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Sildenafil, pulmonary hypertension and bronchopulmonary dysplasia

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ABSTRACT

Pulmonary hypertension (PH) secondary to bronchopulmonary dysplasia (BPD) in infants remains a serious concern and continues to cause significant morbidity despite improvements in both quality of life and survival for patients. One of the potential agents that might help is sildenafil citrate, a phosphodiesterase-V inhibitor used a first line therapy for idiopathic PH. However, only limited evidence exists for its use as either monotherapy or part of a combination approach towards the management of PH in BPD. The evidence and current knowledge is presented for sildenafil alone and in combination with other disease modifying agents to treat PH in the presence of BPD. We have previously suggested that sildenafil appears to be safe and possibly effective in this condition. We present the evidence that if continued until PH resolution, there might be reduced mortality in this debilitating disease.

1. Introduction

Bronchopulmonary dysplasia (BPD) or chronic lung disease, commonly affects preterm babies with respiratory distress syndrome (RDS) requiring mechanical ventilation or oxygen therapy. It can also occur less often, when there are few signs of underlying lung pathology or in babies who are not born preterm or who are not exposed to mechanical ventilation [1]. 13–35% of preterm infants beyond 36 weeks post-conceptional age have BPD. Currently, there is no consensus on best treatment, and there is therefore scope for new ideas [2].

A significant proportion (around 50%) of those children who have BPD, will suffer from pulmonary hypertension (PH) [3]. Sildenafil, a phosphodiesterase-V inhibitor (PDE-Vi), has proven efficacy in PH as both monotherapy and in combination with other medications. This is primarily in children and adults with idiopathic pulmonary hypertension, heritable causes of PH and PH due to congenital heart disease.

2. Bronchopulmonary dysplasia and pulmonary hypertension

The most widely accepted definition of BPD is a need for oxygen therapy at 36 weeks postmenstrual age in an infant who is more than 28 days old [4]. (See Table 1.) Approximately 30% of children born <1000 g will develop BPD [5,6].

Cor Pulmonale is the consequence of preterm delivery, BPD and PH. The right ventricle struggles to cope with the high pulmonary artery pressure and eventually becomes hypertrophied, dilates and fails. As a result the babies will have poor growth and eventually demise. Global hypoxia affects up to 37% of cases with BPD and is thought to be the main cause of such pulmonary vasoconstriction, with disastrous consequences and is seen in 5% of childhood PH [7]. [8].

Doppler echocardiography, with a peak tricuspid valve regurgitant jet velocity >2.8 m/s, is the usual method for screening babies who have BPD in order to determine if they have BPD-PH. This measurement can be difficult to obtain, more so if there is overdilation of the lungs. Hence other methods must be used in addition, in order to avoid missing any cases. Right atrial enlargement, septal flattening, right ventricular hypertrophy or dilatation, and a short right ventricular ejection time (RVET < 60 ms) all have their place. Even more derived is the acceleration time/ejection time ratio with <0.28 being recognised as indicative of severe PH. Ideally, diagnosis should be confirmed by cardiac catheterisation, and include vaso-reactivity testing to nitric oxide and oxygen. Confirmation of PH requires pulmonary vascular resistance (PVR) >3 Wood units × BSA.m^2 with capillary wedge pressures ≤15 mm Hg, to distinguish PH from the hyperkinetic flows of unrepaired congenital heart disease or evidence of stiff left ventricle in systemic hypertension [9,10].

3. Mortality

Recent data based on contemporary treatments suggests BPD-PH survival rates after diagnosis of just 64% at 6-months, and 61% and

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Table 1
Definition of bronchopulmonary dysplasia [34].

Gestational age	<32 weeks	>32 weeks
Time point of assessment	36 weeks postmenstrual age or discharge to home, whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
Treatment with oxygen >21% for at least 28 days plus		
Mild BPD	Breathing room air at 36 weeks postmenstrual age or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need*-for <30% oxygen at 36 weeks postmenstrual age or discharge, whichever comes first	Need-for <30% oxygenat56 days postnatal age or discharge, whichever comes first
Severe BPD	Need-for >30% oxygen and/or positive pressure at 36 weeks postmenstrual age or discharge, whichever comes first	Need-for >30% oxygen and/or positive pressure at 56 days postnatal age or discharge, whichever comes first

52% at 1 and 2-years respectively, PH increasing mortality from BPD 4 fold [3,11].

4. Bpd-ph management strategies

Often, BPD-PH will resolve, but infants need to be kept in oxygen with careful monitoring, to ensure that they have sufficient to minimise the effect of BPD-PH but avoiding toxicity that will cause retrolental fibroplasia. Almost as important, is to avoid gastro-oesophageal reflux, to avoid severe virus infections – for example respiratory syncytial virus, using prophylaxis with palivizumab and precautions to minimise exposure and early treatment of bacterial infections. Babies are often treated in the acute stages of PH with inhaled nitric oxide (iNO), in order to relieve right ventricular afterload and improve ventilation-perfusion mismatch. The other possible pharmacological interventions include prostacyclin analogues and endothelin-receptor antagonists all manipulating different pathways of pulmonary artery physiology.

5. Sildenafil

5.1. Pharmacodynamics

Pulmonary vascular resistance (PVR) is controlled by a balance of constrictors and dilators acting on vascular smooth muscle cells (VSMC) [11,12]. In vivo, endothelial cell nitric oxide diffuses into VSMC's to activate soluble guanylate cyclase (sGC) which converts guanosine monophosphate (GMP) to cyclic GMP. The result is that calcium is sequestered in the cell or ejected from the cell, leading to vaso-relaxation and dilation of the vessel. PDE-Vi's reduce cGMP degradation enhancing local endogenous nitric oxide leading to similar vasodilator effect [13]. A range of novel sildenafil actions leading to lasting PH resolution have been cited. This includes increased matrix metalloproteinase-2, and the modulation of the Rho-associated kinase signalling, reducing VSMC contraction and proliferation [14,15]. In addition, there is evidence supporting improved right ventricular function [16].

5.2. Dosing

After oral administration, maximal serum concentrations are reached within 0.5–1.5 h at 40% bioavailability [17]. Importantly, the 4-hour half-life before metabolism by the cytochrome P450 system allows for variable metabolic rates secondary to agents that either inhibit or induce this system. In practice, this causes plasma concentrations either above or below the targeted therapeutic window. Moreover, a neonatal system of metabolism requires time for maturation after birth, and delays in this cause drug half-lives notably longer than anticipated, increasing the risk of adverse reactions and overdose [18]. Administration every 6 h, starting at 0.5 mg/kg each 6 or 8 h up to a maximum of 8 mg/kg/day, are effective and well tolerated [19,20]. Intravenous sildenafil, although expensive, has become available and is used to cover hospitalised patients that are usually maintained on oral sildenafil but who cannot absorb for a variety of reasons, such as necrotising enterocolitis or acute gastrointestinal disease. Its increased bioavailability means smaller doses, usually 0.25–0.5 mg/kg, are given every 8 h. The usual protocol will include echocardiographic monitoring by an experienced cardiologist every few months. Discontinuing treatment is not yet standardised, most clinicians relying on overnight oxygenation studies combined with echocardiography, in order to manage a customised weaning regime for the individual patient. Therapy can be stopped when a patient has had two negative sequential echocardiography investigations [21].

5.3. Side-effects

The most common adverse reactions are nausea and vomiting, abdominal pain, pyrexia and cough, although migraine and sleep disturbance can also be triggered [22]. Notably, PDE-Vi's have previously been linked with the interference of retinal function, however a 6-month assessment showed no evidence of this, although discontinuation is recommended in the occurrence of visual disturbance and sildenafil in contra-indicated in inherited retinal or auditory pathology [23]. Of 43 patients with BPD-PH treated, just two reported reactions requiring cessation. Systemic hypotension was noted whilst using 0.5 mg/kg/day in an infant, however after a 3-day therapeutic holiday this dose was tolerated and could be titrated up to 4 mg/kg/day [28].

The European medicine agency still supports the use of sildenafil for children, although it has been withdrawn in the USA for children aged 1–16 years (but interestingly not in infants). Follow-up data detailing dose-dependent increases in child mortality with sildenafil led to the FDA withdrawing its recommendation for use in paediatric PH [24,25]. At the current time there is no formal evidence from a randomised controlled trial of the benefit of sildenafil in BPD-PH.

5.4. Sildenafil monotherapy

A case report documenting the successful resolution of BPD-PH in an infant was published in 2010 [26]. This 23-week gestation infant required sildenafil from 5 months age at oral doses up to 8 mg/kg/day alongside prolonged assisted ventilation. Treatment normalised right ventricular morphology (RV:LV end-diastolic diameter ratio 1.25 to <0.7) and resolved PH (pPA 70 mm Hg to <25 mm Hg). Eighteen months after discontinuation of therapy, the patient was asymptomatic and the pulmonary artery pressure had normalised, suggesting long-lasting effects. We have published the evidence from our own unit for the safety of sildenafil in our population [27]. Despite the lack of published evidence for its efficacy, a recent questionnaire of level 3 neonatal units in the UK confirmed that 40 of 43 units were routinely using sildenafil in babies with BPD-PH but without formal guidelines or controls [Herbert S, Bhojnagarwala B, Luyt K, Tulloh RM unpublished data].

5.5. Sildenafil with nitric oxide

Sildenafil has been used in conjunction with inhaled NO therapy in the acute setting, especially in the postoperative cardiac intensive care. [28] A retrospective review into the use of sildenafil with iNO involved 5-years following 21 preterm infants suffering moderate or severe BPD [29]. Sildenafil, titrated to a maximum oral dose of 6 mg/kg/day from a median age of 167 days, produced clinically significant reductions in estimated right ventricular peak systolic pressure (mean 65 mm Hg to 53 mm Hg; $p = 0.01$).

Oral sildenafil, dosed to a maximum of 8 mg/kg/day was initiated at a median age of 184 days (range: 14–615) for a mean duration of

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