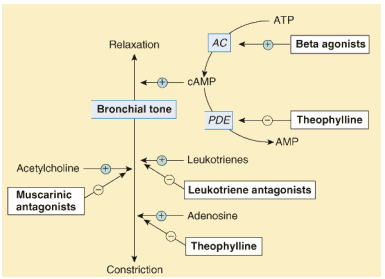
RESPIRATORY PHARMACOLOGY

Asthma is a syndrome characterised by airflow obstruction that varies markedly, both spontaneously and with treatment. Asthmatics harbour a special type of inflammation in the airways that makes them more responsive than non asthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnoea. In allergic asthma, inhaled allergen initiates the inflammatory response by interacting with IgE bound to mast cells and basophils. This leads to a cascade of events involving other immune cells and resulting in the release of numerous inflammatory mediators into the interstitial space, where they influence the growth and function of cell types within the airway wall. The drugs available for the treatment of asthma are targeted at inhibiting the inflammatory responses (of which steroids are the most important) and/or relaxing the bronchial smooth muscle (beta2 agonists).

DRUGS USED IN ASTHMA	
BRONCHODILATORS	ANTI INFLAMMATORIES
Beta2 Agonists	Steroids
Muscarinic antagonists	IgE Antibodies
Theophylline	Antileukotrienes (both)



DRUG CLASS & APPLICATION

Beta 2 Agonists

Short acting (salbutamol) for treatment of acute symptoms of bronchoconstriction

Long acting (salmeterol) for long term control of bronchoconstriction.

Oral/IV preparation (salbutamol) occasionally in children <5 unable to manage inhalers (PO), or status epilepticus (IV)

Muscarinic antagonists

Short acting (ipatropium bromide) is effective in a subset of asthma patients and may give additive effects to Beta2 agonists.

Long acting (tiotropium) is a structural analogue of ipatropium which diffuses more slowly away from the receptor.

Theophylline (Methylxanthines)

Provides modest benefits and now rarely used due to side-effects, narrow therapeutic window and requirement for plasma level monitoring..

It may be used as an additional bronchodilator in patients with severe asthma. At low doses may provide additive anti inflammatory effects to ICS.

Its main application currently is in a slow release preparation for supressing nocturnal asthma.

Corticosteriods

Along with Beta2 agonists these are the mainstay of treatment and are used to suppress the inflammatory response long term in patients with moderate to severe asthma. They do not directly relax smooth muscle and therefore have little effect in direct bronchoconstriction.

Antileukotrienes

Leukotriene receptor antagonists (Montenlukast)

5-lipoxygenase (leukotriene precursor) inhibitors (Zileuton)

Are not as effective as ICS in controlling asthma and have less effect on airway inflammation but may be useful as an add on therapy in some patients with difficult asthma management.

Anti IgE Antibodies (Omalizumab)

Is used selectively in patients with severe asthma not controlled by other modalities to reduce the frequency of exacerbations. The cost of this therapy is prohibitive.

MODE OF ACTION

Beta2 Adrenergic receptors are found throughout the airways and are involved in both smooth muscle relaxation and reducing release of inflammatory cytokines. Beta2 Agonists activate the G-Protien - Adenyl cyclase - CAMP pathway to cause reduced smooth muscle tone. Unlike the smooth muscle effects, anti-inflammatory response is quickly desensitised and therefore not useful to control inflammation long term.

Muscarinic antagonists competitively block M3 muscarinic receptors in the airways and effectively prevent the bronchoconstriction by vagal discharge. They are less effective than Beta2 agonists because they only block the cholinergic component of bronchoconstriction rather than all bronchocontrictor mechanisms.

Methylxanthines are purine derivatives found in beverages, theophylline (tea), caffiene, and theobromine (cocoa). The mechanism of action is inhibition of of Phosphodiesterases (PDE) which results in increased CAMP and therefore bronchodilation. The other mechanism is competitive antagonism at adenosine receptors which has a myriad of effects (possibly reducing bronchoconstriction and inflammation).

Corticosteriods move passively across the cell membrane and act on the nucleus, switching off transcription of multiple activated genes which encode inflammatory protiens such as cytokines, chemokines, adhesion molecules, and inflammatory enzymes including arachidonic acid. They also activate anti inflammatory genes, such as mitogen activated protien (MAP) and increase expression of Beta2-receptors.

Cysteinyl leukotrienes (CysLTs) include leukotriene D4 (LTD4) and E4 (LTE4). All the CysLTs are potent constrictors of bronchial smooth muscle, cause microvascular leakage and eosinophillic and mast cell mediated inflammation. Montelukast is a high affinity competitive antagonist of LTD4 and LTE4.

Omalizumab is a recombinant humanised monoclonal antibody of the IgG subclass, targeted against IgE. IgE bound to omalizumab cannot bind to IgE receptors on mast cells and basophils, thereby preventing the allergic reaction at a very early step in the process.

PHARMACOKINETICS

The mode of delivery is normally inhalation which typically leads to <20% deposition in the lungs. SABA have an onset of action within 1-5 minutes, and are removed from the receptor environment by aqueous diffusion. LABA have slower onset (30 mins) but have a prolonged action due to high lipophilicity and reduced diffusion. Half life for both is 3-5hrs. Hepatic metabolism via hydroxlyation (salmeterol) or sulfation (salbutamol)

The mode of delivery is usually inhalation which results in <20% deposition in the lungs. Ipatropium has an onset of action of 15-30 minutes. Both drugs are minimally absorbed systemically. There is very minor hepatic metabolism but it is mostly excreted in the urine and faeces (not absorbed). The half life of tiotropium is 5-6 days whilst ipatropium is 2 hours.

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Theophylline is delivered orally and is absorbed rapidly and completely. It distributes poorly into body fat and has a small volume of distribution. Metabolism is hepatic via CYP450 into active metabolites including caffiene and 3-methylxanthine. At higher doses follows zero order kinetics. Exceretion via urine. The half life is highly variable and dependent on age, liver and cardiac function, lung disease, diet and smoking.

CS are usually delivered in inhaled form to improve deposition in the lung and reduce systemic effects. They may also be given either as a short burst or long term orally. Oral prednisone is converted to its active metabolite prednisolone. Inhaled budesonide systemic absorption is limited by first pass metabolism. Hepatic metabolism for both steriods takes place through CYP3A4, with a half life around 3 hours., urine excretion.

Monteleukast is administered orally. It is absorbed rapidly with 60-70% bioavailability. At therapeutic concentrations it is highly protien bound (99%). It is extensively metabolised hepatically by CYP3A4 and CYP2C9. The half life is around 3-6 hours. Excereption is primarily via faeces.

Omalizumab is delivered as a single subcutaneous injection every 2-4 weeks. It has a bioavailabilty of 60% reaching peak serum levels after 7-8 days. The serum half life is 26 days, with a clearance rate of 2.5ml/kg/day, which is somewhat faster than that of free IgG. It is metabolised in the liver reticuloendothelial system by the degradation of IgG, some make be excereted in the bile unchanged.

VARIABILITY / SIDE-EFFECTS

Skeletal muscle tremors is a common side effect. The Beta2 selectivity is relative and therefore there is often a degree of Beta1 response usually manifested by tachycardia. There may be a minor decrease in K levels due to increased skeletal muscle takeup. Some studies show an increased risk of asthma mortality with increased use although this may represent worsening asthma control. Lactic acidosis may occur with salbutamol.

The main issue with these drugs in their use for asthmatics is that there is significant variability in response. This is presumably due to the differences in parasympathetic tone and in the degree to which reflex activation of cholinergic pathways participates in generating symptoms in individual patients. Due to minimal systemic absorption there are few side effects beyond a dry mouth. Elderly patients may get urinary retention or glaucoma

Due to the variable half life theophylline, it is not uncommon for four-fold variations of plasma levels. This necessitates monitoring of blood levels. Common side effects include nausea, vomitting and headaches are due to PDE inhibition. Diuresis and palpitations may also occur and at higher concentrations cardiac arrythmias, epileptic seizures, and death may occur due to adenosine receptor antagonism.

Frequent aerosol administration of ICS may result in a minor degree of adrenal supression, however the main side-effects relate to localised candidiasis and dysphonia. Systemic corticosteroid use has many well documented side-effects, although short bursts during exacerbations limit these. SEs include adrenal supression, trunkal obesity, osteoporosis, diabetes, hypertension, gastric ulceration, prox myopathy, and cataracts.

Some patients show an improved response to antileukotrienes but this has not been genomically linked to the leukotriene pathway. The are relatively few side effects to inhibition of leukotriene synthesis or function. This is likely due to the fact that leukotriene production is limited predominately to sites of inflammation.

Omalizumab is generally well tolerated however there was an increased incidence of various types of malignancies during a large study into the drug 5 in 2236 versus 20 in 4127 which requires further study.

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in a progressive increase in vascular resistance and, ultimately, right ventricular failure and death. The abnormal elevation in pressure may be a result of left heart failure, pulmonary parenchymal or vascular disease, thromboembolism or a combination of these factors. In a percentage of patients no cause is found (idiopathic PAH). Cardiac catheterisation is required to diagnose the condition and identify the appropriate treatment strategy. This involves, firstly establishing the pressures are elevated and then introducing either NO, adenosine or the prostacycline epoprostenol and measuring the change in pressure. If the drop is significant then Ca Channel blockers may be trialled as a first line therapy. Other recommended therapies once the diagnosis has been made include diuretic therapy to reduce RV load and anticoagulation to reduce thromboembolic risk. Three major pathways are implicated in the abnormal proliferation and contraction of smooth muscles in the pulmonary vasculature and these provide the therapeutic targets. In addition to Ca Channel Blockers, the main therapies are Endothelin receptor antagonists (Bosentan), Phosphodiesterase type 5 inhibitor (sildenafil) and Prostacyclin derivatives (incl illoprost and epoprostenol).