CHAPTER 6

DRUGS ACTING ON THE RESPIRATORY SYSTEM

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INTRODUCTION

The upper air passageways, nasal cavities, pharynx, and trachea, and also the bronchi and bronchioles, are all part of the respiratory system. The exchange of gases between body tissue and the outside environment is known as respiration. Breathing in air through the respiratory tract, oxygen uptake from the lungs, oxygen transport through the body in the blood stream, oxygen use in metabolic activities, and carbon dioxide elimination from the body are all part of it.

The goal of drug treatment for pulmonary problems is to change certain physiological function. The focus of this chapter will be on drugs used to treat some of the more prevalent respiratory problems, such as bronchial asthma, allergies, and congestion caused by certain respiratory conditions.

Bronchial Asthma

Asthma is defined by increased sensitivity of the trachea and bronchi to numerous stimuli, as well as a large constriction of the airways that changes in severity either spontaneously or as a result of medication. Three bronchial anomalies that induces airflow obstruction in bronchial asthma.

1. Smooth muscle contraction in the respiratory airway
2. Edema and cellular infiltration thicken the bronchial mucosa.
3. Inspissations of excessively thick, viscid mucus plugs in the airway lumen.

A. Pathogenesis

Extrinsic and intrinsic bronchial asthma are the two forms of bronchial asthma.

1. **Extrinsic asthma** is linked to a childhood history of allergies, a family history of allergies, hay fever, or increased IgE levels.
2. **Intrinsic asthma** affects middle-aged people with no allergies in their family, negative skin tests, and normal serum IgE levels.

B. Immunologic model

Asthma is caused by reaginic (IgE) antibodies that attach to mast cells in the airway mucosa. However, the antigen-challenge paradigm cannot account for all aspects of asthma. Bronchial spasm is triggered by non-antigenic stimuli such as viral infections, exercise, and cold air.

The acute phase of allergic asthma, or the initial response to allergen provocation, begins quickly and is mostly caused by bronchial muscular spasm. When allergens

interact with mast cells, histamine, LTC4, and LTD4 are released, causing bronchial spasm.

A. Pharmacotherapy of Bronchial Asthma

The drugs used to treat bronchial asthma can be divided into three categories:

i. Bronchodilators

a) α- Adrenergic agonists:

- **Non selective β_2-agonists** e.g. adrenaline, Epinephrine. Ephedrine, Isoprotenerol
- **Selective agonists** e.g. Salbutamol, terbutaline, metaproterenol, salmeterol, formaterol, etc.

b) Methylxanthines- e.g. Theophylline derivatives

c) Muscuranic receptor antagonists e.g. Ipratropium bromide

ii. Mast cell stabilizers, e.g. Cromolyn sodium, Nedocromil, Ketotifen

iii. Anti-inflammatory agents: Corticosteroids

B. β_2-ADRENERGIC AGONISTS (β_2-SYMPATHOMIMETIC AGENTS)

Mechanism of Action

Adrenergic drugs stimulate adenyl cyclase and hence increases the cAMP formation in the bronchial tissue. They reduce the asthmatic severity by relaxing the smooth muscle, inhibiting the release of broncho-constricting substances or inflammatory mediator from mast cells, preventing the leakage of the microvasculature, and boosting the mucociliary transportation.

a) Non-selective β_2- agonists

Non-selective β2- agonists, like **Epinephrine** is a highly powerful, fast-acting bronchodilator that is especially useful for treating acute bronchial asthma attacks. Since these medications induce higher cardiac stimulation (mediated by a single receptor), they should only be used in exceptional circumstances. These are given by inhalation or subcutaneously.

Side effects: Arrhythmia and worsening of angina pectoris, increase blood pressure, tremors etc

Contraindication: Hypertension, arrhythmia,

Ephedrine has a longer duration of action than epinephrine, but a more pronounced central impact and lower potency. It can be administered orally. Because more effective

and β_2-selective medicines are being developed, the medication is today sparingly utilized.

b) Selective β_2-agonists

Non–selective 2-agonists have mostly been replaced by Selective β2-agonists. They are effective after inhalation or oral administration and have a longer duration of action. They're the most common sympathomimetics. Salbutamol, terbutaline, metaproterenol, pirbuterol, and bitolterol are some of the most often used oral and inhalation medicines. Salmeterol and formeterol are long-acting, new generation β2-selective agonists with duration of action 12 hrs or more. These medications appear to improve asthma management by interacting with inhaled corticosteroids. Adrenoreceptor agonists delivered via inhalation have the greatest local effect on airway smooth muscle while causing the least systemic damage.

Side effects: Tremors, anxiety, insomnia, tachycardia, headache, hypertension and etc.

Contraindications: Sympathomimetics are contraindicated in patients with known hypersensitivity to the drugs

Precautions: Patients with hypertension, heart failure, hyperthyroidism, glaucoma, diabetes, or pregnancy should use them with caution.

A. METHYLXANTHINES

Theophylline, theobromine, and caffeine are the three most significant methylxanthines. Aminophylline is the most often utilized theophylline formulation for medicinal purposes (theophylline plus diethylamine).

Mechanism of Action

1. Inhibit the phosphodiesterase (PDE) enzyme competitively, resulting in an increase in cAMP levels.
2. They compete with adenosine to inhibit its action on adenosine (A1 and A2) receptors (adenosine has been shown to cause contraction of isolated airway smooth muscle and histamine release from airway mast cells).
3. Stop the mast cells from releasing histamines and leukotrienes.

Theophylline has the most selective smooth muscle impact of the three natural xanthines, while caffeine has the most significant central effect. Theophylline is currently mostly reserved for patients whose symptoms are uncontrollable despite

regular treatment with an inhaled anti-inflammatory drug and as-needed usage of a 2 agonist.

Adverse Effects: Anorexia, nausea vomiting, abdominal discomfort, headache, anxiety, insomnia, seizures, arrhythmias

B. MUSCRANIC RECEPTOR ANTAGONISTS

Mechanism of Action

Muscarinic antagonists block the contraction of airway smooth muscle and the rise in mucus secretion that occurs in response to vagal activity, such as atropine sulphate, by competing with acetylcholine at muscarinic receptors.

Urinary retention, tachycardia, loss of accommodation, and agitation are all systemic side effects of rapid absorption, whereas local side effects such severe tongue dryness limit the amount of atropine taken. Ipratropium bromide is poorly absorbed and does not readily penetrate the central nervous system, allowing substantial doses to be delivered to muscarinic receptors in the airways; consequently, it could be used effectively to treat bronchial asthma.

Antimuscranic antagonists appear to be significantly less effective in reversing asthmatic bronchospasm than beta-agonists. In acute severe asthma, ipratropium increases the bronchodilation generated by nebulized albuterol. Antimuscarinic drugs appear to be useful in chronic obstructive lung disorders, probably even more so than in asthma. Patients who are intolerant to beta-agonists may benefit from them as an alternative therapy.

C. ANTI-INFLAMMATORY AGENTS: CORTICOSTEROIDS

Used both for treatment and prophylactic purposes

Mechanism of action

They are thought to work because of their wide anti-inflammatory properties, which are mediated in part by suppression of inflammatory mediator production. They also enhance the effects of beta-receptor agonists and reduce lymphocytic-eosinophilic inflammation of the airway mucosa.

Effects on airway

- ✓ reduces bronchial reactivity
- ✓ increases airway caliber

- ✓ reduces the frequency and severity of asthma exacerbations

Hydrocortisone, predinisolone beclomethasone, triamcinolone, and other corticosteroids are routinely utilised. The medications can be administered via aerosol inhalation, oral administration, or IV administration.

Oral and parenteral corticosteroids are reserved for patients who require immediate therapy and have not responded to bronchodilators due to severe side effects when given persistently. Aerosol therapy is the most effective technique to reduce corticosteroid medication's systemic side effects. Because of the risk of adrenal insufficiency, abrupt withdrawal should be avoided. Following improvement, doses should be reduced. Aerosol corticosteroids provide for more consistent or controlled therapy.

Side effects: Hypothalamic-pituitary-adrenal axis suppression, osteoporosis, sodium retention and hypertension, cataract, growth retardation in children, and susceptibility to infections such as oral candidiasis and tuberculosis

D. MAST CELL STABILIZERS

Mechanism of action

Change the function of the delayed chloride channel in the cell membrane to stabilise mast cells and prevent the release of histamine and other mediators. It serves no purpose once the mediator is freed and is just utilized as a precaution.

Clinical uses: used in exercise and antigen induced asthma and occupational asthma.

Side effects: Since it is poorly absorbed hence effect minimally to human body. Main side effect includes throat irritation, cough, dryness of mouth, chest tightness and wheezing.

Treatment of Status Asthmatics

- **Status asthmatics:** Asthma attack that is severe and persistent and does not respond to standard treatment.
- **Management includes:**
  - ✓ Oxygen administration
  - ✓ Systemic corticosteroid like methyl prednisolone or hydrocortisone IV - Frequent or continuous dosing of aerosolized ß2 agonists like salbutamol
  - ✓ IV infusion of aminophylline
  - ✓ Intravenous fluids to prevent dehydration

- ✓ Antibiotics in the presence of infection evidence

ANTI-TUSSIVES

Coughing is a defensive reaction that allows sputum and other irritating materials to be expelled from the respiratory passage.

Types:

- **Useful productive cough:** Effectively expels fluids and exudates.
- **Useless Un-productive cough:** Chronic cough that is nonproductive due to smoking and local irritants.

Anti-tussives are cough suppressants that help to lessen the severity and frequency of coughing.

Two Types of Anti-tussives:

1. **Central anti-tussives:** The medullary cough centre is suppressed, and it can be divided into two groups:
    - Opoid antitussive e.g. codeine, hydrocodeine, etc
    - Non opoid antitussives e.g. dextromethorphan
2. **Peripheral anti-tussives:** Reduce the amount of stimulation entering the respiratory route through the cough receptor. e.g., Demulcents e.g. liquorices lozenges, honey.

Demulcents cover the inflamed pharyngeal mucosa and provide local pain relief.

Codeine is a narcotic that is less addictive than heroin and is used as a central antitussive agent. Its chief negative effects include dry mouth, constipation, and dependence.

Dextromethorphan is an opoid synthetic antitussive that is essentially free of analgesic and addictive qualities, with respiratory depression being the most common adverse effect.

Expectorants, such as ipecac alkaloid, sodium citrate, saline expectorant, guanfenesin, and potassium salts, help to remove thick, sticky mucus from respiratory passages.

Mucolytics, such as acetylcysteine, liquefy mucus and make expectoration easier.

DECONGESTANTS

Decongestants are medications that relieve nasal congestion, allowing congested nasal passages to open and sinus drainage to improve. e.g phenylephrine, oxymetazoline etc.

Mechanism of Action: Mucus membrane decongestants are β_1-agonists that cause localised vasoconstriction of the nasal membrane's tiny blood vessels. Congestion in the nasal passageways is reduced.

Clinical uses: Used to treat rhinitis, hay fever, allergic rhinitis, and to a lesser extent, the common cold. For a longer duration of action, drugs might be delivered nasally or orally.

Classification:

1. Short acting decongestants administered topically, e.g. phenylepherne, phenylpropanolamine
2. Long acting decongestants administered orally, e.g. ephedrine, pseudoephedrine, naphazoline
3. Long acting topical decongestants, e.g. Xylometazoline, oxymetazoline

Side effects:

1. Nasal congestion that has reappeared
2. Changes in mucus membrane ischemia
3. Nasal stinging, burning, and dryness
4. Hypertension, arrhythmia, anxiety, restlessness, sleeplessness, and impaired vision

Contraindications: Hypertension, severe coronary artery disease

Questions:

i. What are the drugs used to treat bronchial asthma and how are they classified?
ii. Explain mechanism of action and pharmacokinetic properties of methylxanthines.
iii. What are the side effects and contraindications of glucocorticoids?
iv. What are differences between antitussives and expectorants? Give example.
v. Give examples of decongestant drugs and their side effects.

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