Respiratory system: applied pharmacology

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Abstract

Manipulation of respiratory physiology by pharmacological intervention is a significant role of the anaesthetist and intensivist. Successful use of these various agents requires a thorough understanding of their mechanisms of actions, potential side-effects and limitations. These interventions involve changes in airway calibre, secretions and sensitivity of the airway to noxious stimuli. Other agents act to inhibit the depressant effect that sedatives may have on the patient's respiratory drive. The effects, both advantageous and detrimental, may be complicated by the action of other disease processes which affect the metabolism of these drugs. There are multiple possible routes of administration which allows flexibility for the clinician and may reduce systemic effects, thereby limiting side effect profiles. Drugs used specifically in the treatment of acute respiratory distress syndrome attempt to alter pulmonary ventilation and perfusion thereby reduce mismatching and improve diffusion capacity.

Keywords β_2-agonists; acute respiratory distress syndrome (ARDS); anticholinergics; bronchodilators; corticosteroids; respiratory pharmacology; respiratory stimulants; theophyllines

Royal College of Anaesthetists CPD matrix: 1A01, 1A02, 2A12, 2C04, 3C00

Learning objectives

After reading this article, you should be able to:

- explain the action of different medications on respiratory physiology
- discuss some of the current NICE and British Thoracic Society guidance on asthma and chronic obstructive pulmonary disease management
- list the main factors affecting metabolism of theophyllines

The anaesthetist may be presented with patients with chronic obstructive pulmonary disease (COPD), asthma, fibrotic lung disease and cystic fibrosis. In addition, the intensivist encounters acute respiratory distress syndrome (ARDS) and respiratory failure due to sputum retention. Anaphylaxis (with bronchospasm) may occur in both theatre and ICU settings. Knowledge of pharmacology for the respiratory system is essential for successful management of these conditions.

Bronchoconstriction[1]

Bronchial diameter is under direct control of smooth muscle. Its autonomic control is from both sympathetic and parasympathetic efferent nerves, although parasympathetic activity predominates. In health the bronchial tree is in a state of almost maximal dilatation and sympathetic activity has little benefit. ***Cholinergic*** parasympathetic response to inhaled irritants causes bronchoconstriction. This is a rapid defensive reaction but ***non-cholinergic*** parasympathetic nerves probably counteract these responses via peptides (e.g. vasoactive intestinal peptide — VIP) and the production of nitric oxide. Heightened cholinergic parasympathetic activity means that sympathetic noradrenergic pathways now participate in reversing bronchoconstriction.

Local release of prostaglandins (PG) causes both contraction ($PGF_{2\alpha}/TxA_2$) and relaxation (PGE_2) of bronchial smooth muscle. Production of leukotrienes (LT) occurs as part of this inflammatory process. Stimulation of LT-receptors on mast cells, endothelium and eosinophils leads to propagation of inflammation and bronchoconstriction.

Increased airway secretions/oedema[2]

Mucus secretion occurs from goblet cells throughout the respiratory tract under the control of ***non-cholinergic*** parasympathetic nerves (VIP). This traps and removes airway debris by means of the mucociliary apparatus. Triggers of inflammation/irritation can lead to oversecretion of mucus via ***cholinergic*** stimulation leading to airway obstruction. This occurs in asthma/COPD and is exacerbated by ciliary dysfunction. Leukotrienes increase mucus secretion, vascular permeability and chemotaxis of neutrophils.

Bronchodilators

β_2-adrenoceptor agonists cause sympatho-mimetic effects to counteract acute parasympathetic bronchoconstriction (Figure 1). Their effect on mast cells is debated. Some suggest reduced histamine release[3] while others show a subsequent increase in the release of mediators in response to allergens.[4] COPD patients exhibit slower peak therapeutic response than asthmatics.

Preparations exist for intravenous, subcutaneous, nebulized and metered-dose inhaler (MDI) administration. Bambuterol is an oral preparation but systemic effects limit its use.

Adverse effects are predominantly due to β_1 effects at higher doses (arrhythmias, hypertension). Short-acting agents provide 3—5 hours of action (salbutamol, terbutaline) with longer acting preparations providing up to 12 hours due to deposition in smooth muscle cell walls (salmeterol, formoterol). Longer acting agents are first-choice add-on agents for patients over 5 years old who already take inhaled steroids but concerns have been raised over unpredictable bronchial irritation or sensitisation with these drugs.[5] Subcutaneous terbutaline infusion has been used in severe asthma but lacks evidence to support its use. Caution is advised with hyperthyroidism, cardiovascular disease or arrhythmias, QT prolongation or hypertension where symptom exacerbation may occur. β-agonists may also cause ketoacidosis

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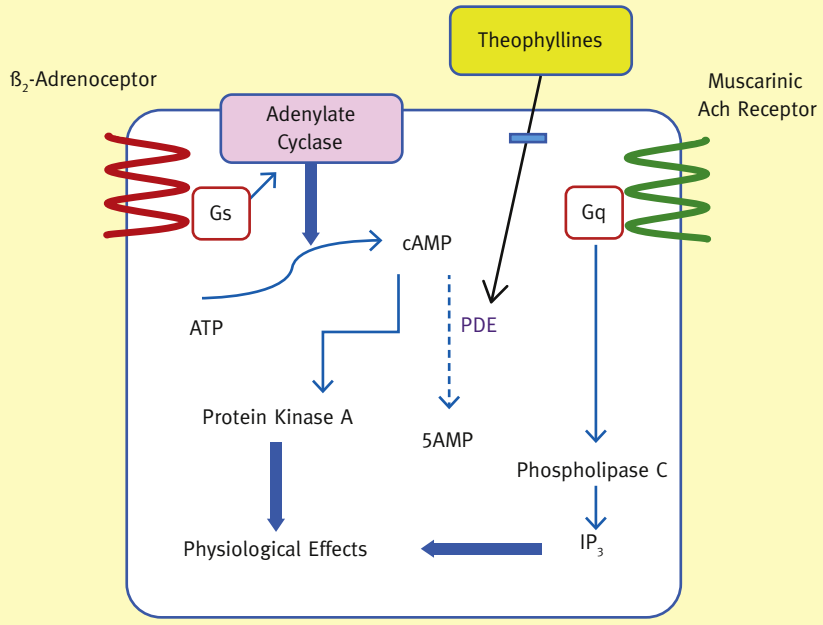

Stimulation of ß$_2$-adrenoceptor acts via Gs protein coupled receptors to activate adenylate cyclase and increase cellular cyclic adenosine monophosphate (cAMP). B$_2$-agonists stimulate this pathway causing smooth muscle relaxation. Phosphodiesterases break down cellular cAMP and are inhibited by theophyllines. Muscarinic acetylcholine receptors (Ach) act via Gq protein coupled receptors to activate phospholipase C and inositol triphosphate (IP$_3$). Muscarinic antagonists block this pathway causing smooth muscle relaxation and reduced airway secretions.

Figure 1

in diabetes. Hypokalaemia may occur especially with potentiation from concurrent theophyllines, corticosteroids, diuretics and hypoxia. Animal and ex-vivo studies have shown accelerated alveolar fluid removal with β_2-agonists but this has failed to prove advantageous in ARDS.[6] Agents such as adrenaline are reserved for anaphylaxis or peri-arrest situations and show no benefit over other selective β_2-agonists when used as an inhaled agent.

Anticholinergic agents block parasympathetic effects causing smooth muscle relaxation (Figure 1). Inhaled effects occur within 30–60 minutes and last up to 6 hours. Both ipratropium and tiotropium are given as nebulized or MDI forms but may cause acute angle closure glaucoma. Atropine or glycopyrrolate can be given as intravenous or subcutaneous preparations but may exhibit marked systemic effects (tachycardia, central anticholinergic syndrome, constipation, urinary retention). They are used for acute and chronic control of COPD and are recommended by the British Thoracic Society for acute asthma in adults and children.[7] Current NICE guidelines[8] suggest some clinical benefit of tiotropium over ipratropium in stable COPD.

Phosphodiesterase inhibitors (PDEi) refer specifically to theophylline. An inhibitor of all five PDE isoforms, it causes smooth muscle relaxation (Figure 1). In addition it inhibits leukotriene synthesis and subsequently reduces inflammation. Increased responsiveness to corticosteroids in smokers is thought to occur due to its reactivation of histone deacytyle.[9] Theophylline may also increase diaphragmatic strength. It also exhibits non-selective adenosine receptor antagonism which assists bronchodilation but increases tachycardic effects. It abolishes hypoxic vasoconstriction and so potentially worsens ventilation-perfusion matching. Other adverse effects include nausea, diarrhoea, arrhythmias and central nervous system excitability (headaches, insomnia, irritability). The narrow therapeutic index (10–20 mg/litre plasma) is complicated by drug interactions and pathologies which disrupt its metabolism (Table 1). Oral theophylline is recommended as add-on therapy for long-term management of asthma in all age groups,[7] while the intravenous preparation is recommended only for acute severe or life-threatening exacerbations refractory to other treatments. Both preparations are also used in the management of COPD.[8]

Magnesium sulphate targets cellular calcium flux to exert its effects on the respiratory system. Both neuronal acetylcholine release and smooth muscle contraction are facilitated by extracellular calcium influx into presynaptic terminal axons and smooth muscle cells respectively. High extracellular magnesium levels impede these processes. The evidence in acute situations is equivocal but response in childhood asthma is more convincing.[10] While unlicensed, its use is supported by the British Thoracic Society guidelines (2012).[7]

Volatile anaesthetic agents may be used to induce bronchodilation but their application is restricted to anaesthetized patients with suitable scavenging systems.

Immunomodulators

Corticosteroids are more effective in asthma control than COPD. Their maximum anti-inflammatory effect occurs at 3–7 days.