Newer Drugs and Their Use in the Treatment of Bronchial Asthma

ORHAN MUREN, M.D.

Professor of Medicine, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

The current knowledge of pathophysiology and new medications, as well as the better use of old ones, has significantly improved the therapy and prognosis of patients with bronchial asthma. However, it should be understood that drug therapy is beneficial only when aggravating or precipitating agents have been eliminated from the patient's environment; these include allergens, such as dust, mold, pollens and other irritants, infection, exercise, psychological disturbances, certain drugs (aspirin), and stimulation of irritant receptors in the respiratory tract.

There are five major classes of drugs used in treating bronchial asthma: (1) adrenergic agents, (2) xanthines, (3) corticosteroids, (4) cromolyn sodium, and (5) parasympatholytic agents. Some adrenergic agents, such as terbutaline and metaproterenol, offer advantages over others, such as epinephrine, isoproterenol and ephedrine. Among the xanthines the measurement of theophylline blood levels has resulted in the more effective use of aminophylline and other theophylline compounds. The development of a topical steroid, beclomethasone, has been useful in treating steroid-dependent chronic asthmatics. The drugs described below are prescribed to eliminate wheezing and dyspnea; however, other types of therapy such as antibiotics for infections, hyposensitization for allergic factors, and counseling for emotional disturbances should also be considered.

Correspondence and reprint requests to Dr. Orhan Muren, Box 472, Medical College of Virginia, Richmond, VA 23298.

Adrenergic Drugs

Adrenergic agents reduce bronchial obstruction by activating the enzyme adenylcyclase, which increases cyclic adenosine monophosphate (cAMP) in bronchial smooth muscle and mast cells. Adrenergic drugs have alpha- and beta-stimulating effects. The stimulation of alpha receptors causes vasoconstriction. Beta receptors are divided into $beta_1$ and $beta_2$ receptors. The stimulation of $beta_1$ receptors causes cardiac stimulation; stimulation of $beta_2$ receptors is responsible for bronchodilatation, as well as other effects. Terbutaline and metaproterenol are primarily "$beta_2$-selective," but they also stimulate the heart minimally.

Terbutaline (Brethine; Bricanyl), which comes in tablets and ampules is, as noted above, a selective $beta_2$ agent. The most common side effect is tremor, which is caused by stimulation of $beta_2$ receptors in the skeletal muscle. It is recommended that this drug be started at 2.5 mg every eight hours. Tremor may disappear after continuation of the medication; thereafter the dose can be increased to 5 mg every eight hours. However, it should be kept in mind that an injection dose of 0.25 mg of terbutaline may also cause a significant degree of cardiac stimulation.

Metaproterenol (Alupent) is available as a syrup, in tablets and as an aerosol; tremor is a common side effect. The usual oral dose is 10 to 20 mg q.8.h.

Isoetharine (Bronkosol; Bronkometer) is available as an aerosol.

Epinephrine and ***isoproterenol*** have been used for a long time in the management of

patients with bronchial asthma. Epinephrine has both alpha- and $beta_1$- and $beta_2$-stimulating effects. Isoproterenol stimulates both $beta_1$ and $beta_2$ receptors. Epinephrine may also improve symptoms by constricting vessels in the bronchial mucosa, thus decreasing edema. However, epinephrine increases blood pressure, and large doses of this agent or isoproterenol can cause angina pectoris and cardiac arrythmias. It has been observed that cardiac stimulation may increase blood flow in some regions of the lung where there may be poor ventilation. This may cause lowering of arterial O_2 tension.

Ephedrine. This drug was the first adrenergic agent used and it stimulates both alpha and beta receptors. However, its bronchodilatation activity is less than that of the new $beta_2$ agents. Ephedrine may increase blood pressure and may cause CNS stimulation (insomnia, nervousness). It may be responsible for urinary retention in patients with some degree of prostatic obstruction. Ephedrine and isoproterenol have more $beta_1$ (cardiac stimulation) than the newer medications. Insomnia, palpitations, and anxiety limit their use in bronchial asthma.

Xanthines

Theophylline is 1,3 dimethylxanthine. Methylxanthines increase intracellular cAMP by inhibiting phosphodiesterases, enzymes responsible for the breakdown of cAMP. Theophylline has been used for many years in combination with ephedrine and a sedative. The combination medications provide one fourth to one half the proper dose of theophylline and less bronchodilatation.

Aminophylline is theophylline ethylenediamine and is used more often than theophylline itself. Since the difference between therapeutic and toxic doses of theophylline compounds may be narrow, it is desirable to start with a small dose and increase it as required. Plasma theophylline levels should be obtained if patients do not respond to the usual doses; the optimum serum level is between 10 and 20 μg/ml.[1] Patients with chronic liver disease should be treated carefully, since theophylline is detoxified in the liver. Serum theophylline levels greater than 20 μg/ml are usually associated with toxic side effects, such as nausea, vomiting, anorexia, headache, tachycardia and CNS irritation. Levels greater than 30 to 40 μg/ml may lead to serious cardiac arrythmias and seizures.

An oral loading dose of approximately 5 to 6 mg/kg of aminophylline, anhydrous theophylline, or elixophylline will supply therapeutic theophylline levels within 30 to 45 minutes and will usually be effective against a mild-to-moderate degree of bronchospasm. In cases of severe bronchospasm 6 mg/kg aminophylline should be given intravenously in a drip over 20 minutes.

The usual recommended intravenous (IV) maintenance of theophylline is 0.9 mg/kg/hr aminophylline. Serum theophylline levels should be checked at 18 to 24 hours and proper adjustments made as needed. In patients with congestive heart failure or liver disease, the dose should be reduced by half or more if indicated. In elderly people intravenous maintenance of theophylline is 0.7 mg/kg/hr.

For long-term maintenance of theophylline an average-size adult patient with bronchial asthma requires approximately 800 to 1200 mg/day aminophylline. The serum levels should be checked after three days on this therapy, and proper adjustments should be made to maintain levels between 10 to 20 μg/ml. The slow-release preparations of theophylline can be given every 12 hours and can be effective against early-morning bronchospasm.

Corticosteroids

Steroids are very useful in the treatment of asthma but should be used only when conventional bronchodilating agents fail to relieve bronchospasm. Some of the undesirable side effects of steroids include acne, peptic ulcer, osteoporosis, growth retardation, hypertension, adrenal suppression and opportunistic infections. The exact mechanism of steroid action in asthma is not definitely known. Large doses appear to potentiate beta agonists and cause bronchodilatation. As soon as symptoms are relieved with up to 60 to 80 mg/day of prednisone or prednisolone, the dose is tapered to the smallest effective dose, 5 to 10 mg/day or 10 to 20 mg every other day.

Beclomethasone dipropionate (Vanceril) is a topically active, inhaled steroid (50 μg/puff, 8 to 20 puffs per day). When used properly it has no, or only minimal, systemic effects and is especially useful in steroid-dependent chronic asthmatics. It is most effective

when the patient is relatively free of asthma. The usual dose is two puffs four times a day. The patient continues to take all previous medications. If the patient improves after two weeks, steroids should be decreased slowly. If no improvement takes place, the dosage may be increased to four puffs four times a day and then decreased after two weeks of symptomatic improvement. Sixteen hundred micrograms or greater per day causes adrenal suppression. By proper administration of beclomethasone in many steroid-dependent asthmatics, the steroid dose can be significantly reduced and even discontinued. The main possible adverse effects of this agent are nasopharyngeal candidiasis and, in patients who have been on long-term systemic steroids, adrenocortical insufficiency as adrenal suppressive doses of corticosteroids are decreased. Oral candidiasis can be minimized by rinsing the oral cavity after each use with plain water; if candidiasis occurs, nystatin (Mycostatin) rinse three times a day will eradicate the infection.

Cromolyn Sodium

Cromolyn blocks the release of chemical mediators from the sensitized mast cells; it has no antihistamine, bronchodilator or anti-inflammatory characteristics and should not be used during an acute asthmatic attack. It has only prophylactic value. The main indication in the asthmatic appears to be as a steroid-sparing agent. It is most useful in young patients with extrinsic or exercise-induced asthma. The usual dose is 20 mg four times a day by a special inhaler.[2] If after four weeks of therapy, no improvement occurs, the drug should be discontinued. The adverse side effects include cough, throat irritation, skin rashes, occasionally bronchospasm, and eosinophilic pneumonia.

Parasympatholytic Agents

A parasympatholytic agent, such as ipratropium (SCH-1000/Atrovent, 40 μg/puff) may give bronchodilatation in asthma and chronic bronchitis. It is not available in the United States at the present time.

Combination of Drugs

A beta agonist such as terbutaline can be given with theophylline, and lower doses of the two together may be as effective or less toxic than higher doses of either drug alone. Oral bronchodilating agents are usually continued when patients receive corticosteroids or cromolyn sodium.

Indications of Severity of Bronchial Asthma

Significant reduction in FEV_1 (less than 1.0 liter) associated with one or more abnormalities such as marked scalene muscle contractions, mental confusion, pulse rate greater than 130/min, pulsus paradoxus greater than 10 mm Hg, marked overdistension of the lungs on chest x-ray, central cyanosis, arterial PCO_2 greater than 40 mm Hg, pneumothorax, or pneumomediastinum, indicate a severe attack of asthma.[3] If FEV_1 is less than 25% predicted, there is a tendency to CO_2 retention. Pulsus paradoxus of more than 10 torr is associated with FEV_1 less than 25% predicted; scalene muscle contractions and intercostal retractions suggest FEV_1 less than 1.0 liter.[4]

Patients with these abnormalities should be hospitalized immediately, and receive proper therapy (IV aminophylline, high doses of steroids, supportive and specific care).

Status asthmaticus is defined as a severe asthma attack unresponsive to inhaled or injected sympathomimetic amines. The cornerstone of management of status asthmaticus is the administration of IV aminophylline and large doses of corticosteroids. Supportive care and specific therapy for any complication should also be undertaken.

Indications for Intubation and Mechanical Ventilation in Asthma.

1. Arterial PCO_2 over 50 to 60 torr in the absence of chronic hypercapnea.
2. An arterial PO_2 under 60 torr on 6 liters of O_2 by nasal cannula.
3. Evidence of marked increase in the work of breathing judged by physical examination, even in the presence of near-normal arterial gas studies.
4. Respiratory arrest.

It should be emphasized that during the acute episode of an asthma attack, there is a lowering of arterial PO_2 and PCO_2. Perfectly normal PCO_2 such as 40 torr indicates fatigue of the patient and the necessity of aggressive therapy.

Treatment Failures

Patient compliance and understanding are important for the successful management of

asthma. Hidden environmental hazards should be eliminated. Not every wheezing represents bronchial asthma; left-sided heart failure, chronic obstructive pulmonary disease, pulmonary emboli, hypersensitivity pneumonitis, mediastinal node compression, foreign body in a large bronchus, or bronchial carcinoid can be responsible for diffuse wheezing masquerading as asthma. Finally, inadequate medication may be the cause of failure to improve. Readings of serum theophylline at the level obtained one hour after a dose has been given, and one hour before the next dose, are helpful indications of whether an adequate amount has been given. There is a tendency to underuse corticosteroids in severe acute respiratory failure. It is better to overuse the steroids for a short period than to have the patient suffer cardiac, respiratory or neurologic damage if complications arise.

REFERENCES

1. MITENKO PA, OGILVIE RI: Rational intravenous doses of theophylline. *N Engl J Med* 289:600–603, 1973.

2. IRANI FA, JONES NL, GENT M, ET AL: Evaluation of disodium cromoglycate in intrinsic and extrinsic asthma. *Am Rev Resp Dis* 106:179–185, 1972.

3. AUSTEN KF, LICHTENSTEIN LM: *Asthma: Physiology, Immuno-Pharmacology, and Treatment*. New York and London, Academic Press, 1973.

4. REBUCK AS, READ J: Assessment and mangement of severe asthma. *Am J Med* 51:788–798, 1971.