Endothelin Receptor Antagonists

**Dual action** - Bosentan is used for patients who are New York Heart Association II-III, other PDE 5 inhibitors include vardenal and tadala/fil.

**Phosphodiesterase type 5 inhibitor**
- Tadalafil is a selective PDE 5 inhibitor which inhibits cyclic GMP breakdown and improves V/Q matching. When inhaled it preferentially dilates the vessels of the skin and decreases the surface area which leads to an improvement of V/Q matching.
- Sildenafil, the primary product of arachidonic acid in the vascular endothelium, induces relaxation of vascular smooth muscle by stimulating the production of cAMP and inhibiting the growth of smooth muscle cells. It is used as a powerful inhibitor of platelet aggregation.
- Nitric oxide is the main product of iNOS.
- Epoxyprostenol may only be delivered by IV infusion, it has a very short half life of 6-9 minutes, and is often delivered via infusion pump through a central line. It is rapidly metabolised by hydrolysis and mostly excreted in the urine. It is a chemically stable prostacycline analogue delivered by inhaler. It has a short half life of approximately 30 minutes therefore requiring frequent dosing (q6h).

**Pharmacokinetics**

- The main issue with Bosentan is there is dose dependent deranged liver function with transaminates of up to eight times the normal levels. This necessitates monthly monitoring of LFTs in patients on Bosentan. It strongly induces CYP3A4 and 2C9 and therefore may reduce the efficacy of other drugs metabolised by this pathway.

Nitric Oxide therapy

**Nitric oxide** is a powerful modulator of many aspects of bodily function. It is synthesised from L-arginine and molecular O2 by NO synthase (NOS). There is usually an abundance of L-arginine so it is the NOS that limits the reaction. NOS currently in use.

- Nitric oxide is rapidly inactivated by haemoglobin in blood (hence its limited systemic effects). NO formation is inhibited by high concentrations of oxygen with oxymoglobin. Almost 70% of NO is excreted as nitrate in the urine within 24 hours. When high conc NO2 is combined with NO it forms the toxic NO2, therefore delivering it with a high FiO2 is not recommended.
- Prostacyclines are inhibitors of platelet aggregation and may be required in patients with a bleeding diathesis.

**Pharmacology of oxygen** oxygen may be regarded as a drug. It is a colourless, odourless and tasteless drug which is present in normal air at a approximately 21% of the total pressure. The delivery of oxygen is determined primarily by a decrease in the oxygen cascade from a normal pO2 at sea level of 158 mmHg down to the mitochondrial level where the partial pressure may be as low as 2-3 mmHg. Oxygen is primarily transported throughout the body bound to Hb but a small percentage is dissolved in the blood. The dissolved component may be increased at supranormal pressures such as those observed in hyperbaric oxygenation. The main purpose of O2 in the body is to participate in oxidative phosphorylation which produces the high levels of energy required for cellular function. Oxygen may be delivered in a range of methods, either via nasal prongs or a face mask where the inspired amount is variable on tidal volumes and rates, or in fixed amounts via closed circuits or fixed intake valves such as venturi valves which entrain air at a set proportion. Oxygen has a range of therapeutic uses, by far the most common is treatment of hypoxia. Other less common treatments are usually delivered at increased pressures and include treatment of air embolism, non healing diabetic foot ulcers, osteoradionecrosis of the jaw, and ventilation room. Very high doses may lead to significantly increased methemoglobin levels.

Surfactant

- Surfactant is currently only indicated in neonatal respiratory distress syndrome and severe meconium aspiration syndrome in newborns. There is some research supporting its use in ARDS although no benefit in outcome has yet been proven.
- Surfactant forms a mono layer due to its structure with a hydrophilic head adjacent to the cell wall and the hydrophobic tail facing inwards towards the air. Surfactant has a 15-30 half hour life and in addition to its primary role of reducing surface tension also prevents transudation into the the alveolus (less pressure inside alveolus) and has an immunological role. The exact mechanism of how it reduces surface tension is unknown but the main hypothesis is that it packs closer together when the alveolus reduces in size the action is accentuated, causing a greater decrease in surface tension with decreases in radius.

The major issue with Surfactant administration are the transient hypoxia, hypotension and bradycardia and the risk of blockage of the ETT. There is some association with pulmonary haemorrhage.