Current and Emerging Drugs in Pulmonary Vascular Pharmacology

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DM Seminar

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Pulmonary Hypertension

- A mean pressure of greater than 25 mm Hg at rest (normal ~14 mm Hg) or greater than 30 mm Hg during exercise.
- At rest
  - sustained vasoconstriction/remodelling
- During exercise
  - Reduced distensibility / recruitment of vessels

Diagnostic Classification

- WHO 1998
- Diagnostic and treatment oriented
- Five descriptive classes
- PPH clubbed with CVD etc
- Heterogeneous group of disorders

I Pulmonary Arterial Hypertension

- Primary pulmonary hypertension
- Related to:
  - CVD
  - Systemic-pulm shunt
  - Portal HT
  - HIV
  - Drugs/toxins
  - Persistent pulm HT of newborn
  - Others

II Pulm Venous Hypertension

- Lt sided atrial/ventricular heart disease
- Lt sided valvular heart disease
- Ext compression of pul veins
  - Fibrosing mediastinitis
  - Adenopathy/tumours
- Pulm veno-occlusive disease
- Other

III Pulm HT associated with hypoxia

- COPD
- ILD
- Sleep disorders
- Alveolar hypoventilation
- High altitude
- Neonatal lung disease
- Others

IV PHT due to chronic PTE

- Obst of prox pulm arteries
- Obst of distal pulm arteries
  - PE (thrombus,tumour,parasites,foreign matter)
  - Insitu thrombosis
  - Sickle cell disease

V PHT : Disorders affecting Pulmonary Vasculature

- Inflammatory
- Schistosomiasis
- Sarcoidosis
- Others

- Pulm capillary hemangiomatosis

Functional Classification

- I PHT No limitation of activity
- II PHT Slight limitation
- III PHT Marked limitation
- IV PHT Inability to carry out any activity.

- Dyspnoea,pain,near syncope, RT HF

Table 2. **Functional Classification of Pulmonary Arterial Hypertension.***

Class	Description
Class I	Pulmonary arterial hypertension without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Pulmonary arterial hypertension resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
Class III	Pulmonary arterial hypertension resulting in a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near-syncope.
Class IV	Pulmonary arterial hypertension resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

Pulmonary Arterial Hypertension

- Vasoconstriction
- Vascular remodelling
- In situ arteriolar thrombosis
- Treatment difficult
- CCBs
- Prostacyclin analogues
- Endothelin 1 Receptor antagonists
- Phosphodiesterase inhibitors

Vasodilators

- Vasoconstriction
- Diagnostic and therapeutic
- ?? reactive pulm bed
- Not selective except NO / prostacyclin
- Role debated in established PAH
- Improve survival despite remodelling

Right heart cath with vasodilator testing

- Vasoreactive ?
- A reduction in PAP without a negative impact on cardiac output or systemic vascular resistance
- CCB not used for testing, short acting agents preferred

Acute vasodilator challenge

- Inhaled NO, prostacyclin, adenosine
- Baseline, supine, room air
- No vasodilators/ inotropes for 36 hrs
- NO by face mask/IV adenosine/IV prostacyclin
- Reduction of PAP and Pulm vasc resistance by 20% to initiate CCB
- Sustained benefit not predicted

Calcium channel blockers

- Most often used
- Responders
- Dose decided by HD monitoring
- Vasodilator and antiproliferative effects
- Diltiazem and nifedipine preferred
- Verapamil compromises rt vent output
- Survival at 5 yrs 94% vs 55%

Prostacyclin analogues

- Prostacyclin
- Product of vascular endothelium
- Vasodilator, antithrombotic,antiproliferative
- Prostacyclin vs thromboxane in PAH
- Induces NO
- Analogues:Epoprostenol IV
- Treprostinil SC
- Beraprost oral
- Iloprost inh/IV

Epoprostenol IV

- Product of arachidonic acid metabolism
- Induces smooth muscle relaxation (cAMP)
- Inhibits growth of smooth muscle cells
- Used initially in 80s
- Lack of immediate benefit vs long term benefit

Epoprostenol

- Prospective, randomized, open trial
- 81 patients Class III/IV
- Conv therapy -warf, diuretic,O2,vasodilator
- 12 weeks
- SMWT 32m vs -15m
- MPAP -8% vs +3%
- MPVR -21% vs 9%
- Death 0 vs 8
- Obviated need for lung transplant in 66%

N Engl J Med 1996;334:296-302.

Epoprostenol IV

- Obviated need for lung transplant in 66%
- Scleroderma worse than PPH
- Half life 3 min : need for continuous IV inf.
- Portable pump and subclavian cath
- Complicated, uncomfortable, costly
- Jaw pain, headache, flushing, diarrhea
- Cath related sepsis/ pump failure/ cath dislocation
- Pulm edema/ death in PVOD/PCH (increased perfusion with downstream obstruction)

Treprostinil SC

- Stable analogue can be given SC
- Improved all indices of function
- Largest benefit with largest dose
- Pain at site main side effect (85%)
- 8% discontinued due to pain
- Alternative to IV epoprostenol

Oral Beraprost

- First stable orally administered analogue
- Absorbed rapidly, peak 30 min
- Half life of 35-40 min
- 80 µg QID
- 25-46m increase in SMWT
- Approved in Japan

Inhaled Iloprost

- Stable analogue
- MMD 0.5-3 µm
- 6-12 times/day
- 36m-59m increase in SMWT
- Cough, syncope,vasodilatation
- Approved in Europe

Nitric oxide

- Potent vasodilator
- Increases cGMP
- eNOS/nNOS/iNOS
- Inadequate NO to oppose vasoconstriction
- Inhaled NO/NTG/nitroprusside
- Improves exercise tolerance
- Methemoglobin/peroxynitrite-DNA damage
- Not approved in US

Phosphodiesterase inhibitors

- Increases cGMP levels, decreases HPV
- Sildenafil acutely decreases PAP and improves CO
- Synergestic with NO and prostacyclin
- More selective than CCB/prostacyclin
- Less selective than NO

SUPER Study Group

- Double blind placebo controlled study
- 278 patients
- Placebo,20, 40, 80 mg TDS X 12 weeks
- SMWT, MPAP, Func class
- 45,46,50 m/decreased PAP/improved class
- 222 pts 1yr 51m

N Engl J Med 2005;353:2148-57.

More vasodilators

- α and β receptors mediate cons/dilat
- Hydralazine conflicting reports/no trials
- ACEI
- 5-HT2A ketanserin, sarpogrelate – no effect

Endothelin-1 receptor antagonists

- Endothelin-1: potent vasoconstrictor/mitogenic activity
- ET A & B receptors
- Blockade attenuates HPV in rats
- Decreased clearance/increased production in PAH
- 213 pts- placebo/125mg/250mg bosentan
- All indices improved at 16 wks

Bosentan

- Used in Class II/III
- Combination with epoprostenol tried
- May interfere with endothelin clearance
- Selective ET A antagonists may be better
- Sitaxsentan and ambrisentan being tried (LFT monitoring essential)

Adjuvant therapies

- Anticoagulation: in situ thrombosis/no trials
- Digoxin: in RHF/ no trials
- Diuretics: in RHF. Aldactone mortality benefits not known in RHF

Potential Therapies

- Rho-kinase inhibitors
- Statins
- Aspirin

Rho-kinase inhibitors

- Mediates Ca sensitisation and contraction of vascular smooth muscle
- Regulates migration and proliferation
- Y-27632/Fasudil reverse PHT
- Fasudil- CAD,cerebral vasospasm

Statins

- Commonly used lipid lowering agents
- Improve endothelial dysfunction
- Anti-thrombotic effects
- Promote fibrinolysis
- Decrease inflammation
- Reduce oxygen radicals
- No trials/reports yet

Aspirin

- Inhibits thromboxane-(vasoconstrictor)
- Terbogrel- thromboxane antagonist- no clinical use due to side effects .
- Aspirin may safely improve prostacyclin thromboxane ratios

Assessing response

- Generally poor prognosis
- Median survival of 2.8 years
- 68%, 48%, 34% at 1,3 and 5 years
- Survival benefit shown only for epoprostenol and bosentan
- Improvement in functional class
- 6-min walk test

The Future

- Mechanisms regulatng tone & structure
- More effective agents to prevent and reverse PAH
- Ideal agent(s):
  - Vasodilatory
  - Antitrophic
  - Anti-inflammatory
  - Anti-thrombotic
  - Selective for pulm vasculature