families of phosphodiesterases (PDE), the enzymes catalyzing hydrolysis of cyclic (c) nucleoside monophosphates, namely, 3'5'-cAMP (cAMP) and 3'5'-cGMP (cGMP), have been identified and characterized in recent years.[26] Since selective pharmacological inhibitors of isoform 5 (a cGMP-specific PDE), such as sildenafil, tadalafil, or vardenafil, have become available, the physiological function and interaction of different PDE isoforms,[27] their tissue distribution,[27] and the therapeutic potential of PDE-5 inhibition have attracted increasing interest.[28] To date, at least 11 isoforms of PDE have been discovered,[29]and the differential distribution of PDE isoforms in various tissues as well as the selectivity of pharmacological agents is the basis for potential tissue-specific effects of PDE inhibitors.

Apart from smooth muscle cells of the penile corpora cavernosa, PDE-5 is expressed in various other tissues, such as the arterial vasculature, including pulmonary and coronary arteries, veins, skeletal muscles, visceral and tracheobronchial muscles, and platelets.[26,27,30,31] Relaxation of arterial smooth muscle occurs after stimulation of the enzyme guanylate cyclase by nitric oxide released from nonadrenergic-noncholinergic nerves and endothelial cells, with subsequent formation of cGMP.[29]cGMP activates a cGMP-dependent protein kinase, which leads to phosphorylation of ion channels with the final consequence of a reduced cytosolic calcium concentration.[32]Sildenafil inhibits the breakdown of cGMP and maintains relaxation of arterial smooth muscle.[33] Sildenafil is highly selective for the cGMP-hydrolyzing isoform 5 with a half-maximal inhibition (IC_{50}) of PDE-5 activity at a concentration of 3.5 nmol/L, followed by IC_{50} values of 34 to 38 nmol/L for PDE-6 (cGMP-hydrolyzing PDE in the retina) and 280 nmol/L for PDE 1 (cAMP- and cGMP-hydrolyzing PDE isoform).[27,31] The cAMP-hydrolyzing PDE 3 and 4 and the cAMP- and cGMP-hydrolyzing isoform 2, as well as PDE 7 to 11, are inhibited by sildenafil with an IC_{50} of >2600 nmol/L.

PULMONARY VASCULATURE AND INHIBITION OF PHOSPHODIESTERASE 5

In human pulmonary circulation, the isoforms 1, 3, 4, and 5 of PDE are involved in regulating pulmonary resistance.[20,34]Thus, the blood pressure-lowering effects of sildenafil in the pulmonary circulation are of special interest.

In a study by Zhao and associates, 100 mg of oral sildenafil markedly reduced the rise in arterial pulmonary pressure in response to breathing 11% inspiratory oxygen in healthy volunteers, which paralleled their findings in a mouse model of hypoxia-induced pulmonary hypertension.[35] In a lamb model of acute pulmonary hypertension, inhalation of nebulized sildenafil reduced pulmonary artery pressures significantly and had a synergistic effect with inhalation of nitric oxide, whereas pulmonary right-to-left shunt volume did not increase after sildenafil.[36] However, a recent study performed in normal pigs described an increase in right-to-left shunt volume and subsequently a decrease of systemic arterial oxygen tension, along with reduced pulmonary arterial pressure after sildenafil.[37]

These experimental data suggest that at least in certain conditions causing pulmonary hypertension, PDE-5 inhibition might be of benefit, and the possibility of additional inhalative application of other agents used to lower pulmonary artery pressure might provide a unique approach to achieve site-specific, additive, or even supra-additive effects.[23]

In patients with severe primary or secondary pulmonary hypertension who were evaluated for potential heart-lung transplantation, a reduction of pulmonary vascular resistance that was similar in extent to that observed after iNO was reported after use of sildenafil.[22] In addition, sildenafil slightly increased cardiac index and decreased pulmonary capillary wedge pressures. The combination of iNO and sildenafil seemed to be effective in a synergistic manner.[22,38]Additive effects of inhaled iloprost with 25 mg oral sildenafil in lowering pulmonary artery pressure were reported without major adverse events in a series of patients with primary pulmonary hypertension.[24] Comparison of iNO in combination with either intravenous epoprostenol or with oral sildenafil in patients with pulmonary hypertension due to fibrotic lung disease revealed a marked reduction of pulmonary arterial pressure by both treatments; however, a decreased ratio of pulmonary to systemic vascular resistance was only measured in patients who received nitric oxide and sildenafil. Importantly, the ventilation/perfusion mismatch, and subsequently the right-to-left shunt, deteriorated with epoprostenol/nitric oxide, but the ventilation/perfusion mismatch was unaltered with a sildenafil/nitric oxide combination, which was accompanied by an even slight reduction in right-to-left shunting.[39] If achievable on a long-term basis, these effects on the pulmonary circulation might favorably influence symptoms, similar to the improved exercise capacity in patients with congestive heart failure, as reported by Bocchi and colleagues.[40]

Besides classical primary pulmonary hypertension and pulmonary hypertension due to cardiac disease, some benefit might also exist for patients with pulmonary hypertension of relatively rare etiology,[41] or postoperative pulmonary hypertension, and difficult weaning problems in mechanical respiration.[42,43] The weaning of iNO, which is often followed by a rebound phenomenon, might especially be a target for PDE 5 inhibition.[43]However, these sporadic reports are based on small numbers of patients and need confirmation by large, randomized studies.

PULMONARY HYPERTENSION DUE TO CONGENITAL HEART DISORDERS

Pulmonary hypertension results from large number of untreated congenital heart disorders and complicates the postoperative course of many patients receiving surgery for congenital heart disease. Intrauterine pulmonary vascular disease is unusual, and it generally starts at birth.[44] The rate of change depends on the type of intracardiac abnormality, but some exceptional children appear to be genetically predisposed to develop an accelerated form of pulmonary vascular disease. Endothelial cell damage, medial smooth muscle cell hyperplasia, hypertrophy, and site specific changes in cell phenotype are well described in early infancy.[44] Respiratory unit arteries, about half of which normally form after birth, are reduced in size and number. This is the morphological substrate of pulmonary hypertensive crises, which most often occur in the presence of potentially reversible structural abnormalities. Endothelial dysfunction is present early. In potentially operable children the relaxation response to acetylcholine is impaired, basal NO production may be raised initially but then decreases, and the ratio of thromboxane to prostacyclin is raised, tipping the balance in favour of vasoconstriction and platelet aggregation. Impaired endothelial-dependant relaxation occurs later in association with elevation in resistance and more advanced structural disease. Dilatation and plexiform lesions contain abundant vascular endothelial growth factor (VEGF) which co-localises with transforming growth factor-beta (TGFβ1). VEGF induces endothelium dependent relaxation, which may help ensure continued perfusion of the capillary bed. But it is also a potent angiogenic factor, and TGFβ upregulates its angiogenic activity in vitro. The VEGF in the plexiform lesions could in theory stimulate angiogenesis. As intimal obstruction develops, flow becomes more turbulent and in vitro studies suggest that this is likely to have an unfavourable influence on gene transcription. Laminar flow is associated with activation of genes such as eNOS and cyclo-oxygenase COX2 but turbulent flow is associated with the localised upregulation of VCAM-1 and ICAM-1, encouraging leucocyte recruitment and activation.[45] Changes in mechanical stress also alter expression of specific genes in the smooth muscle cell, such as platelet drived growth factor.[46]

PULMONARY HYPERTENSION AFTER SURGERY FOR CONGENITAL HEART DISORDERS

Pulmonary hypertension after surgery for congenital heart disorders may occur for a number of reasons. Several factors peculiar to cardiopulmonary bypass may raise pulmonary vascular resistance: microemboli, atelectasis, endothelial dysfunction, vasoconstriction, and adrenergic events.[47,48] Anatomic factors that impose either obstruction to pulmonary blood flow or residual left-to-right shunting such as mitral valve disease or left ventricular dysfunction, pulmonary venous obstruction, branch pulmonary artery stenosis, or surgically induced loss of the pulmonary vascular cross-sectional area all can lead to pulmonary hypertension following surgery for congenital heart disorders. Similarly, a significant residual left-to-right shunt can raise pulmonary artery pressure postoperatively and should be surgically addressed.

SILDENAFIL FOR PULMONARY HYPERTENSION DUE TO CONGENITAL HEART DISORDERS

In the hierarchy of clinical evidence, the randomized controlled trial (RCT) is generally considered the best approach to ascertain the value of a particular therapy. To date only one randomized trial[49] to investigate the acute effects of intravenous sildenafil on haemodynamics and oxygenation, and its interaction with inhaled nitric oxide (iNO) in infants at risk of pulmonary hypertension early after cardiac surgery has been performed. In this trial by Stocker et al, sixteen ventilated infants early after closure of ventricular or atrioventricular septal defects were randomly assigned to one of two groups.[49]The study was completed in 15 infants. Studies were commenced within 7 h of separation from bypass. Seven infants received iNO (20 ppm) first, with the addition of intravenous sildenafil (0.35 mg/kg over 20 min) after 20 min. Eight infants received sildenafil first, iNO was added after 20 min. Vascular pressures, cardiac output and a blood gas were recorded at 0, 20 and 40 min. In infants receiving iNO first, iNO lowered the pulmonary vascular resistance index (PVRI) from 3.45 to 2.95 units (p=0.01); sildenafil further reduced PVRI to 2.45 units (p<0.05). In those receiving sildenafil first, PVRI was reduced from 2.84 to 2.35 units (p<0.05) with sildenafil, and fell to 2.15 units (p=0.01) with the addition of iNO. In both groups, sildenafil reduced the systemic blood pressure and systemic vascular resistance (p<0.01) and worsened arterial oxygenation and the alveolar-arterial gradient (p<0.05).

In a prospective non randomized study, Schulze-Neick et al[50] compared the effects of inhaled NO before and after the specific inhibition of the PDE-5 by intravenous sildenafil (Viagra™) in pre- and postoperative children with increased pulmonary vascular resistance (PVR) because of congenital heart disease. 12 children with congenital heart disease (age 0.2 to 15.7 years, median 2.4 years) and increased mean pulmonary arterial pressure, and 12 postoperative children (age 0.11 to 0.65 years, median 0.32 years) with increased PVR (8.3±1.0 Wood Units*m2) were studied during cardiac catheterization (“cath laboratory”), or within 2 hours after return from cardiac surgery (“post op”), respectively. All were sedated, tracheally intubated and paralyzed. During alveolar hyperoxygenation (FiO_2=0.65), the effects of inhaled NO (20 ppm) were compared before and after the stepwise infusion of sildenafil (“cath laboratory”, 1 mg/kg; post op, 0.25 mg/kg). Intravenous sildenafil more effectively reduced PVR than NO (11.5% versus 4.3% in the “cath laboratory” patient group, P <0.05, and 25.8% versus 14.6% in the post op patient group, p =0.09). The increase in cGMP in response to NO was potentiated (2- to 2.4-fold) by PDE-5 inhibition. While the vasodilating effects of sildenafil showed pulmonary selectivity, its infusion was associated with increased intrapulmonary shunting in the postoperative patients (Q_s/Q_t=16.5±4.7% to 25.5±18.2%; p =0.04).

Description of the use of oral sildenafil for treating pulmonary hypertension secondary to congenital heart disease or paediatric cardiac surgery is limited only to case reports and nonrandomized studies. [51,52,53,54] Kothari et al[54] reported the outcome of chronic oral sildenafil therapy in 14 patients, five of whom had surgery for congenital heart disease. The drug was started in low dose and empirically increased. Finally, a median dose of 87.5 mg/day was used in children weighing less than 30 kg, and 150 mg/day in those with weight more than 30 kg. The patients were followed up by assessing their functional status, six-minute walk test, Doppler echocardiography and hemodynamic study (in selected cases). On mean follow-up of 7.3±2.4 months (range 3–14 months), New York Heart Association functional class improved from 3.31±0.75 to 2.00±0.71 (p<0.002). There was a remarkable improvement on the six-minute walk test from a baseline of 264.1±193.7 m to 408.2±156.97 m at 3 months (p<0.001) and 453.2 ±159.81 (p<0.0001) at 6 months. The right ventricular systolic pressure estimated echocardiographically declined from 112.40±45.21 mmHg to 101.86 ±47.86 mmHg (p<0.002). The mean pulmonary artery pressure decreased from 62 mmHg to 47 mmHg in 4 patients of primary pulmonary hypertension recatheterized after a mean of 7 months of sildenafil treatment. Clinical improvement was seen even when no decrease in pulmonary artery pressure was demonstrated in one patient with secondary pulmonary artery hypertension. 2 patients died during follow-up despite clinical improvement.

CAUTIONS AND CONCERNS

There are limited data available to suggest dosage regimens in children. Due to the paucity of data a cautious approach must be adopted to the introduction of sildenafil. Following a 0.5 mg/kg test dose oral sildenafil should be administered six hourly, with increments of 0.5 mg/kg/dose, and a target maintenance dose of 2 mg/kg six hourly.[51] Although the biological half life of sildenafil is relatively short (four hours), evidence suggesting more frequent administration is not available presently.

Data on adverse effects and interactions in pediatric patients are also not robust. Sildenafil produces mild decreases in systolic and diastolic blood pressure and an array of minimal side effects due to the inhibition of other types of phosphodiesterase.[55] Drug interactions involving the concurrent use of sildenafil with nitrates and nitrites are well-documented and can produce profound hypotension leading to decreased coronary perfusion and myocardial infarction.[55]Sildenafil is metabolized in the liver through cytochrome P-450. This enzymatic system can be inhibited by cimetidine, ketoconazole or erythromycin. These drugs can increase plasma concentrations of sildenafil.[56] Adverse events considered to be related to sildenafil treatment include headache, nausea, and dyspepsia.[57] Most available literature on the use of sildenafil in children states that complications include nausea, flushing, rashes, reduced systemic blood pressure, worsened arterial oxygenation and the alveolar-arterial gradient. Short lived erections may also occur in pediatric patients.[51] Recent studies have identified other potential oral treatments for pulmonary hypertension. In particular, the endothelin receptor antagonists bosentan[9] and sitaxsentan[58] have been reported to be effective in treating pulmonary hypertension. It remains to be seen if they are safer, more effective or even complementary to sildenafil. Moreover, since sildenafil augments the cGMP levels but does not increase NO synthesis by itself, patients with defective NO synthesis may not respond as well to it.

Sildenafil is expensive.[51] The cost for a 50 mg (2 mg/kg) six hourly dose is £19.34 per day or £7059 per annum (approximately equivalent to €27 or US$32 per day, or €9913 or US$11 664 per annum).[51]However, this compares favourably with the estimated costs of one year's treatment with intravenous epoprostenol (£25 342, €35 590, or US$41 873) or inhaled prostacyclin (£17 520, €24 604, or US$28 947) in the same patient. Moreover, patients remain unhindered by infusion pumps, the inherent difficulties of permanent intravenous lines, or the inconvenience of four hourly nebulisers.

Available evidence on the use of sildenafil for the treatment of pulmonary hypertension due to congenital heart disease suggests that theoretic rationale exists for the beneficial effects of sildenafil in this category of patients. Clearly further work, ideally a large multicentre randomised controlled trial, needs to be done to establish the safety and efficacy of sildenafil in children with pulmonary hypertension due to congenital heart disorders. However, given the poor prognosis and lack of other proven treatments, we conclude that even though evidence currently available is not sufficient to recommend the routine use of sildenafil in pediatric patients with severe pulmonary hypertension secondary to congenital heart disease, sildenafil should be used as a last resort, after failure of standard treatment.

AUTHORS' CONTRIBUTIONS

SGR did literature search, conceived and drafted the article. SKM, AS and AH did literature search and contributed in the design of the article. MP critically reviewed the manuscript. All authors read and approved the manuscript

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