

PHARMACOLOGIC TREATMENT OF ASTHMA

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INTRODUCTION

This summary of the drug treatment of asthma emphasizes on the separation of medications into controllers and relievers, and the use of a step approach to treatment. Reliever medications are those that act quickly to relieve bronchoconstriction and its accompanying symptoms. Controller medications are those that are used daily to achieve and maintain control of persistent asthma. This summary will also focus on the issues about asthma that are of particular concern to the primary care practitioner.

RESCUE DRUGS

a) Rapid acting inhaled β_2 -agonists

Examples include salbutamol (ventolin), terbutaline (bricanyl). They relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability and may modulate mediator release from mast cells. They are the treatment of choice for acute exacerbations of asthma. Increased use or even daily use is a warning of deterioration of asthma and indicates the need to institute or intensify regular anti-inflammatory therapy. Side effects, cardiovascular stimulation, muscle tremor and hypokalemia are less frequent with inhaled than oral therapy.

b) Inhaled anticholinergics

An example is inhaled ipratropium bromide (Atrovent). They are bronchodilators that block the effect of acetylcholine released from cholinergic nerves in the airways, resulting in bronchodilation by reducing vagal cholinergic tone. In asthma, inhaled anticholinergics are less potent bronchodilators than inhaled β_2 -agonists. Side effects are a bitter taste and dry mouth.

c) Systemic steroids

They can be administered orally or parenterally. Onset of action is 4-6 hrs. They prevent progression of asthma exacerbation and decrease hospitalization or early relapse after emergency treatment. They are usually given 3-10 days following initial treatment. The usual dose is 0.5-1 mg/kg prednisolone.

ANTI-INFLAMMATORY DRUGS

a) Inhaled steroids

Currently, they are the most effective anti-inflammatory medications for the treatment of asthma. They have proven efficacy in improving lung function, decreasing airway responsiveness, reducing symptoms, reducing frequency and severity of exacerbations and improving quality of life. The various preparations differ in potency and bioavailability with 200-500 mcg Beclomethasone (Becotide) equal to 200-400 mcg Budesonide (Pulmicort) or 100-250 mcg Fluticasone (Flixotide). Side effects include oropharyngeal candidiasis, dysphonia and coughing from upper airway irritation but these effects may be prevented by using spacer devices. Mouth washing after inhalation may also prevent candidiasis.

b) Cromones eg Nedocromil sodium and sodium cromoglycate

The mechanism of action is thought to be the inhibition of IgE mediator release from mast cells. In adults with asthma, nedocromil sodium improves symptoms and lung function and reduces airway responsiveness, although it is less effective than inhaled steroids. A 4-6 week trial is required to determine efficacy in individual patients. Side effects of these drugs are minimal.

c) Long acting inhaled β_2 -agonists (LABA)

Agents include formoterol (Oxis) and Salmeterol (Serevent). These drugs have bronchodilator action (more than 12 hrs compared to 4 hrs for rapid acting inhaled β_2 agonists) and relax airway smooth muscle, enhance mucociliary clearance, decrease vascular permeability and possibly modulate mediator release. Such drugs are often given alone to prevent exercise-induced bronchospasm.

d) Inhaled combination drugs (steroids and LABA)

The greater efficacy of adding an inhaled long acting β_2 agonist to an inhaled steroid than increasing the dose of inhaled steroid has led to the development of fixed dose combination inhalers (eg fluticasone plus salmeterol or budesonide plus formoterol). Fixed combination inhalers are also more convenient for patients, increasing compliance and are less expensive.

e) Leukotriene modifiers

The classic leukotriene modifier Montelukast is a cysteinyl leukotriene 1 receptor antagonist. These drugs have a small and variable bronchodilator effect, reduces symptoms, improve lung function and reduce asthma exacerbations. The effects of leukotriene modifiers are less than low dose inhaled steroids. Data shows that leukotriene modifiers used

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as add-on therapy reduce the dose of inhaled steroids required. However, they are less effective than LABA. The greatest advantage of these drugs is their tablet preparation. Aspirin sensitive asthma patients specifically do well with such therapy.

f) Methylxanthines

Theophylline is a bronchodilator that may have extrapulmonary effects, including anti-inflammatory effects. At low doses, it may be used in patients with milder disease and as an add-on therapy to low or high doses of inhaled steroids when further control is required. Monitoring serum levels is generally recommended (target 5-15 mcg/ml) especially when conditions known to alter theophylline metabolism exist, eg febrile illness, pregnancy, congestive heart failure and use of certain drugs (eg cimetidine, certain quinolones, certain macrolides).

CLASSIFICATION OF ASTHMA SEVERITY BEFORE TREATMENT

Step 1: Intermittent

Symptoms less than once a week

Brief exacerbations

Nocturnal symptoms not more than twice a month

FEV1 or PEFr \geq 80% predicted

FEV1 or PEFr variability \leq 20%

Step 2: Mild Persistent

Symptoms more than once a week but less than once a day

Exacerbations may affect activity and sleep

Nocturnal symptoms more than twice a month

FEV1 or PEFr \geq 80% predicted

FEV1 or PEFr variability 20-30%

Step 3: Moderate Persistent

Symptoms daily

Exacerbations may affect activity and sleep

Nocturnal symptoms more than once a week

Daily use of inhaled short acting beta 2 agonists

FEV1 or PEFr 60-80% predicted

FEV1 or PEFr variability \geq 30%

Step 4: Severe Persistent

Symptoms daily

Frequent exacerbations

Frequent nocturnal asthma symptoms

Limitation of physical activities

FEV1 or PEFr \leq 60% predicted

FEV1 or PEFr variability \geq 30%

STEP APPROACH TO TREATMENT

Control of asthma is defined as:

a) Minimal symptoms

b) Minimal exacerbations

Recommended medications by level of severity

Level	Daily Controller	Other options
1	None necessary	
2	Inhaled steroid (\geq 500mcg BDP)	a) Slow release theophylline b) Cromone c) Leukotriene modifier
3	Inhaled steroid (200-1000 mcg BDP) Plus LABA	a) Inhaled steroid (500-1000mcg BDP) plus Slow release theophylline b) Inhaled steroid at higher doses (\geq 1000mcg BDP) c) Inhaled steroid (500-1000mcg BDP) plus leukotriene modifier
4	a) Inhaled steroid (\geq 1000mcg BDP) plus LABA plus either b) Slow release theophylline c) Leukotriene modifier	

Note that once control is achieved for about 3 months, reduction in therapy can be considered. Reduction should be done gradually by reducing the daily steroid dose by 25% every 3 months.

- c) No emergency visits
- d) Minimal use of prn beta agonists
- e) No limitation of activities
- f) Normal lung function
- g) Minimal (or no) adverse effects of medication.

SPECIAL SITUATIONS

a) Pregnancy

1/3 of patients with asthma become worse during pregnancy. Although concern exists with the use of medications in pregnancy, poorly controlled asthma can have an adverse effect on the foetus. However, well-managed asthma during pregnancy usually results in an equally good outcome as those without asthma. For this reason, using medications to obtain optimal control is justified, even when their safety in pregnancy has not been unequivocally proven.

b) Physical activity

Exercise-induced asthma (EIA) usually indicates that the patient's asthma is not well controlled. Therefore, appropriate anti-inflammatory therapy generally results in amelioration of symptoms. For those who still in whom EIA is the only manifestation, the inhalation of rapid acting beta₂-agonists before exercise is the most effective treatment. Many other compounds including sodium cromoglycate, LABA, leukotriene modifiers have also been found to be effective. It is important to recommend that sports and physical activity should not be avoided in those with EIA.

c) Occupational Asthma Anaphylaxis and asthma

This is defined as asthma caused by exposure to an agent encountered in the work environment. The diagnosis can be suggested when the symptoms improve when away from work and worsen on returning to work. A detailed occupational history is of crucial importance. Once the diagnosis is made, complete avoidance of the relevant exposure is ideal. Occupations associated with a high risk include painting (spray painting), plastic manufacturing, cleaning and janitorial work.

d) Anaphylaxis and asthma

Anaphylaxis is a potentially life threatening condition that can mimic asthma. If there is any doubt that anaphylaxis is involved in an "asthma attack", epinephrine is the bronchodilator of choice. Identifying the cause is crucial in preventing a recurrence.

e) Gastroesophageal reflux

This condition is common in patients with asthma but its contribution to asthma symptoms remains controversial. Diagnosis is confirmed by monitoring esophageal pH. Medical management includes H₂ antagonists and proton pump inhibitors. Concurrent lifestyle changes includes eating smaller, more frequent meals, avoiding supper, alcohol and elevating the head of the bed.

f) Aspirin induced asthma

It is important to recognize that in this condition, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) cause asthma exacerbations in about 20% of adults with asthma. Nasal polyposis is also a strong association with this syndrome. Inhaled steroids remain the mainstay of treatment for this condition and leukotriene modifiers are useful if additional control is desired.

g) Rhinitis and Sinusitis

Asthma and rhinitis often coexist in the same patient and, indeed, is often thought of as the same disease affecting different parts of the airway. Treatment of rhinitis may improve asthma symptoms.

ALTERNATIVE MEDICINE

It is important for the practitioner to recognize that many patients are using alternative medicine to treat their asthma, often because of the frustration that conventional treatment has not been able to provide a long lasting complete cure of their condition. Most of these traditional therapies have not been rigorously studied using conventional methods. The impact of a psychotherapeutic placebo effect from these alternative treatment modalities cannot be excluded. Examples are described below:

- a) Acupuncture – most of the clinical trials that were performed were poorly designed especially with respect to choice of controls.
- b) Herbal medicine – various types of herbal medication are available especially in countries where there are lax regulations.
- c) Ayurvedic medicine – This is a complex of a few types of medicine that includes transcendental meditation and yoga.
- d) Buteyko – this is a breathing technique consisting of a set of exercises in which subjects control the depth and rate of respiration. This is often practiced in Russia, UK, Australia and New Zealand.

Learning Points:

- Rescue drugs are rapid acting inhaled beta₂-agonists, inhaled anticholinergic, and systemic steroids.
- Anti-inflammatory drugs are inhaled steroids, cromones, LABA, Leukotriene modifiers, and methylxanthines.
- Asthma severity before treatment is classified as intermittent (step 1); mild persistent (step 2); moderate persistent (step 3); and severe persistent (step 4).
- Special situations exist in the context of asthma.
- Alternative medicine is used by patients to treat their asthma.

REFERENCES

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