CHAPTER

Drugs Used to Treat Asthma

1

Introduction

Asthma is physiologically characterized by increased responsiveness of trachea and bronchi to various stimuli and by widespread narrowing of the airways. Most common chronic condition in children. Death rate up 50% from 1980 to 2000. Death rate up 80% in people under 19. Morbidity and mortality highly correlated with poverty, urban air quality, indoor allergens, lack of patient education and inadequate medical care. Usually associated with airflow obstruction of variable severity. Airflow obstruction is usually reversible, either spontaneously, or with treatment. The inflammation associated with asthma causes an increase in the baseline bronchial hyper responsiveness to a variety of stimuli.

Asthma Triggers

1. Allergens
   (a) Dust mites, mold spores, animal dander, cockroaches, pollen, indoor and outdoor pollutants, irritants (smoke, perfumes, cleaning agents)
2. Pharmacological agents (β-blockers)
3. Physical triggers (exercise, cold air)
4. Physiologic factors
   (a) Stress, GERD, viral and bacterial URI, rhinitis

Diagnostic Testing

Peak Expiratory Flow (PEF)

- Inexpensive
- Patients can use at home
  - May be helpful for patients with severe disease to monitor their change from baseline every day
  - Not recommended for all patients with mild or moderate disease to use every day at home
  - Effort and technique dependent
- Should not be used to make diagnosis of asthma

Spirometry

Recommended to do Spirometry pre and post use of an albuterol MDI to establish reversibility of airflow obstruction. > 12% reversibility or an increase in *forced expiratory volume* (FEV1) of 200cc is considered significant.

Obstructive pattern: Reduced FEV1/FVC ratio

Restrictive pattern: Reduced FVC with a normal FEV1/FVC ratio

Can be used to identify reversible airway obstruction due to triggers.

Can diagnose Exercise-induced asthma (EIA) or Exercise induced bronchospasm (EIB) by measuring FEV1/FVC before exercise and immediately following exercise, then for 5-10 minute intervals over the next 20-30 minutes looking for post-exercise bronchoconstriction.

Methacholine Challenge

Most common bronchoprovocative test in US. Patients breathe in increasing amounts of methacholine and perform Spirometry after each dose. Increased airway hyper responsiveness is established with a 20% or more decrease in FEV1 from baseline at a concentration < 8 mg/dl. Diagnostic trial of anti inflammatory medication

(preferably corticosteroids) or an inhaled bronchodilator. It is especially helpful in very young children unable to cooperate with other diagnostic testing. There is no one single test or measure that can definitively be used to diagnose asthma in every patient.

Classification of Antiasthmatics.

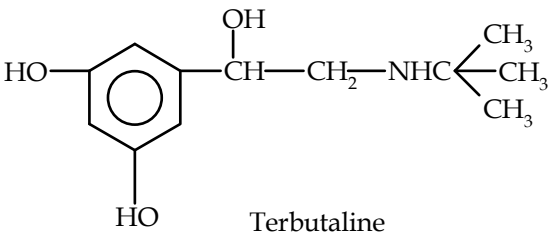
1. Brochodilators:
   (a) β_2 adenergic receptor agonists.
   Ex : Salbutamol, Fenuterol, Bitolterol Salmetaol and formoterol.
   (b) Phosphodiesterase Inhibitors
   Ex : Theophylline
   (c) Anti cholinergics: Ipratropiumbromide
2. Anti - Inflammatory drugs :
   (a) Glucocorticoids
   (b) Leukotriene (LT) modifiers :
   Lt Syntesis inhibitors : Zileuton
   Lt Antagonists : Monteleukast, Zajirleukast
   (c) Mast cell stabilizers :
   Sodium cromoglycae, Nedocromil
   (d) PAF Antagonists : Ketotifen.

Pharmacotherapy

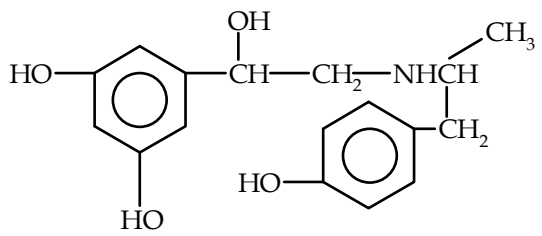
Asthma therapies are divided into two categories: Short-term relievers and long-term controllers.

Short-Term Relievers: β-adrenoceptor stimulants, theophylline, antimuscarinic agents, leukotriene antagonists.

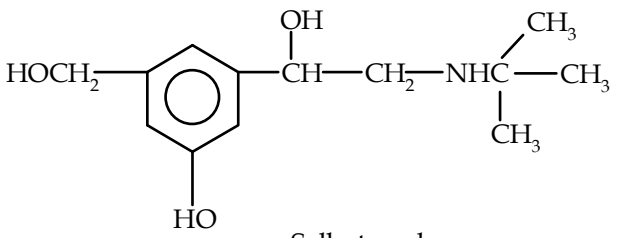
Long-Term Controllers: Anti-inflammatory agents, inhibitor of mast cell degranulation.



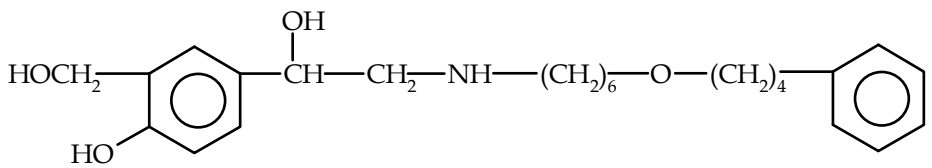
Terbutaline



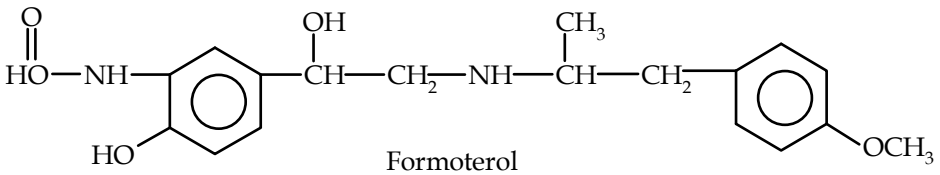
Fenoterol



Salbutamol



Salmeterol



Formoterol

Fig 1-1: Beta adrenoceptor agonists.

Adrenoceptor Agonists

β_2 agonists (Fig 1-1) are bronchodilators that act on the bronchial smooth muscle by combining with β_2-adrenergic receptors to cause bronchial muscle relaxation and, thus, bronchodilation. Bronchodilation occurs regardless of the mechanism for the bronchial constriction and β_2 agonists also provide protection against bronchial constriction; however, they do not significantly alter the progression of the inflammatory process. In other words, they dilate the bronchial muscle even though the inflammation is occurring. Bronchial smooth muscle contains β_2-adrenergic receptors, whereas the heart contains both, β_1 receptors and β_2 receptors. Consequently, no therapeutic rationale exists for using nonselective β_2 agonists (i.e., agents that are not selective for β_2 receptors relative to β_1 receptors); such agents (e.g., isoproterenol, metaproterenol, epinephrine) have an increased incidence of sympathetic stimulatory effects, including increased heart rate and force of contraction. Since these cardiac effects could improve exercise performance, nonselective β agonists are not allowed in Olympic competition, and only selected β_2 agonists (albuterol, terbutaline, salmeterol) by inhalation are allowed upon written notification before competition. The β-agonist components of over the counter oral and inhalation asthma products are nonselective and, thus, a poor choice to treat asthma. Inhaled β_2 agonists are the only agents providing an immediate response for acute asthma attacks (rescue therapy).

They are also the most effective medication to prevent an anticipated attack, such as immediately before exercise, without the onset of significant cardiac or other systemic effects. After inhalation of short-acting β_2 agonists, onset of action is usually within 5 minutes and maximal bronchodilation occurs within about 15 minutes. Duration of action is 4 to 8 hours, depending upon the agent, although a shorter period of protection (2 to 4 hours) is experienced during exercise. When given at equipotent doses, all of the β_2 agonists will produce the same intensity of bronchodilation; their main difference is the duration of action. Some agents are effective orally, but the oral route delays onset of action and is less selective for bronchial muscle, thus increasing the incidence of side effects.

Salmeterol

Is a long acting β_2 agonist available by inhalation, but its slower onset of action (up to 20 minutes) and time for maximal effect (1 to 4 hours) preclude its use as rescue therapy for treatment of acute attacks. Users of salmeterol must clearly understand that it is not effective for treatment of acute bronchospasms and that the dose should not exceed 2 puffs every 12 hours. Depending upon the duration of the athletic activity, some athletes may benefit from salmeterol, which has a longer duration of action (12 hours) as compared with albuterol (4 hours). Patients who suffer from nocturnal asthma may also benefit from the longer acting β_2 agonist. Regularly scheduled, daily use of a short acting β_2 agonist is generally not recommended, since there is no apparent advantage over use on an as needed basis. If the frequency of β_2- agonist use increases or if use exceeds 1 canister of β_2 agonist (e.g., 200 dosage of the drug puffs of albuterol) per month to control exacerbations, asthma control is poor, and reevaluation of the anti-inflammatory therapy is necessary. Regular use of short acting β_2 agonists has not demonstrated a clinically significant tolerance to the pulmonary effects, although daily use of salmeterol has resulted in a shorter duration of protection from exercise induced bronchoconstriction (EIB). Regular use of a long acting β_2 agonist is recommended for some patients with moderate to severe asthma, especially to control night time symptoms, in conjunction with corticosteroid therapy. The most frequent side effects from inhalation of β_2 agonists are tachycardia and muscle tremor, although these are more pronounced with the nonselective agents and with oral use. During an acute asthma attack, the dose of the short-acting β_2 agonists can be increased several fold to counter the bronchoconstriction without toxicity. However, if an athlete has escalating symptoms of asthma that are no longer being

alleviated by the normal regimen of β_2 agonist, adjustment of the anti-inflammatory therapy may be required.

Albuterol

Like many drugs, including all currently available selective β_2 agonists, it is an equal mixture of R and S isomers. These isomers are mirror images of each other and interact differently at receptor sites. The R isomer, originally thought to be the only bioactive form, produces virtually all of the bronchodilation; the S isomer appears to dosage of the drug contribute to some adverse effects (e.g., nervousness and tremor) and has a longer duration because it is metabolized more slowly. Levalbuterol (Xopenex, Sepracor Inc, Marlborough, MA) is (R)-albuterol and is available for use with a nebulizer. Since levalbuterol contains only the active isomer, it provides comparable or better FEV1 values than albuterol, with a lower incidence of side effects and at a smaller dose. R isomers of other β_2 agonists are also being investigated.

Anticholinergics

Another group of bronchodilators is the anticholinergic agents (Fig 1-2). Rather than activating adrenergic receptors, these drugs inhibit the cholinergic receptors of the parasympathetic system, which, through the vagus nerve, maintain normal bronchial smooth muscle tone. The use of these agents has diminished over the years as the inhaled β_2 agonists have become available and because these agents cause significant anticholinergic side effects (e.g., urinary retention, blurred vision, nasal congestion) and sedation through their central nervous system actions. Part of the bronchoconstriction caused by some asthma-inducing stimuli is mediated through the parasympathetic system, but the extent of this involvement varies significantly among patients. Anticholinergics are only effective in reducing bronchoconstriction mediated through this system.

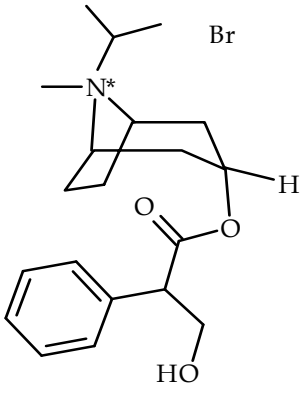


Fig 1-2: Ipratropium bromide

Ipratropium bromide is a newer anticholinergic agent without sedative properties due to poor distribution into the central nervous system. It is available by inhalation for a more selective response. Onset of action is slower than that for the β_2 agonists, and peak bronchodilation dosage occurs in 1 to 2 hours. The effectiveness of ipratropium varies considerably among asthmatic patients, although it does provide additional bronchodilation when combined with a short acting β_2 agonist. It has limited effectiveness in preventing EIB.

Methylxanthines

Theophylline is a methylxanthine bronchodilator (Fig 1- 3). Caffeine and theobromine are also members of this chemical group, but they are not used therapeutically to treat asthma since

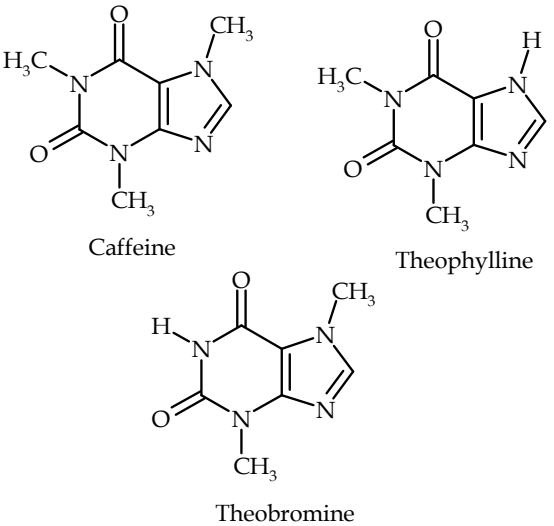


Fig 1-3: Methylxanthines

they have only a mild bronchodilating effect. The mechanism by which theophylline relaxes bronchial smooth muscle is not clearly understood, for all the drugs the dosage should provide but the inhibition of phospho-diesterase and subsequent increase in intracellular cyclic adenosine monphosphate may be a contributor.

Theophylline is used orally since it is not effective by inhalation and it is available in immediate and sustained release formulations. A major disadvantage of theophylline is that it has a narrow therapeutic window; that is, the blood level between too little and too much is narrow. Consequently, routine monitoring of theophylline blood levels is a standard procedure to prevent toxicity during long term use. Potential side effects at the upper end of the normal therapeutic blood level include anorexia, nausea, vomiting, headache and anxiety. As blood levels increase, seizures, arrhythmias and death can occur. Complicating the problem is patient variability in the rate of excretion by the kidney and the potential for several other drugs (e.g., erythromycin, cimetidine, zileuton) to alter the metabolism rate of theophylline by the liver, thus intensifying the need for blood-level monitoring. For most patients, theophylline is less effective than other bronchodilators. Nonetheless, long-term use at appropriate steady state blood levels will maintain significant bronchodilation and it is recommended as a second or third line of treatment for moderate to severe asthma in adults and children and to treat nocturnal asthma. For patients who do not respond to β_2-agonist therapy for prevention of EIB, theophylline offers an alternative. Long term therapy is effective in preventing EIB, and, for some patients, protection from EIB is obtained from a single dose of theophylline before exercise.

Anti Inflammatory Agents

Since asthma is a chronic inflammatory disease, long term use of anti-inflammatory agents is an important part of therapy to control inflammation (Fig 1-4) and to prevent exacerbations. The cellular mechanism for airway inflammation includes the activation of phospholipase, an enzyme that releases arachidonic acid from membrane bound phospholipid in the mast cell. Arachidonic acid is the precursor to prostaglandins and leukotrienes, which are mediators released by several cell types, including T lymphocytes, macrophages and mast cells of the lung. These mediators contribute to bronchoconstriction, edema and mucous production. These cells also release an array of other compounds (e.g., histamine, platelet activating factor, cytokines) that contribute to the inflammatory process, which includes increased vascular permeability, increased mucus secretion and structural changes in the airways. The anti-inflammatory drugs affect 1 or more of the steps in the inflammatory process, thereby diminishing the destructive effects of chronic inflammation. Use of corticosteroids early in the disease can preserve lung function for a longer time compared with delayed use of these drugs.

Anti-inflammatory agents can be grouped in the following categories: Corticosteroids, mast cell-stabilizing agents and antileukotrienes. Specific agents in all 3 groups are used as long term therapy to prevent the onset of recurring asthma symptoms and to reduce the frequency of acute exacerbations, thus also reducing β_2-agonist usage for quick relief. Poor asthma outcomes are often a result of underuse of these agents for long term therapy.

Phospholipase A_2 catalyzes the release of membrane-bound arachidonic acid, which can be converted to prostaglandins, prostacyclin, or thromboxanes by the action of cyclooxygenase (COX) or converted to cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) by the action of 5-lipoxygenase. The leukotrienes and COX products are released in the lung by mast cells, as well as other cell types, and contribute to symptoms of asthma. The sites of action of NSAIDs and antiasthma drugs (corticosteroids, antileukotrienes, and mast cell-stabilizing agents) are shown in Fig 1-4.

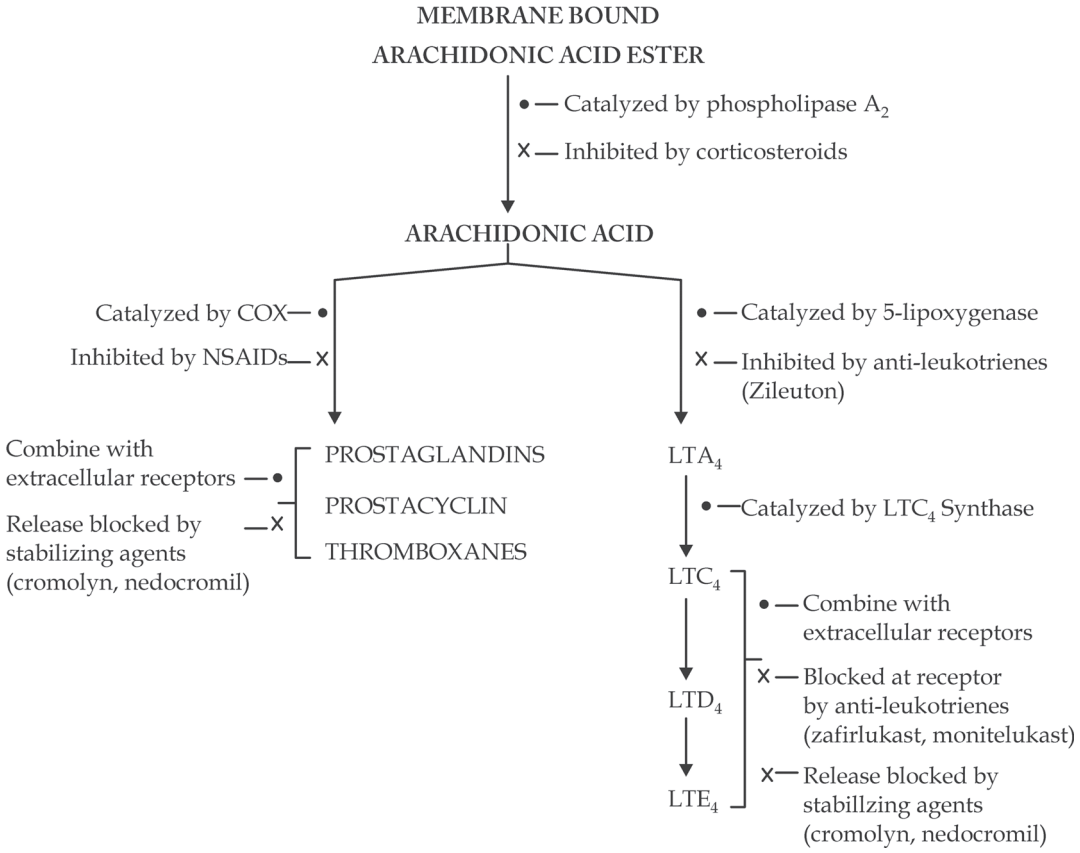


Fig 1-4: The sites of action of anti-inflammatory agents

Corticosteroids

The corticosteroids (Fig 1-5) have multiple mechanisms of action that contribute to their use in asthma. For example, they inhibit the production of prostaglandins and leukotrienes by inhibiting the action of phospholipase; inhibit cytokine gene transcription; and increase gene transcription of β receptors, which increases the responsiveness to β agonists. These drugs are effective in suppressing inflammation when used on a regular dosing schedule as long term therapy. Inhaled corticosteroids are recommended as the first line agents to control mild, moderate and severe asthma, with dosage adjustment according to the severity of the disease. Benefit from inhalation corticosteroid therapy occurs over several weeks and may require 3 months for maximal effect. Consequently, inhalation corticosteroids are not beneficial on an as-needed basis to prevent EIB or to treat acute attacks (rescue therapy). As the cornerstone of long term anti inflammatory therapy, however, inhaled corticosteroids have been shown to reduce both symptoms and the number of acute exacerbations of chronic asthma, thus also reducing the reliance on β_2 agonists. In addition, long-term use of inhaled corticosteroids is effective in managing nocturnal asthma and in providing protection against EIB symptoms. The potential for systemic side effects is minimized with long-term use of inhaled compared with oral corticosteroids and even more so with lower doses of inhaled corticosteroids. There is some concern that inhaled corticosteroids may reduce linear growth or delay growth in children, but generally the benefits of low-dose inhaled corticosteroids outweigh the risks. The most frequent side effects of inhaled corticosteroids

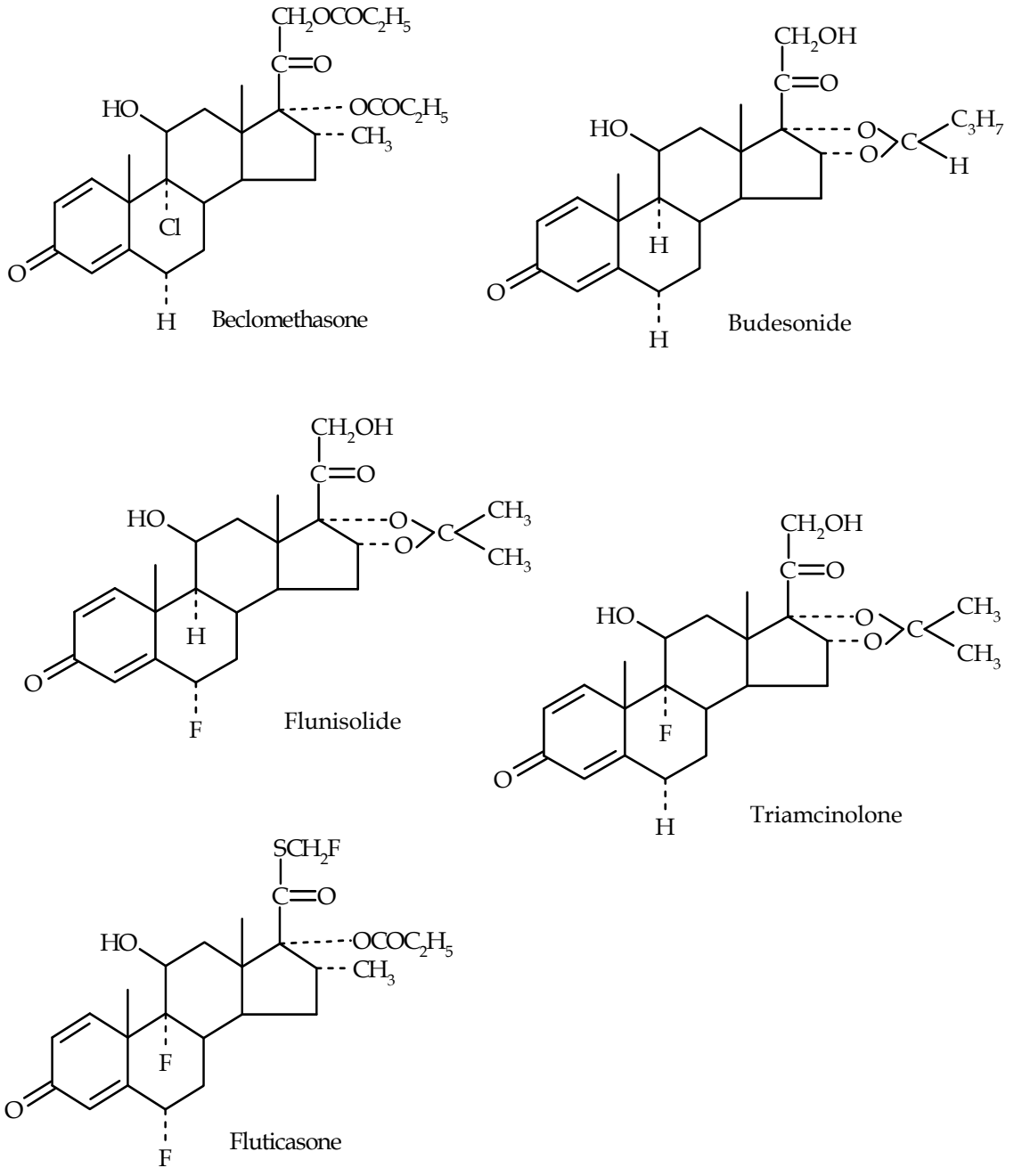


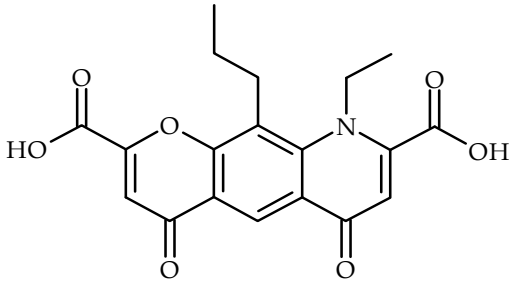
Fig 1-5: Corticosteroids

are dysphonia (hoarseness), cough and the potential for the development of oral fungal (candidiasis) infection. The incidence of these effects depends upon the total daily dose of corticosteroid in the oropharynx. Consequently, the incidence can be significantly reduced by the use of a spacer and by rinsing the mouth with water and spitting after every use; these

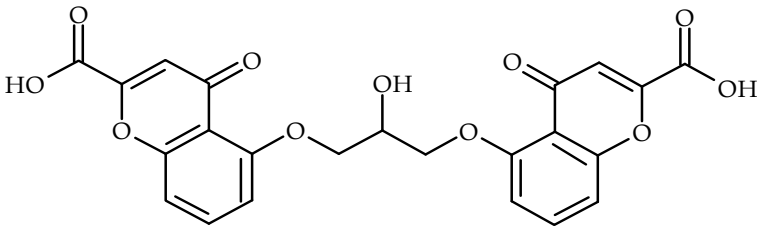
procedures also reduce the amount of corticosteroid swallowed, which may otherwise contribute to systemic effects. The cough may be due to throat irritation from additives in the MDI and is less frequent with DPI. For some asthmatic patients, once per day, low dose inhalation of corticosteroids may provide appropriate management of stable, mild to moderate asthma and may further diminish side effects. At equipotent doses, generally no corticosteroid appears to be significantly more efficacious than another. However, the 2 newest inhaled corticosteroids, budesonide and fluticasone, are potent and consequently require fewer puffs per day, thus providing an advantage for compliance in patients who require higher doses of inhaled corticosteroids. Budesonide and fluticasone also have the advantage of rapid metabolism by the liver compared with other inhaled corticosteroids, which reduces the potential for systemic side effects, especially in patients who require higher dosages. Additionally, fluticasone is poorly absorbed orally, thus further diminishing the potential for systemic side effects from drug swallowed after inhalation. Long term use of oral corticosteroids is not recommended except for the control of severe asthma. Long-term oral use for treatment of severe persistent asthma presents the potential for an array of systemic side effects, such as fluid and electrolyte abnormalities, hyperglycemia, behavioral disturbances, osteoporosis, fat redistribution, cataracts, glaucoma and growth suppression. Short term use of oral or parenteral corticosteroids, however, is useful as a beneficial adjunct to β_2 agonists for the treatment of acute exacerbations. The duration of systemic therapy for treatment of acute exacerbations depends upon the patient's response, but 3 to 10 days of therapy can reduce the effects of acute episodes. These short bursts of systemic corticosteroid therapy do not produce serious toxicities, although mood disturbances and loss of glucose control in diabetic patients may occur. Any adrenal suppression (i.e., decrease in physiological production of steroids) is readily reversible in a few days after therapy. Tapering of corticosteroid therapy is unnecessary in acute asthma therapy. Because systemic corticosteroids have an array of metabolic effects, some of which could provide an advantage in competitive sports, their use is carefully monitored. However, inhalation corticosteroids (e.g., Beclomethasone, Budesonide, Flunisolide, Fluticasone, Triamcinolone) are permissible in Olympic competition upon written notification before competition.

Mast Cell-Stabilizing Agents

Two mast cell-stabilizing agents (Fig 1-6) (also referred to as khellin derivatives) are currently available: Cromolyn and Nedocromil. These drugs are only effective by inhalation and are used primarily to prevent allergen-induced bronchospasm and EIB. They are most effective in maintaining protection when used 2 to 4 times daily and although initial improvement is observed in 1 to 2 weeks, about 4 weeks of therapy are necessary to obtain maximal benefit. Since they do not produce bronchodilation, mast cell stabilizing agents are not effective in



Nedocromil



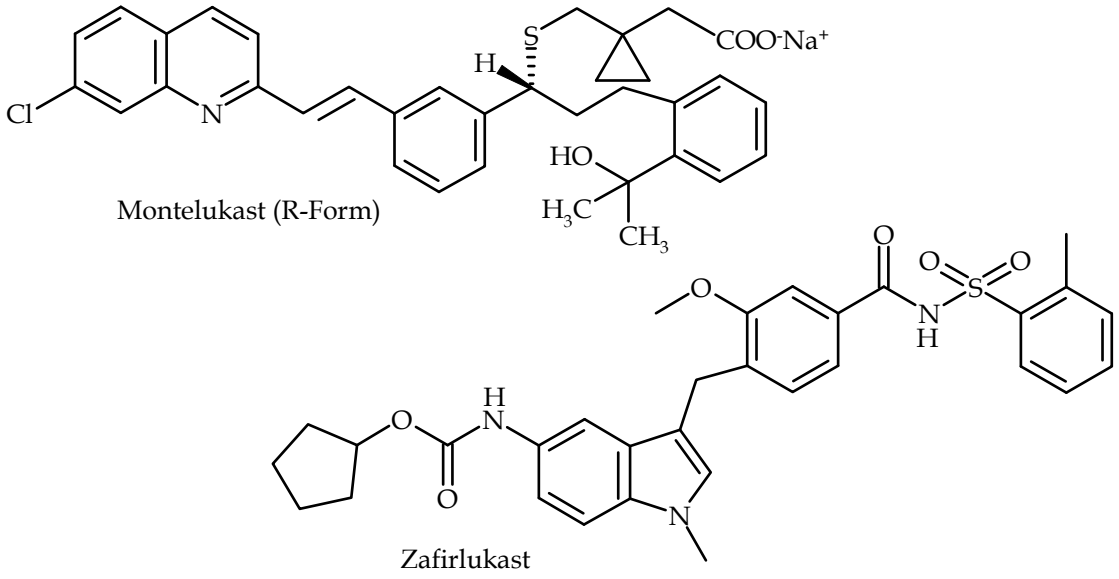
Cromolyn

Fig 1-6: Mast cell-stabilizing agents

alleviating acute asthmatic attacks. Although the exact mechanism of action of the mast cell stabilizing agents is unknown, they appear to stabilize the membrane to prevent the release of inflammatory mediators (e.g.,leukotrienes, prostaglandins, cytokines) from the cell. These mediators play an important role in the hyperreactivity response, especially as a result of exposure to allergens and exercise. At equipotent doses, cromolyn and nedocromil are equally effective. They are not as effective as inhaled corticosteroids for the prevention of asthma symptoms, but they have fewer potential side effects and virtually no systemic toxicity. These drugs are recommended for prevention of EIB and are frequently added if inhaled β_2 agonist alone before exercise is insufficient to block the bronchospasms. They are also used for the treatment of mild persistent asthma, especially in children, since they lack the potential to delay growth. Reduced effectiveness with daily use has not been demonstrated. Some patients experience minor mouth and throat irritation, which can be alleviated by drinking water immediately after use. Additionally, some patients complain that nedocromil has such a bad taste that they discontinue the therapy.

Antileukotrienes

The antileukotrienes (also known as leukotriene modifiers) (Fig 1-7) are the newest group of antiasthma drugs available. These drugs either



Montelukast (R-Form)

Zafirlukast

Fig 1-7: Antileukotrienes

decrease the synthesis of cysteinyl leukotrienes by inhibiting 5-lipoxygenase (e.g., zileuton) or by inhibiting the binding of leukotrienes at the receptor (e.g., montelukast, zafirlukast). In either case, these agents diminish the effect of leukotrienes, which contribute to broncho-constriction, edema and mucous production. Antileukotrienes are effective for long term control of mild to moderate asthma, especially in asthma induced by allergens, exercise and aspirin. These drugs are only available for oral use and are not effective to treat acute asthma attacks.

All 3 of the antileukotrienes are well tolerated orally. The most frequent side effects have been headaches and gastrointestinal disturbances. A potential problem associated with zileuton is an increase in blood alanine aminotransferase, an indicator of potential liver toxicity. Consequently, alanine aminotransferase should be checked monthly for the first 3 months and then every other month for the first year to monitor for hepatic toxicity. In addition, Churg Strauss syndrome has been associated with the use of leukotriene receptor antagonists in a few patients. This syndrome is a vasculitis that primarily affects the respiratory tract during the early stages and can develop into a life-threatening systemic vasculitis. Most, but not all, of these reports have been in patients being withdrawn from corticosteroid therapy after being maintained on a leukotriene receptor antagonist. Therefore, there is some question as to whether undiagnosed Churg-Strauss syndrome existed before antileukotriene therapy and the symptoms, which include asthma, were masked by the corticosteroid therapy.

In addition to side effects, other differences exist among the antileukotrienes. The oral absorption of zafirlukast, the first of the leukotriene receptor antagonists approved for asthma therapy, is reduced significantly by food, and, thus, the medication should be taken either 1 hour before or 2 hours after meals. It has been approved for use in children as young as 7 years old. Zafirlukast acts as an inhibitor of CYCYP450 enzymes; these enzymes are important for the metabolism (inactivation) of many drugs. Consequently, the potential exists for zafirlukast to increase the blood level of other drugs as a result of the inhibitory action on the CYP450 enzymes. Warfarin is a drug that is metabolized by these same CYP450 enzymes, and, as a result, drug-dosing modifications may be necessary when patients are taking zafirlukast concurrently with warfarin or other drugs metabolized by selected CYP450 enzymes.

Zileuton, the inhibitor of 5-lipoxygenase, is similar to zafirlukast in that it inhibits the ability of CYP450 enzymes to metabolize many drugs, such as warfarin, but also theophylline. Zileuton should not be used in children less than 12 years old. The absorption of zileuton from the gastrointestinal tract is not affected by food. Montelukast, like zafirlukast, inhibits the binding of leukotrienes to the receptor. Montelukast can be taken without regard to food, can be used to treat children at least 6 years old, and is available as a chewable tablet. Unlike zileuton and zafirlukast, montelukast does not inhibit the CYP450 enzymes and, thus, does not have the same potential for drug interactions. Since antileukotrienes are relatively new agents for the treatment of asthma, their usefulness has not been clearly identified. Some patients respond well to therapy with these agents, whereas others do not. The reason for this difference is not certain, but the agents causing the asthma symptoms in some patients may not significantly affect the leukotriene pathway; other asthmatic patients may have a genetic disposition determining their response to these drugs. For example, asthma patients with diminished expression of the 5-lipoxygenase gene may not respond adequately to drug therapy targeting that pathway alone. Alternatively, some patients with aspirin induced asthma (AIA) may have an enhanced expression of 5(S)-hydroxy-6(R)-S-glutathionyl-7,9- trans-11, 14-cis-eicosatetraenoic acid (LTC4) synthase and, therefore, respond well to leukotriene receptor antagonists.

Exercise Induced Bronchoconstriction (EIB)

Since most asthmatic patients (70% to 90%) experience some degree of EIB, the treatment of athletes for EIB is of obvious importance to the athletic trainer. Of additional importance is that

many athletes have no other history of asthma and are thus unaware that they have EIB. Symptoms of airway obstruction typically occur as a result of 5 to 8 minutes of strenuous exertion, but the time period of exercise free symptoms can be extended somewhat with a warm-up period of 15 to 30 minutes of submaximal exercise. Maximal airway obstruction occurs 5 to 15 minutes after exercise cessation. Symptoms include coughing, wheezing, prolonged recovery times after exercise and chest tightness. Airflow returns to baseline levels during the following 20 to 60 minutes. Some athletes experience a subsequent refractory period of 2 to 4 hours, in which exercise results in diminished bronchoconstriction, possibly due to depletion of mast cell mediators. A late asthmatic response 3 to 9 hours after exercise causes additional bronchoconstriction in some athletes, but is typically less severe. In athletes with EIB, inhalation of a β_2 agonist 5 to 15 minutes before exercise offers protection. If symptoms develop during exercise, puffs can be repeated. Increased use of a β_2 agonist by an athlete could indicate a need for additional anti inflammatory therapy. Use of salmeterol, a long-acting inhaled β_2 agonist, provides protection against EIB for as long as 12 hours, although long term daily use has been shown to diminish the duration of effect. Nonetheless, a long acting inhaled β_2 agonist may be specifically advantageous for the athlete who is active for longer periods. The mast cell-stabilizing agents, cromolyn and nedocromil, have also demonstrated good effectiveness in protecting against EIB when administered before exercise. The duration of protection is dose dependent but similar to that of short acting β_2 agonists (about 2 to 4 hours), and the low incidence of side effects make them appealing. In addition, cromolyn and nedocromil can alleviate the late asthmatic response and can be used in combination with a β_2 agonist for enhanced protection if 1 agent alone is not sufficient. The antileukotrienes have also demonstrated protective effects against EIB; they have the convenience of oral use and no tolerance to the protective effects with long-term use. Inhaled corticosteroid given immediately before exercise is of no benefit, but daily, long term use may reduce the severity of EIB. Factors that reduce the effectiveness of all drugs used to treat EIB are increased intensity and duration of the exercise and exercise in cooler, drier air. Inhaled corticosteroids and albuterol, terbutaline and salmeterol by inhalation are allowed in Olympic competition upon advance written notification. Cromolyn, nedocromil, ipratropium, theophylline and all the antileukotrienes are allowed by the US Olympic Committee without prior notification.

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