Respiratory Pharmacology

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Key Points

- Medications used to manage the pulmonary "pathologic triad" include bronchodilators and anti-inflammatory medication. Bronchodilators include beta 2 adrenergic receptor agonists and cholinergic/muscarinic acetylcholine receptor antagonists. Anti-inflammatory medications include leukotriene modifier drugs, mast cell stabilizers, and immunoglobulin E blockers.
- Bronchodilators are essential in the treatment of airway disorders. They are a mainstay treatment for the management of chronic obstructive lung disease (COPD) and are critical in the symptomatic management of asthma.
- There is a uniform distribution of β(beta)-adrenoreceptors on the alveolar wall with 2:1 ratio of β(beta)1/β(beta)2 receptors.
- β(beta) 2 adrenergic agonists should be used with caution in patients with hyperthyroidism and cardiovascular disease due to the potential for QT prolongation and arrhythmias.
- Airway tone is mainly controlled by parasympathetic nerves carried by the vagus nerve.
- There are 5 different subtypes of muscarinic acetylcholine receptors (M1-M5), which are expressed in almost every cell type of the airway and lung tissue, including airway and vascular smooth muscle, different glandular and surface epithelium cells, endothelial cells, and inflammatory cells.
- Steroids are considered first-line medications in the treatment of asthma. Using the inhaled rather than intravenous forms can reduce their side effects.
- Low-dose inhaled steroids in regular daily doses are highly effective in reducing asthma symptoms and reducing the risk of asthma-related exacerbations, hospitalization, and death.
- Headache is a common side effect in patients receiving leukotriene-modifying drugs.
- The use of the immunoglobulin E blocker omalizumab can reduce the requirements for steroids and improve quality of life in asthmatic patients with frequent asthma exacerbation. Its use is reserved for severe uncontrolled asthmatic patients despite best available therapy.
- Combination therapy combines a medication from 2 or more classes. Combination therapy, by using a lower dose of medication from each class, can reduce systemic side effects.

12.1 Introduction

The pathological triad of pulmonary disease consists of: bronchospasm, airway inflammation, and retained secretion. Respiratory pharmacology deals with agents used to treat this "pathological triad." Medications used to treat these conditions can be divided into different categories based on their mechanism of action. They include bronchodilators, anticholinergics, corticosteroids, mucolytics, and decongestants just to name a few. Other agents used to treat pulmonary disease such as oxygen, antibiotics, local anesthetics, respiratory stimulants, and muscle relaxers are beyond the scope of this chapter.

12.2 Bronchodilators

Bronchodilators are essential in the treatment of airway disorders. They are the primary treatment for the management of chronic obstructive pulmonary disease (COPD) and are critical in the symptomatic management of asthma. Bronchodilators work through a direct relaxation effect on airway smooth muscle cells. Three major classes of bronchodilators exist at the present time: β(beta)2-adrenoreceptor (AR) agonists, cholinergic receptor antagonists, and xanthines. This chapter will discuss the first 2 treatments, which can be used individually or in combination, as is currently preferred in order to minimize systemic effects. Fast- and short-acting agents are best used for acute symptom relief, whereas long-acting agents are best for maintenance therapy. Treatment adherence has been improved by new formulations that allow once-daily administration.

Understanding the neurological innervation of the airway is key to understanding how bronchodilators work. Airway tone is mainly controlled by parasympathetic nerves carried by the vagus nerve. Postganglionic parasympathetic cholinergic and non-noradrenergic noncholinergic (NANC) fibers innervate airway smooth muscles (ASM), providing the dominant control of the muscle tone and airway caliber as well as airway glands and microvasculature.

There is no direct sympathetic innervation of ASM, but there is innervation of the airway vasculature. Acetylcholine (ACh) is the classic neurotransmitter of the parasympathetic nervous system at both the ganglionic and neuroeffector junctions, which then activate the cholinergic/muscarinic receptors.

Five different subtypes of muscarinic receptors (mAChRs) have been identified (M1-M5), and they are expressed in almost every cell type of the airway and lung tissue, including airway and vascular smooth muscle, different glandular and surface epithelium cells, endothelial cells, and inflammatory cells.

β(beta)-ARs are present in high concentrations in lung tissue and are divided into 3 types: β(beta)1, β(beta)2, and β(beta)3. The majority of pulmonary β(beta)-ARs are of the β(beta)2-AR subtype, localized in the ASM, epithelium, vascular smooth muscle, and submucosal glands. They are more prevalent in small airways than large airways but are also expressed on many inflammatory and immune cells, whereas β(beta)1-ARs are located in the gland and alveoli. There is a uniform distribution of β(beta)-ARs on the alveolar wall with a 2:1 ratio of β(beta)1/β(beta)2.

β(beta)2-ARs are coupled to Gs (part of the G protein-coupled receptors), where stimulation by β(beta)2-AR agonist activate the adenyl cyclase and increase cyclic adenosine monophosphate (cAMP) levels, which in turn increase protein kinase A (PKA) activity. This reduces the intracellular calcium level and activates large conductance potassium channels leading to relaxation of airway smooth muscle.

12.3 β(beta)-Adrenergic Receptors Agonists

Ephedrine from the plant ephedra equisetina was used for more than 2000 years for the short-term treatment of respiratory symptoms. The discovery of epinephrine and isoproterenol followed, but due to the fact that these drugs were non-selective alpha- and beta-adrenergic receptor agonists, they caused unwanted side effects and warranted the need of selective β(beta)-AR receptors agonist.

12.3.1 Short-Acting β(beta)2-Adrenergic Receptors Agonists

Short-acting β(beta)2-AR agonists (SABA) can be divided into 2 groups dependent on the duration of action using conventional doses: (1) very short acting, duration 1–2 h (isoproterenol and rimiterol); and (2) short acting, duration 3–6 h (fenoterol, albuterol, and terbutaline).

Albuterol

Albuterol has greater selectivity between β(beta)2 and β(beta)1-AR than any other product previously available. It also has negligible α(alpha)-AR activity. It causes maximum bronchodilation but with minimal cardiovascular responses compared to isoproterenol. After inhalation, its maximum effect can be seen in 15 min. However, albuterol weakly binds to the receptor and quickly diffuses to the microcirculation, which accounts for the short action of duration (4–6 h), but it is the drug of choice to relieve symptoms of bronchospasm. It also can be used intravenously if the inhalation response is reduced or absent.

Levalbuterol ([R]-Albuterol), an isomer of albuterol, can be used instead of albuterol. It may reduce hospitalization, have fewer adverse effects, and provide similar bronchodilators effects at reduced dose, but recent studies have questioned these benefits.

Fenoterol

Fenoterol has a similar effect to albuterol, with β(beta)2-AR selectivity and minimal α(alpha)-AR stimulation. The only difference is that it can exhibit slightly longer duration of action. A 200 microgram dose was required to produce a maximal response.

Terbutaline

Synthetic sympathomimetic amine has a greater specificity for β(beta)2-AR. Due to it structure, with a dihydroxybenzene group at the β(beta)-carbon atom, it has a longer duration of action (4–6 h).

Terbutaline is administered by aerosol inhalation. When given parenterally, it loses much of its selectivity, and cardiovascular effects similar to isoproterenol are observed. Compared to epinephrine, subcutaneous terbutaline can induce more bronchodilation for a longer period of time but with more side effects.

Bambuterol is an oral terbutaline prodrug with prolonged duration of bronchodilator action.

12.3.2 Long-Acting β(beta)2-Adrenergic Receptor Agonists

Long-acting β(beta)2-AR agonists (LABA) such as salmeterol and formoterol provide 12-h bronchodilation.

Salmeterol

Salmeterol binds specifically to the β(beta)2-AR via albuterol "head group"—the molecule of which is >10,000 times more lipophilic than albuterol. The process of its diffusion to reach the active site of the β(beta)2-AR is slow (>30 min) and accounts for the slow onset of action on the airway smooth muscle (ASM). Salmeterol does not induce desensitization or internalization of receptors, which may also contribute to its long therapeutic duration of action.

Studies have shown that salmeterol is a partial agonist, which may attenuate the effects of β(beta)2-AR agonist with greater efficacy, thus raising the possibility of pretreatment with this drug.

The onset of action is approximately 10 min. Maximal bronchodilation may take hours to achieve.

Formoterol

Due to its structural molecule, formoterol has greater affinity to the β(beta)2-AR and has the highest bronchoselectivity among the LABA.

Formeterol has a faster onset of action compared to salmeterol and has been shown in a concentration dependent to inhibit antigen-induced mediator release from human lung fragments.

Formoterol has the same effect of salmeterol at a lower dose (50 microgram vs 12 microgram).

12.3.3 Ultra-Long-Acting β(beta)2-Adrenergic Receptors Agonists

Ultra-long acting β(beta)2-ARs were developed in an attempt to simplify the treatment to 1 dose daily so that patients can adhere to their treatment.

Indacaterol

Indacaterol is a highly lipophilic drug that is retained in the lipid rafts of the plasma membrane, an area particularly rich in β(beta) receptors. This means that these receptors are repeatedly stimulated by this drug and for a long period of time, achieving an effect that lasts 24 h. Indacaterol has high intrinsic activity, which explains the rapid onset of action within 5 min of administration. Mild cough is the only significant side effect, which may lead to discontinuation of the treatment.

Multiple studies have shown the superiority of daily dose indacaterol over formoterol, salmeterol, and tiotropium bromide in improving trough forced expiratory volume 1 (FEV1). It also provides significant health-related quality of life.

Olodaterol

Olodaterol is a potent β(beta)2 receptor agonist with high intrinsic activity. This ultra-LABA binds moderately to lipid rafts, although its dissociation half-life is about 18 h. It has a 2-stage profile of dissociation from β(beta)2 receptors. Its slow component has a dissociation half-life of 12 h. These 2 features explain the fact that the bronchodilator effect lasts 24 h.

Vilamterol

Vilamterol has greater intrinsic activity than salmeterol and appears to be more potent than indacaterol. All doses of vilamterol were associated with low incidence of treatment-related side effects.

Carmoterol

Carmoterol is over 100 times more selective for bronchial muscle than myocardial tissue. It displays a fast onset and long duration of action.

Carmoterol has better improvement of trough FEV1 than salmeterol, and it has no side effects.

12.3.4 Intravenous β(beta)2-Adrenergic Receptors Agonists

Bedoradrine

Many patients with acute exacerbation of asthma are non-responders to inhaled β(beta)-adrenergic agonists. Intravenous bedoradrine is a highly selective β(beta)2-AR agonist. In a recent study to show the efficacy of bedoradrine, there was no significant difference in % FEV1 at 3 h between the bedoradrine compared to the placebo groups. The dyspnea scores were significantly improved for patients treated with bedoradrine.

12.3.5 Side Effects of β(beta)2-Adrenergic Receptors Agonists

Because of the widespread distribution of β(beta)2-AR, a number of side effects are noted when β(beta)2-AR agonists are absorbed into the systemic circulation. The number of side effects is the greatest when β(beta)2-AR are administered orally or parenterally.

Increased heart rate and palpitation are less common with the selective β(beta)2-AR agonists than the nonselective, but they can cause reflex tachycardia secondary to vasodilation. Some of these atrial and ventricular effects could be the result of β(beta)2-AR receptors that may be present in the atria and ventricles.

All agonists should be used with caution in patients with hyperthyroidism or cardiovascular disease (arrhythmias, hypertension, QT-interval prolongation).

Transient mild decrease in partial pressure of oxygen in arterial blood could result from the administration of β(beta)2-AR agonists despite concomitant bronchodilation. This could be attributed to pulmonary vasodilation and increased blood flow to poorly ventilated lung region, which causes a ventilation-perfusion mismatch.

In diabetics, β(beta)2-AR agonists should be used with caution because of the risk of ketoacidosis. β(beta)2-AR agonists stimulate liver glycogenolysis, which results in increase glucose blood level.

Hypokalemia is a risk secondary to stimulation of the Na+/K+ pump in skeletal muscle, which causes an extracellular shift of sodium in exchange for potassium, thereby lowering potassium plasma levels.

Selective β(beta)2-AR agonists can cause fine tremors of skeletal muscles, particularly the hands.

β(beta)2-AR agonists can induce the mobilization of triglycerides resulting in elevated blood levels of fatty acids and glycerol.

Albuterol, terbutaline, and fenoterol can induce mild appetite suppression, headache, nausea, and sleep disturbances due to their ability to cross the blood-brain barrier.

12.4 Cholinergic/Muscarinic Acetylcholine Receptors Antagonists

Inhaled muscarinic acetylcholine receptors (mAchR) antagonists have been used for many years. The smoking of plant alkaloids was recommended in the seventeenth century for the treatment of asthma in India, and it was later introduced in the nineteenth century to Great Britain.

Atropa belladonna and *Datura stramonium* are rich in anticholinergic alkaloid, atropine, and stramonium. If dried and smoked, they relieve the symptoms of asthma.

Atropine is well absorbed into the systemic circulation and can cross the blood-brain barrier. It therefore has multiple unmanned side effects, but the modification of its chemical molecule lessens the amount of mucosal absorption and blood-brain barrier crossing.

12.4.1 Short-Acting Muscarinic Acetylcholine Receptors Antagonists

Short-acting mAchR agents have duration of action of 6–8 h, but compared to SABAs they have a slower onset of action.

Atropine Methonitrate

Quaternary ammonium of atropine, a more potent bronchodilator, reaches its peak effect in 40–60 min and duration of action can last up to 6 h.

Ipratropium Bromide

Unlike atropine, ipratropium bromide has low lipid solubility, does not cross the blood-brain barrier, and is poorly absorbed by the mucosa or the gastrointestinal tract.

It is a nonselective antagonist of M1, M22, and M3 mChRs and starts acting within 15–30 min with peak concentration in 3 h. The duration of action is approximately 6 h when given as inhalation. It has little or no systemic side effects.

Oxitropium Bromide

Oxitropium bromide's base molecule is scopolamine. It has a longer duration of action than ipratropium, but peak bronchodilation may take 60–90 min. It has a slight clinical advantage over ipratropium, but at higher doses it causes tachycardia.

12.4.2 Long-Acting Muscarinic Acetylcholine Receptors Antagonists

Tiotropium Bromide

Tiotropium bromide is a long-acting AChR antagonist (LAMA) with higher affinity to the mAChRs than ipratropium by (6- to 20-fold). It binds to all the M receptors but dissociates faster from the M2 receptors. Its long duration of action can be explained by the slow dissociation from M1-M3 mAChRs.

It has a very long half-life of approximately 35 h, which allows for once-daily dose. It is rapidly absorbed into the circulation with peak plasma concentration within 5 min followed by rapid fall within 1 h to a steady state and a terminal half-life of 5–6 days. Peak onset occurs between 1 and 3 h with improvement in FEV1 for more than 24 h. Recently, tiotropium bromide has been shown to be more effective than salmeterol in preventing COPD exacerbation.

12.4.3 Novel Long-Acting Muscarinic Acetylcholine Receptors Antagonists

Glycopyrronium Bromide

Glycopyrronium bromide is an mAChR antagonist and has a fast onset that is sustained over 24 h. Fifty micrograms of glycopyrronium bromide once daily produces immediate and significant improvement in exercise tolerance from day 1. It also improves inspiratory capacity and trough FEV1 in patients with COPD.

Aclidinium Bromide

Aclidinium bromide exhibits M3/M2 selectivity. Its action is related to its inhibition of M3 receptors with resultant bronchodilation. The major route of metabolism of aclidinium bromide is hydrolysis, which occurs both chemically and enzymatically by esterases.

It has a faster onset and shorter duration of action than tiopropium bromide.

Umeclidinium Bromide

Umeclidinium bromide is a long-acting muscarinic antagonist (LAMA) that blocks action of acetylcholine at muscarinic receptors (M1–M5) in the bronchial airways (M3) by preventing increases in intracellular calcium concentration. This leads to relaxation of airway smooth muscle, improved lung function, and decreased mucous secretion. It dissociates slowly from M3 muscarinic receptors, extending its duration of action.

Primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (eg, glucuronidation) to inactive metabolite. It is mostly secreted in the feces.

Trospium

Trospium is currently used as a urinary antispasmodic drug, but when used as inhaler it induces a fast onset of bronchdilation with an onset of 15 min and duration of 24 h.

12.4.4 Side Effects of Muscarinic Acetylcholine Receptors Antagonists

All of the mChR antagonists are very well tolerated because they are very poorly absorbed after inhalation.

If these agents contact the eye, they can cause papillary dilation and blurred vision. In patients with glaucoma, they can cause an acute angle-closure glaucoma.

In patients with prostatic hyperplasia, they should be used with caution, since the risk of further increase and acute urinary retention can follow.

Patients with moderate to severe renal impairment should be monitored under the treatment of tiotropium bromide because it is mainly excreted by the kidneys.

Bad breath or dry mouth is another side effect of the treatment, though usually well tolerated in the long-term treatment.

Paradoxical bronchoconstriction could occur with these drugs. One possible cause is the blockade of prejunctional M2 mChRs on airway cholinergic nerves, which normally inhibits the release of ACh.

Recent systemic reviews and meta-analyses showed that tiotropium bromide inhaler is associated with increased risk of cardiovascular morbidity and mortality. A possible explanation is that new formulation and device may lead to greater systemic absorption.

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12.5 Steroids

Corticosteroids are very useful when the common bronchodilators are less effective. Previously they were used as rescue medication, but presently they are considered a first-line medication for asthma.

Corticosteroid are primarily anti-inflammatory by reducing the numbers of inflammatory cells in the airway, such as eosinophils, T lymphocytes, mast cells, and dentritic cells. Corticosteroids inhibit the recruitment of inflammatory cells by reducing chemotaxis and adhesion, phagocytosis, and the production of inflammatory mediators such as cytokines and eicosanoids. Corticosteroids also increase the expression of 2-adrenergic receptors in the lung and prevent their down-regulation and uncoupling in response to 2-agonists.

The primary effects of corticosteroids are at the genetic level, activating transcription of anti-inflammatory gene while repressing pro-inflammatory genes. The steroid hormone is initially taken up by the target cell before binding to specific cytoplasmic receptor proteins. This "steroid-receptor complex" is then transported to the nucleus of the cell. There it binds to a specific acceptor site on the DNA molecule. Messenger RNA is then formed from the DNA. The messenger RNA is transported to the cytoplasm where it causes new protein synthesis along the ribosomes. The new protein then gives a cellular response to the steroid, promoting vasoconstriction in areas of inflammation and decreasing capillary permeability. This decreases edema fluid in the airway, which will decrease the wall thickness, increase lumen size, and decrease airway resistance. Steroids stabilize cell membranes resulting in a decrease in synthesis, storage, and release of histamine. This makes it useful in preventing allergic bronchospasm.

Steroids are administered orally, intravenously, or aerosolized for respiratory symptoms. Intravenous formulations include hydrocortisone or methylprednisolone. Oral choices are prednisone or prednisolone. Aerosolized steroids are beclomethasone dipropionate, flunisolide, triamcinolone acetone, and fluticasone. It may take 4–6 h to have a noticeable improvement in asthmatic symptoms.

Between 10% and 60% of inhaled corticosteroid (ICS) is deposited in the lung, where it is absorbed into the circulation and cleared by the liver. The remainder of the dose is deposited in the oropharynx and may cause local side effect.

Oral steroid undergoes absorption into the portal circulation and undergoes first-pass elimination.

- **Hydrocortisone** is administered parenterally and rarely aerosolized. The dose ranges from 300 to 2000 mg.
- **Prednisone** has 3–4 more inflammatory potency than hydrocortisone, ineffective when aerosolized.
- **Prednisolone** is a synthetic steroid, rarely aerosolized. Its half-life is 2–4 h and its duration of action can be up to 36 h.
- **Methylprednisolone** is 4–5 times more potent than prednisone. It has little effect on electrolyte balance. It is used for severe shock, persistent asthma, acute respiratory distress syndrome (ARDS), and aspiration pneumonia. Onset is fast, and its half-life is 78–188 min, with duration of action lasting up to 36 h.
- **Dexamethasone** – With 30 times the anti-inflammatory potency than hydrocortisone, it is as effective as an aerosolized steroid but does not potentiate the effect of β(beta)2 agonists. It also may cause adrenal insufficiency.
- **Triamcinolone** – As a synthetic steroid, it may cause sodium and water diuresis. It has a similar potency to methylprednisolone. Its half-life is 3 h, and duration can last up to 48 h. Prolonged use can cause muscle weakness and depression.
- **Beclomethasone Dipropionate** – This is 100 times more potent that hydrocortisone. The major side effect is fungal infection of the oropharynx. The maximum adult daily dose is 840 mcg. Pediatric dosing is half of that.
- **Flunisolide** is several hundred times more potent than hydrocortisone. Maximum dose is 2 mg, and pediatric dosage is half that dose.
- **Fluticasone** – The highest recommended dose is 440 mcg daily, which may be doubled if the patient is taking oral steroid.

12.5.1 Side Effects of Steroid Treatment

Usually, side effects are more common with systemic steroids than with inhaled agents. These side effects can be improved with reducing the dosage or treatment duration, if possible.

Long-term use can be associated with weight gain, increase susceptibility to infection secondary to immunosuppression, osteoporosis, and growth retardation in kids.

Bone health is adversely affected in systemic steroid utilization, and it is related to daily use, prolonged duration of use, and high cumulative lifetime dose. This can be manifested as osteoporosis, osteoporotic fractures, and avascular osteonecrosis. These complications are seen with doses as low as 5–7.5 mg/day of prednisone.

Adrenal insufficiency is another side effect from systemic steroid. This risk seems minimal with inhaled steroidal agents. Morning cortisol level suppression does occur with inhaled steroid, but it is clinically not significant.

When a systemic steroid is prescribed in higher doses and for a prolonged period of time, it carries a risk for *Pseudomonas*, *Pneumocystis* infections, tuberculosis, and herpes zoster. This is all secondary to immunosuppression.

Inhaled steroids can cause deposition of the drug in the oropharynx, which in turn can increase the risk of fungal infection, such as oral candidiasis. Rinsing the mouth after taking the medication may reduce the incidence of fungal infection. Inhaled steroid may cause dysphonia.

The TORCH (Towards a Revolution in COPD Health) trial found an increased frequency of pneumonia among patients receiving inhaled steroids. Proper education of patients in the utilization of the inhaled steroid and washing of the mouth after use can reduce the side effects mentioned previously.

Patients also should be referred for routine ophthalmologic exams, as secondary glaucoma or cataracts may develop while on chronic use of systemic steroids. Routine checkups for cardiovascular side effects are also recommended to monitor for hypertension, hyperglycemia, and hyperlipidemia.

Bone density measurements should be done routinely in patients on chronic steroid therapy, and they should be encouraged to perform weight-bearing exercise and take calcium supplements with vitamin D.

Avoidance of nonsteroidal anti-inflammatory drugs (NSAIDs) is appropriate in patients receiving steroid therapy, due to increase risk of stomach ulcer and gastrointestinal bleeding.

Psychiatric symptoms should be monitored, if any, and they should be managed by reducing the dose or adding an additional treatment targeting the psychiatric symptoms.

12.6 Leukotriene Modifier Drugs

Leukotrienes are formed from arachidonic acid that is released from the cell-membrane phospholipid bilayer by phospholipase A2 (PLA2). The liberated arachidonic acid may then be metabolized by one of several pathways: the cyclooxygenase pathway, to generate prostaglandins, thromboxanes, and prostacyclin; or the 5-lipoxygenase pathways, to generate the cysteinyl leukotrienes C4, D4, and E4. In humans, 5-lipoxygenase is present only in myeloid cells (ie, monocytes, eosinophils, basophils, alveolar macrophages, and mast cells).

Leukotrienes can impair mucociliary clearance, enhance mucus secretion, chemotactically attract leukocytes to the airways, and cause edema by facilitating pulmonary vascular permeability. Inhaled leukotrienes C4 and D4 can cause airflow obstruction 1000 times more potently than histamine in normal subjects. In patients with asthma, the airways are 100 to 1000 times more sensitive to inhaled leukotrienes D4 and E4 than are the airways of normal subjects.

Two approaches have been developed to decrease the action of leukotrienes. One is by enzyme inhibition to block leukotriene synthesis, and the other is by blocking the binding of a leukotriene to its receptor.

Inhibitors of leukotriene synthesis block the formation of both the cysteinyl leukotrienes and leukotriene B4. These inhibitors can be grouped on their site of action into 2 groups. Inhibitors of 5-lipoxygenase prevent the formation of leukotriene A4, which is the unstable intermediate. Zileuton is a representative 5-lipoxygenase inhibitor.

Alternatively, leukotriene synthesis can be inhibited by blocking the action of the 5-lipoxygenase-activating protein. These agents are still under investigation.

Leukotriene modifiers also work as competitive antagonists of the leukotriene B4 receptor.

12.6.1 Zafirlukast

Zafirlukast (Accolate®) is a synthetic peptide leukotriene-receptor antagonist recommended for children 7 years of age and older. It is used for the management of mild, persistent asthma, a step-up therapy for moderate persistent asthma, treatment of exercise-induced asthma, and management of allergic rhinitis. It inhibits the binding of leukotrienes that are responsible for smooth muscle constriction and hyperresponsiveness after contact with an allergen challenge including exercise. The dose is 10 mg for 7–12 years old twice a day. For older patients it is 20 mg BID.

Headache is the major side effect. Nausea, abdominal pain, diarrhea, rash, and elevated liver functions tests (LFTs) have occurred in clinical trials. Patients on warfarin treatment should be monitored closely because this drug may affect the warfarin level and increase prothrombin time.

12.6.2 Montelukast

Montelukast (Singulair®) is also a leukotriene-receptor antagonist. It is used for the long-term management of children with asthma over the age of 2 years. Montelukast is recommended as an alternative medication to inhaled corticosteroids or as adjunctive therapy for the treatment of mild and moderate persistent asthma.

The rapid onset, safety of the drug in children, ease of administration, once daily dose, and chewable tablets are all advantages to using this drug. Headaches are the major side

effect affecting 18–19% of patients. Cough, abdominal pain and increased LFTs, diarrhea, and rash are other side effects of this drug.

12.6.3 Zileuton

Zileuton (Zyflo®) is a 5-lipoxygenase inhibitor. Zyflo is indicated for children greater than 12 years of age for the treatment of chronic asthma. Headaches are a side effect experienced by 25% of patients taking zileutin. Additional reported side effects include unspecified pain, dyspepsia, nausea, and abdominal pain. Increase in LFT is reported, so it is contraindicated in children with liver disease or elevated LFTs.

Leukotriene modifiers drugs are effective treatment against exercise-induced bronchospasm and aspirin-induced asthma. They are not recommended in acute exacerbations of asthma, but should be continued during acute episodes.

12.7 Mast Cell Stabilizer

Mast cell stabilizing drugs inhibit the release of allergic mediators from mast cells and are used clinically to prevent allergic reactions to common allergens.

Mast cells play a fundamental role in the occurrence and maintenance of allergic disease in response to substances that induce an allergic reaction.

This allergic reaction begins with the allergen interacting with immunoglobulin E (IgE) complex, expressed on the surface of the sensitized mast cell, through complex signaling cascade. It leads to calcium influx and release of preformed chemical mediators such as histamine from mast cells, which induces the production of cytokine and chemokines. The effect of these mediators on surrounding cells and tissues are responsible for the symptoms and the severity of an allergic reaction.

Mature mast cell are widely distributed throughout the body where they reside in vascularized tissue, including nerves, smooth muscle cells, mucus production glands, and hair follicles. They are also found in sites that are directly exposed to the environment including the skin, airway, and gastroenterology tract.

Mast cells are classified into 2 subtypes depending on their location: (1) connective tissue mast cells, which reside in tissue such as skin, small bowel submucosa, and peritoneal cavity; and (2) mucosal mast cells, which mature in mucosal tissue such as the intestine and in the airways.

An allergic reaction may be prevented or attenuated by interfering with certain signaling molecules within the signaling cascade of the mast cell. Agents that prevent mediator release from the mast cells are termed mast cell stabilizers. They can be natural, semisynthetic, and synthetic products.

12.7.1 Cromolyn Sodium

One of the earliest mast cell stabilizers, cromolyn sodium inhibits release of histamine, leukotrienes, and slow-reacting substance of anaphylaxis from mast cells by inhibiting degranulation following exposure to reactive antigens.

Peak onset is 15 min with duration of action of 6 h and half-life 80–90 min.

Multiple side effect have been reported, most of which are diarrhea, headache, angioedema, and neutropenia. Inhalation of cromolyn sodium has side effects including cough, nasal congestion, nausea, and wheezing.

12.7.2 Nedocromil Sodium

Nedocromil sodium has been shown to inhibit the activation of, and mediator release from, a variety of inflammatory cell types associated with asthma, including eosinophils, neutrophils, macrophages, mast cells, platelets, and monocytes. In humans, nedocromil sodium has been shown to inhibit acutely the bronchoconstriction response to several kinds of allergens.

At higher concentrations, nedocromil sodium showed more effective inhibition of histamine release from mast cells isolated from the lung, and tonsillar and adenoid tissues than cromolyn sodium.

Systemic absorption of nedocromil sodium administered as an inhaled aerosol is low.

Studies have shown that nedocromil sodium improved symptom control and pulmonary function when it was added to an as-needed inhaled beta 2-adrenergic bronchodilator regimen, and a beneficial effect could be detected within 2 weeks.

12.7.3 Ketotifen

Ketotifen is another mast cell stabilizer drug, but is currently not available in the United States.

The aforementioned drugs are used mainly as prophylaxis, and they cannot be used in the acute phase of any bronchoconstriction events.

12.8 Immunoglobulin E Blockers

In recent years, evidence suggests that bronchial asthma and other allergic conditions have become more common worldwide, in both developed and developing countries.

It is estimated that more than 50% of asthma is related to allergy and the majority of patients with severe asthma have allergic-atopic asthma. Immunoglobulin E(IgE) antibodies, allergen type 2 helper T cells derived cytokines and eosinophils play a major role in the development of chronic airway

disease, even in mild forms of the disease. This airway inflammation is the pathogenesis of bronchial asthma, which causes an increase in airway responsiveness to many trigger factors such as aeroallergens alone or in combination with other triggers such as air pollution and viruses.

Elevated levels of specific IgE toward common environmental allergens are the main component in the pathogenesis of allergic asthma. IgE antibodies cause chronic airway inflammation through effector cells activated by 2 IgE receptors: high affinity and low affinity.

Corticosteroids have been the main treatment for asthmatic patients, suggested by the Global Initiative for Asthma (GINA), but there are asthmatic patients who continue to have severe symptoms with multiple regimen treatments. These patients have increased recurring hospitalizations and mortality within 1 year of initial hospitalization. These conditions also have high economic and social costs.

Anti-IgE monoclonal antibody (omalizumab) binds IgE at the same site where the antibody binds, resulting in the inhibition of IgE effector function. This means that in allergic subjects, omalizumab prevents the activation of cellular response and the occurrence of asthma symptoms.

Treatment with omalizumab reduces airway wall thickness in patients with severe persistent asthma treated with conventional treatment. The use of omalizumab also has resulted in decreased corticosteroid use and improved quality of life in asthmatic patients.

Omalizumab treatment is reserved for the severe uncontrolled asthmatic patients despite best available therapy. Multiple studies have shown that adding omalizumab reduces asthma exacerbation, total emergency visits, hospitalizations, and steroid utilization, thus improving quality of life.

Omalizumab is very safe with few side effects. The most frequent side effects are nasopharyngitis and sinusitis. No data exist about patients with renal or hepatic dysfunction prior to starting omalizumab, thus caution should be used in administering this drug in these patients.

12.9 Combination Therapy

Combination therapy is used when airway symptoms are not controlled by maintenance monotherapy. Moreover, combining 2 or more classes allows the use of lower doses to achieve the same result. Combination therapy with a long-acting beta agonist (LABA) and inhaled corticosteroid (ICS) is an essential approach to patients with frequent exacerbation.

The combinations present in clinical use are:

1. Combining β(beta)2-adrenergic receptors agonist and muscarinic acetylcholine receptor antagonists
2. Combining β(beta)2-adrenergic receptor agonists and inhaled corticosteroid
3. Combining muscarinic acetylcholine receptor antagonists and inhaled corticosteroid

12.10 Conclusion

Inhaled bronchodilators are the primary drugs for the management of COPD, and they are critical in the symptomatic management of asthma.

According to the guidelines for the management of COPD by the British National Institute for Health and Clinical Excellence (NICE), the treatment choice after initial SAMA or SABA bronchodilators for persistent breathlessness or exacerbations is determined by the level of post bronchodilator FEV1.

International guidelines on asthma management recommend the utilization of rapid onset inhaled β(beta)2-AR agonists alone for symptom relief and pretreatment of exercise induced asthma.

The field of obstructive lung disease treatment is currently undergoing major development in pharmacogenetic studies, which could target the use of specific medications in populations most likely to benefit.

12.11 Questions and Answers

Questions (Choose the Most Appropriate Answer)

1. Airway tone is mainly controlled by which of the following
   - A. Parasympathetic nerves carried by the vagus nerve
   - B. Parasympathetic nerves carried by the phrenic nerve
   - C. Sympathetic nerves carried by the vagus nerve
   - D. Sympathetic nerves carried by the phrenic nerve
2. How many subtypes of muscarinic receptors are present in the airways?
   - A. 3
   - B. 4
   - C. 5
   - D. 6
   - E. 7
3. Levalbuterol has advantage over albuterol in which category
   - A. Duration
   - B. Side effect
   - C. Hospitalization
   - D. All of the above
4. Side effects of B2 adrenergic receptors agonists include all of the following EXCEPT
   - A. Tachycardia
   - B. Transient increase in partial pressure of oxygen
   - C. Risk of ketoacidosis in patients with diabetes mellitus
   - D. Hypokalemia
   - E. Fine tremor
5. Which of the following is a side effect of muscarinic acetylcholine receptors antagonists?
   - A. Dry mouth
   - B. Urinary retention

C. Paradoxical bronchoconstriction
D. Blurred vision
E. All of the above

Answers

1. **A**. Airway tone is mainly controlled by parasympathetic nerves carried by the vagus nerve.
2. **C**. There are 5 subtypes of muscarinic receptors in the airways.
3. **D**. Levalbuterol may reduce hospitalization, have fewer adverse side effects, and provide similar bronchodilators effects at reduced dose compared to albuterol.
4. **B**. Transient mild decrease (rather than an increase) in partial pressure of oxygen in arterial blood could result from the administration of β(beta)2-AR agonists despite concomitant bronchodilation.
5. **E**. All are side effects:
   - Bad breath or dry mouth is a side effect, though usually well tolerated in long-term treatment.
   - In patients with prostatic hyperplasia, these agents should be used with caution, since the risk of further increase and acute urinary retention can follow.
   - Paradoxical bronchoconstriction could occur with these drugs. One possible cause is the blockade of prejunctional M2 mChRs on airway cholinergic nerves, which normally inhibits the release of ACh.
   - If these agents contact the eye, they can cause papillary dilation and blurred vision.

Suggested Reading

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775–89.