An Overview of the Pathogenesis and Treatment of Pulmonary Hypertension: Part 2

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Abstract: The pathoaeiology of pulmonary hypertension (PHT) was reviewed in Part I of this article. The discovery that an imbalance of the various vasomotor mediators, particularly prostacyclin (down-regulated), and endothelin (up-regulated), has led to the development of novel treatment for this potentially deadly disease. It is now possible to not only relieve the signs and symptoms of PHT but also to prolong the quality life years of sufferers of this condition.

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Introduction

Before considering the various drugs and other technical approaches that can be used to treat pulmonary hypertension (PHT), it must be emphasised that certain general measures can have significant influence on the development and outcome of the disease. Of particular importance is the close counselling of patients and their relatives. The seriousness of the disease, life expectancy, therapeutic options including transplantation, and possible complications should be discussed in an open and congenial atmosphere. The patient should be helped to fully understand the diagnostic and therapeutic measures to be taken, as this helps in tolerating the sometimes unpleasant and strenuous procedures.

Traditionally, drug treatment of PHT has involved the use of high dose systemic vasodilators notably calcium channel blockers such as nifedipine, diltiazem and felodipine, diuretics, inotropic agents e.g. digoxin, anticoagulation with warfarin, and long term oxygen therapy. Treatment of the underlying condition such as specific therapies for systemic lupus erythematosus (SLE) and certain infections may also delay the progression of PHT. Surgical interventions, the most commonly carried out one being atrioseptostomy, may also improve the patient's symptoms. Cardio-pulmonary transplantation may be considered for advanced cases. Unfortunately, there is often a lack of randomised controlled trials to prove the efficacy of these therapeutic measures, which is generally thought to be low or at most moderate. This, in addition to their many associated side-effects, have led clinicians into a search for novel therapeutic agents for PHT. The improvement in our understanding of the pathophysiology of PHT has made this possible.

Recent Advances in the Treatment of Pulmonary Hypertension

PGI₂ Therapy

Systemic PGI₂

The beneficial effects of PGI₂ therapy were first reported in 1996 by Barst and his colleagues.1 In this study, patients who were given epoprostenol (exogenous PGI₂) plus conventional
therapy had improved survival and exercise tolerance, increased cardiac output, and decreased pulmonary vascular resistance when compared with patients who were treated with conventional therapy only. Subsequent studies have confirmed the sustained positive effects of continuous infusion of epoprostenol in patients with primary PHT as well as those with systemic sclerosis (SSc) associated PHT. However, epoprostenol therapy is complicated by the need for continuous intravenous infusion. The drug is unstable at room temperature and at acidic pH, and has a very short half-life in the bloodstream (less than 6 minutes). Further, abrupt or inadvertent interruption of the epoprostenol infusion may, in some patients, lead to a rebound worsening of their PHT with symptomatic deterioration and perhaps even death.

Some of the above-mentioned problems associated with epoprostenol may be circumvented by the use of treprostinil, a stable analogue of PGI2, with a half-life of 3 hours and similar haemodynamic effects of epoprostenol. However, this treatment is not without its own complications. Like epoprostenol, treprostinil has to be given continuously though it is administered subcutaneously. Injection site reaction is not an uncommon adverse reaction of treprostinil treatment, and like epoprostenol, systemic side-effects including headache, diarrhoea, flushing, jaw pain and foot pain are often reported.

Inhaled Iloprost

To evade the systemic side-effects of PGI2 and analogues treatment, administration of these agents through inhalation was explored. The rationale for this mode of administration is based on the fact that intra-acinar pulmonary arteries are tightly surrounded by alveolar surfaces and it is possible to vasodilate these vessels by means of an alveolar deposition of a prostanoid.

Iloprost is a PGI2 analogue and has the same biologic profile as the natural substance with respect to PG receptor binding and cellular effects, as well as clinical efficacy in PHT. However, iloprost has significant better chemical stability than PGI2. Initial evidence for the inhalation of aerosolised iloprost was reported by Olschewski and his colleagues. It was found to have similar effects in the reduction of pulmonary arterial pressure, but without significant systemic hypotensive effects, when compared with intravenous iloprost.

In a large randomised double-blind placebo-controlled European multicentre study with inhaled iloprost, a total of 203 patients with primary and other forms of PHT in NYHA class III or IV were enrolled. The primary endpoint of the study, defined as an improvement in NYHA class, combined with at least 10% improvement in the 6-minute walking test, and no prior deterioration or death (combined clinical endpoint) was reached by 3.4 times (16.8% vs 4.9%) more patients in the iloprost than in the placebo group. Treatment effects did not differ between patient subgroups. This effect was achieved with a mean inhaled iloprost dose of 0.37 ng/kg/min. In the 6-minute walking test the treatment effect was 36.4 m in favour of iloprost. There was also a significant treatment effect on NYHA functional class, quality of life, and the clinical symptomatology of the patients studied. Haemodynamics significantly deteriorated in the placebo group, whereas in the iloprost group pre-inhalation values were unchanged compared to baseline and post-inhalation values were significantly improved. Importantly, the number of patients remaining on the study medication, a measure corresponding to event-free survival, was significantly higher in the iloprost than in the placebo group. Over 3 months of therapy, there was no indication of tachyphylaxis, which is a significant advantage to the systemically administered PGI2 and analogues. The overall side-effects were mild and mostly transient. The authors concluded that inhalation of iloprost is an effective and safe therapy for severe primary and non-primary PHT. This approach combines efficacy with excellent tolerability and safety, with no evidence of tachyphylaxis during a 3-month treatment period. On-going open label multi-centre long-term study (up to 2 years) of inhaled iloprost in PHT is currently underway and results have thus far been encouraging. However, inhalational iloprost treatment is not without its potential drawbacks, the most important of which is the fact that the haemodynamic effects level off within 30 to 90 minutes, and that 6 to 9 inhalations per day are needed to achieve good clinical results.

Endothelin Receptor Antagonist

Since endothelin (ET) has an important pathogenic role in PHT, new treatment for this condition could act by blocking ET receptors. Bosentan is an orally active non-peptide antagonist of both ET receptor subtypes (ETa and ETb). It has been shown to decrease inflammatory reactions, prevent increase in permeability of pulmonary vessels, and prevent
development of fibrosis in animals with pulmonary inflammation.\textsuperscript{11-12} The use of bosentan in human PHT was first evaluated by Channick and his colleagues\textsuperscript{13} in a double-blind placebo-controlled trial involving 32 patients with primary or SSc associated PHT. After 12 weeks treatment with bosentan, there was significant improvement in the 6-minute walking distance, cardiac index, pulmonary vascular resistance, dyspnoea index and WHO functional class.

The positive effects of bosentan in patients with PHT was later confirmed by a large multicentre double-blind, placebo-controlled study.\textsuperscript{14} Two hundred and thirteen patients with primary or connective tissue disorder associated severe PHT were assigned to receive orally placebo or 62.5 mg of bosentan twice daily for 4 weeks followed by either of the two doses of bosentan (125 mg or 250 mg twice daily) for a minimum of 12 weeks. The primary end point was the degree of change in exercise capacity. Secondary end points included the change in the Borg dyspnoea index, the change in the WHO functional class, and the time to clinical worsening. At week 16, patients treated with the active drug showed an improvement in their exercise capacity. The mean difference in 6-minute walking distance between the placebo group and the combined bosentan groups was 44 m. Bosentan also improved the Borg dyspnoea index, WHO functional class and the time to clinical worsening. Treatment with 125 mg of bosentan twice daily was not associated with a significant increase in adverse events or with a change in their nature when compared with placebo. However, increasing the dose to 250 mg twice daily led to a greater frequency of increased aminotransferase levels. The authors concluded that 125 mg twice daily is the clinically preferable dose. Bosentan is now approved for the treatment of PHT.

Although bosentan is a major advance in the treatment of PHT, a number of issues relating to ET receptor blockade remain to be addressed. These include: (1) the long term effects of bosentan in PHT; (2) whether selective ET\textsubscript{A} receptor-blocking agents are superior to non-selective agents; and (3) whether combination therapies, for example a prostanoid coupled with ET-blocker, produce greater benefits in PHT compared to single agent approaches. These important questions are under investigations, and the answers will undoubtedly lead to further progress in the quest for improved treatments for this devastating disease.

Other Experimental Agents

Phosphodiesterases (PDEs) are a superfamily of enzymes that inactivate cyclic adenosine monophosphate and cyclic guanosine monophosphate, the secondary messengers of PGI\textsubscript{2} and nitric oxide (NO). The PDEs have different tissue distributions and substrate affinities; in particular, PDE-5 is abundantly expressed in lung tissue.\textsuperscript{15} Inhibition of PDE may augment and prolong prostanoid- and NO-related vascular effects. Sildenafil is a novel selective PDE-5 inhibitor approved for treatment of erectile dysfunction. It has also recently been used in patients with PHT. Short term application of sildenafil during right heart catheterisation showed the potential to reduce pulmonary vascular resistance in a dose dependent manner.\textsuperscript{16} In combination with inhaled iloprost, augmentation of the pulmonary vasodilatory effect of each single agent was noted.\textsuperscript{16,17} Combination prostanoids and PDE-5 inhibitor treatment could prove to be an appealing concept for future treatment of PHT.

Other experimental therapeutic agents for PHT include L-arginine, a substrate for NO through the NO synthase pathway; dicloroacetate, an activator of the cellular potassium (K\textsubscript{v}) channels; and agents targeting anti-remodelling such as serotonin, elastase blockers, vascular endothelial growth factor inhibitors and cholesterol-synthase inhibitors. It is beyond the scope of this article to review the evidence for these agents in PHT.

Conclusion

PHT is an uncommon but devastating and life-threatening disease. Treatment options were limited in the past. However, recent research has shown new light onto the factors which contribute to the mechanisms underlying the pathophysiology of PHT and enabled the development of novel treatment for this condition. It is now possible to not only treat the debilitating symptoms of PHT, but potentially target the trigger factors that are fundamental to the pathogenesis of this disease and result in a better prognosis.

References


