Drugs Used in Asthma

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Reference: Basic & Clinical Pharmacology: Bertrum G. Katzung and Anthony J. Treveror, 13th edition, 2015, chapter 20, p. 336-351

Learning Objectives:

At the end of session, the student should be able to:

1. Explain the goals of drug therapy in asthma.
2. Classify drugs used in asthma.
3. Explain the role of each class of drugs in asthma.
4. Explain the routes of administration of drugs in asthma.
5. Describe mechanism of actions, uses and side effects of corticosteroids in asthma.
6. Name inhaled corticosteroids used in asthma
7. Describe mechanism of action and uses of cromolyn in asthma.
8. Describe mechanism of action and uses of leukotriene pathway inhibitors.
9.

Drugs Used in Asthma

The clinical features of asthma are recurrent bouts of shortness of breath, chest tightness, and wheezing, often associated with coughing. Its hallmark physiologic features are widespread, reversible narrowing of the bronchial airways and a marked increase in bronchial responsiveness to inhaled stimuli; and its pathologic features are lymphocytic, eosinophilic inflammation of the bronchial mucosa. In mild asthma, symptoms occur only intermittently, as on exposure to allergens or air pollutants, on exercise, or after viral upper respiratory infection. More severe forms of asthma are associated with more frequent and severe symptoms, especially at night. Chronic airway constriction causes persistent respiratory impairment, punctuated by frequent acute asthmatic attacks, or "asthma exacerbations."

Goals of drug therapy in asthma

1. To reverse acute attack
2. To prevent recurrence

To achieve the above goals, drugs used in asthma can be classified into two groups: bronchodilators and antiniflammatory drugs. The major use of bronchodilators in asthma is for quick relief of symptoms of acute bronchoconstriction, known as **"short-term relievers**", while anti-inflammatory drugs are mainly used for reduction in symptoms and prevention of attacks, known as "**long-term controllers**". Bronchodilators are categorized into sympathomimetics, antimuscarinics and methylxanthines. Antiinflammatory drugs include corticosteroids, mediator stabilizers, leukotriene inhibitors and anti-IgE antibody.

Route of drug administration in asthma

In general, the best route of drug administration in asthma is by inhalation. This results in the greatest local effect on airway smooth muscle with the least systemic toxicity. Aerosol deposition depends on the particle size, the pattern of breathing, and the geometry of the airways. Even with particles in the optimal size range of 2–5 mm, 80–90% of the total dose of aerosol is deposited in the mouth or pharynx. The use of a spacer with metered-dose inhaler or rinsing mouth with water after each inhalation decreases side effects of drugs due to mouth deposition. Particles under 1–2 μm remain suspended and may be exhaled. Bronchial deposition of an aerosol is increased by slow inhalation of a nearly full breath and by 5 or more seconds of breath-holding at the end of inspiration.

Anti-inflammatory Drugs

Corticosteroids

Mechanism of Action

Corticosteroids have long been used in the treatment of asthma and are presumed to act by their broad anti-inflammatory efficacy, mediated in part by inhibition of production of inflammatory cytokines. They do not relax airway smooth muscle directly but reduce bronchial hyperreactivity and reduce the frequency of asthma exacerbations if taken regularly. Their effect on airway obstruction is due in part to their potentiation of the effects of β-receptor agonists, but their most important action is inhibition of the infiltration of asthmatic airways by lymphocytes, eosinophils, and mast cells.

Clinical Uses

Clinical studies of corticosteroids consistently show them to be effective in improving all indices of asthma control: severity of symptoms, tests of airway caliber and bronchial reactivity, frequency of exacerbations, and quality of life.

Inhaled Corticosteroids

Inhalational treatment is the most effective way to avoid the systemic adverse effects of corticosteroid therapy. Examples of the ICS are **beclomethasone, budesonide, fluticasone and mometasone.** A special problem caused by inhaled topical corticosteroids is the occurrence of oropharyngeal candidiasis. This is easily treated with topical cotrimazole, and the risk of this complication can be reduced by having patients gargle water and expectorate after each inhaled treatment. Hoarseness can also result from a direct local effect of ICS on the vocal cords. In children, ICS therapy has been shown to slow the rate of growth by about 1 cm over the first year of treatment, but not the rate of growth thereafter, so that the effect on adult height is minimal. The risks of systemic toxicity from chronic use of ICS are negligible compared with those of the oral corticosteroid. Nonetheless, chronic use of ICS may increase the risks of osteoporosis and cataracts.

Because of the efficacy and safety of inhaled corticosteroids, national and international guidelines for asthma management recommend their prescription for patients who require more than occasional inhalations of a β □agonist for relief of symptoms. Inhaled corticosteroids are not curative. In most patients, the manifestations of asthma return within a few weeks after stopping therapy. Thus, inhaled corticosteroids are properly labeled as "controllers." They are effective only so long as they are taken.

Systemic Corticosteroids

Because of severe adverse effects when given chronically, oral and parenteral corticosteroids are reserved for patients who require urgent treatment, ie, those who have not improved adequately with bronchodilators or who experience worsening symptoms despite maintenance therapy. When asthma becomes under control, systemic corticosteroids are replaced with ICS. Indeed, one of the cautions in switching patients from oral to ICS therapy is to taper oral therapy slowly to avoid precipitation of adrenal insufficiency. Regular or "controller" therapy is maintained with ICS in all but the most severely affected individuals.

CROMOLYN & NEDOCROMIL

Cromolyn sodium (disodium cromoglycate) and nedocromil sodium were once widely used for asthma management, especially in children, but have now been supplanted so completely by other therapies that they are mostly of historic interest. Both have low solubility, are poorly absorbed from the gastrointestinal tract, and must be inhaled as a microfine powder or microfine suspension. These drugs have no effect on airway smooth muscle tone and are ineffective in reversing asthmatic bronchospasm but effectively inhibit both antigen- and exercise-induced asthma.

Mechanism of Action

Cromolyn and nedocromil are thought to alter the function of delayed chloride channels in cell membranes, inhibiting cell activation. This action on airway nerves is thought to mediate inhibition of cough; on mast cells and eosinophils, the drugs inhibit the early and the late response to antigen challenge.

Clinical Uses

Acute protective effect: Pretreatment with cromolyn or nedocromil blocks the bronchoconstriction caused by allergen inhalation, exercise, sulfur dioxide, and a variety of causes of occupational asthma. Cromolyn is useful for administration shortly before exercise or before unavoidable exposure to an allergen.

Chronic use: When taken regularly (2-4 puffs 2-4 times daily) both agents modestly but significantly reduce symptomatic severity and the need for bronchodilator medications, particularly in young patients with allergic asthma. These drugs are not as potent or as predictably effective as ICS, and the only way of determining whether a patient will respond is by a therapeutic trial of 4 weeks' duration.

Cromolyn and nedocromil solutions are also useful in reducing symptoms of **allergic rhinoconjunctivitis.** Applying the solution by nasal spray or eye drops several times a day is

effective in about 75% of patients, even during the peak pollen season. Because the drugs are so poorly absorbed, adverse effects of cromolyn and nedocromil are minor and are localized to the sites of deposition. These include throat irritation, cough, and mouth dryness, and, rarely, chest tightness and wheezing. Inhalation of a β2-adrenoceptor agonist before cromolyn or nedocromil treatment can prevent some of these symptoms. Serious adverse effects are rare.

Its place in treatment of childhood asthma has lately diminished, because of the significantly greater efficacy of even low-dose corticosteroid treatment and because of the availability of an alternate nonsteroidal controller class of medication, the leukotriene pathway inhibitors (see below).

LEUKOTRIENE PATHWAY INHIBITORS

Because of the evidence of leukotriene involvement in many inflammatory diseases and in anaphylaxis, considerable effort has been expended on the development of drugs that block their synthesis or interaction with their receptors. Leukotrienes result from the action of 5-lipoxygenase on arachidonic acid and are synthesized by a variety of inflammatory cells in the airways, including eosinophils, mast cells, macrophages, and basophils. Leukotriene B4 (LTB4) is a potent neutrophil chemoattractant, and LTC4 and LTD4 exert many effects known to occur in asthma, including bronchoconstriction, increased bronchial reactivity, mucosal edema, and mucus hypersecretion.

Two approaches to interrupting the leukotriene pathway have been pursued: inhibition of 5-lipoxygenase by **zileuton**, thereby preventing leukotriene synthesis; and inhibition of the binding of LTD4 to its receptor on target tissues by **zafirlukast** and **montelukast**, thereby preventing its action. Efficacy in blocking airway responses to exercise and to antigen challenge has been shown for drugs in both categories. All have been shown to improve asthma control and to reduce the frequency of asthma exacerbations in clinical trials. Their

effects on symptoms, airway caliber, bronchial reactivity, and airway inflammation are less marked than the effects of ICS, but they are more nearly equal in reducing the frequency of exacerbations. Their principal advantage is that they are taken orally; some patients—especially children—comply poorly with inhaled therapies. Montelukast is approved for children as young as 12 months.

Trials with leukotriene inhibitors have demonstrated an important role for leukotrienes in aspirin-induced asthma. It has long been known that in 5–10% of patients with asthma, ingestion of even a very small dose of aspirin causes profound bronchoconstriction and symptoms of systemic release of histamine, such as flushing and abdominal cramping. Because this reaction to aspirin is not associated with any evidence of allergic sensitization to aspirin or its metabolites and because it is produced by any of the nonsteroidal anti-inflammatory agents, it is thought to result from inhibition of cyclooxygenase, shifting arachidonic acid metabolism from the prostaglandin to the leukotriene pathway, especially in platelets adherent to circulating neutrophils. Of these agents, montelukast is by far the most prescribed, probably because it can be taken without regard to meals, because of the convenience of once-daily treatment, and because of patient fear of inhaled corticosteroids. Zileuton is the least prescribed because of reports of liver toxicity. The receptor antagonists appear to have little toxicity.

Anti-IgE Monoclonal Antibodies

Omalizumab inhibits binding of IgE to mast cells. Because its specific target is the portion of IgE that binds to its receptors (Fcε-R1 and Fcε-R2 receptors) on mast cells and other inflammatory cells, omalizumab inhibits the binding of IgE but does not activate IgE already bound to mast cells and thus does not provoke mast cell degranulation.

Omalizumab's use is restricted to patients with evidence of allergic sensitization, and the dose administered is adjusted for total IgE level and body weight. Given by subcutaneous

injection every 2–4 weeks to asthmatic patients, it lowers free plasma IgE to undetectable levels and significantly reduces the magnitude of both early and late bronchospastic responses to antigen challenge.

Omalizumab's most important clinical effect is reduction in the frequency and severity of asthma exacerbations, even while enabling a reduction in corticosteroid requirements. It also lessens asthma severity and improves coincident nasal and conjunctival symptoms of allergic rhinitis. Combined analysis of several clinical trials has shown that the patients most likely to respond are those with a history of repeated exacerbations, a high requirement for corticosteroid treatment, and poor pulmonary function. Similarly, the exacerbations most prevented are the ones most important to prevent: omalizumab treatment reduced exacerbations requiring hospitalization by 88%. These benefits justify the high cost of this treatment in selected individuals with severe disease characterized by frequent exacerbations. There is also evidence of effectiveness of omalizumab treatment for chronic urticaria (for which the drug is now approved) and peanut allergy.

Bronchodilators

Sympathomimetic Agents

Adrenoceptor agonists are mainstays in the treatment of asthma. Their binding to β2□receptors—abundant on airway smooth muscle cells—stimulates adenylyl cyclase and increases the formation of intracellular cAMP, thereby relaxing airway smooth muscle and inhibiting release of bronchoconstricting mediators from mast cells. They may also inhibit microvascular leakage and increase mucociliary transport.

Sympathomimetic agents that have been widely used in the treatment of asthma include epinephrine, ephedrine, isoproterenol, and albuterol and other β2-selective agents. Because epinephrine and isoproterenol increase the rate and force of cardiac contraction (mediated mainly by β1 receptors), they are reserved for special situations.

Beta2-Selective Drugs

The β2-selective adrenoceptor agonist drugs, particularly albuterol (salbutamol), are now the most widely used sympathomimetics for the treatment of the bronchoconstriction of asthma. They are effective after inhaled or oral administration and have a longer duration of action than epinephrine or isoproterenol.

Albuterol and terbutaline are available as metered-dose inhalers. Bronchodilation is maximal within 15 minutes and persists for 3–4 hours. They can be diluted in saline for administration from a hand-held nebulizer. Because the particles generated by a nebulizer are much larger than those from a metered-dose inhaler, much higher doses must be given (2.5–5.0 mg vs 100–400 mcg) but are no more effective. Nebulized therapy should thus be reserved for patients unable to coordinate inhalation from a metered-dose inhaler.

Albuterol and terbutaline are also available in oral form. This route of administration presents no advantage over inhaled treatment and is rarely prescribed. Terbutaline is also available for subcutaneous injection (0.25 mg). The indications for this route are similar to those for subcutaneous epinephrine—severe asthma requiring emergency treatment when aerosolized therapy is not available or has been ineffective—but it should be remembered that terbutaline's longer duration of action means that cumulative effects may be seen after repeated injections.

A newer generation of long-acting β2-selective agonists includes **salmeterol** (a partial agonist) and **formoterol** (a full agonist). These long-acting β_2-agonists (LABA) are potent selective β2 agonists that achieve their long duration of action (12 hours or more) as a result of high lipid solubility. These drugs appear to interact with inhaled corticosteroids to improve asthma control. Because they have no anti-inflammatory action, they should not be used as monotherapy for asthma.

Adverse effects

The principle adverse effects include tachycardia, skeletal muscle tremor, nervousness, occasional weakness and decreases in serum potassium levels.

Toxicities

A reduction in the bronchodilator response to low-dose β2-agonist treatment can indeed be shown after several days of regular β2-agonist use, but maximal bronchodilation is still achieved well within the range of doses usually given. Tachyphylaxis is more clearly reflected in a loss of the protection afforded by acute treatment with a β2agonist against a later challenge by exercise or inhalation of allergen or an airway irritant. It was speculated that a genetic variant of β2 receptor may underlie the report of an increase in asthma mortality from regular use of a long-acting β2 agonist.

Antimuscarinic Agents

Mechanism of Action

Muscarinic antagonists competitively inhibit the action of acetylcholine at muscarinic receptors. In the airways, acetylcholine is released from efferent endings of the vagus nerves, and muscarinic antagonists block the contraction of airway smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity. In the doses given, antimuscarinic agents inhibit only that portion of the response mediated by muscarinic receptors, which varies by stimulus, and which further appears to vary among individual responses to the same stimulus.

Clinical Uses

Antimuscarinic agents are effective bronchodilators. Even when administered by aerosol, the bronchodilation achievable with atropine, the prototypic muscarinic antagonist, is limited by absorption into the circulation and across the blood-brain barrier. Greater bronchodilation, with less toxicity from systemic absorption, is achieved by treatment with a selective quaternary ammonium derivative of atropine, **ipratropium bromide.** Ipratropium can be

delivered in high doses by this route because it is poorly absorbed into the circulation and does not readily enter the central nervous system.

Antimuscarinic agents are especially useful for patients intolerant of inhaled β2-agonist agents. Although antimuscarinic drugs appear to be slightly less effective in reversing asthmatic bronchospasm, the addition of ipratropium enhances the bronchodilation produced by nebulized albuterol in acute severe asthma.

Methylxanthine Drugs

The three important methylxanthines are **theophylline, theobromine,** and **caffeine.** Their major source is beverages (tea, cocoa, and coffee, respectively). The methylxanthines have effects on the central nervous system, kidney, and cardiac and skeletal muscle as well as smooth muscle. Of the three agents, theophylline is most selective in its smooth muscle effects, whereas caffeine has the most marked central nervous system effects. A theophylline preparation commonly used for therapeutic purposes is **aminophylline,** a theophyllineethylenediamine complex.

Mechanism of Action

Several mechanisms have been proposed for the actions of methylxanthines, but none has been firmly established. At high concentrations, they can be shown in vitro to inhibit several members of the phosphodiesterase (PDE) enzyme family thereby increasing concentrations of intracellular cAMP and, in some tissues, cGMP. Another proposed mechanism is inhibition of cell surface receptors for adenosine. These receptors modulate adenylyl cyclase activity, and adenosine has been shown to provoke contraction of isolated airway smooth muscle and histamine release from airway mast cells. A third mechanism of action may underlie theophylline's efficacy is enhancement of histone deacetylation. Acetylation of core histones is necessary for activation of inflammatory gene transcription.

Clinical Uses

Of the xanthines, theophylline is the most effective bronchodilator. It relieves airflow obstruction in acute asthma and reduces the severity of symptoms in patients with chronic asthma. Tolerance does not develop to bronchodilation produced by the methylxanthines. Typically, theophylline is rarely used as monotherapy (see below) and, when prescribed, is most commonly used as add-on therapy when treatment with other agents, principally ICS, is inadequate

Methylxanthines improve contractility of skeletal muscle and reverse fatigue of the diaphragm in patients with COPD. This effect—rather than an effect on the respiratory center—may account for theophylline's ability to improve the ventilator response to hypoxia and to diminish dyspnea even in patients with irreversible airflow obstruction.

The use of theophylline, once a mainstay of asthma treatment, has waned with demonstration of the greater efficacy of inhaled adrenoceptor agonists for acute asthma and of inhaled anti-inflammatory agents for chronic asthma. Accelerating this decline in theophylline's use are 1) the requirement for monitoring serum levels because of the narrowness of its therapeutic index and inter-individual variations in drug metabolism; 2) its side effects and toxicities. Anorexia, nausea, vomiting, abdominal discomfort, headache, and anxiety, insomnia, tremor may occur at concentrations of 15 mg/L and become common at concentrations more than 20 mg/L. Higher levels (>40 mg/L) may cause seizures or arrhythmias; these may not be preceded by gastrointestinal or neurologic warning symptoms.