

# Asthma Medications: Basic Pharmacology and Use in the Athlete

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**Objective:** Asthma is a chronic disease that affects athletes at all levels of sport. Several categories of drugs, including relatively new agents, are available to treat the asthmatic patient. By understanding the appropriate uses and effects of these drugs, the athletic trainer can assist the asthmatic athlete in improving therapeutic outcomes from the asthma therapy. The appropriate use of these medications includes not only the use of the appropriate drug(s), but also appropriate technique for administration, compliance with the prescribed dosing intervals, and sufficient care to avoid side effects.

**Data Sources:** I searched MEDLINE and CINAHL from 1982 to 1999 and International Pharmaceutical Abstracts from 1990 to 1999. Terms searched were "asthma," "athlete," "athletic," "exercise-induced," "exercise," "performance," "therapy," and "treatment."

**Data Synthesis:** Bronchodilators include  $\beta_2$  agonists, anticholinergics, and methylxanthines. Of these, the  $\beta_2$  agonists used by inhalation are the drugs of choice to treat an acute asthma attack or to prevent an anticipated attack (such as before exercise). Anti-inflammatory agents include corticoste-

roids, mast cell-stabilizing agents, and antileukotrienes. Corticosteroids by inhalation are the drugs of choice for long-term treatment to curb the inflammatory process in the lung. Each of these drug categories has a unique mechanism of action. The athletic trainer who understands the appropriate use of these medications can help the athlete to obtain optimal results from drug therapy. Encouraging the athlete to comply with appropriate therapy, monitoring the effectiveness of the therapy, and recognizing the stimuli that initiate asthmatic attacks can improve the patient's therapeutic outcomes.

**Conclusions/Recommendations:** The athletic trainer has an opportunity to play a key role in ensuring that the asthmatic athlete achieves the desired outcomes from treatment. The athletic trainer can help to minimize the effect of asthma on athletic performance by ensuring that the athlete uses inhaler devices properly, is compliant with the prescribed drug therapy, monitors pulmonary function appropriately, uses medications properly before exercise, and is aware of the factors that initiate asthma symptoms.

**Key Words:** exercise induced, therapy, bronchospasm

Asthma is a chronic inflammatory disorder of the airways that affects approximately 15 million people in the United States, with an increase in incidence of over 75% from 1982 to 1995.<sup>1,2</sup> This inflammatory disease results in a hyperresponsiveness of the airways that can be initiated by exposure to various stimuli, including allergens, exercise, cold temperatures, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), viral infections, or other irritants. In addition, many asthmatic patients have nocturnal asthma, with symptoms that awaken them during the night or affect them upon awakening in the morning.<sup>3,4</sup> Symptoms of asthma include episodic wheezing, chest tightness, shortness of breath, and cough. A discussion of the pathophysiology of asthma is available elsewhere.<sup>3-5</sup>

Drug therapy plays an important role in the proper management of asthma. However, 1 study<sup>6</sup> revealed that fewer than 20% of asthmatic patients received appropriate drug therapy.<sup>6</sup> Inadequate patient education, poor patient compliance, and a communication gap between the patient and health care providers are major causes for inadequate therapeutic outcomes.<sup>7-9</sup> Athletic trainers have the opportunity to influence these areas of deficiency and, thus, improve therapeutic outcomes. Consequently, it is important that athletic trainers have

a basic understanding of the effects and appropriate use of the drugs available to treat athletes who have asthma, as well as knowledge of other related factors that may have an impact on the performance of these athletes.

## GOALS OF THERAPY

The National Heart, Lung, and Blood Institute (NHLBI) established general goals of asthma therapy<sup>10</sup>:

- Prevent chronic asthma symptoms and asthma exacerbations during the day and night.
- Maintain normal activity levels, including exercise and other physical activities.
- Have normal or near-normal lung function.
- Be satisfied with the asthma care received.
- Have no or minimal side effects while receiving optimal medications.

For the athlete, whether casual or competitive, maintenance of normal activity levels includes athletic performance, but a recent survey<sup>7</sup> found that 48% of people with asthma say their asthma limits their ability to take part in sports or recreation. Ultimately, the athlete must determine an acceptable response from therapy, but to maximize the effectiveness of the therapy, the athletic trainer can help ensure that the athlete is compliant with the medication dosing schedules, is using inhaler devices appropriately, and is adequately monitoring the effectiveness of drug therapy. To achieve the best combination of medication and dosing, athletes not ideally managed may require a referral

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to their prescribing physician to adjust the selection of drugs, drug dose, dosing interval, or route of administration. The general concepts regarding these and other pharmacologic principles are described elsewhere.<sup>11</sup>

Another goal of therapy is to ensure that the athlete is not using any asthma medication banned by an agency regulating the athlete's participation. As discussed later, the US Olympic Committee, for example, only allows the use of some asthma medications by inhalation to minimize the systemic effects that may impart an advantage to the athlete (eg, central nervous system stimulation).

## INHALERS AND PULMONARY FUNCTION TESTS

Inhalation of antiasthmatic medication provides a topical application of the drug in the airways and is the most effective route to administer the drugs of choice for quick relief of acute attacks (ie,  $\beta_2$  agonists) and for long-term therapy (ie, corticosteroids). The most popular device used for inhalation of these drugs is the metered dose inhaler (MDI). These devices contain the drug in a pressurized container with a metering valve. When the device is pressed appropriately, it releases a propellant, which forces a metered amount of drug as an aerosol into the patient's mouth. The drug is either in solution or a suspended micronized powder. One disadvantage of the MDI is that the patient must be skilled in coordinating the activation of the MDI with inhalation to maximize delivery of drug to the lung. Even with good technique, only 10% to 20% of the drug reaches the lungs; most of the drug is deposited in the oropharynx.<sup>12-14</sup> A spacer (or holding chamber) is a device that attaches to the MDI. The inhaler is discharged into the spacer, and the patient inhales from it. Some propellant evaporates as it travels through the spacer, resulting in smaller particles that have a better chance of reaching the lung. The spacer also reduces the speed of the drug so that some of the larger particles lose their momentum before reaching the oropharynx. When spacers are used with inhaled corticosteroids, the diminished amount of oropharyngeal deposition of the drug results in a lower incidence of hoarseness and fewer oral candidiasis infections (thrush). Rinsing the mouth with water and spitting after use of the inhaler also may reduce these localized side effects.<sup>4,12,14</sup> The design of some spacers more effectively facilitates an increase in the number of particles reaching the lung.<sup>15</sup> Use of a spacer also eliminates the need to precisely coordinate inhalation with activation of the MDI. Therefore, use of a spacer with the MDI decreases the precision necessary, improves inhaler technique, and increases the delivery of drug to the lungs in those patients who have difficulty achieving proper technique without the spacer.<sup>16-18</sup> Spacers are especially recommended for asthmatics who cannot master hand-lung coordination, have developed local side effects, or require a large dose of the inhaled drug.<sup>19</sup>

Dry powders can be inhaled with the use of a dry powder inhaler (DPI). The powdered drug is placed in the DPI in a

capsule or other package form, and the inhaler is used to break open the package. There is no propellant, but the process of inhalation through the inhaler causes the powder to reach the lung. This eliminates the need for hand-lung coordination but requires a higher inspiratory flow. DPIs tend to cause more drug to be deposited at the oropharynx and, thus, may necessitate patients rinsing their mouths, especially when using corticosteroids.

Nebulizers are used to deliver an aerosol of drug to the patient's lungs, but these are larger devices and are primarily used in hospitals and clinics and in homes for parents to administer drugs to young patients. Nebulizers use liquid drug and a stream of compressed air that forms the droplets of drug, which are inhaled during normal breathing by the patient. No hand-lung coordination is needed, and less drug is deposited in the mouth.

Another device that facilitates appropriate drug therapy is a peak flow meter (PFM), which measures the peak expiratory flow (PEF). The purpose of the PFM is to assess the patient's pulmonary function as a means of monitoring the effectiveness of the drug therapy. The handheld device can be used as a daily routine check of pulmonary function. The patient's personal best is established over 2 to 3 weeks of good asthma control. All other PFM tests are then compared with that value. Daily results can be used to evaluate the response to adjustments in acute, as well as long-term, therapy or to signal that an acute attack is imminent even before symptoms arise. For example, if the PEF is 80% to 100% of the personal best, the existing treatment should be maintained. If the PEF is 50% to 80% of the personal best, the treatment should be adjusted, as previously determined by the physician. A medical alert is indicated if the PEF is less than 50%; a short-acting inhaled bronchodilator should be used and medical attention obtained immediately. The NHLBI recommends the use of the PFM for patients with moderate to severe persistent asthma or a history of severe exacerbations as a means to obtain optimal drug therapy outcomes.<sup>3,10</sup>

Another pulmonary function test is the forced expiratory volume in 1 second ( $FEV_1$ ). This can be measured using a forced expiratory spirometer, which allows a determination of the rate of forced expiratory volume after maximal inspiration. A comparison of  $FEV_1$  with normal predicted values can be part of the criteria used to determine the severity of the asthma. Table 1 is the classification of the severity of asthma as defined by the NHLBI.<sup>10</sup> Long-term therapy is modified based upon these classifications (Table 2).<sup>10</sup> Patients at any level of severity may have acute exacerbations that range from mild to severe.

## CATEGORIES OF ASTHMA DRUGS

Drugs used to treat asthma can be grouped in 2 broad pharmacologic categories: bronchodilators and anti-inflammatory agents. Within these categories, subgroups exist based

**Table 1. Classification of Asthma Severity: Clinical Features Before Treatment<sup>10</sup>**

Classification	Days with Symptoms	Nights with Symptoms	PEF or $FEV_1$ *	PEF Variability
Step 4 (Severe persistent)	Continual	Frequent	$\geq 60\%$	$> 30\%$
Step 3 (Moderate persistent)	Daily	$\geq 5$ /month	$> 60\%$ to $< 80\%$	$> 30\%$
Step 2 (Mild persistent)	3 to 6/week	3 to 4/month	$\geq 80\%$	20 to 30%
Step 1 (Mild intermittent)	$\leq 2$ /week	$\leq 2$ /month	$\geq 80\%$	$< 20\%$

\* Percentage of patient's best PEF or percentage of predicted values for  $FEV_1$ .

**Table 2. Stepwise Approach for Managing Asthma in Adults and Children >5 Years of Age<sup>10</sup>**

Asthma Classification	Daily Medication(s) (preferred treatments are in bold)
Step 4 (Severe persistent)	<ul style="list-style-type: none"> <li>• <b>Anti-inflammatory: inhaled corticosteroid (high dose)</b> and</li> <li>• Long-acting bronchodilator: <b>long-acting inhaled <math>\beta_2</math> agonist</b>, sustained-release theophylline, or long-acting <math>\beta_2</math> agonist tablets and</li> <li>• Corticosteroid tablets or syrup long term; make repeated attempts to reduce systemic corticosteroid and maintain control with high-dose inhaled corticosteroid</li> </ul>
Step 3 (Moderate persistent)	<ul style="list-style-type: none"> <li>• <b>Anti-inflammatory: inhaled corticosteroid (medium dose)</b> or</li> <li>• <b>Inhaled corticosteroid (low to medium dose)</b> and add a long-acting bronchodilator, especially for nighttime symptoms: <b>long-acting inhaled <math>\beta_2</math> agonist</b>, sustained-release theophylline, or long-acting <math>\beta_2</math>-agonist tablets</li> </ul> <p>If needed:</p> <ul style="list-style-type: none"> <li>• Anti-inflammatory: <b>inhaled corticosteroids (medium to high dose)</b> and</li> <li>• Long-acting bronchodilator, especially for nighttime symptoms; <b>long-acting inhaled <math>\beta_2</math> agonist</b>, sustained-release theophylline, or long-acting <math>\beta_2</math>-agonist tablets</li> </ul>
Step 2 (Mild persistent)	<ul style="list-style-type: none"> <li>• <b>Anti-inflammatory: either inhaled corticosteroid (low dose)</b> or</li> <li>• <b>Cromolyn or nedocromil</b> (children usually begin with either cromolyn or nedocromil)</li> <li>• Sustained-release theophylline to serum concentration of 5 to 15 mcg/mL is an alternative, but not preferred, therapy. Zafirlukast or zileuton may also be considered for those <math>\geq 12</math> years old, although their use in therapy is not fully established.</li> </ul>
Step 1 (Mild intermittent)	<ul style="list-style-type: none"> <li>• No daily medication needed.</li> </ul>

\* For quick relief for all patients, short-acting bronchodilator: inhaled  $\beta_2$  agonist (2 to 4 puffs) as needed for symptoms. Intensity of treatment will depend on severity of exacerbation. Step down: Review treatment every 1 to 6 months. Gradually decrease treatment to the least medication necessary to maintain control. Step up: If control is not maintained, consider step up. Inadequate control is indicated by increased use of short-acting  $\beta_2$  agonists. Review patient inhaler technique, compliance, and environmental avoidance of allergens or other precipitant factors.

upon the mechanism of action of the drug. According to the NHLBI recommendations, asthmatic patients with any level of persistent asthma require at least 1 drug from each pharmacologic category.<sup>3</sup> From a therapy viewpoint, asthma drugs can be categorized differently: as drugs aimed at quick relief of acute asthma attacks or as drugs for long-term therapy to prevent recurrent attacks.

## BRONCHODILATORS

### $\beta_2$ Agonists

$\beta_2$  agonists are bronchodilators that act on the bronchial smooth muscle by combining with  $\beta_2$ -adrenergic receptors to cause bronchial muscle relaxation and, thus, bronchodilation. Bronchodilation occurs regardless of the mechanism for the bronchial constriction, and  $\beta_2$  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  $\beta_2$ -adrenergic receptors, whereas the heart contains both  $\beta_1$  receptors and  $\beta_2$  receptors. Consequently, no therapeutic rationale exists for using nonselective  $\beta_2$  agonists (ie, agents that are not selective for  $\beta_2$  receptors relative to  $\beta_1$  receptors); such agents (eg, isoproterenol, metaproterenol, epinephrine) have an increased incidence of sympathetic stimulatory effects, including increased heart rate and force of contraction.<sup>4,20</sup> Since these cardiac effects could improve exercise performance, nonselective  $\beta$  agonists are not allowed in Olympic competition, and only selected  $\beta_2$  agonists (albuterol, terbutaline, salmeterol) by inhalation are allowed upon written notification before competition.<sup>21</sup> The  $\beta$ -agonist components of over-the-counter oral and inhalation asthma products are nonselective and, thus, a poor choice to treat asthma.<sup>22</sup>

Inhaled  $\beta_2$  agonists are the only agents providing an immediate response for acute asthma attacks (rescue therapy).<sup>20</sup>

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.<sup>3,23</sup> After inhalation of short-acting  $\beta_2$  agonists, onset of action is usually within 5 minutes, and maximal bronchodilation occurs within about 15 minutes.<sup>24,25</sup> 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.<sup>4,25</sup> Table 3 lists some short-acting  $\beta_2$ -adrenergic agonists and a typical adult dose. When given at equipotent doses, all of the  $\beta_2$  agonists will produce the same intensity of bronchodilation; their main difference is the duration of action.<sup>4</sup> 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  $\beta_2$  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 clearly understand that it is not effective for treatment of acute bronchospasms and that the dose should not exceed 2 puffs every 12 hours.<sup>3,24</sup> 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  $\beta_2$  agonist.

Regularly scheduled, daily use of a short-acting  $\beta_2$  agonist is generally not recommended, since there is no apparent advantage over use on an as-needed basis.<sup>26,27</sup> If the frequency of  $\beta_2$ -agonist use increases or if use exceeds 1 canister of  $\beta_2$  agonist (eg, 200 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  $\beta_2$  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).<sup>3,4,27,28</sup> Regular use of a long-acting  $\beta_2$  agonist is recommended for some patients with moderate to severe asthma,

**Table 3. Characteristics of Some Drugs for Relief of Acute Symptoms<sup>3,20,26</sup>**

Generic Name	Trade Name	Category	Formulation; Typical Adult Dosage
Albuterol	Ventolin	$\beta_2$ agonist, SA*	MDI <sup>†</sup> ; 2 puffs (90 mcg each) tid to qid prn <sup>‡</sup> DPI <sup>§</sup> ; 1 to 2 capsules (200 mcg each) qid to q4h prn
Bitolterol	Tornalate	$\beta_2$ agonist, SA	MDI; 2 puffs (370 mcg each) tid to qid
Ipratropium	Atrovent	Anticholinergic	MDI; 2–3 puffs (18 mcg each) qid
Methylprednisolone	Medrol	Corticosteroid	Oral; 40 to 60 mg/day for 3 to 10 days
Pirbuterol	Maxair	$\beta_2$ agonist, SA	MDI; 2 puffs (200 mcg each) tid to qid
Prednisolone	Prelone	Corticosteroid	Oral; 40 to 60 mg/day for 3 to 10 days
Prednisone	Prednisone	Corticosteroid	Oral; 40 to 60 mg/day for 3 to 10 days
Terbutaline	Brethaire	$\beta_2$ agonist, SA	MDI; 2 puffs (200 mcg each) tid to qid prn

\* SA, short acting.

† MDI, metered dose inhaler.

‡ prn, as needed for relief.

§ DPI, dry powder inhaler.

especially to control nighttime symptoms, in conjunction with corticosteroid therapy.<sup>3</sup>

The most frequent side effects from inhalation of  $\beta_2$  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  $\beta_2$  agonists can be increased severalfold 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  $\beta_2$  agonist, adjustment of the anti-inflammatory therapy may be required.

Albuterol, like many drugs, including all currently available selective  $\beta_2$  agonists, 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 contribute to some adverse effects (eg, 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 FEV<sub>1</sub> values than albuterol, with a lower incidence of side effects and at a smaller dose. *R* isomers of other  $\beta_2$  agonists are also being investigated.<sup>29–31</sup>

### Anticholinergics

Another group of bronchodilators is the anticholinergic agents. 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.<sup>4,20</sup> The use of these agents has diminished over the years as the inhaled  $\beta_2$  agonists have become available and because these agents cause significant anticholinergic side effects (eg, 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.

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  $\beta_2$

agonists, and peak bronchodilation 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  $\beta_2$  agonist. It has limited effectiveness in preventing EIB.<sup>23,24,26</sup>

### Methylxanthines

Theophylline is a methylxanthine bronchodilator. Caffeine and theobromine are also members of this chemical group, but they are not used therapeutically to treat asthma since they have only a mild bronchodilating effect. The mechanism by which theophylline relaxes bronchial smooth muscle is not clearly understood, but the inhibition of phosphodiesterase and subsequent increase in intracellular cyclic adenosine monophosphate may be a contributor.<sup>4</sup>

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 (eg, erythromycin, cimetidine, zileuton) to alter the metabolism rate of theophylline by the liver, thus intensifying the need for blood-level monitoring.<sup>4,12,32</sup>

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.<sup>3</sup> For patients who do not respond to  $\beta_2$ -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.<sup>33</sup>

### ANTI-INFLAMMATORY AGENTS

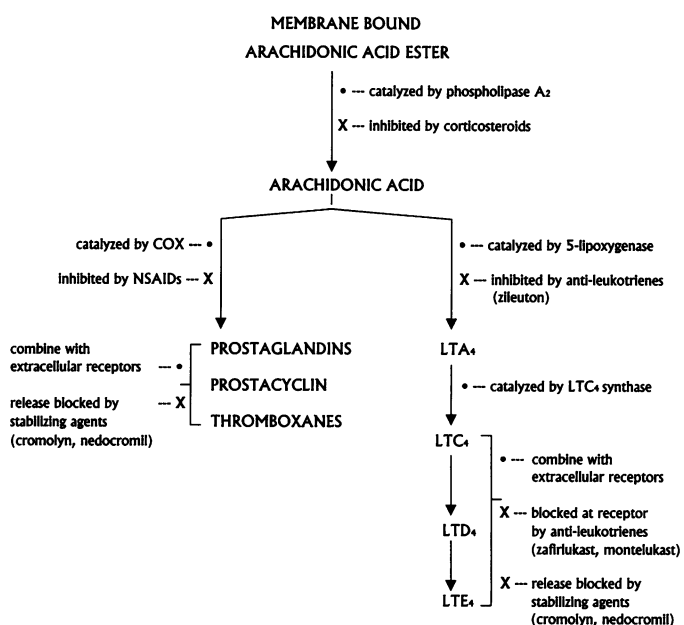
Since asthma is a chronic inflammatory disease, long-term use of anti-inflammatory agents is an important part of therapy

to control inflammation 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 (Figure). 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.<sup>13</sup> These cells also release an array of other compounds (eg, 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.<sup>13</sup>

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  $\beta_2$ -agonist usage for quick relief. Poor asthma outcomes are often a result of underuse of these agents for long-term therapy.<sup>6</sup>

## Corticosteroids

The corticosteroids 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



**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.**

action of phospholipase; inhibit cytokine gene transcription; and increase gene transcription of  $\beta$  receptors, which increases the responsiveness to  $\beta$  agonists.<sup>13,19</sup> 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.<sup>3</sup> Benefit from inhalation corticosteroid therapy occurs over several weeks and may require 3 months for maximal effect.<sup>13</sup> 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  $\beta_2$  agonists. In addition, long-term use of inhaled corticosteroids is effective in managing nocturnal asthma and in providing protection against EIB symptoms.<sup>13,20,33,34</sup>

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.<sup>13,20,35</sup> 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.<sup>3</sup> The most frequent side effects of inhaled corticosteroids are dysphonia (hoarseness), cough, and the potential for the development of oral fungal (candidiasis) infection.<sup>13</sup> 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.<sup>13,14,19</sup> The cough may be due to throat irritation from additives in the MDI and is less frequent with DPI.<sup>13</sup> 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.<sup>36</sup>

At equipotent doses, generally no corticosteroid appears to be significantly more efficacious than another.<sup>13,20</sup> 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.<sup>13,14</sup>

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  $\beta_2$  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 (ie, decrease in physiologic production of steroids) is readily reversible in a few days after therapy.<sup>4,20</sup> Tapering of corticosteroid therapy is unnecessary in acute asthma therapy.<sup>20,37</sup>

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 (eg, beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone) are permissible in Olympic competition upon written notification before competition.<sup>21</sup>

### Mast Cell-Stabilizing Agents

Two mast cell-stabilizing agents (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.<sup>3,4</sup> Since they do not produce bronchodilation, mast cell-stabilizing agents are not effective in 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 (eg, 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.<sup>4,12,20</sup>

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.<sup>3,4</sup> These drugs are recommended for prevention of EIB and are frequently added if inhaled  $\beta_2$  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.<sup>10,33</sup> 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) are the newest group of antiasthma drugs available. As shown in the Figure, these drugs either decrease the synthesis of cysteinyl leukotrienes by inhibiting 5-lipoxygenase (eg, zileuton) or by inhibiting the binding of leukotrienes at the receptor (eg, montelukast, zafirlukast).<sup>26,38,39</sup> In either case, these agents diminish the effect of leukotrienes, which contribute to bronchoconstriction, 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.<sup>4,26,40</sup> These drugs are only available for oral use and are not effective to treat acute asthma attacks.<sup>39,41</sup>

Use of these agents may allow for decreased dose of corticosteroids and decreased reliance on  $\beta$ -agonist inhalers.<sup>38</sup>

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.<sup>39</sup> 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.<sup>39,42-45</sup> 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 P450 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 P450 enzymes. Warfarin is a drug that is metabolized by these same P450 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 P450 enzymes.<sup>32,39</sup>

Zileuton, the inhibitor of 5-lipoxygenase, is similar to zafirlukast in that it inhibits the ability of P450 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.<sup>26</sup>

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 cytochrome P450 enzymes and, thus, does not have the same potential for drug interactions.<sup>26,38,46</sup>

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.<sup>47-49</sup> For example, asthma patients with diminished expression of the 5-lipoxygenase gene may not respond adequately to drug therapy targeting that pathway alone.<sup>47</sup> Alternatively, some patients with aspirin-induced asthma (AIA) may have an enhanced expression of 5(S)-hydroxy-6(R)-S-glutathionyl-7,9-

**Table 4. Examples of Over-the-Counter Products Containing Aspirin or Other NSAIDs<sup>22</sup>**

Brand-Name Product	Analgesic Component
Actron	Ketoprofen
Advil Cold & Sinus	Ibuprofen
Aleve	Naproxen
Alka-Seltzer Plus Sinus Medicine	Aspirin
Anacin	Aspirin
Arthritis Pain Formula	Aspirin
Ascriptin Regular Strength	Aspirin
BC Sinus-Cold	Aspirin
Buffaprin	Aspirin
Buffasal	Aspirin
Buffets II	Aspirin
Buffinol	Aspirin
Cope	Aspirin
Dristan Sinus	Ibuprofen
Ecotrin Regular Strength	Aspirin
Excedrin Extra Strength	Aspirin
Excedrin Migraine	Aspirin
Motrin IB	Ibuprofen
Nuprin	Ibuprofen
Orudis KT	Ketoprofen
Ultraprin	Ibuprofen
Valprin	Ibuprofen
Vanquish	Aspirin

*trans*-11,14-*cis*-eicosatetraenoic acid (LTC<sub>4</sub>) synthase and, therefore, respond well to leukotriene receptor antagonists.<sup>49</sup>

## THERAPY CONSIDERATIONS

### General Principles

Several nondrug measures should always be a part of asthma therapy. Physical training, for example, has been shown to decrease the severity of asthmatic symptoms other than EIB and to reduce the number of emergency room visits.<sup>50-52</sup> Adequate education concerning the proper use of the MDI and the PFM can also reduce symptoms of asthma. A seemingly obvious nondrug measure is to avoid contact with stimuli that have the potential to initiate asthma symptoms. These causative agents include animal allergens from pets, indoor fungi, house dust mites, tobacco smoke, viral infections, outdoor

allergens such as pollen, and occupational exposure to chemical irritants. Patients can be tested to assess their sensitivity to various allergens and irritants. Athletes who exercise outdoors and are hyperresponsive to outdoor allergens can reduce their exposure to these allergens by adjusting their exercise routine to an indoor, air-conditioned environment during peak pollen season or by avoiding outdoor exercise during midday, when allergen levels are typically higher.<sup>3</sup>

Along with animal and environmental stimuli of hyperresponsiveness in the asthmatic patient, from 3% to 39% of asthmatic patients have AIA. The incidence of AIA increases with age and with asthma severity.<sup>4,10,12,49</sup> These asthmatics are also likely to be sensitive to other NSAIDs. Care should be taken when selecting over-the-counter analgesic products, since NSAIDs are components of many such products (Table 4).<sup>22</sup> Aspirin desensitization is an option for people who require routine therapy with NSAIDs. The use of acetaminophen may be effective for treatment of minor pain for athletes with AIA. However, in 1 study,<sup>53</sup> one third of asthmatics with AIA who were treated with 1000 to 1500 mg of acetaminophen experienced some degree of cross-reaction with acetaminophen. The bronchospastic reactions were dose dependent and milder than when induced by aspirin. Consequently, the authors indicate that the use of 650 mg or less of acetaminophen poses only a small risk of bronchospasm. In addition to being a major ingredient in many over-the-counter analgesic products, acetaminophen is also a component of many cold, cough, and allergy medications, although the amount of acetaminophen is usually not over 650 mg per dosage unit.<sup>22</sup>

When reviewing the athlete's asthma drug therapy, it is beneficial to group the drugs in therapeutic categories of agents either for quick relief (Table 3) or for long-term therapy to prevent recurring attacks (Table 5). As indicated in Table 2, the NHLBI guidelines<sup>10</sup> recommend a stepwise course of long-term therapy based upon the severity of the asthma. The initial objective of this therapy is to gain control of the asthma symptoms by using sufficiently aggressive drug therapy. Subsequently, treatment should be reviewed and drug therapy gradually reduced to the least medication necessary to maintain control. For mild to moderate persistent asthma, use of a short-acting  $\beta_2$  agonist on a daily basis or more than 3 to 4 times in 1 day indicates a need for a step up in therapy, assuming the patient is compliant with prescribed therapy, has

**Table 5. Characteristics of Some Drugs for Long-Term Asthma Control<sup>2,20,26</sup>**

Generic Name	Trade Name	Category	Formulation; Typical Adult Dosage
Albuterol	Proventil	$\beta_2$ agonist, LA*	Oral; extended release; 4 mg q12h
Beclomethasone	Beclvent	Corticosteroid	MDI; 6 to 10 puffs/day (84 mcg each)
Budesonide	Pulmicort Turbuhaler	Corticosteroid	DPI; 2 to 3 inhalations/day (200 mcg each)
Cromolyn	Intal	Mast cell stabilizer	MDI; 2 to 4 puffs (800 mcg each) tid to qid
Flunisolide	AeroBid	Corticosteroid	MDI; 4 to 8 puffs/day (250 mcg each)
Fluticasone	Flovent	Corticosteroid	MDI; 2 to 6 puffs/day (110 mcg each)
Fluticasone	Flovent Rotadisk	Corticosteroid	DPI; 3 to 6 inhalations/day (100 mcg each)
Montelukast	Singulair	Antileukotriene	Tablets; 10 mg qd
Nedocromil	Tilade	Mast cell stabilizer	MDI; 2 to 4 puffs (1.75 mg each) bid to qid
Salmeterol	Serevent	$\beta_2$ agonist, LA	MDI; 2 puffs (21 mcg each) q12h
Salmeterol	Serevent Diskus	$\beta_2$ agonist, LA	DPI; 1 inhalation (50 mcg) every 12 hours
Theophylline	Theo-Dur	Methylxanthine	Oral; extended release; 300 mg bid
Triamcinolone	Azmacort	Corticosteroid	MDI; 10 to 20 puffs/day (100 mcg each)
Zafirlukast	Accolate	Antileukotriene	Tablets; 20 mg bid
Zileuton	Zyflo	Antileukotriene	Tablets; 600 mg qid

\* LA, long acting.



appropriate inhaler technique, and is avoiding known precipitating factors. Inhaled  $\beta_2$  agonists are the drugs of choice for quick relief of acute attacks, whereas inhaled corticosteroids are the drugs of choice for long-term control. The addition of another anti-inflammatory agent to inhalation corticosteroid therapy may allow for a reduction of the corticosteroid dose or may be necessary without reduction of the corticosteroid dose to achieve desired control.

### 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.<sup>4,12,54</sup> Of additional importance is that many athletes have no other history of asthma and are thus unaware that they have EIB.<sup>24</sup> 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.<sup>3,23,54</sup> 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.<sup>4,54</sup> A late asthmatic response 3 to 9 hours after exercise causes additional bronchoconstriction in some athletes, but is typically less severe.<sup>24</sup>

In athletes with EIB, inhalation of a  $\beta$  agonist 5 to 15 minutes before exercise offers protection. If symptoms develop during exercise, puffs can be repeated.<sup>3,23,24</sup> Increased use of a  $\beta_2$  agonist by an athlete could indicate a need for additional anti-inflammatory therapy. Use of salmeterol, a long-acting inhaled  $\beta_2$  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.<sup>28</sup> Nonetheless, a long-acting inhaled  $\beta_2$  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  $\beta_2$  agonists (about 2 to 4 hours), and the low incidence of side effects make them appealing.<sup>4,25</sup> In addition, cromolyn and nedocromil can alleviate the late asthmatic response and can be used in combination with a  $\beta_2$  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.<sup>39,55</sup> 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.<sup>23</sup>

Inhaled corticosteroids and albuterol, terbutaline, and salmeterol by inhalation are allowed in Olympic competition upon advance written notification.<sup>21</sup> Cromolyn, nedocromil, ipratropium, theophylline, and all the antileukotrienes are allowed by the US Olympic Committee without prior notification.<sup>26</sup> The

National Collegiate Athletic Association permits most asthma medications except for oral  $\beta_2$  agonists.<sup>26</sup>

### Considerations for the Athletic Trainer

The athletic trainer has the opportunity to play a key role in ensuring that the asthmatic athlete achieves the desired therapeutic outcomes, including minimizing the effect of asthma on athletic performance. To accomplish this, the athletic trainer should consider the following:

- Ensure that asthmatic athletes are aware that asthma is a chronic inflammatory disease requiring compliance to the prescribed drug therapy to obtain maximal benefit (eg, not skipping doses or taking daily medication on an as-needed basis).
- Be certain that athletes are using the inhaler device(s) properly, including a spacer if good inhalation technique is not being achieved with the MDI.
- Remind athletes of the appropriate use of a prescribed  $\beta_2$ -agonist or mast cell-stabilizing agent (or both) before exercise for EIB and the value of 15 to 30 minutes of submaximal warm-up activity.
- Refer the athlete to a physician if the asthma is not being controlled at an acceptable level. Be especially alert to overuse of  $\beta_2$ -agonist inhalers, which may signal the need for adjustment in long-term anti-inflammatory therapy.
- Observe the routine use of the PFM in athletes with moderate to severe asthma, ensure they understand the importance of tracking their PEF, assist them in monitoring the results, and know the predetermined plan for making appropriate adjustments if PEF is below 80% of the athlete's personal best.
- Be sure that athletes are aware of the stimuli that have the potential to initiate asthmatic symptoms and that cooler, drier air and more strenuous exercise increase the severity of EIB.
- Be alert to athletes not diagnosed with EIB but experiencing symptoms, who may require evaluation for diagnosis and treatment.
- Ensure that athletes with AIA understand that aspirin and other NSAIDs, which can also be found in over-the-counter combination products, must be avoided.
- Monitor each athlete's drug therapy to ensure that the medications being used are not banned at the athlete's level of competition.
- Reassure asthmatic athletes that proper therapy can allow them to compete at the level of nonasthmatic patients. In the 1996 Summer Olympic Games, the US Olympic athletes who had been told that they had asthma or had taken asthma medications fared as well as nonasthmatic athletes in winning team and individual medals.<sup>56</sup>

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