

# Current Treatment For Pulmonary Hypertension

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## Citation

H Kiran, S Vidyasagar, U Shashikiran. *Current Treatment For Pulmonary Hypertension*. The Internet Journal of Pulmonary Medicine. 2004 Volume 4 Number 2.

## Abstract

Pulmonary hypertension is a fatal disease. When left untreated, it progresses to death from right heart failure. Prostaglandins and their analogues are the mainstay of treatment. Intravenous Prostaglandins, Epoprostenol and calcium channel blockers are in use since many years. Several recent trials have established the efficacy of newer drugs. Trepostinil is a prostacyclin analogue which can be given as subcutaneous infusion. Iloprost is a prostaglandin analogue which can be given through intravenous as well as inhalational route. Beraprost can be used orally. Bosentan is a nonselective dual Endothelin receptor antagonist while Sitaxsentan is an oral selective Endothelin A receptor blocker. L Arginine, a precursor of Nitric Oxide can be used orally. Sildenafil, a phosphodiesterase inhibitor appears promising. Several options are now available for the treatment of pulmonary hypertension in addition to other adjunctive therapies. Present treatment options for pulmonary hypertension are discussed. However, further studies are required to evaluate the long-term efficacy of these drugs.

## INTRODUCTION

Pulmonary hypertension is a common cardiac problem seen by medical specialists in day-to-day practice. The incidence of secondary pulmonary hypertension due to lung diseases, congenital heart diseases, or chronic pulmonary thromboembolism is much higher than primary pulmonary hypertension, which is an uncommon disease characterized by increased pulmonary artery pressure and pulmonary vascular resistance. The incidence of this disorder has been estimated at approximately 2 cases per million

Progressive obliteration of the pulmonary vascular bed is the hallmark of pulmonary hypertension. If it is not treated, it progresses to death from right heart failure. Mean survival from the time of diagnosis is only 2 years in untreated patients with severe pulmonary hypertension.

## PATHOPHYSIOLOGY AND BASIS OF TREATMENT

Recent insights into the pathogenesis have resulted in newer approaches to its treatment. Pulmonary hypertension involves vasospasm and later intimal fibrosis, thrombosis in situ, proliferation of smooth muscles and medial hypertrophy. Normally there is a balance between the endothelium derived relaxing factors (Nitric oxide NO and prostacyclin) and endothelium derived constricting factors Endothelin-1 (ET-1) etc). Any imbalance of these factors promotes endothelial smooth muscle proliferation, induces

vascular remodeling and incites thrombosis. Pulmonary hypertension is thus, nowadays, considered as a vasoproliferative rather than a vasoconstrictive disorder. This has led to a major change in the approach to treatment, which has evolved, from vasodilators to antiproliferative agents (1)

In this article we will attempt to summarize the results of clinical trials on new treatments and provide an approach to treatment of pulmonary hypertension.

The diagnostic classification of Pulmonary Hypertension is given in Table 1.

Table 1: Diagnostic Classification Of Pulmonary Hypertension (PH) (WHO- 1998) (2)

- Pulmonary Arterial hypertension
  - Primary pulmonary hypertension
  - PH associated with:
    - Collagen vascular diseases
    - Portal hypertension
    - Congenital systemic to pulmonary shunts
    - Drugs/toxins

- HIV infection
  - Persistent PH of newborn
- Pulmonary venous hypertension
- PH associated with disorders of respiratory system and / or hypoxemia
- PH due to chronic thrombosis and/or embolic disease
- PH due to disorders affecting pulmonary vasculature.

Table 2: assessment of improvement (outcome measures)

Assessment of Improvement in various trials included the following parameters.

1. 6-minute walk test - Measures how far a patient can walk in 6 min.
2. Borg dyspnea index – A measure of perceived breathlessness on a scale of 0 to 10
3. Pulmonary hemodynamics – Pulmonary Artery pressure
4. NYHA class

### OPTIONS FOR TREATMENT OF PULMONARY HYPERTENSION

#### VASODILATOR THERAPY

In the past, several vasodilators (i.e. hydralazine, diazoxide, isosorbide dinitrate, Alpha blockers, Beta agonists like Isoprenaline) etc. have been tried without much success. Currently, Calcium Channel Blockers and PGI<sub>2</sub> analogues are the only effective vasodilators.

**CALCIUM CHANNEL BLOCKERS (CCBs):** Calcium channel blockers are vasodilators of systemic and pulmonary circulations. Among the various CCBs, long acting vasoselective dihydropyridines and slow release, heart rate regulating CCBs are preferred. Before starting long term CCBs, “Responders” should be identified by measuring Pulmonary artery pressure (PAP) and Pulmonary venous resistance (PVR) in response to short acting vasodilators (e.g. inhaled NO, intravenously Adenosine or intravenously PGI<sub>2</sub>) (3). A positive response is 10mm Hg or more fall in Mean Pulmonary artery pressure (MPAP) with either no

change or an increase in Cardiac output and or decrease in PVR of approx. 25%. Rich et al (4) have shown that high doses of CCBs resulted in a 5-year survival of more than 90% in “responders” i.e. in patients who showed an acute response to vasodilators. It should be noted that only 10-15% of patients come under this “responder” category. The patients who respond to CCBs need large doses (eg. Nifedipine upto 300mg/day, Diltiazem upto 720mg/day).

The adverse affects are due to their negative inotropic effect and fall in systemic blood pressure, which may be an important limiting factor in their use. Hence CCBs should not be used in patients with overt right ventricular failure and those with systemic hypotension.

**PROSTAGLANDINS:** The prostacyclins act through an increase in Cyclic AMP, which produces vasodilatation.

**EPOPROSTENOL:** Epoprostenol is a potent pulmonary vasodilator. Its other mechanisms of benefit are unclear. It may also result in a positive inotropic effect, has some amount of systemic vasodilatation and antiplatelet effect by which it may reverse vascular damage (5)

Prospective randomized trials by Barst et al (6) and McLaughlin et al (7) have demonstrated improved exercise tolerance and survival in patients with primary pulmonary hypertension treated with Epoprostenol. The survival benefit was seen in patients with NYHA class 3 & 4 heart failure. The optimal dose is yet to be clearly defined. However, starting Epoprostenol at a dose of 2-4ng/kg/min intravenously is recommended followed by increments of 1-2ng/kg/min until either clinical improvement is seen or further increment is not possible due to side effects.

Epoprostenol has a very short half life ( $t_{1/2}$ ). Therefore, a permanent central venous access is needed for administration and hence a risk of potentially serious complications thereof. Common side effects are flushing, headache, diarrhoea, nausea, jaw pain, leg pain. Sudden withdrawal may result in rebound rise in PAP leading to Acute RV failure. Epoprostenol is unstable in aqueous solution and has a  $t_{1/2}$  of 1-2 minutes. Hence any interruption of the infusion may lead to sudden life threatening loss of its effect. Therefore, a more stable PGI<sub>2</sub> analogue like Iloprost offers theoretical advantages.

**ILOPROST:** Iloprost is a stable prostacyclin analogue with a  $t_{1/2}$  of 20-30min. given intravenously; its effects are similar to intravenous epoprostenol. Dosing of intravenous iloprost is lower than that of intravenous epoprostenol. The normal

starting dose is 0.5–1 ng/kg/min and maintenance dose is 2–4 ng/kg/min. Iloprost can be given by inhalation also. By inhalation route, less of the drug reaches systemic circulation thus making it a “pseudoselective pulmonary vasodilator”.

Currently, intravenously prostaglandins are the first line of treatment for patients in New York Heart Association (NYHA) class III & IV. However, in the future, patients with less severe disease (NYHA II, III) may be initially treated with one of the novel prostaglandins.

### SUBCUTANEOUS TREPOSTINIL

The propensity for serious central venous catheter related infections in case of intravenous epoprostenol led to the development of Trepostinil, a stable prostacyclin analog for subcutaneous infusion. It is given as a continuous subcutaneous infusion by a mini pump that has been used for insulin. It has a  $t_{1/2}$  of 3–4 hours.

A 12-week, double blind, randomized placebo controlled multicenter trial (in 470 patients with PH either primary or associated with connective tissue disease, congenital systemic to pulmonary shunts) showed that continuous subcutaneous Trepostinil improved indices of dyspnea, signs and symptoms of pulmonary hypertension and hemodynamics (<sub>8</sub>). It was given through a micro infusion pump with catheter placed in the subcutaneous tissue of abdominal wall at an initial dose of 1.25ng/kg/min. During the course of this study, the drug was increased to a maximum dose at which PH signs and symptoms were improved. The maximum allowed dose was 22.5ng/kg/min. The most common side effect was infusion site pain (85%). 3 patients had gastrointestinal (GI) bleed.

### ORAL BERAPROST

Oral Beraprost another prostacyclin analogue appears to be beneficial in the treatment of PPH (<sub>9,10</sub>). A study of oral Beraprost in 13 patients with severe PH (given treatment for 1 year) concluded that oral Beraprost might result in long-lasting clinical and hemodynamic improvement (<sub>9</sub>). A placebo controlled multicenter trial (ALPHABET) of 130 patients showed that oral Beraprost decreased mean pulmonary artery pressure in many patients. This study included patients with primary PH, PH associated with collagen vascular disease, congenital systemic to pulmonary shunts, portal hypertension and HIV. A median dose of 80ug was given 4 times/day.

### INHALED ILOPROST

Inhaled Iloprost also appears to be beneficial (<sub>11,12</sub>). In a study involving 203 patients with severe pulmonary hypertension (including PH with scleroderma and chronic thrombo embolic PH) inhaled Iloprost was found to be useful (<sub>12</sub>). 2.5–5 ug of Iloprost (6–9 times/day – median inhaled dose 30 ug/d) was compared with placebo and was found to be effective in decreasing the signs and symptoms of PH. Inhaled Iloprost has the disadvantage of short duration of action and hence requires frequent (<sub>6,7,8,9,10,11,12</sub>) inhalations per day. It may hence disturb patient’s lifestyle and may be cumbersome.

### ENDOTHELIN RECEPTOR ANTAGONISTS

Endothelin – 1 mediates vasoconstriction and smooth muscle cell proliferation through ETA receptor. It also induces vasodilatation through ETB receptor.

**BOSENTAN:** Bosentan is an oral, dual endothelin receptor antagonist. It blocks both Endothelium A and Endothelium B receptors (and hence it is non selective). It is thus an antiproliferative agent and may be most useful in PPH. A double blind randomized placebo-controlled study showed that oral Bosentan increases exercise capacity and improves hemodynamics in patients with PH (<sub>13</sub>). The results of BREATHE-1 (Bosentan: Randomized trial of Endothelin receptor Antagonist Therapy for Pulmonary Hypertension) concluded that Bosentan is beneficial in patients with PH and is well tolerated at a dose of 125mg twice daily (<sub>14</sub>). Elevation of liver enzymes was observed in 14% patients (transient in most cases and necessitated discontinuation of treatment in only 3 patients). The mechanism responsible for this is not clear. An accumulation of bile acids in hepatocytes due to competitive inhibition of bile salt-export pump may be the reason.

**SITAXSENTAN:** It is an oral, selective ETA receptor blocker. A 12-week open label trial by Barst et al showed that Sitaxsentan is beneficial in PH (<sub>15</sub>). It was given orally at a dose of 100–500mg bd. It also resulted in elevated liver enzymes in some patients.

**NITRIC OXIDE (NO) & L – ARGININE:** Vasodilators including inhaled NO act through Cyclic GMP

**NO:** Inhaled NO is an effective acute pulmonary vasodilator in PH. It requires a continuous inhalation device. Though NO is a potent and selective pulmonary vasodilator, its long-term use is limited by its short half-life. Inhaled NO is currently used to identify “responders” (who respond to CCBs). 80ppm of NO is usually the maximum dose used in

acute vasodilator setting (<sub>16</sub>). Long-term therapy with NO is not practical or viable at present.

**L-ARGININE:** NO is synthesized from the amino acid L-Arginine. Hence L-Arginine supplementation may be beneficial in PH. The first ever randomized placebo controlled study to examine the effects of short term oral administration of L-Arginine (<sub>17</sub>) showed that oral L-Arginine significantly decreased mean PAP and PVR associated with significant increase in citrulline and improved exercise capacity. It was used at a dose of 0.5g/kg body weight

**PHOSPHODIESTERASE INHIBITOR – SILDENAFIL:** PH is associated with a defect in endothelial nitric oxide production and hence nitric oxide dependent pulmonary artery dilation. Therapeutic approaches have been devised to reverse this relative deficiency of nitric oxide. This has been tried using L-Arginine, the substrate required for nitric oxide synthesis and administration of nitric oxide as mentioned earlier. An alternative approach for enhancing the endogenous nitric oxide in PH is to increase nitric oxide – dependent, cGMP mediate pulmonary artery vasodilatation by inhibiting the breakdown of cGMP by PDE5 (Phosphodiesterase5). Sildenafil increases cGMP level by inhibiting PDE5, an enzyme that hydrolyses cGMP.

There are few data on long term Sildenafil treatment barring a few case reports. Michelakis et al (<sub>16</sub>) have demonstrated that Sildenafil is as effective and selective a pulmonary vasodilator as inhaled Nitric Oxide. Studies that have been done so far are in a small number of patients.

Kothari and Duggal (<sub>18</sub>) have demonstrated that oral Sildenafil is effective in PH. They studied 14 patients with severe PH (9 patients with primary PH & 5 patients were operated Congenital heart disease patients). Oral Sildenafil was started at low dose and then increased. It was used at a dose of 87.5mg/day in children < 30kgs and at a dose of 150mg/day in patients > 30kgs. They observed remarkable improvement in 6 min walk test, NYHA class and Mean pulmonary artery pressure (MPAP)

Bharani et al (<sub>19</sub>) studied 10 patients with PH of varied etiology (PPH, left to right shunts, pulmonary thromboembolism and interstitial lung disease) They used Sildenafil at a dose of 25mg Q8H in their randomized double blind placebo controlled cross over study, and showed that Sildenafil was useful in PH of varied etiology.

Ghofrani et al (<sub>20</sub>), in a randomized controlled open label trial showed that Sildenafil causes preferential pulmonary vasodilation and improves gas exchange in patients with severe lung fibrosis and secondary pulmonary HT.

Sastry et al (<sub>21</sub>) studied the efficacy of sildenafil in 29 patients with PPH. Sildenafil was started at a dose of 25mg tid & increased upto 100mg tid. There was a significant improvement in functional class, 6min walk test and MPAP.

However, the experience with Sildenafil is limited and remains preliminary and more studies are required to establish its efficacy and safety.

The most commonly reported side effects of Sildenafil are due to vasodilatation. It can cause flushing, nasal congestion, headache, dizziness, hypotension. It can cause relaxation of lower esophageal sphincter resulting in dyspepsia and reflux related symptoms and transient visual abnormalities such as blurred vision and increased light perception due to inhibition of PDE6 in rods and cones in retina (<sub>22</sub>) It is contraindicated in patients with ischemic heart disease (IHD) who are on nitrates.

A current option for treatment of Pulmonary Hypertension has been summarized in Table 3.

Table 3: Current Options for Treatment of Pulmonary Hypertension

### VASODILATORS:

- Calcium channel Blockers: Nifedipine, Diltiazem
- Continuous intravenously infusion: Epoprostenol
- Continuous subcutaneous infusion: Trepostinil
- Dual Endothelin receptor antagonist: Bosentan
- Investigational therapy
  - Selective Endothelin receptor antagonist: Sitaxsentan
  - Inhaled Nitric Oxide
  - Stable prostacyclin analogues:
    - Oral Beraprost
    - Inhaled Iloprost
  - Oral Phosphodiesterase 5 inhibitor: Sildenafil

## OTHER ADJUNCTIVE THERAPIES:

- Supplemental O<sub>2</sub>
- Anticoagulation
- Diuretics
- Digoxin
- Intravenous inotropes: low dose  
Dobutamine/Dopamine in severe right heart failure  
With hypo perfusion.
- Transplantation: Lung Heart – lung (PH sec. to complex CHD).
- Atrial Septostomy (investigational)

## RECENT ADVANCES IN THE TREATMENT OF SECONDARY PH

The treatment of secondary PH depends on the cause and this involves treatment of the primary disease as hypoxia causes pulmonary vasoconstriction. Oral anti-coagulation is the mainstay of treatment for chronic pulmonary thromboembolism.

Present treatment includes long-term oxygen therapy for COPD, and treatment of underlying diseases.

Oral Bosentan and subcutaneous Trepostinil are not restricted for the use in only primary pulmonary hypertension. They have been approved for other causes of PH as well (23). Sildenafil also has been shown to be useful in patients with severe lung fibrosis and secondary hypertension (20).

## OTHER ADJUNCTIVE THERAPIES

Long-term anticoagulation with warfarin is advised in all patients since it has been shown to reduce mortality by decreasing the incidence of intravascular thrombosis in situ.

Supplemental O<sub>2</sub> is useful in hypoxic patients. Patients with right heart failure should be treated with diuretics and digitalis intravenously. Dobutamine or dopamine may be used for short-term treatment of severe right heart failure. Pulmonary endarterectomy may be done in cases of chronic thromboembolic PH. Atrial septostomy, as palliative procedure can be tried in patients with severe precapillary PH but it is risky.

## AN APPROACH TO TREATMENT OF PULMONARY HYPERTENSION ( ), ( )

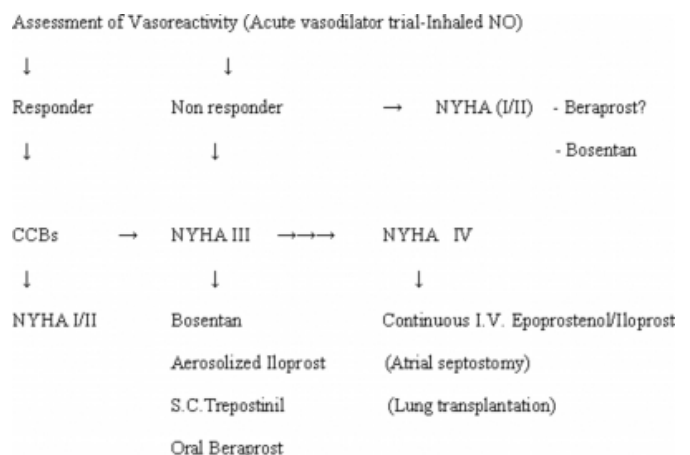
There are no long-term data comparing different drugs. Hence the choice of drug therapy depends on experience, affordability and availability of drugs.

All patients should be treated with oral anticoagulants if there are no contraindications. In patients with mild to moderate PH, in NYHA I & II and who come under the category of “Responder” (following a response to acute vasodilator trial), Calcium channel blockers are the first line of treatment. “Non Responders” in NYHA class II and who are stable may be observed. If necessary, oral Beraprost or Bosentan can be given.

For patients in NYHA class III, oral/inhaled/ subcutaneous prostaglandins or ET antagonist Bosentan could be given as first line of treatment. For patients with severe PH (NYHA-IV) the treatment of choice is intravenously prostacyclin. Current approach to treatment of pulmonary hypertension is given in flow chart in table 4.

**Figure 1**

Table 4: Flow chart for treatment options in pulmonary hypertension



## FUTURE OPTIONS

A gene for familial PH, which codes for BMPR-2, a receptor in the TGF-B family has been discovered. This is also seen in some patients with sporadic PH. This discovery may lead to specific therapies directed at the origin of the disease.

There were no placebo-controlled trials in the treatment of pulmonary hypertension prior to 1999. There are few studies evaluating the long-term efficacy of the drugs mentioned so far and their effects on survival. However, these drugs appear promising. Also, in future, a combination of 2 drugs from different groups may be tried. Trials of this kind are

currently under progress, and hold out promises of hope for patients with irreversible pulmonary hypertension.

### References

1. Rubin L.J. Therapy of Pulmonary Hypertension: The Evolution from vasodilators to Antiproliferative agents. *Am J Respir Crit Care Med* 166: 1308-1309
2. Chatterjee K, De Marco T, Alperi JS. Pulmonary Hypertension. *Arch Intern Med* 2002; 162: 1925-1933
3. Rich S. Primary Pulmonary hypertension. *Curr Treat Options Cardiovasc Med* 2000; 2:135-139
4. Rich S, Kaufman E, Levy PS. The Effect of high doses of Calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992; 327:76-81
5. Galie N, Mannes A, Brauzi A et al. A medical therapy of pulmonary hypertension, the prostacyclins. *Clin.Chest Med* 2001; 22: 529-537
6. Barst RJ, Rubin LJ, Long WA, et al. for the primary pulm Hypertension study group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension *N Engl J Med* 1996; 334: 298-302
7. Mc Laughlin VV, Genthner OE, Panella MM. et al. Reduction in Pulmonary vascular resistance with long term epoprostenol (Prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med*. 1998; 338: 273-277.
8. Simonneau G, Barst RJ, Galie N et al. Continuous subcut. Infusion of Trepstinil, a prostacyclin analogue in patients with pulmonary arterial hypertension: a double blind randomized control trial. *Am J Respir Crit Care Med* 2002;165: 800-804
9. Vizza CD, Sciomer S, Morelli S Long term treatment of pulmonary Hypertension with Beraprost, an oral prostacyclin analogue. *Heart* 2001; 86, 661-665
10. Galie N, Humbert M, Vachiery JL et al. Effect of Beraprost Sodium, an oral prostacyclin analogue, in patients with pulm arterial hypertension, a randomized, double blind placebo controlled trial. *J Am Coll Cardiol* 2002; 38:1496-1502
11. Hoeper MM, Schwarze M Ehlerding S et al. Long term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000; 342; 1866-1870
12. Olschewski H, Simonneau G Galie N et al Inhaled Iloprost for Severe pulm HT, *N Engl J Med*: 2002; 347: 322-329.
13. Channick RN, Simonneau G, Sitbon O et al. Effects of the dual Endothelin receptor antagonist bosentan in patients with pulm HT: a randomized placebo controlled study. *Lancet* 2001; 358: 1119-1123.
14. Rubin LJ, Badesch DB, Burst RL et al. Bosentan in patients with pulmonary arterial HT: a randomized placebo controlled multicenter study. *N Engl J Med* 2002; 346: 896-903.
15. Barst J, Rich S, Widlitz A et al. Clinical efficacy of Sitaxsentan, an Endothelin A Receptor antagonist, in patients with pulm arterial HT. Open label pilot study *Chest* 2002; 121: 1860-1868.
16. Michelakis E, Tymchal W, Lien D et al. Oral Sildenafil is an Effective and specific pulmonary vasodilator in patients with pulm Arterial HT. Comparison with inhaled nitric oxide. *Circulation*. 2002;105:2378-2403
17. Nagaya N, Uematsu M, Oya H et al. Short-term oral administration of L-Arginine improves hemodynamic and exercise capacity in patients with precapillary pulm. HT. *Am J Respir Crit care Med* 2001; 163; 887-891
18. Kothari SS, Duggal B. Chronic oral Sildenafil therapy in severe PAH. *Indian Heart J*. 2002 Jul-Aug 54(4): 404-9
19. Bharani A, Mathew V, Sahu A et al. Efficacy and tolerability of Sildenafil in patients with moderate to severe PH. *Indian Heart J*. Jan 1 2003;55(1): 55-4
20. Ghofrani HA, Wiedermann R, Rose F et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension. A randomized controlled trial *Lancet* 2002; 360: 895-900
21. Sastry BKS, Narasimhan C, Reddy NK et al. A Study of Clinical Efficacy of Sildenafil in patients with PPH. *Indian Heart J* 2002; 54:410-414.
22. Reffelmann T, Kloner RA. Therapeutic potential of phosphodiesterase5 inhibition for cardiovascular disease. *Circulation* 2003; 108: 239-244.
23. Maloney J. Advances in the treatment of secondary pulmonary hypertension.
24. *Opin.Pul Med* 2003 9(2): 139-143
25. Sharma S. Treatment of Pulmonary Arterial Hypertension. A step forward. *Chest*, July 2003 124; 8-11.
26. Hoeper M, Galie N, Simonneau et al. New treatments for pulmonary arterial Hypertension. *Am J Respir Crit Care Med* 2002; 165: 1209-1216.

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