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Pulmonary Arterial Hypertension Agents

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OVERVIEW

Pulmonary artery hypertension (PAH) is marked by proliferation of vasculature and remodeling of small pulmonary arteries which causes an increase in pulmonary vascular resistance. The resultant pulmonary artery hypertension can lead to right heart failure and death. Both endothelial and smooth muscle cells appear to play a role in the development and progression of PAH. The underlying cause of most cases of PAH is unknown, but some cases are associated with autoimmune diseases such as scleroderma or systemic sclerosis. PAH is also a complication of chronic lung diseases such as chronic bronchitis and emphysema and interstitial lung diseases such as sarcoidosis. Agents used for PAH, however, are largely effective in patients with idiopathic forms of this condition who do not have major structural damage to the lungs (secondary PAH).

Pharmacotherapy of PAH has recently advanced with the development of specific antagonists and inhibitors of receptors and pathways involved in the modulation of smooth muscle tone in the pulmonary vasculature. Three major classes of agents are used: prostaglandins, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors.

Prostacyclin is a **prostaglandin** that is produced by endothelial cells in the lungs and directly relaxes the smooth muscle cells in the pulmonary vasculature. In idiopathic PAH, there is reduced production of prostacyclin. Stable analogues of prostacyclin have been developed which can be given by infusion or inhalation and result in temporary decrease in pulmonary artery pressure.

The **endothelin receptor antagonists** inhibit the binding of endothelin, a vasoconstrictive peptide, to its receptors on smooth muscle cells which results in vasodilation. Endothelin receptors are relatively enriched in pulmonary vasculature and their inhibition results in a decrease in pulmonary vascular pressure. In patients with idiopathic PAH, the endothelin receptor antagonists have been shown to improve exercise tolerance and slow progression of disease.

The **phosphodiesterase type 5 (PDE5) inhibitors** cause vasodilation by blocking the breakdown of intracellular cyclic guanosine monophosphate (cGMP), which results in prolongation of the action of mediators of vasodilation including nitric oxide (NO). The type-5 phosphodiesterases are isoforms of this enzyme that are found primarily in the penis and lung. For these reasons, the two major actions of the PDE5 inhibitors are to prolong penile erection and decrease pulmonary vascular pressure. They have little effects on the systemic vasculature.

Drug induced liver injury is uncommon with most agents used to treat idiopathic PAH. The exceptions are the endothelin receptor antagonists bosentan and sitaxsentan which have been implicated in several cases of clinically apparent acute liver injury. Bosentan has a boxed warning about liver injury and a requirement for

monitoring liver enzymes; sitaxsentan was withdrawn from use largely because of its potential for causing severe liver injury.

The individual agents used to treat PAH are discussed individually, but references are given in the Overview sections:

- Pulmonary Arterial Hypertension Agents
  - Endothelin Receptor Antagonists
    - Ambrisentan, Bosentan, Macitentan
  - Phosphodiesterase Type 5 (PDE5) Inhibitors
    - Avanafil, Sildenafil, Tadalafil, Vardenafil
  - Prostacyclin Analogs
    - Epoprostenol, Iloprost, Treprostinil
  - Miscellaneous
    - Riociguat, Selexipag