Pediatr Cardiol (2008) 29:1082–1086
DOI 10.1007/s00246-008-9260-x

ORIGINAL ARTICLE

Treatment of Pulmonary Hypertension in Children with Chronic Lung Disease with Newer Oral Therapies

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Received: 1 January 2008 / Accepted: 6 June 2008 / Published online: 2 July 2008

Abstract Chronic lung disease (CLD) is often complicated by chronic pulmonary vascular changes and pulmonary hypertension (PH) in young children. Current therapies for severe PH in such patients, including oxygen, inhaled nitric oxide, and parenteral prostacyclin, are often suboptimal, cumbersome, and expensive. Recently, oral endothelin receptor blockers and phosphodiesterase-5 inhibitors have been used successfully to control and reverse pulmonary vascular disease in idiopathic PH, but the use and efficacy of these agents in pediatric CLD have not been previously reported. We report a series of six children with CLD and severe PH treated with bosentan (six of six) and sildenafil (four of six). Vascular reactivity was assessed by cardiac catheterization prior to and after 6 months of therapy. Serial echocardiography was also used to assess response. Patients have been treated for 2.1–2.9 years (mean, 2.53 years). Response to therapy has included improvement in oxygenation, symptoms, echocardiographic parameters, and hemodynamics by cardiac catheterization. Transiently elevated liver enzymes were noted associated with viral respiratory infections in two subjects; no other adverse effects were noted. Three patients with large cardiac right-to-left shunts prior to therapy had subsequent shunt reversal, two of whom underwent shunt closure later. Oral therapy with bosentan alone or in combination with sildenafil improves PH in patients with CLD over a period of 3–4 years.

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Keywords Bronchopulmonary dysplasia · Pulmonary hypertension · Bosentan · Sildenafil

Chronic lung disease (CLD) in infancy is commonly associated with bronchopulmonary dysplasia (BPD), which results from a cycle of injury and repair in the immature lung following premature birth [4]. CLD can also result from prolonged mechanical ventilation for treatment of respiratory failure due to multiple etiologies [4, 7, 10]. Persistence of pulmonary hypertension (PH) with CLD is associated with a high mortality [1, 6, 11]. Premature babies with intracardiac shunts and CLD, sometimes develop rapidly progressive pulmonary vascular disease (PVD) [1]. CLD is associated with frequent exacerbations of inflammation in the damaged lung parenchyma, which is a potent vasoconstrictor stimulus to the endothelium [1]. Traditional therapies used to treat idiopathic pulmonary hypertension (IPAH) include oxygen (O_2), calcium channel blockers, inhaled NO (iNO), and IV prostacyclin. Because of the underlying parenchymal lung disease in CLD, there may be a significant ventilation-perfusion (V/Q) mismatch at baseline. Potent pulmonary vasodilators such as parenteral prostacyclin can worsen this V/Q mismatch. Inhaled NO may be effective in maintaining V/Q matching and improving oxygenation, however, it is an expensive and cumbersome therapy for long-term use [2, 13]. Recently developed oral vasodilators, including sildenafil and bosentan, have favorable pulmonary vascular effects, similar to those of iNO [2, 8, 13, 14]. We report a case series describing the use of these medications in six patients with severe PH secondary to lung disease, demonstrating short- and medium-term efficacy as well as safety.

Patient Characteristics

Six patients with significant lung disease and severe PVD were treated with oral medications. Age ranged from 1.6 to 7.7 years (mean, 3.2 years) at the start of therapy. All had failed to improve with conventional therapies, including oxygen, calcium channel blockers, and cardiac failure therapy, and remained in severe heart failure. Clinical characteristics of the six patients are described in Table 1. Baseline cardiac catheterization was performed in all patients, with evaluation of hemodynamics and vasoreactivity testing with O_2, calcium channel blockers, iNO, and oral sildenafil (Table 2). Pulmonary angiography was performed to rule out vascular obstruction as well as pulmonary venous disease. Left heart catheterization was performed to measure shunts, evaluate for left ventricular dysfunction complicating CLD [14], and rule out any left heart abnormality leading to PH. Therapy was initiated with oral bosentan at 31.25 to 62.5 mg BID (6/6), and oral sildenafil at 3–4 mg/kg (combination therapy), in four of six patients (nos. 1, 4, 5, and 6). Sildenafil treatment was not possible in the other two subjects due to reimbursement issues. Liver enzymes and blood counts were monitored every 4 weeks. Echocardiograms were performed on a 6- to 8-weekly basis to monitor right ventricular (RV) function and pressures. Repeat cardiac catheterization was performed after 6 months of therapy (Tables 2 and 3, Fig. 1). High-resolution CT scans of the lung, performed at onset of oral therapy, demonstrated severe parenchymal disease in all patients.

Patients 1 to 4 were born extremely premature (gestational age, <26 weeks) and had severe CLD. They had spent 18–24 weeks in the neonatal nursery, with 12–16 weeks on mechanical ventilation. Echocardiograms during their neonatal intensive care (NICU) stay had demonstrated severe PH as well as RV dysfunction. All had been transferred to a chronic care facility upon discharge from the NICU and subsequently had recurrent acute intensive care hospitalizations for exacerbations of lung disease and Ross functional Class 4 congestive heart failure symptoms [9]. These exacerbations were associated with cyanosis from right-to-left intracardiac shunting due to pulmonary hypertensive crises and right heart failure.

Patient 1 had a large atrial septal defect (ASD), which shunted entirely right to left at baseline, and had presented with severe right heart failure. Baseline hemodynamic data revealed systemic pulmonary artery (PA) pressures and elevated pulmonary vascular resistance (PVR). After 6 months of combination treatment, he had significant

Table 1 Clinical characteristics of patients at baseline and follow-up

Patient no.	Age (yr) at start of therapy	Diagnosis	Treatment period (yr)	Baseline Ross class	Current Ross class	Drug(s)	Current management plan
1	2.0	BPD, ASD	2.8	Class 4	Class 1–2	B, S	ASD closure planned
2	3.6	BPD, VSD	2.5	Class 4	Class 1	B	VSD closed
3	1.6	BPD	2.2	Class 4	Class 1	B	Off O_2
4	2.9	BPD, hypoplastic left lung	2.8	Class 4	Class 1	B, S	Decreased O_2
5	2.1	CLD (CMV), PDA	2.1	Class 4	Class 1–2	B, S	PDA closed
6*	7.7	CLD (GVHD)	2.9	Class 4, cyanosis	Class 1 (36 mo), [a]Class 3 (3 mo)	B, S	Off O_2 for 2.5 yr; [a]on O_2 for past 3 mo

Note: BPD, bronchopulmonary dysplasia; ASD, atrial septal defect; VSD, ventricular septal defect; B, bosentan; S, sildenafil; CLD, chronic lung disease; CMV, cytomegalovirus; PDA, patent ductus arteriosus; GVHD, graft-versus-host disease

[a] Recent worsening

Table 2 Cardiac catheterization data (mean ± SD) at baseline and 6 months of therapy

	Baseline O_2 saturation (%)	mPA/mAo pressure	Qp/Qs	PVR (Wood units)	PVR/SVR
Baseline					
FiO_2, 0.21	76.2 ± 8.4	0.84 ± 0.29	0.95 ± 0.13	10.8 ± 2.8	0.83 ± 0.36
20–80 ppm nitric oxide	98–100	0.60 ± 0.38	1.9 ± 0.71	5.8 ± 4.4	0.37 ± 0.31
Follow-up					
FiO_2, 0.21	93.6 ± 3.2	0.53 ± 0.22	1.57 ± 0.58	5.3 ± 2.5	0.31 ± 0.13
20–80 ppm nitric oxide	100	0.47 ± 0.2	3.1 ± 1.74	3.27 ± 2.0	0.17 ± 0.08

Note: mPA/mAo, mean pulmonary/mean aortic pressures; Qp/Qs, pulmonary/systemic blood flow; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; FiO_2, fractional inspired oxygen concentration; ppm, parts per million

Table 3 Hemodynamic parameters in all subjects at baseline and follow-up catheterization after 6 months of therapy

Pt no.	Baseline data				6-mo follow-up data			
	Mean PA/Ao pressure: FiO_2, 0.21	PVR (WU): FiO_2, 0.21	Mean PA/Ao pressure: NO, 80 ppm	PVR (WU): NO, 80 ppm	Mean PA/Ao pressure: FiO_2, 0.21	PVR (WU): FiO_2, 0.21	Mean PA/Ao pressure: NO, 80 ppm	PVR (WU): NO, 80 ppm
1	0.8	9.8	0.5	3	0.5	5.7	0.4	3.4
2	0.75	6.8	0.25	1.6	0.35	2.8	0.34	1.3
3	0.62	8.2	0.46	3.8	0.4	5.6	0.36	1.7
4	1.46	15	1.35	15	0.75	10.4	0.72	8.4
5	0.9	14.8	0.8	7	0.75	12.2	0.7	3.7
6	0.6	12.5	0.25	4.4	0.37	2.5	0.26	2.1

Note: Pt, patient; FiO_2, fractional inspired oxygen concentration; PA, pulmonary artery; Ao, aortic; PVR, pulmonary vascular resistance; WU, Wood units; NO, nitric oxide; ppm, parts per million

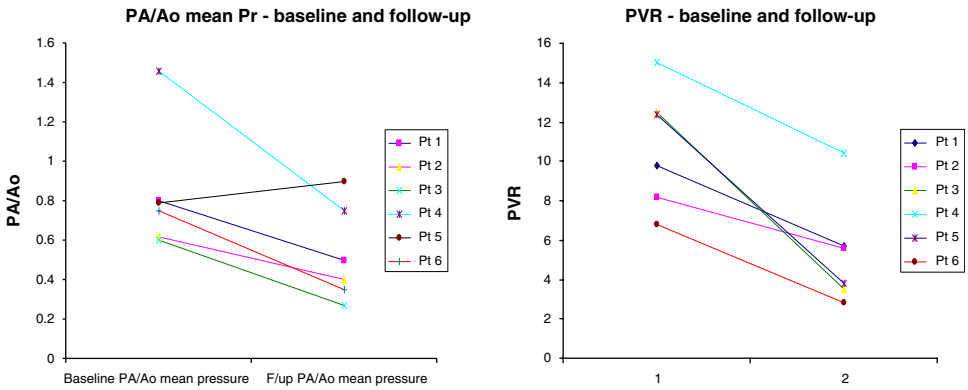

Fig. 1 Change in ratio of mean pulmonary artery (PA)/aortic (Ao) pressures and pulmonary vascular resistance (PVR) at baseline and after 6 months of therapy

clinical improvement as well as a reduction in PA pressures and PVR on cardiac catheterization and the ASD shunts left to right. He is currently doing well, and transcatheter closure of the ASD is planned.

Patient 2 had a moderate ventricular septal defect (VSD) and small ASD, both shunting right to left, and severe CLD at 3.8 years of age. He had significant cyanosis and right heart failure. After 1 year of bosentan therapy, he had 100% O_2 saturation in room air, with improved effort tolerance. Repeat catheterization revealed that the VSD was now shunting left to right, with increased pulmonary flow, less than half systemic right-sided pressures, and a markedly decreased PVR. The patient underwent successful surgical VSD closure, leaving a small atrial shunt open. Currently he has near-normal hemodynamics by echocardiogram and is asymptomatic.

Patient 3 had a complicated course during infancy, with multiple resuscitations for cardiac arrests associated with suprasystemic elevations of PH documented on echocardiography. He was initially given parenteral prostacyclin and iNO, prior to starting oral therapy, with temporary improvement. He had required prolonged mechanical ventilation followed by continuous positive airway pressure (CPAP) via a tracheostomy. Within 3 months of oral therapy with bosentan, he was weaned off CPAP. He had normal pulmonary hemodynamics on follow-up cardiac catheterization at 6 months. Currently, he is scheduled for decannulation of his tracheostomy. The patient had a transient threefold increase in liver enzymes coincident with a viral respiratory infection, which normalized on discontinuing bosentan for 1 week and remained normal after reintroduction of the medication.

Patient 4 was diagnosed with hypoplastic left lung, in addition to CLD of prematurity. He has a diminutive left PA supplying the hypoplastic lung on pulmonary angiography. With combination therapy there was marked clinical improvement, and 1 month later, he was finally discharged home, after prolonged ventilation and intensive care hospitalization for nearly 3 years of life, with no subsequent readmissions. The patient still requires minimal nasal oxygen, for his lung disease. He had suprasystemic PA pressures on baseline cardiac catheterization and elevated PVR, which decreased significantly at cardiac catheterization after 6 months of combination therapy. There was a transient elevation of liver enzymes during an intercurrent viral respiratory infection, which resolved with temporary cessation of bosentan therapy.

Patient 5 was born at 35 weeks of gestation, diagnosed with severe intrauterine congenital cytomegalovirus infection associated with interstitial lung disease. She spent 6 months in neonatal intensive care, was mechanically ventilated for 2 months, and then was weaned to nasal

CPAP. She had frequent hospitalizations subsequently for pulmonary exacerbations and cyanosis. Baseline cardiac catheterization showed a very large right-to-left patent ductus arteriosus (PDA) and multiple small muscular VSDs. She had significantly elevated PVR. She was weaned off CPAP to nasal oxygen after 3 months of combination therapy. Follow-up cardiac catheterization revealed a significant reduction in PVR 6 months after therapy. Following balloon occlusion of the PDA, PA pressures fell by 30 mm Hg, with no worsening of the RV pressure or function. The PDA was closed nonsurgically by transcatheter approach, with complete occlusion and resultant PA pressure less than two-thirds systemic. Currently, at 1 year after PDA closure, the patient shows continued clinical improvement.

Patient 6 presented with seizures and cyanosis, 4 months after bone marrow transplantation for aplastic anemia. Clinical exam suggested RV failure. There was severe RV hypertrophy on ECG, and systemic RV pressures suggested on echocardiogram. He had developed respiratory failure following transplant, requiring mechanical ventilation for 5 weeks. Lung biopsy revealed significant interstitial lung disease suggestive of graft-versus-host disease and stage 2–3 Heath Edwards changes. Cardiac catheterization revealed near systemic but reactive PH. Follow-up hemodynamics on cardiac catheterization after 6 months of combination therapy revealed normal pulmonary pressures and resistance. The patient had a recent relapse of respiratory symptoms, after 2.6 years of complete resolution of PH, and his recent echocardiograms on therapy revealed elevated PA pressures. A repeat lung biopsy as well as a high-resolution CT scan showed marked worsening of interstitial lung disease and vascular disease. He is on high-dose steroid therapy for the lung disease, and on an increased dose of bosentan, and will be closely followed for pulmonary hypertensive status.

Results

The patients were followed up for 2.1 to 2.9 (mean, 2.53) years. All subjects showed substantial clinical improvement in symptoms with resolution of cardiac failure (Ross Class 4 to Class 1) (Table 1). Follow-up CT scans obtained for all subjects 6–18 months into therapy did not show substantial improvement in the parenchymal/interstitial lesions to account for symptomatic or hemodynamic improvement in these subjects. Within 2 months of therapy, five of six patients were discharged home from the chronic care facility, and the sixth remained in hospital longer for social reasons. Four of six patients were weaned off oxygen over 6 months. There were no significant adverse effects noted except for transient elevations of liver enzymes coincident with viral infections in two patients, which resolved with recovery and temporarily withholding of bosentan. Table 2 reports the marked improvement in hemodynamic parameters at 6 months after treatment. Figure 1 describes changes in individual mean PA/aortic pressure ratios and changes in PVR, at baseline and repeat catheterization after 6 months of therapy.

Discussion

Children with CLD differ from patients with IPAH in their clinical course and response to therapy. The clinical course is complicated by both interstitial lung disease and pulmonary hypertensive crises [1]. Newer oral medications like sildenafil and bosentan are now first-line therapeutic agents in IPAH, but there has not been much experience with these drugs in secondary PH in children. Sildenafil has been shown to improve pulmonary hemodynamics in small groups of adult patients with CLD [5, 6]. It is possible that treatment with phosphodiesterase and ET-1 inhibitors could decrease the progression of vascular disease (acting synergistically at the cellular level), reverse the inflammatory endothelial damage, and cause vascular remodeling as well as reduction in RV hypertrophy in patients with CLD [12]. Both bosentan and sildenafil have been shown to improve perfusion selectively to the healthier lung tissue, thereby improving VQ matching [2, 14].

In this series, marked improvement in respiratory status was seen in all patients within the first 3 months of initiation of these newer agents, suggesting the possibility of an additional direct effect on the pulmonary parenchymal disease in these patients. Improved V-Q matching could play a role in reducing oxygen requirements. Sildenafil, a phosphodiesterase inhibitor, acts on vascular, cardiac, and bronchial smooth muscle through cGMP-mediated release of NO and is shown to have beneficial effects on both pulmonary vasculature and parenchyma and on reversal of RV hypertrophy [2, 13]. Bosentan, a nonselective endothelin receptor antagonist, has been shown to reverse endothelin-induced smooth muscle constriction, hypertrophy, and hyperplasia [8, 14]. PH has been described previously in the setting of graft-versus-host disease, but the response to therapy has not been encouraging [3]. It appears that the combination of medications had a positive effect on our patient with PH related to graft-versus-host disease, and further long-term follow-up to assess durability of therapy is required, in light of recent worsening parenchymal and vascular disease. We included this subject in our series, though the lung pathology did not stem from the neonatal period, since this was yet another example of secondary PH associated with lung disease that showed an impressive response to oral agents.

Three subjects had additional cardiac shunts, however, these shunts were entirely right to left since the neonatal period secondary to CLD and PH. Hence, their lungs were never subjected to increased pulmonary blood flows secondary to the shunts. All patients tolerated the therapies well, with minimal side effects. It is possible that intercurrent viral infection may increase the vulnerability of hepatocytes to bosentan, hence close monitoring of aminotransferase levels is indicated. The ease of administration, as well as the low incidence of side effects, improves patient compliance to therapy.

It may be argued that clinical improvement in these subjects could have been a result of improvement in their CLD. However, that appears unlikely given the presenting condition of the subjects before initiation of the oral therapies and the rapid improvement. Indeed, though there were no significant parenchymal/interstitial changes on CT, one could speculate that these agents may even help in the improvement of the lung parenchymal/interstitial disease in these subjects over the long term by mechanisms yet unknown.

In conclusion, this study demonstrates that oral bosentan and sildenafil may be useful in the management of CLD with PH in young children. Longer-term, controlled studies with larger number of subjects is needed to evaluate the sustained effect of these medications.

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