QUESTION 70 Respiratory

Bosentan is one of a number of new pharmacological therapies for pulmonary hypertension. Which of the following best describes the predominant mechanism of action of bosentan?

A. Thromboxane-receptor antagonism.
B. Inhibition of platelet aggregation.
C. Phosphodiesterase inhibition.
D. Endothelin-receptor antagonism.
E. Reversal of hypoxic vasconstriction.

Answer D.

Definition of PH:
Mean PAP > 25mmHg at rest or 30mmHg with exercise

Classification of pulmonary hypertension (WHO classification)

1) Group 1 Pulmonary arterial hypertension
   a) sporadic IPAH
   b) familial IPAH
   c) PAH due to diseases that localize to small pulmonary muscular arterioles, including collagen vascular diseases, congenital systemic to pulmonary shunts, portal hypertension, HIV and anorexigens

2) Group 2 pulmonary venous hypertension
   a) L atrial disease,
   b) L ventricular disease
   c) L valvular disease

3) Group 3 PH (disorders of respiratory system or hypoxemia)
   a) interstitial lung disease
   b) COPD
   c) Sleep disordered breathing

4) Group 4 PH (chronic thrombotic or embolic disease)
   a) thrombotic occlusion
   b) nonthrombotic pulmonary embolism – schistosomiasis

5) Group 5 PH (inflammation, mechanical obstruction or extrinsic compression of pulmonary vasculature)
   a) sarcoidosis
   b) histiocytosis X
   c) fibrosing mediastinitis

History
Symptoms: exertional dyspnea, lethargy & fatigue
As PH progresses and RVF develops, exertional CP, exertional syncope and peripheral oedema develops.

Pathogenesis
Elevated pressure → damage to pulmonary vasculature → narrows pulmonary vascular bed → R ventricle hypertrophies →
Vascular injury accelerates presence of elevated PAP → increases R ventricular afterload → R ventricular dilation

Primary therapy

Group 1 PAH
No primary therapy
Advanced therapy required

Group 2 PAH
Treatment of underlying disease
If due to mitral stenosis- valve replacement beneficial
Advanced therapy may be detrimental and should be avoided
Group 3 PAH
- Treatment of underlying cause of hypoxemia
- O2 is the only modality with proven mortality benefit
  2 trials:
  a) O2 decreased 5 yr mortality however survival advantage did not appear until after 500d of therapy. Pulmonary vascular resistance increase in the no therapy group but not the O2 group
  b) Nocturnal O2 therapy Trial (NOTT)
    3 yr mortality rate lower with continuous O2 vs nocturnal ass with slight reduction of pulmonary vascular resistance

- Advanced therapy appropriate for pts with NYHA class 3 or 4, should be administered cautiously due to its potential to worsen ventilation-perfusion mismatch and increase hypoxaemia

Group 4 PAH
- Anticoagulation although data suggesting that it is beneficial is lacking
- Surgical thromboendarterectomy
  a) perioperative mortality < 10%
  b) 3 mth period of anticoagulat ion required and pt must be severely incapacitated

- Advanced therapy in pt with NYHA 3 or 4 after anticoagulation or thromboendarterectomy

Group 5 PAH
- Directed at underlying cause

All groups
1) Diuretics
2) O2 therapy
   - Definitely beneficial in Group 3 PH
   - considered for pt with PH and hypoxia
3) Anticoagulation
   - indicated in pt with IPAH, familial PAH, group 4 PH or who are at high risk for throboembolism
   - warfarin ass with improved survival in IPAH pts not responding to Ca channel blockers’
4) Exercise

Advanced therapy
Promote vasodilation and are antiproliferative
1) prostanoids (epoprostenol, treprostinil, iloprost)
2) Endothelin receptor antagonists (bosentan)
3) Phosphodiesterase 5 (PDE5) inhibitors (sildenafil/ viagra)
4) Calcium channel blockers (nifedipine)

Abit more about Bosentan
Nonselective endothelin receptor antagonists
Attractive due to its oral administration.
Adverse effect: hepatotoxicity
LFTs should be closely monitored
Potent teratogen