Drug Therapy in the Management of Asthma

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In the past decade there has been substantial improvement in the quality of drug therapy for asthma. In part, this reflects the greater sophistication and confidence in the use of bronchodilator drugs, after their role in modifying the intracellular concentration of cyclic nucleotides was discovered. Another advance has come from the appearance of adequate information on theophylline blood levels and half-lives and their variability in man. The increasing availability of theophylline blood levels has aided not only in the selection of therapeutic doses but also in determining the effectiveness of newer products that, for example, promise to have a more sustained effect when given by mouth. The plight of asthmatic patients dependent on oral glucosteroid therapy has been substantially eased with the development of new steroid-sparing drugs that are effective by inhalation.

ASTHMA can be defined as a symptom complex involving paroxysmal episodes of wheezing respirations and difficulty breathing. The symptoms are caused by spasm of the bronchial and bronchiolar smooth muscle, swelling of the mucosa from edema, and mucous gland hypertrophy. The bronchioles most affected are those from 2 to 5 mm in diameter. In those patients with more continuous and severe disease, the smooth muscle hypertrophies, the basement membrane thickens, and mucous plugs occlude the bronchioles and bronchi; eosinophils, lymphocytes, histiocytes, and plasma cells infiltrate the submucosa; and many surface epithelial cells are shed into the lumen. Small collapsed areas occur that, together with obstruction from tenacious mucous plugs, account for much of the observed hypoxia due to ventilation/perfusion (V/Q) abnormalities. Fortunately, appreciable tissue destruction (fibrosis, loss of alveolar septa) is rare. Thus, asthma can also be defined physiologically as a *reversible* form of diffuse obstructive lung disease.

In an asthmatic patient there are various triggers that will initiate or aggravate symptoms, such as allergen exposure, infection, emotional stress, and primary irritants (smoke, smog, cold air, irritating chemicals). The possibility that a single common abnormality exists that makes an asthmatic patient susceptible to these diverse triggers is being studied actively by several investigators.

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An acute exacerbation of bronchial asthma that is persistent and does not respond to repeated doses of epinephrine or to intravenous theophylline is defined as status asthmaticus. Factors that may precipitate status asthmaticus or lead to its development include one or more of the following: respiratory infection (1, 2); termination of corticosteroid therapy (1, 3); undermedication with drugs such as theophylline (3, 4); overuse of nebulized sympathomimetic drugs (5-7); failure of the patient or his physician to recognize the severity of the asthma attack (8); reaction to inhaled allergen (9, 10) (alone, rarely precipitates status asthmaticus); reaction to aspirin or indomethacin in susceptible patients; metabolic acidosis (11, 12); and acute emotional stress (13).

The properly managed asthmatic patient should rarely need hospitalization if the above factors are anticipated and avoided. Proper management usually means the proper use of drugs, particularly in the many adult asthmatic patients in whom a causative factor cannot be identified and avoided.

The rationale for the use of many anti-asthma drugs has been reinforced in recent years by the results of research on the role of intracellular cyclic nucleotides in regulating biochemical and physiologic activity. Since this work is now so well known, it will be mentioned only briefly here. The nucleotides are cyclic 3′5′ adenosine monophosphate (cyAMP) and cyclic 3′5′ guanosine monophosphate (cyGMP). These are converted from the triphosphates by the enzymes adenylate cyclase and guanylate cyclase, respectively. These cell-membrane associated enzymes can be activated by several drugs. For the purpose of this discussion, activation has significant effects at two points: in the mast cell and in bronchial smooth muscle. Activation of adenylate cyclase results in an inhibition of the antigen-induced release of mediators of asthma (histamine, anaphylactic slow-reacting substance, eosinophil chemotactic factor, and possibly others) by mast cells (14). Similar activation in bronchial smooth muscle causes muscle relaxation. Activation of guanylate cyclase has the opposite effect and, thus, would be clinically detrimental.

Beta Adrenergic Agonists

Sympathomimetic drugs may stimulate alpha receptors (vasoconstrictors) or beta receptors (cardiac stimulants

and bronchodilators), and some do both. In recent years, beta adrenergic drugs have been developed that have a selective effect on bronchial smooth muscle on one hand and cardiac receptors on the other. This has led to the assumption that there are two beta receptors: the β_1 in heart muscle and the β_2 in mast cells and bronchial smooth muscle. This selectivity extends to other tissues as well (15). These drugs are thought to act through a beta adrenergic receptor by activating adenylate cyclase and increasing intracellular cyAMP.

Until recently the only drugs available in this country were epinephrine, isoproterenol, and ephedrine. The first two are catecholamines, that is, they have hydroxyl groups on the 3 and 4 carbons in the aromatic ring. They are rapidly degraded, particularly in the liver, by the enzyme catechol-o-methyl transferase (COMT) and for this reason are ineffective when given by mouth; their duration of action is only a few minutes. Epinephrine has alpha, β_1, and β_2 adrenergic effects, whereas isoproterenol, with a larger alkyl substitution on the amino group, has little or no alpha effect.

Ephedrine has no hydroxyl groups on the aromatic ring, is thus resistant to catechol-o-methyl transferase, and is effective by mouth. It has a direct effect on beta adrenergic receptors and also has some alpha adrenergic activity, exerted in part at least by its ability to release stored norepinephrine. Since 1924, ephedrine has been a mainstay of oral asthma therapy and is contained in numerous fixed-dose combinations with theophylline, a sedative, or both.

The new drugs that are now available or soon will be are relatively free of β_1 activity and, thus, are safer to use in terms of cardiac toxicity. These were developed through two fundamental structural modifications of isoproterenol (Figure 1). One was the change in the hydroxyl substitution from 3,4 to 3,5. This accomplished two things: the drug was somewhat more β_2 selective, and it was resistant to catechol-o-methyl transferase and thus could be effective by mouth with a relatively long duration of action. Metaproterenol, now available for oral and for aerosol therapy, is the result of this simple change. The second change was to increase the size of the alkyl substitution on the amino group. Substitution of a tertiary butyl for the isopropyl group of metaproterenol produced terbutaline, which is now available in oral or injectable form and has very little β_1 activity. One catecholamine, isoetharine, by virtue of an ethyl substitution on the alpha carbon, is more β_2 selective but is relatively short-acting. It is available only in combination with phenylephrine (an alpha adrenergic drug) for aerosol therapy.

Several other β_2 selective drugs have been developed and are now marketed abroad. One, salbutamol, is representative of the group of drugs that are resistant to catechol-o-methyl transferase because of the substitution of an ethyl group for the hydroxyl group on the number 3 carbon atom. It has been subject to extensive controlled clinical trials in this country but is not yet on the market. Carbuterol, also under investigation, differs only in the nature of the 3-carbon substitution. A third investigational drug undergoing clinical trials in this country is called fenoterol. It was derived from metaproterenol by the addition of a hydroxyphenyl group to the side chain. This enlargement of the side chain on the amino group enhances further the β_2 specificity of the compound. Several other drugs are being developed abroad (15) in the hope of finding the ideal β_2 selective agent.

The most bothersome side effect from treatment with the newer adrenergic drugs is muscle tremor. Unfortunately, this is the result of a beta adrenergic action—facilitation of skeletal muscle nerve transmission—and probably cannot be reduced very much by further structural modifications.

Alpha Adrenergic Antagonists

Phenylephrine and, to a lesser extent, norepinephrine, in the presence of propranolol (a beta adrenergic blocking agent), enhance the antigen-induced release of mediators from passively sensitized human lung in vitro and reduce the concentration of cyAMP (16). Several clinical studies have followed this observation, indicating that (in special circumstances) blocking alpha adrenergic receptors with phentolamine or thymoxamine may be beneficial in circumstances where beta adrenergic drugs are ineffective or make matters worse (17, 18). Such circumstances are so unusual, however, that the use of such drugs will remain experimental for some time to come, for lack of controlled clinical trials.

Parasympathetic Antagonists

The regulation of bronchial smooth muscle tone, in normal subjects as well as in asthma, is largely under parasympathetic control via the vagus nerve. Even antigen-induced bronchoconstriction appears to be mediated in part by cholinergic activity (19). Anticholinergic therapy for asthma has a long history. Indeed, breathing smoke from burning stramonium leaves was a common treatment for asthma long before epinephrine or ephedrine were introduced, and atropine cigarettes have been used for treatment through most of this century (20). Yet some authorities consider atropine contraindicated in asthma because of its adverse effect on sputum viscosity. Recently, there has been a renewed interest in the use of anticholinergic therapy. This has come about for two reasons: an increased recognition that vagal innervation is important in regulating bronchomotor tone; and the discovery that cholinergic agents increase the concentration of cyGMP and enhance the antigen-induced release of mediators from isolated sensitized lung tissue, while atropine has an oppo-

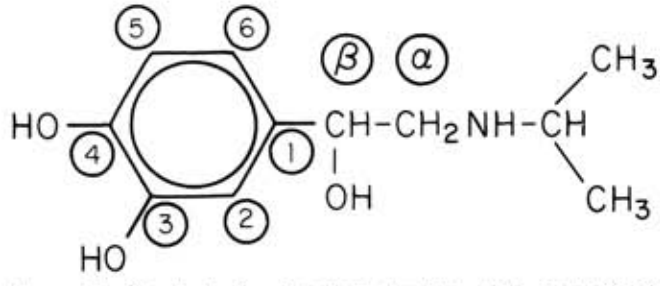

Figure 1. Catecholamine chemical structure with conventional carbon-position symbols (*encircled*). This is the structure of isoproterenol.

Table 1. Single-Drug Methylxanthine Preparations

	Dose Form
Anhydrous theophylline	
Short-acting	
Aerolate®	Elixir: 160 mg/15 ml
Bronkodyl®	Elixir: 80 mg/15 ml
	Capsules: 100 and 200 mg
Elixophyllin®	Elixir: 80 mg/15 ml
	Capsules: 200 mg
Slo-phyllin®	Syrup: 80 mg/15 ml
	Capsules: 60 mg
	Tablets: 100 and 200 mg
Theolair®	Tablets: 125 and 250 mg
Theophyl®	Elixir: 225 mg/30 ml
	Tablets: 225 mg
Long-acting	
Aerolate	Capsules: 65, 130, and 250 mg
Slo-phyllin	Capsules: 125 and 250 mg
Theodur®	Tablets: 100 and 300 mg
Theobid®	Capsules: 260 mg
Aminophylline (85% theophylline)	
Short-acting	
Aminophylline*	Tablets: 100 and 200 mg
Somophyllin®	Oral liquid: 315 mg/15 ml
	Rectal solution: 300 mg/5 ml
Long-acting	
Aminodur®	Tablets: 300 mg
Oxytriphylline (64% theophylline)	
Choledyl®	Elixir: 100 mg/5 ml
	Tablets: 100 and 200 mg
Theophylline Monoethanolamine (74% theophylline)	
Fleet's enema®	Rectal solution: 250 and 500 in 30 ml (delivered)
Theophylline Sodium Glycinate (50% theophylline)	
Synophylate®	Elixir: 330 mg/15 ml
	Tablets: 330 mg
Dyphylline (dihydroxypropyl theophylline) (not converted to theophylline)	
Lufyllin®	Elixir: 100 mg/15 ml
	Tablets: 200 mg
Dilor®	Elixir: 160 mg/15 ml
	Tablets: 200 and 400 mg

* Generic name.

site and protective effect (14). Furthermore, the suspected deleterious effect of atropine on sputum viscosity has not been confirmed in controlled clinical trials (21). However, atropine does inhibit mucociliary transport. Most treatment in this country has been with atropine sulfate by aerosol. At least 1 mg is necessary to produce an effect, and up to 0.1 mg/kg may be necessary to inhibit exercise-induced asthma (22). Side effects (mouth dryness and difficulty in voiding) are relatively common. Since the adrenergic agents are as effective or more so, there appears to be little need to use atropine for chronic use except in the occasional patient refractory to conventional therapy. However, a new drug is now under investigation in this country that appears to be effective in doses of 40 to 80 μg by nebulizer without significant side effects. It does not alter mucociliary transport, for example. Called Sch 1000, it is an isopropyl-substituted derivative of atropine (23). It could be particularly useful in glucosteroid-dependent patients who do not respond to beta adrenergic drugs, but the necessary controlled clinical trials in this country cannot be done until stability problems have been solved.

Phosphodiesterase Inhibitors

Phosphodiesterase is the enzyme that catalyses the degradiation of cyAMP to 5′ AMP. Methylxanthines, particularly theophylline, inhibit the action of this enzyme, thus acting to sustain any beneficial increase in cellular cyAMP produced by beta adrenergic stimulation. However, this mechanism has been found only in systems involving the antigen-induced release of mediators from mast cells or basophils in vitro. Whether it is also responsible for relaxation of bronchial smooth muscle is not yet established.

Theophylline ethylenediamine (aminophylline) is the most commonly used form, and theophylline is also available in other forms such as choline theophyllinate (oxytriphylline) and ethanolamine. The first is 85% theophylline; the second, 64%; and the third, 74%. This must be taken into account when the effectiveness of the various compounds is compared. Until recently, these compounds were thought to be better absorbed and produce less gastrointestinal irritation than U.S.P. theophylline (which is only slightly soluble in water) and appeared to be most bioavailable as alcoholic elixirs.

Innovations in methylxanthine therapy have come not from new chemical formulations but from changes in the physical state of the drugs—and changes in therapeutic attitudes supported to a large degree by the use of the theophylline blood level as a check on bioavailability. Several companies now provide anhydrous theophylline in a microcrystalline form, which is rapidly and completely absorbed after oral administration. Furthermore, several sustained-action preparations are now available that can sustain blood levels in the therapeutic range for up to 12 h (24). As physicians have gained more confidence in the administration of theophylline on a schedule that will maintain a therapeutic blood level (10 to 20 μg/ml), reliance on fixed-dose combinations with ephedrine and other drugs has diminished. Some of the preparations of theophylline or its salts are listed in Table 1. Those interested in the theophylline concentrations and other ingredients in some fixed-dose combinations should see Bergner and Bergner's paper (25). Note that two rectal solutions are included but not aminophylline suppositories, which have been known for more than a quarter century to produce inadequate blood levels (26).

The optimum mean oral dose (as theophylline) to achieve and maintain a therapeutic blood level was found to be 4.8 mg/kg · 6 h by Piafsky and Ogilvie (27) in adults. This can range from 1000 to more than 2000 mg daily, depending on patient size. However, a few individuals deviate markedly from the mean in their theophylline half-life and may require as little as 400 or as much as 3200 mg/day to maintain adequate serum theophylline levels (28). For adequate control of these individuals, one may have to determine the optimum dose by trial and error. This is done

by increasing the dose to the point of toxicity (nausea, abdominal pain, nervousness, headache, tachycardia) and then reducing it slightly. The process is much easier, though, if serum levels are measured during the adjustment process. Theophylline levels should be available in most medical centers with toxicology laboratories.

The usefullness of long-acting preparations (Table 1) in maintaining therapeutic blood levels with two or three doses daily is being investigated and looks promising from the evidence available so far (24).

Cromolyn sodium (disodium cromoglycate) is one of several synthetic derivatives of a natural substance called khellin. It is a bischromone, which turned out to have a highly selective action in blocking bronchospasm produced by antigen or exercise. The mechanism of action, until recently, was thought to be a temporary stabilization of the mast-cell membrane. While this probably is still the case, Lavin, Rachelefsky, and Kaplan (29) have reported that lymphocytes of subjects being treated with cromolyn had lower phosphodiesterase, and higher cyAMP, concentrations than the cells of control subjects. Despite this phosphodiesterase inhibition, cromolyn is so different from theophylline that it should properly be in a class by itself. It is ineffective by mouth and is used only as an inhaled powder, while theophylline is ineffective by inhalation. Cromolyn is not a bronchodilator and produces none of the theophylline side effects. It is particularly useful in young asthmatic patients who are sensitive to inhaled allergens and who are poorly controlled by, or have intolerable side effects from, sympathetic drugs or theophylline. For optimal effect, it is often necessary to improve the patient's ventilation first with a short period of oral glucosteroid treatment. It is also used in the management of glucosteroid-dependent asthma patients to reduce their reactivity to antigen or exercise, or both, and thus permit the steroid treatment to be reduced or stopped*. It is not effective in treatment of acute asthma.

For optimum effect, cromolyn must be taken without interruption and is expensive, costing $25 to $30 per month when inhaled in the usual dose of 20 mg, four times daily. It is effective in only a small percentage of patients with adult-onset asthma, most of whom are not reactive to inhaled allergens. Until recently, a 1-month therapeutic trial of cromolyn treatment for such patients, particularly those who were steroid-dependent, would have been appropriate. However, such treatment has been largely supplanted by treatment with a topical glucosteroid (*see* below).

Another group of drugs, xanthones, share cromolyn's pharmacologic action and are somewhat similar in structure, but may be effective by mouth (30). They are undergoing controlled clinical trials now in this country.

Prostaglandins

Prostaglandins are 20-carbon hydroxy fatty acids and are found in many body tissues. One prostaglandin, $F_2\alpha$, is a potent bronchoconstrictor and has been implicated in the pathogenesis of some forms of asthma. The E prostaglandins (PGE_1 and PGE_2), also found in lung tissue, are bronchodilators (31). They stimulate cyclic AMP formation in some tissues, including lung, via a different receptor than that for beta adrenergic agonists. Thus there is reason to hope that E prostaglandins might be effective in patients who are unresponsive to the beta adrenergic drugs. Both PGE_1 and PGE_2 are investigational drugs now undergoing controlled clinical trials. They are inhaled, and their usefulness may be limited by the frequent occurrence of pharyngeal irritation.

Glucosteroids ("Steroids")

These are the most potent antiasthmatic agents and may produce dramatic improvement in patients with chronic airway obstruction who do not respond adequately to bronchodilators. Such patients may need continuous steroid treatment and are subject to the side effects of osteoporosis, purpura, diabetes, hypertension, weight gain, adrenal suppression, and—in children—growth retardation. At maintenance doses of 10 mg (as prednisone) or less, these side effects are uncommon. There is no convincing evidence that steroids activate tuberculosis, or peptic ulcer disease, or that they produce fetal abnormalities (32-34). Prednisone (or prednisolone) is the standard drug used for oral therapy; other glucosteroids usually have no significant advantage and are more expensive. For obscure reasons, a few patients will be significantly better controlled with one of the others than with an equivalent prednisone dose.

Much has been written about the mechanism of action of steroids in asthma, but it is still poorly understood. To the degree that tissue inflammation contributes to airway obstruction, the action of steroids in decreasing the number and activity of inflammatory cells is a reasonable mechanism for improvement. The long-held belief that steroids act by stabilizing lysozomal membranes probably does not apply in vivo (35). Steroids have no effect on antigen-induced histamine release, and, although release of anaphylactic slow-reacting substance may be partially inhibited in vitro, steroids do not diminish acute antigen-induced bronchospasm significantly. However, there exists some reasonable evidence that steroid therapy may enhance the effect of beta adrenergic drugs on cyAMP production (36).

Therapy is initiated with 30 to 60 mg of prednisone per day, and the daily dose is lowered gradually after symptoms have abated. If the condition is self-limited, steroid therapy can be discontinued in a week or 10 days. Otherwise, symptoms may return at some dosage level, usually 10 mg/day or less. Low doses may not cause adrenal suppression if taken in the early morning. However, adrenal suppression can better be avoided by converting to every-other-day therapy, which can be achieved by tapering 1 day's dose downward and the alternate day's dose upward by the same amount. Even if this is done slowly, however, about half of the patients experience intolerable symptoms on the off-day. Long-acting steroids (dexamethasone, betamethasone) should not be used if one is trying to avoid adrenal suppression. Adrenal suppression is also avoided in those fortunate patients who can be adequately controlled with intermittent short courses of daily prednisone treatment.

* This must be done cautiously; fatalities have occurred because unwarranted confidence in the protective effect of cromolyn led to abrupt cessation of steroid therapy.

The most appropriate form of therapy for the steroid-dependent asthmatic patient would be to inhale the drug. However, the usual water-soluble glucosteroids, when used in effective doses, caused adrenal suppression because about 70% of the dose was swallowed and absorbed from the gastrointestinal tract (37). Lipid-soluble steroids, developed originally for dermatologic use, are poorly absorbed when swallowed. Three such drugs have been subject to extensive clinical trials: beclomethasone diproprionate (37, 38), triamcinolone acetonide (39), and betamethasone valerate (40). Only beclomethasone has been approved for use in this country so far. The usual dose of 100 μg (two inhalations), four times daily, can allow a dramatic reduction in oral-steroid dosage for most steroid-dependent patients: a few patients may need to take up to 2000 μg/day of the inhaled drug. Oropharyngeal candida or aspergillus infection is the only significant direct side effect. Much more important, however, are the side effects resulting from stopping oral steroid therapy. Allergic rhinitis and nasal polyposis may flare up. All patients should be warned about the appearance of adrenal insufficiency, and reducing the dose of prednisone below 5 mg daily should be done slowly for all patients who have been on continuous treatment for any length of time. If any withdrawal symptoms develop (fatigue, weakness, arthralgias, nausea, dizziness), the patient should be given a replacement steroid dose that can be tapered slowly and stopped when the 0800-h plasma cortisol exceeds 10 μg/dl (41). Each patient who has stopped oral steroid therapy should be given a warning card indicating the need for supplementary steroid therapy during stress. The patient should be advised that full recovery of adrenal function may not occur for more than 9 months after oral glucosteroid therapy has stopped. One can establish that earlier recovery has occurred, if desired, by measuring the plasma cortisol response to synthetic adrenocorticotrophic hormone (41).

As with cromolyn, the nebulized steroids are ineffective and should not be used for relief of acute asthma symptoms.

General Therapeutic Principles

Despite warnings on abuse of nebulized adrenergic drugs, a substantial number of patients with mild, intermittent asthma symptoms require nothing else and suffer no adverse effects from this mode of treatment over many years. Those who are used to treatment with isoproterenol or epinephrine should be warned, though, about the possibility of cumulative side effects if they change treatment to one of the long acting B_2 selective drugs, such as metaproterenol.

If a patient needs to use the nebulizer more than twice daily or if nocturnal symtoms cause loss of sleep, then therapy with one of the oral theophyllines should be started, and the patient should take the drug on a regular basis. A typical adult program is 200 to 400 mg of aminophylline two or three times daily, plus up to 600 mg of the more expensive long-acting theophylline at bedtime. The estimated daily dose should be about 20 mg/kg and adjusted upward or downward with the aid of serum theophylline levels, if necessary.

The next step in treatment would be to give an oral adrenergic drug such as metaproterenol or terbutaline. One of these drugs should be tried if methylxanthine treatment is associated with intolerable side effects. Occasionally, they provide additional benefit when given along with aminophylline. Side effects of tremor, nervousness, headache, and palpitations limit the usefulness of oral adrenergic drugs; in most situations, the route of choice is inhalation.

Despite optimum bronchodilator therapy, some patients are still so obstructed as to be partially or completely disabled. Glucosteroid therapy is appropriate for these patients and should consist of oral prednisone to the point of maximum improvement. Nebulized beclomethasone dipropionate treatment is then begun, and the prednisone dose is reduced to zero over a week's time if the patient has not been on chronic steroid therapy.

If prednisone therapy cannot be discontinued and the patient is allergic to a substantial load of environmental allergens, treatment with inhaled disodium cromoglycate powder should be added as another aid to steroid withdrawal.

Hospital Management of Asthma

By the time the asthmatic patient is admitted to the hospital, all conventional drug therapy usually has been tried and has failed. Nevertheless, most patients will improve in the hospital within a few hours with simple medical treatment. Despite the usual favorable response, each patient should be observed carefully and examined periodically around the clock. Unless obvious clinical improvement occurs promptly, the patient should be monitored with periodic blood gases and a ventilatory function test such as the peak expiratory flow rate.

Adequate hydration is of *paramount* importance and is one of the first steps to take. Practically all patients initially are hypovolemic due to increased insensible water loss, diuretic effect of drugs, and poor oral intake (42). An average of 4000 ml of D5W with the appropriate amounts of sodium and potassium added should be given to replace the deficit. Adequate hydration may aid in sputum liquification and should prevent further accumulation of mucous plugs. Precipitation of congestive heart failure in susceptible individuals should be considered when fluids are given. Alkali administration may be important in the treatment also, when metabolic acidosis as well as respiratory acidosis has developed. There is some evidence that acidosis inhibits the action of beta adrenergic drugs (11). If the pH falls below 7.25, 45 to 90 meq of sodium bicarbonate should be administered. Respiratory acidosis alone is best treated, however, by ventilatory support.

Adequate oxygenation is important, especially at the time bronchodilators are given (43). Oxygen in sufficient quantities should be administered to keep the arterial PO_2 above 60 torr. Usually, it can be delivered effectively by nasal prongs. Occasionally an oxygen mask, such as the Venturi mask, is necessary because of mouth breathing. In all but rare instances, hypercarbia will not occur with O_2 administration to the asthmatic patient. However, if the patient tires, loss of the hypoxic drive may lead to this dangerous state. Therefore, blood gas determinations

should be repeated 30 to 60 minutes after beginning oxygen treatment to insure adequate oxygenation and anticipate possible hypercarbia.

Aqueous epinephrine in doses of 0.3 mg (in the adult), given subcutaneously, can be very helpful early in the attack. If there is no response to two doses 30 minutes apart, further repeated injections are usually futile. Recently experimental evidence has suggested an epinephrine reversal effect: epinephrine may cause bronchial constriction, due to its alpha stimulating effect, if beta receptors become unresponsive. The β_2 selective drug, terbutaline, is now available in injectable form. The usual dose is 0.25 mg, which can be repeated once if there is no response in 30 minutes but should be used no more frequently than every 4 h thereafter.

The usual method of giving an adrenergic drug is by aerosol. Epinephrine, isoproterenol, and isoetharine are available as solutions for nebulizer use, the last only in combination with phenylephrine. It is good rule not to use isoproterenol during the first 24 h in a patient who has been using it excessively without benefit prior to hospitalization. Its overuse, in fact, may have aggravated the problem (5-7). Isoproterenol has also caused a decrease in the arterial Po_2 despite improved ventilatory function (43). Presumably, this occurs by increasing perfusion of underventilated alveoli. This is not a significant problem in the hospitalized patient receiving oxygen therapy. Whatever is used, the aerosolized bronchodilator can be delivered effectively by oxygen or compressed air. There is little evidence that intermittent positive pressure breathing offers any advantage for the treatment of most patients with obstructive lung disease (44).

Occasionally the careful infusion of isoproterenol intravenously has been effective after other methods have failed (45). Intravenous treatment with β_2 selective drugs is still in the experimental phase.

Aminophylline is very useful if sufficient doses are used. Six mg/kg should be given intravenously over 20 minutes initially. If this is well tolerated, another 3 mg/kg can be given, which should achieve a therapeutic blood level of 10 to 20 μg/ml (27). Good blood levels can be maintained in most patients by giving 1 mg/kg·h by continuous intravenous drip. Because of the biologic variation in theophylline half-life, theophylline blood levels, if available, should be checked and the rate of administration adjusted accordingly (28).

Systemic glucosteroid therapy is usually necessary if the patient is sick enough to be hospitalized. The effects of steroids may not be clinically significant for several hours after administration; therefore, consideration of their use should be made early. A patient who has previously been treated with a steroid should have treatment started immediately, using 4 mg/kg (as hydrocortisone) every 4 h with appropriate potassium supplementation (46). If the patient has not previously received such treatment, it should be started if no significant improvement occurs within the first 8 to 12 h with the other modes of treatment. A dose of 4 mg/kg (hydrocortisone) every 12 h is usually adequate, somewhat less than that for the steroid-dependent patient. After the start of steroid therapy, the responsiveness of the patient to a beta adrenergic drug is usually restored (47). After substantial improvement, the steroid therapy can be changed from intravenous to oral and the dose tapered as described earlier.

Generally, narcotics, barbiturates, or other sedatives should not be used because these may depress respiration and the cough reflex. A reasonable exception to this is the use of mild sedation with one of the benzodiazepines for an overt anxiety reaction, especially with hyperventilation alkalosis. Generally, though, sedation is contraindicated in management of the hospitalized asthmatic patient. On one hand, it may lead to a paradoxic increase in agitation and a disoriented, uncooperative patient. On the other hand, sedation may work too well and lead to a false sense of security. It has also been associated with sudden death. (For the patient *in extremis* requiring intubation and machine-cycled ventilation, the rules are different.)

Most asthmatic patients have an arterial Pco_2 that is somewhat low. If the patient is not responding to treatment and the arterial Pco_2 is more than 40 torr, the patient may be developing respiratory failure and needs close monitoring. A rising arterial Pco_2, particularly if it exceeds 55 torr, is an indication for intubation and machine-cycled ventilation.

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