EMERGENCY ROOM MANAGEMENT OF ACUTE ASTHMA

Gary R. Hart, M.D.

Medical Grand Rounds

"When all at once from indolence to toil
You spring, the fibres by the hasty shock
Are tir'd and crack'd, before their unctuous coats
Compress'd can pour the lubricating balm.
Besides, collected in the passive veins,
The purple mass a sudden torrent rolls,
O'erpow're the heart, and deluges the lungs
With dang'rous inundation: oft the source
Of fatal woes; a cough that foams with blood,
Asthma ---

--John Armstrong

March 19, 1981
Department of Internal Medicine
University of Texas Health Science Center
at Dallas, Texas

Acute asthma is one of the most common reasons for admission to adult or pediatric emergency rooms. Nationwide, approximately 4% of ER visits are for acute asthma. In the medicine emergency room at Parkland, there are, on the average, four visits per day for this indication, or 1500 visits per year.

It is curious that the frequency of this complaint has not always resulted in well-reasoned approaches to its management. There have been a variety of protocols for estimating severity of the attack, formulating pharmacologic therapy and selecting patients needing hospitalization. Unfortunately, in most hospitals objective measurements of lung function are not obtained and recent advances in the use of bronchodilator drugs are not utilized in planning the pharmacologic approach.

This discussion will review current understanding of the changes in lung function in acute asthma, of the rate of resolution of abnormalities with treatment, the clinical pharmacology of the two major classes of drugs useful in management and the estimation of severity and likely outcome of any episode. The immuno-physiology of asthma and the management in hospital of status asthmaticus (ventilator therapy, corticosteroids, etc.) will not be discussed.

The definition of asthma proposed by the Committee on Diagnostic Standards of the American Thoracic Society (1) will be used here:

> *Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airway that changes in severity either spontaneously or as a result of therapy. The term asthma is not appropriate for the bronchial narrowing which results solely from widespread bronchial infection, e.g. acute or chronic bronchitis; from destructive disease of the lung, e.g., pulmonary emphysema; or from cardiovascular disorders.*

In some patients, it may be difficult in the emergency room setting to differentiate between true asthma and a decompensation of chronic obstructive lung disease. This distinction, however, is very important in planning the therapeutic approach and estimating the severity of illness.

Our discussion will begin with consideration of two issues pertinent to the management of acute asthma: precipating factors for the acute attack and mortality in asthma.

Precipitating Factors in Acute Asthma

Adult patients with asthma are susceptible to provocation of acute attacks by all those etiologic agents well-described in children. Those most often mentioned include allergens (pollens, dustmites, drugs, etc.), occupational exposures (toluene, textile dust, etc.), drugs (propranolol, reserpine), exercise, irritants (air pollution, cold air, tobacco smoke), infection, emotions or stress and others.. Though any one or more of these may be incriminated in any acute attack, in adults there will often be no precipatating factor identified.

Many adult asthmatics present to the emergency room not after the sudden development of dyspnea, but after a slow and progressive increase in symptoms culminating in the necessity of physician intervention. Not only does slow progression of illness make identification of a precipitating factor difficult, but it probably also changes the responsiveness of the disease to therapy. Airways obstruction in asthma is thought to be the result of a combination of bronchospasm, mucosal edema, and mucous secretions. McFadden has emphasized that the duration of the attack influences the ease with which the process can be reversed (2). Figure 1 shows the rate of response to therapy of the FEV_1 in one patient seen on three different occasions for acute asthma. Though initial FEV_1 was similarly reduced in each attack, the response to therapy varied markedly. There was rapid improvement in FEV_1 following the attack of four hours, but improvement required a number of days of intensive therapy when the acute attack had been present 90 hours prior to the onset of treatment. It is likely that when attacks are present for a long period of time prior to definitive therapy, mucosal edema and mucous impactions are present; airways obstruction due to these elements is much slower to resolve than that due to bronchospasm.

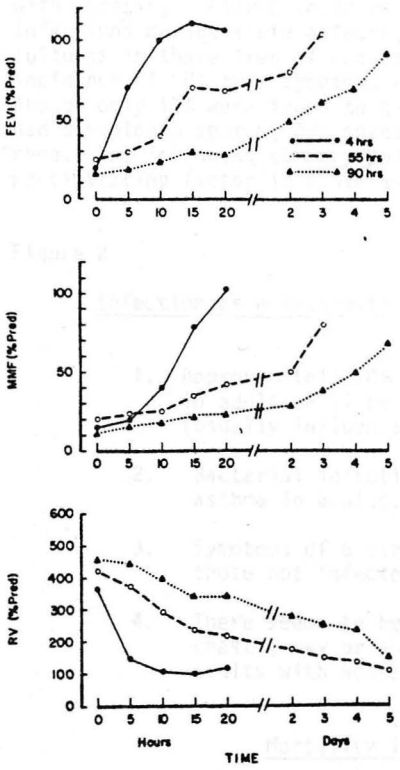


Figure 1. Rate of resolution in one patient on three different episodes. (Ref. 2)

An important question for the physician treating acute asthma is whether or not infection is playing a role in precipitation of the attack. In children, as many as 50% of acute exacerbations may be associated with viral URIs; even so, some asthmatic children with the same viral infection will not experience decompensation (3). In adults, infection as an inciting factor seems to be considerably less frequent. Hudgel (4) in Denver studied 19 adult asthmatics during acute exacerbations and periods of good control and found that 11% of acute exacerbations were associated with viral URIs; 9% of acute attacks were associated with pathogenic bacteria (this number is no different from the number of sputums positive for bacteria during the period of good control). Only half of the viral infections identified were associated

with wheezing. Clarke found an 11% incidence of viral and bacterial infections during acute attacks, and again noted many positive bacterial cultures in those free of wheezing (5). Interestingly, he found a high incidence of URI-type symptoms even in those with no apparent infection. Though only 11% were found to have a respiratory tract infection, 48% had discolored sputum, 20% sneezing, 45% sore throat, and 28% rhinorrhea. The following summary points can be made about infection as a precipitating factor in acute asthma in adults:

Figure 2

Infection as a Precipitant of Acute Asthma in Adults

1. Approximately 10% of exacerbations of asthma in adults will be associated with viral URI (usually influenza A or rhinovirus).
2. Bacterial infections are rare precipitants of asthma in adults.
3. Symptoms of a viral URI are common even in those not infected.
4. There seems to be no indication for routine chest x-ray or antibiotic administration in adults with acute asthma.

Mortality in Acute Asthma

It has been the opinion of many eminent clinicians throughout medical history that asthma is a disease of considerable morbidity but trivial mortality. This belief was evinced by Osler, who wrote:

"The asthmatic pants into old age."

(Ref. 6)

However, in the 20th century, there have been numerous reports of fatal asthma and there has been concern about the iatrogenic nature of some of these deaths.

In the United States, asthma deaths occur at a rate of approximately 0.5-1.0 per 100,000 persons. Mortality for hospitalized asthmatics is approximately 1%. Many of the deaths occur outside the hospital and are sudden and unexpected. There is accumulating evidence that patients at risk for this complication can be detected if objective measures are used to follow the course of disease. Figure 3 shows the result of multiple daily recording of peak expiratory flow rate in a woman who died suddenly of asthma (7). Notice the marked diurnal swings in PEFR. This pattern has been associated with a propensity to sudden death in several studies (7,8). Simple and reliable peak flow meters are now available for home use and ideally all patients with a history of severe asthma should monitor their flow rates at home and notify their physician of changes in pattern.

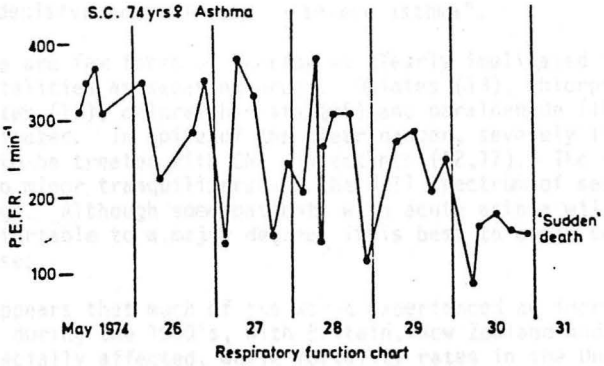


Figure 3. Daily PEFR and sudden death in asthma. (Ref. 7)

In-hospital deaths may occur for a number of reasons. In some cases, the disease process may be tenaciously resistant to therapy, with death due to alveolar hypoventilation or hypoxemia. Such cases are unusual, however. In the last twenty years, the prevention of death from asthma has focused on four major issues: early recognition of the severity of the illness and aggressive treatment, the complications of sedative use, excessive use of beta-adrenergic agonists and fatal complications of IPPB use.

It is unfortunate that failure to promptly hospitalize patients with severe asthma and treat them aggressively continues to be a common problem. It is well-known that patients who have previously been hospitalized for status asthmaticus are at risk for mortality, and mortality rates can be reduced by a special arrangement for self-admission for patients with severe asthma (9). Once patients are hospitalized, the most common therapeutic error appears to be failure to institute or intensify corticosteroid therapy. In one study, the majority of hospitalized patients dying of asthma received no corticosteroids though many had been taking them at home in the preceding month (10). All five fatalities reported by Karetzky in 1975 had received inadequate corticosteroid therapy (11). Cooke reported that over half of all patients with severe asthma referred to his hospital had received no corticosteroids from their physician (12). As he stated, "It is difficult to avoid the conclusion that many doctors fail to grasp the vital importance of decisive drug therapy in severe asthma".

There are few forms of therapy as clearly implicated in iatrogenic asthma fatalities as sedating drugs. Opiates (13), chlorpromazine (14), barbiturates (13), chloral hydrate (15) and paraldehyde (16) have all been implicated. In spite of the clear danger, severely ill asthmatics continue to be treated with CNS depressants (12,17). The danger likely extends to minor tranquilizers and the full spectrum of sedative-hypnotic drugs. Although some patients with acute asthma will be anxious and uncomfortable to a major degree, it is best to avoid sedative drugs in all cases.

It appears that much of the world experienced an increase in asthma mortality during the 1960's, with Britain, New Zealand and Australia being especially affected, while mortality rates in the United States were constant (18-22). Figure 4 illustrates cumulative mortality rates for the years 1960-1974 in six major countries. It is still not clear why some countries experienced this increase in mortality, though the suggestion has been made that it was due to the misuse of pressurized isoproterenol cannisters. There is no doubt that self-administration of these aerosols does entail some risk, including worsening of hypoxemia (23), emergence of tolerance (24), cardiotoxicity (25,26) and delay in seeking physician aid.

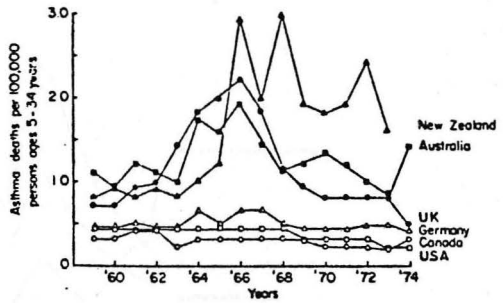


Figure 4. Cumulative asthma mortality in patients age 5-34 in six countries. (Ref. 27)

Figure 5 (27) demonstrates the correlation between sales of isoproterenol products and the increase in mortality rates in England and Wales. Of special interest are the sales of Isuprel-Forte®, a product dispensing five times the dose of isoproterenol provided by the regular isoproterenol cannister. The three countries most often noted as being spared the increase in asthma deaths (the United States, Canada and Germany) did not allow sales of these high dose products. As sales of isoproterenol products declined, mortality rates fell, coincident with an increase in sales of more β_2 selective agonists (metaproterenol, terbutaline, salbutamol).

Figure 6 shows similar data for Australia. Of interest here is the fact that mortality began to return to its previous level even while sales of both regular and high dose isoproterenol continued to climb. Figure 7, data for Canada, shows that despite considerable sales of regular isoproterenol, mortality did not change. Data thus remains suggestive, but by no means conclusive, that the recent epidemic of asthma deaths in some countries may have been due to the overuse of isoproterenol inhalers, particularly the high dose variety.

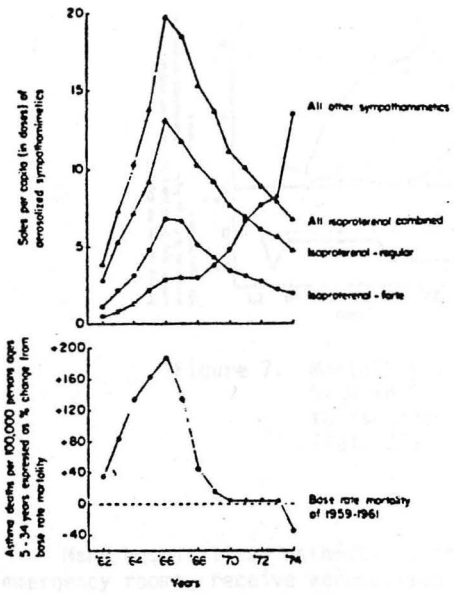


Figure 5. Mortality age 5-34 in relation to isoproterenol sales in England and Wales. (Ref. 27)

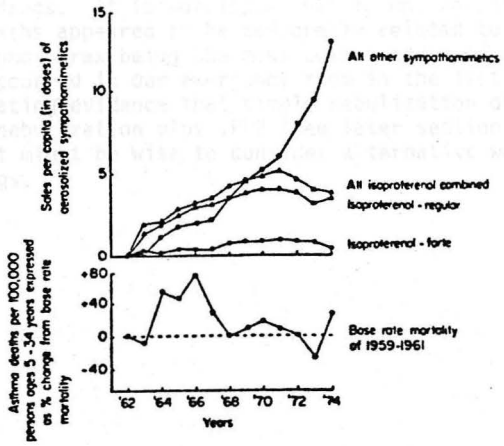


Figure 6. Mortality age 5-34 in Australia related to isoproterenol sales. (Ref. 27)

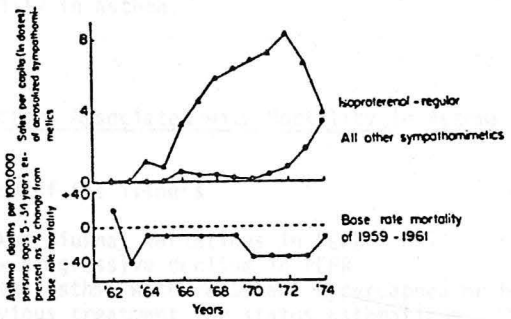


Figure 7. Mortality in patients aged 5-34 in Canada in relation to isoproterenol sales. (Ref. 27)

Many hospitalized asthmatics, or those treated and released from emergency rooms, receive aerosolized beta-adrenergic agonists delivered by IPPB devices. The evidence that IPPB is of benefit in acute asthma is unimpressive, and a number of alternatives exist for nebulizing adrenergic drugs. It is worrisome that in one recent review (11), most hospital deaths appeared to be temporally related to IPPB therapy, with tension pneumothorax being the most common cause of death. One such death has occurred in our emergency room in the last year. In view of the accumulating evidence that simple nebulization of drugs is as effective as nebulization plus IPPB (see later section on beta agonist therapy), it might be wise to consider alternative ways to administer inhaled drugs.

Figure 8 summarizes those factors thought to be associated with increased morality in asthma.

Figure 8

Factors Associated with Mortality in Asthma

1. Course of the illness

   -Marked diurnal variations in PEFR
   -Slow progressive decline in PEFR
   -Status asthma with resistant hypercapnea or hypoxemia
   -Previous treatment for status asthmaticus
   -Duration of illness less than one year

2. Pharmacologic pitfalls

   -Use of sedating drugs
   -Excessive use of isoproterenol aerosols
   -Theophylline toxicity
   -Delay in use of corticosteroids
   -Complications of long term steroid therapy
   -Inadequate oxygen therapy

3. Ventilation - related problems

   -Delay in instituting mechanical ventilation
   -Complications of mechanical ventilation, esp. pneumothorax

4. Physician pitfalls

   -Failure to recognize the severity of illness and provide aggressive therapy.

Lung Function in Acute Asthma

Pathophysiologic changes in lung function in acute asthma are complex and nonuniform and not entirely understood. It is important to try to understand them in order to fully appreciate therapeutic principles and changes in pulmonary function with the course of disease.

Many of the important changes in function in acute asthma are not detectible by routine clinical methods, and require plethysmography or inert gas techniques available only in specialized pulmonary function

laboratories. Though these will be considered in the following discussion, emphasis will be placed on those aspects of lung function which can be assessed in the clinical arena of the emergency room. We will discuss these major areas of dysfunction: abnormalities of air flow, abnormalities of lung volume, and alterations in gas exchange.

Abnormalities of Air Flow in Asthma

Increased resistance to air flow is a hallmark of asthma. The increase in resistance is probably due to a variable combination of increased bronchomotor tone, mucosal edema and mucous secretions. The relative contribution of each of these probably depends to some degree on the duration of the attack (Ref. 2, pg. 259).

Figure 9 demonstrates the typical pattern of spirometric abnormalities in a severe attack of asthma. All of the listed variables can be derived from a simple forced expiration requiring a minimum of sophisticated equipment. Of greatest interest are the FEV_1 and PEFR, which are both severely reduced, but increase greatly with adequate therapy. The maximum midexpiratory flow (MMF, the slope of a line connecting the first and last 25% of the FVC) is initially quite reduced and does not respond to therapy as dramatically as does the PEFR. Also note that even when the patient became asymptomatic, the FEV_1 was still only 55% of predicted.

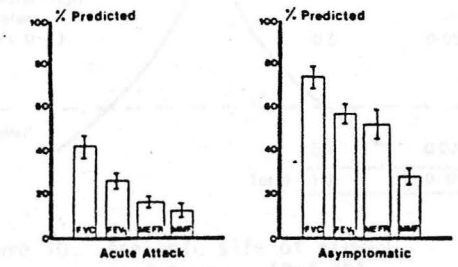


Figure 9. Measures of airway obstruction in acute asthma. (Ref. 28)

The disturbances demonstrated above should be explored in more detail. Figure 10 (Ref. 29) demonstrates the anatomic site of airways resistance in the normal lung. Over 80% of total airways resistance is contributed by bronchi with a diameter greater than 2 mm. However, the greatest cross-sectional area of airways is in those which contribute the least to airways resistance, i.e., those with a diameter less than 2 mm. A considerable portion of these airways can be obstructed without seriously affecting airways resistance. The MMF tends to reflect changes in peripheral airways better than do the PEFR or FEV_1, which are more reflective of changes in the large airways. This figure, as well as other data, suggest that changes in peripheral airways may take longer to resolve than the changes in larger, more central bronchi. To some extent then, at any point in the disease process, measures of large airway function alone may underestimate the severity of disease and extent of involvement. This is a problem in many drug trials in asthma, as FEV_1 or PEFR alone are often utilized to follow the course of therapy. For example, as will be discussed in a later section, parenteral terbutaline may produce the same improvement in PEFR as aerosolized terbutaline, but may differ in providing a greater improvement in measures of small airway function. If only PEFR is measured, then the two treatments will falsely appear equivalent.

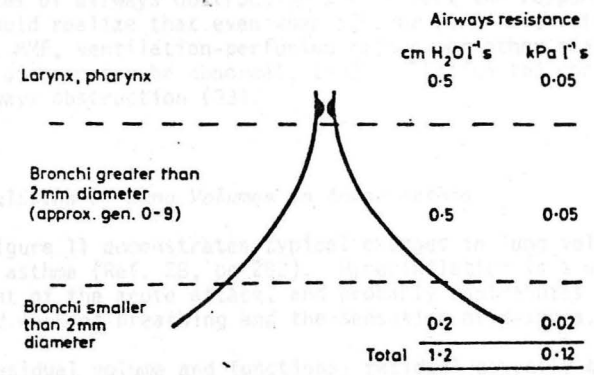


Figure 10. Anatomic site of airway resistance. (Ref.29)

Another common complaint regarding spirometric measurements is their effort dependence. It cannot be denied that PEFR and FEV_1 do have large effort dependent components. However, the majority of the forced expiratory curve is effort independent and measures such as the MMF can be considered to be largely free of effort dependence. In spite of the effort dependence of the FEV_1 and PEFR, these measures appear to be fairly reproducible within subjects. Though they are not sensitive to small changes in peripheral airways, they are usually sufficient for following therapy in patients with acute bronchospasm.

Other measures of airway obstruction can be obtained in the pulmonary function laboratory. Airways resistance, and its reciprocal, conductance (usually expressed as specific conductance, or conductance at specified lung volume) can be assessed by plethysmographic techniques and are sensitive indicators of large airways disease. Closing volume is a sensitive indicator of peripheral airways disease, but need not be measured in those with airway disease detectible by easier tests. Frequency dependence of compliance may also detect small airways disease but again is difficult to perform and is unnecessary if other measures of airway function are abnormal.

In summary, in patients with acute bronchospasm FEV_1 measured by a spirometer or PEFR measured by a peak flow meter provide reasonable estimates of airways obstruction and reflect the response to therapy. One should realize that even when FEV_1 or PEFR have returned to near normal, MMF, ventilation-perfusion ratios, or other measures of small airway disease may be abnormal, thus reflecting the continued presence of airways obstruction (33).

Abnormalities of Lung Volumes in Acute Asthma

Figure 11 demonstrates typical changes in lung volumes in acute severe asthma (Ref. 28, pg 282). Hyperinflation is a well known concomitant of the acute attack, and probably contributes greatly to increased work of breathing and the sensation of dyspnea.

Residual volume and functional residual capacity are almost uniformly increased in patients with acute asthma, though changes in total lung capacity are more variable and usually less marked. Residual volume often exceeds normal FRC during the acute attack. Since TLC increases less, vital capacity must decrease. In occasional patients, TLC may increase dramatically, actually doubling in rare cases.

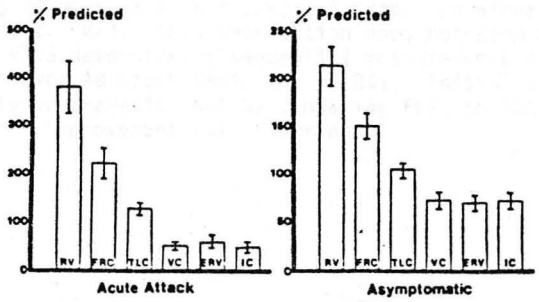


Figure 11. Lung volumes in acute asthma. (Ref. 28)

The mechanisms underlying these changes are poorly understood. There is no clear appreciation of what actually determines TLC, RV and FRC in the normal state. It is tempting to speculate that as airway obstruction occurs, expiratory time and respiratory rate both increase, thus limiting the time available for expiration. These factors together may prevent expiration of a normal amount of air and thus increase FRC. The increase in RV is more difficult to explain but undoubtedly trapping of air behind obstructed small airways is important. Neural influences, changes in the elastic properties of the lung and chest wall, and persistent inspiratory muscle contraction during expiration all may play a role in the abnormalities of lung volumes (30).

For the time being, our knowledge of the abnormalities in lung volumes in acute asthma is predominantly descriptive. One should recall that persistent abnormalities in RV and FRC are common once the patient becomes asymptomatic and that changes in RV probably reflect small airways disease. It should also be acknowledged that increased lung volumes may alter measures of airway obstruction greatly, as hyperinflation may increase transbronchial pressure and provide a dilating effect. The clinical implications of this have been pointed out by Woolcock and Read (31,32). If lung volumes are markedly increased, initial response to therapy may be underestimated if only PEFR or FEV_1 is monitored, the often noted phenomenon of clinical improvement not reflected in spirometric improvement. Figure 12 demonstrates that as obstruction is

relieved, lung volumes fall, and tractive forces on airway walls decrease (Ref. 2, p. 282). Thus obstruction does not seem to have improved. Figure 13 demonstrates sequential measurements of TLC and FEV_1 in one patient over 48 hours (Ref. 28, p 284). Initial changes in FEV_1 did not seem to be dramatic, but by comparing FEV_1 to TLC it can be seen that appreicable improvement was occurring.

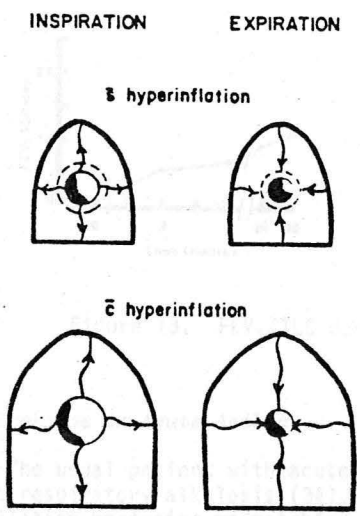


Figure 12. Effect of lung volumes on obstruction. (Ref. 2)

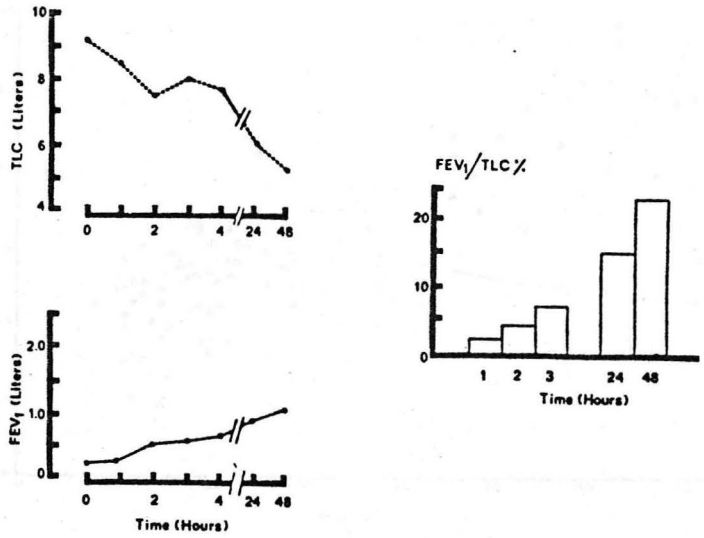
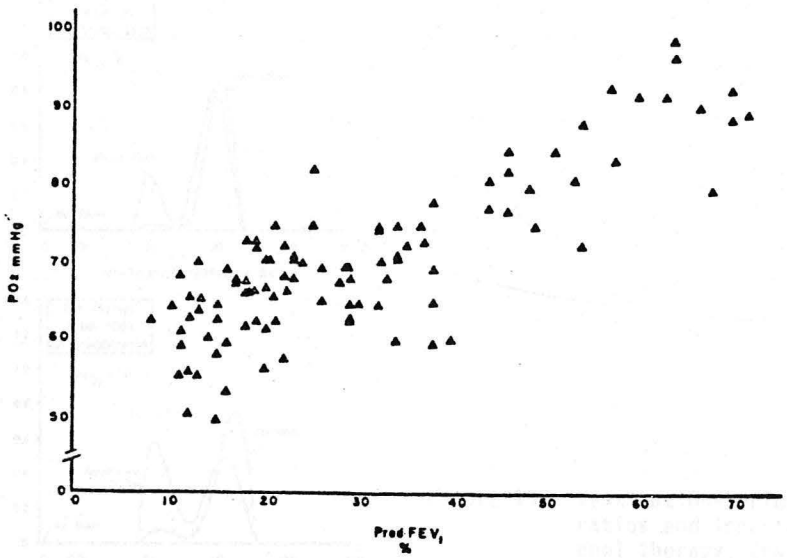


Figure 13. FEV_1/TLC during treatment. (Ref. 28)

Gas Exchange in Acute Asthma

The usual patient with acute asthma will have moderate hypoxemia and a respiratory alkalosis (34). The hypoxemia is usually due to ventilation-perfusion mismatching, though occasional patients may be hypoventilating. Figure 14 demonstrates the relationship between arterial PO_2 and FEV_1. As can be seen, PO_2 tends to fall as FEV_1 declines, but there is wide variation at any given level of FEV_1. The patient with an FEV_1 40% of predicted may have a PO_2 ranging from 58 to 78 mm Hg, thus, initial FEV_1 does not reliably predict need for supplemental oxygen. By analogy, the PO_2 does not necessarily provide a good estimate of the degree of impairment of FEV_1 or PEFR.



Ref. 14. Arterial PO_2 compared to FEV_1. (Ref. 34)

The response of arterial PO_2 to bronchodilators is clinically very important. In some cases, PO_2 will actually fall when such drugs are administered (35). Figure 15 demonstrates distribution in ventilation-perfusion ratios in asthmatics at baseline and after aerosolized isoproterenol (36). After the isoproterenol was given, there was a marked increase in blood flow to the poorly ventilated lung areas, which was accompanied by a fall in arterial oxygen tension. PO_2 returned to baseline after 10 minutes although improvements in MMF persisted. This decline in arterial oxygen tension has been reported with most beta agonists, given parenterally or by aerosol, and theophylline (37-39). In most patients, the fall in PO_2, if it occurs, will be less than 5 mm Hg and probably clinically insignificant. However, for those patients who start with serious hypoxemia, even small falls in PO_2 could be disastrous. Since the hypoxemia is due to ventilation perfusion mismatching, one would expect that it could be easily reversed with a moderately enhanced F_IO_2.

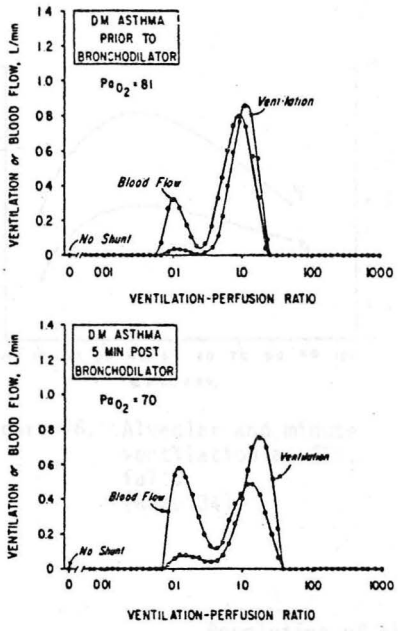


Figure 15. Ventilation-perfusion ratios and isoproterenol therapy. (Ref. 36)

Figure 16 demonstrates the response of minute and alveolar ventilation to progressive declines in FEV_1 (34). Alveolar hyperventilation, leading to hypocapnea, does occur but note that alveolar ventilation does not increase as dramatically as does minute ventilation. Thus, much of the increased respiratory work goes to ventilating dead space. A point is eventually reached at which ventilation declines precipitously and respiratory failure ensues. In most patients, this point will not be reached until FEV_1 has fallen to 30-35% of its predicted value.

Figure 17 compares PCO_2 to FEV_1 (40). PCO_2 does not usually exceed 45 mm Hg until FEV_1 is below 35% of predicted. Hypercapnea is thus an ominous sign in acute asthma.

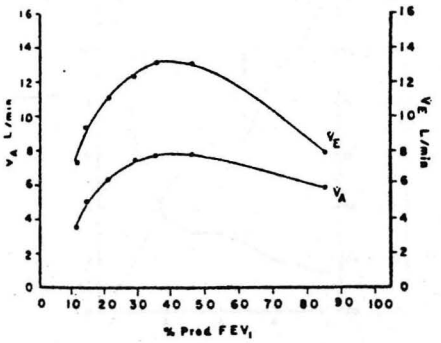


Figure 16. Alveolar and minute ventilation as FEV_1 falls. (Ref. 34)

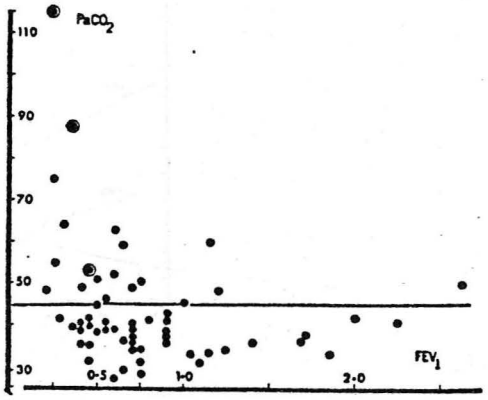


Figure 17. P_aCO_2 and FEV_1 in asthma. (Ref. 40)

Resolution of the Acute Attack of Asthma

Though there is wide variability in the rates at which patients with acute asthma respond to therapy, the response generally follows a similar progression. It appears that those measures which reflect large airways obstruction, i.e. PEFR, FEV_1, R_{aw} and specific conductance, return toward normal most quickly. Those measures which reflect small airways disease, i.e., RV, PO_2 and MMF tend to respond much more slowly. Figure 18 demonstrates the rate of resolution of these variables in a patient with a severe acute attack (Ref. 2, p 272). Over the course of eight hours of therapy, FEV_1 increased to a value which would be considered near normal while MMF was still less than 50% of predicted. This figure also reiterates that even when the patient is asymptomatic (point 2), or the physician judges the patient to be well (point 3), considerable abnormality of lung function remains and should influence discharge planning. Figure 19 illustrates once again the prolonged therapy which may be necessary to return MMF, RV and PaO_2 to normal (Ref. 2, p. 271).

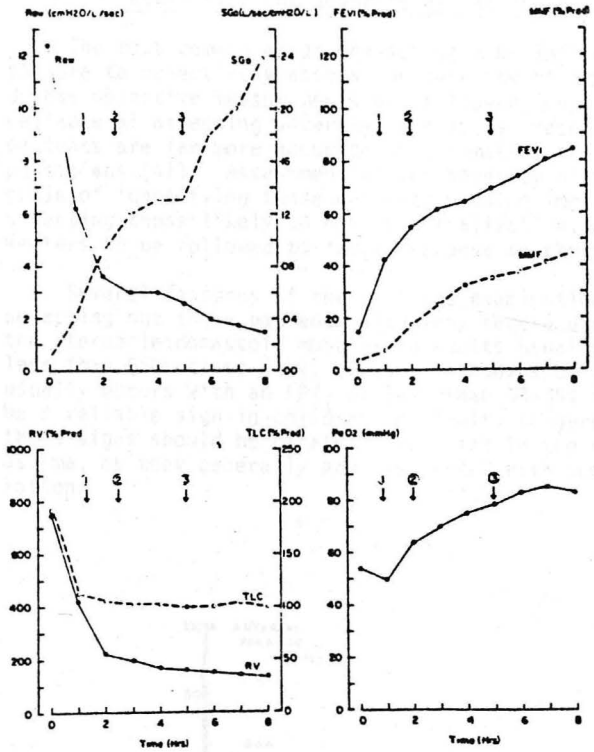


Figure 18.
Rate of resolution of various parameters.
(Ref. 2)

Analysis of Physiological Data When Signs and Symptoms Have Disappeared

Clinical State	R_{aw}	SG_a	$FEV_{1.0}$*	MMF*	TLC*	RV*	Pa_{O_2}
Use of accessory muscles of respiration ended	5.3	0.06	39	10	115	360	50
Attack subjectively ended	3.4	0.10	56	18	105	220	64
Attack objectively ended	2.6	0.13	70	35	100	160	78
Values at end of study	1.5	0.24	85	46	100	130	83
Values after one week of therapy	1.0	0.35	94	88	96	110	97

Figure 19. Rate of resolution of acute attack-PO_2
(Ref. 2)

Estimating the Severity of the Acute Attack of Asthma

The most common error physicians make in treating acute asthma is failure to objectively assess the severity of dysfunction present. Unless objective measurements are followed, physicians are quite unreliable at assessing severity, and it has recently been shown that patients are far more accurate in estimating their PEFR than are their physicians (41). Assessment of the severity of an acute attack has the goals of identifying those patients needing immediate intensive therapy, selecting those likely to need hospitalization, and establishing parameters to be followed to judge response to therapy.

Several features of the physical examination may be helpful in selecting out those patients with very severe disease. Retractions of the sternocleidomastoid muscles in adults usually reflect an FEV_1 of less than 650 cc/sec (42). Pulsus paradoxus of greater than 10 mm Hg usually occurs with an FEV_1 of less than 30-35% predicted and appears to be a reliable sign in children and adults (Figure 20, Ref. 40). Both of these signs should be carefully assessed in the patient with acute asthma, as they generally are associated with necessity of hospitalization.

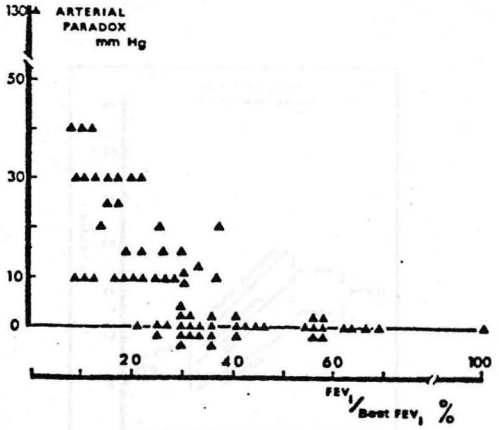


Figure 20. Pulsus paradoxus and FEV_1 (Ref. 40)

If arterial blood gases are measured, P_aCO_2 is the most reliable measure of severity of obstruction and all patients with PCO_2 > 45 mm Hg should be promptly admitted and managed very aggressively. If the P_aCO_2 is normal, one cannot be sure whether this reflects such mild obstruction that alveolar hyperventilation has not yet occurred or whether the patient is so severely obstructed that alveolar ventilation is now on the descending portion of Figure 16. Proper interpretation will require input from physical examination and other objective measurements of lung function.

All emergency rooms treating a significant number of asthmatics should have available either a peak flow meter or a spirometer. When these devices are used, there appear to be several good guidelines to identify those who require admission. Banner suggested that asthmatics whose initial PEFR was less than 16% of predicted or those who failed to respond to one injection of 0.3 cc of 1:1000 epinephrine with at least a 16% improvement, required hospitalization (43). Nowak and associates have published guidelines for admission using FEV_1 as the objective measure of lung function and Figure 21 demonstrates their results (44). They noted that patients who presented with an FEV_1 < 600 cc or who had an FEV_1 < 1600 cc after ER treatment did poorly if sent home, and usually returned to the hospital within 48 hours with severe obstruction. They also noted that failure to significantly increase FEV_1 after an injection of terbutaline .25 mg subcutaneously was a characteristic of patients requiring admission.

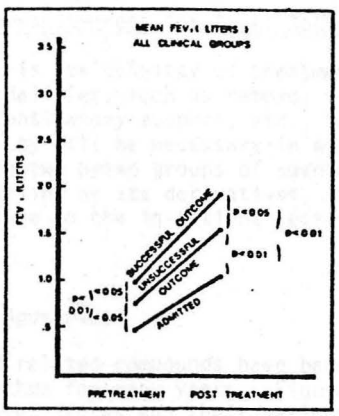


Figure 21. FEV_1 and outcome of acute attack. (Ref. 44)

Figure 22 summarizes those signs which indicate need for hospitalization in acute asthma. It should be emphasized that these are not sole criteria for admission, but sufficient ones. In other words, some patients who do not exhibit any of these signs will need admission. This is especially the case with those who have returned to the ER frequently over a short period of time and those who are already on maximal home pharmacologic therapy.

Figure 22

Signs of Need for Hospitalization in Acute Asthma

1. Retraction of SCM muscles
2. Pulsus paradoxus > 10 mm Hg
3. P_aCO_2 > 45 mm Hg
4. PEFR < 16% predicted
5. Failure of FEV_1 or PEFR to respond to β-agonists
6. Initial FEV_1 < 600 cc or post-treatment FEV_1 < 1600 cc

Pharmacotherapy for Acute Asthma

Pharmacotherapy is the mainstay of treatment for the acute attack of asthma. Other modalities, such as removal from exposure to allergen, emotional support, ventilatory support, etc., may be required in some cases, but drug therapy will be necessary in essentially all patients. ER therapy focuses on two broad groups of agents, the beta-adrenergic agonists and theophylline or its derivatives. We will not discuss agents more appropriate to the in-patient setting, for example, corticosteroids.

The Beta-Adrenergic Agonists

Epinephrine and related compounds have been used to treat both acute and chronic asthma for many years. Figure 23 lists the agents now available in the United States and their various routes of administration. In the ER, we must decide which drug to give, which route to use, and whether to begin with beta-adrenergic or theophylline therapy. Both groups of drugs are thought to mediate bronchodilation by increasing the concentration of cAMP in the smooth muscle cell, theophylline by inhibiting the activity of phosphodiesterase (which degrades cAMP) and beta-agonists by stimulating adenyl cyclase, thus increasing production of cAMP.

Figure 23

Beta-Adrenergic Agonists Now Available in the U.S.

Generic Name	B_1	B_2	Duration of Action	Cannister Inhaler	Solution for Nebulization	Parenteral
Epinephrine	+++	+++	60-90 min	Yes	No	Yes
Isoproterenol	+++	+++	60-90 min	Yes	Yes	Yes
Isoetharine	++	+++	2-3 hrs	Yes	Yes	No
Metaproterenol	+	+++	3-6 hrs	Yes	Yes	No
Terbutaline	0-+	+++	4-8 hrs	No	No	Yes

Both epinephrine and terbutaline are available for parenteral use, and are generally given subcutaneously. Isoproterenol is available for intravenous use but is rarely administered by that route to adults. The advantages usually claimed for parenteral administration include rapid onset of action, lack of dependence on patient cooperation, and potential delivery to parts of the lung which are not well ventilated. While onset of action is usually within five minutes for subcutaneous epinephrine or terbutaline, it is only slightly slower for inhaled adrenergic agonists. It indeed is difficult for some patients, especially children, to effectively use inhaled drugs, and parenteral agents are preferred for them.

The third possible advantage should be discussed in more detail. When measures of large airway function such as FEV_1, PEFR or R_{aw} are used, appropriate doses of parenteral and inhaled beta-adrenergic agonists are generally equally effective. In a recent study comparing inhaled versus subcutaneous terbutaline, no significant difference was found in improvement in PEFR and SG_{aw} between the modes of administration (45). However, when sensitive measures of small airways function (capacity of isoflow and ratio $V_{max\ 50}$) were used, it was found that only parenteral terbutaline had effects on both large and small airways. If these observations are confirmed, one clear advantage for parenteral therapy would be present.

In choosing between the two drugs, epinephrine has the possible advantage of many years of widespread use. Increases in PEFR usually

begin within five minutes after a subcutaneous injection, are maximal by 30 minutes and may persist as long as 90-180 minutes. It is generally recommended that 1.0-1.5 ml of a 1:1000 solution be given in three divided doses over a one hour period. A history of hypertension or ischemic heart disease, a pulse rate greater than 130, or age greater than 45-50 years are often said to be contraindications to such therapy.

In isolated organ systems, terbutaline appears to have a far more selective agonist effect on β_2 receptors in lung and skeletal muscle than on β_1 receptors in the heart. It was thus hoped that parenteral terbutaline would confer the advantage of less tachycardia, less increase in contractility (and presumably myocardial oxygen demand) and lower risk of arrhythmia than parenteral epinephrine. This does appear to be the case for aerosol administration. However, when these drugs are given parenterally, and probably to a lesser extent when given orally, much of the β_2 specificity is lost. Figure 24 compares equally effective doses of subcutaneous and aerosol terbutaline and reveals an increase in heart rate with the parenteral form and relatively no change with aerosol (46). Figure 25 shows that when effective doses of terbutaline and epinephrine subcutaneous are compared, tachycardia is a more prominent feature of terbutaline than epinephrine (47). Finally, figure 26 demonstrates the dramatic increases in cardiac output that may occur when this "β_2 selective" agent is given subcutaneously (48). This loss of selectivity with parenteral injection appears to be a feature of all β_2-selective agonists, as salbutamol given by IV infusion has been shown to cause tachycardia whereas more effective doses by aerosol did not (49).

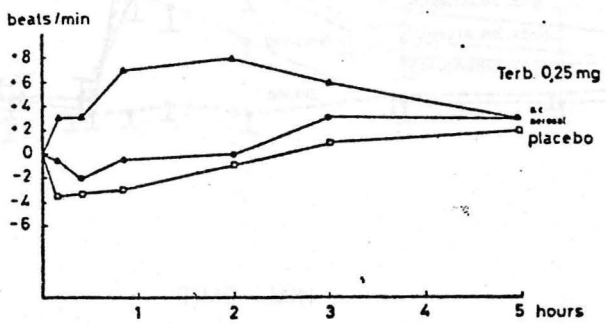


Figure 24. Subq and aerosol terbutaline - increases in heart rate. (Ref. 46)

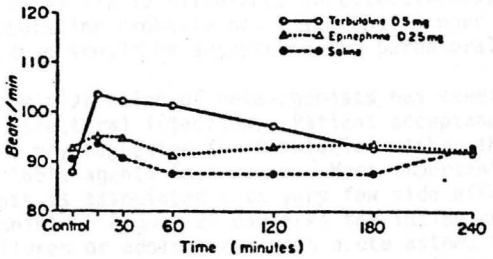


Figure 25. Increase in heart rate with subcutaneous terbutaline and epinephrine. (Ref. 47).

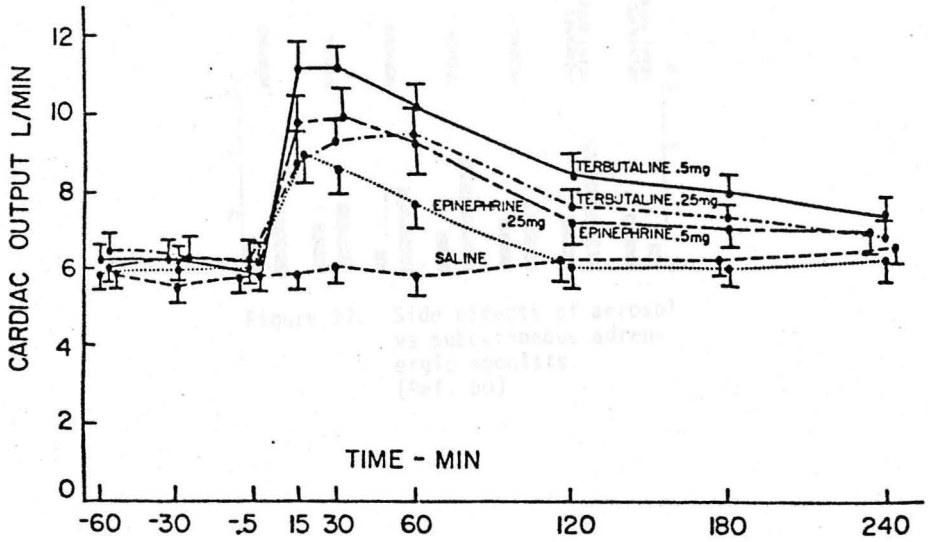


Figure 26. Effect of subcutaneous terbutaline on cardiac output. (Ref. 48)

Thus, when parenteral terbutaline and epinephrine are compared, there appears to be little difference in effectiveness and in cardiac response. Terbutaline probably has a somewhat longer duration of action. Either drug should be acceptable for parenteral use.

Aerosol administration of beta-agonists has several potential advantages over parenteral injection. Patient acceptance, especially among children, may be better for inhalation rather than injection. The choice of available agents is broader. Most important, inhalation of β_2 selective agents is associated with very few side effects compared to parenteral agonists. Figure 27 compares the incidence of various side effects in children or adolescents with acute asthma treated with subcutaneous epinephrine or terbutaline or aerosol isoetharine (50). These three regimens provide equivalent increases in FEV_1 but tremor and nervousness were considerably more frequent with the parenteral agents. Since effective doses of aerosols provide equal bronchodilatation with fewer side effects, they may be the preferred mode of administration for beta-agonists in acute asthma. If studies suggesting a more diffuse site of action for injected terbutaline than aerosol are confirmed, this will have to be reassessed.

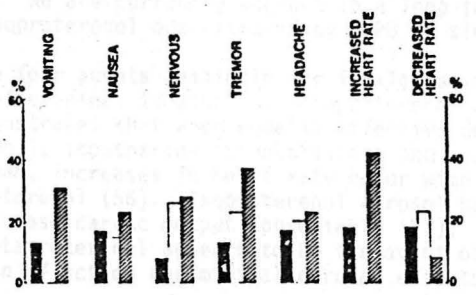


Figure 27. Side effects of aerosol vs subcutaneous adrenergic agonists. (Ref. 50)

A potential disadvantage of aerosol administration is the difficulty some patients have with inhalation therapy. It has recently been reported that 47% of adult patients hospitalized for acute asthma used cannister nebulizers incorrectly (51). Even after teaching, 50% who improved their technique reverted to the incorrect method. Some patients also have trouble utilizing IPPB therapy, particularly if the person administering IPPB is not highly skilled. If patients have trouble utilizing inhalation therapy correctly, then parenteral therapy may be preferred.

Before comparing the drugs available for inhalation, we should consider the various techniques by which aerosols may be produced and inhaled. There are three techniques commonly used today: pressurized cannisters, simple nebulization and inhalation, and nebulization combined with IPPB. The latter technique is probably the one used most frequently. All create adequate particle size for penetration into airways. A number of studies in stable asthmatics demonstrate that all three techniques produce equal improvement in FEV_1 and PEFR, though measures of small airways obstruction have not usually been reported (52-55). Many feel that IPPB may have the advantage of decreasing the work of breathing in acute asthma, but this has not been rigorously demonstrated. Given the concern about pneumothorax in association with IPPB, there appears to be little reason to prefer this technique over the other two. We are currently engaged in a long term study to compare efficacy of isoproterenol administered by IPPB or simple nebulization.

There are four agents available for inhalation through pressurized cannisters (epinephrine, isoetharine, isoproterenol and metaproterenol). Figure 28 demonstrates that when equally effective doses of metaproterenol (Alupent), isoetharine (Bronchilator) and isoproterenol (Medihaler) are given, increases in heart rate occur with all preparations except metaproterenol (56). Isoproterenol aerosol has also been demonstrated to increase cardac output appreciably (57). If cannisters are to be used, metaproterenol appears to be the agent of choice for its longer duration of action and minimal cardiac effects.

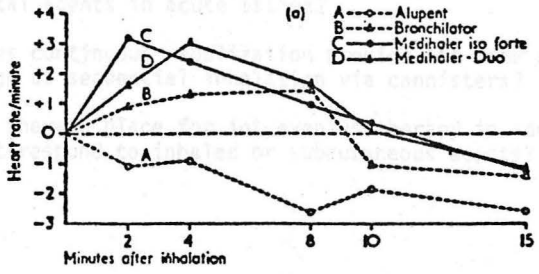


Figure 28. Changes in heart rate with various adrenergic aerosols. (Ref. 56)

There is considerable controversy over whether cannister aerosols should be administered in a single large dose or as multiple sequential inhalations. Heimer and associates (58) recently compared one large inhalation of metaproterenol (1.95 mg) to three sequential inhalations of .65 mg ten minutes apart (total dose, 1.95 mg). They found a significantly better response in FEV_1 with sequential administration than with a single large dose, an effect which they attribute to improved penetration of sequential doses of the drug. The same has been suggested for isoproterenol (49). In summary, metaproterenol, one puff each ten minutes for three doses appears to be the most reasonable choice for cannister therapy.

Isoproterenol, isoetharine, and metaproterenol are available for nebulization via hand held nebulizers, gas powered nebulizers and IPPB. The above comments on selectivity and duration of action hold. Metaproterenol, 0.3 cc in 2-2½ cc saline, appears to be a reasonable choice for nebulization. Nebulization should occur over 10-15 minutes to allow for sequential penetration.

In summary, the beta-agonists are rapidly effective and when appropriate choices of agent and route of administration are made, are reasonably free of side effects. Figure 29 poses several unanswered questions of importance regarding beta-agonist therapy.

Figure 29

Unanswered Questions - Beta-Agonist Therapy

1. Will newer, more selective β_2 agonists (salbutamol, fenoterol) provide an advantage over currently available drugs?
2. Is there any rationale for combining aerosol and parental agents in acute asthma?
3. Does continuous nebulization provide the same advantage as sequential inhalation via cannisters?
4. Is there a place for intravenous therapy in adults who do not respond to inhaled or subcutaneous agents?

Theophylline Therapy in Acute Asthma

Theophylline and its salts are widely used in the management of bronchospastic diseases, and have been demonstrated to be effective in chronic asthma (60). For emergency room use in adults, the drug is generally given intravenously, and our discussion will be confined to IV aminophylline, the most widely used parenteral product. Aminophylline is the ethylenediamine salt of theophylline and is approximately 85% as potent as theophylline on a weight basis. Theophylline is metabolized in the liver and half-life in adults is usually 4-8 hours. Unfortunately, there is tremendous inter-individual variation in rates of metabolism, and to some degree, in volume of distribution. Thus, it is very difficult to individualize intravenous aminophylline therapy without guidance from serum levels, which correlate well with effectiveness and toxicity. The necessity for intravenous infusions, constant infusion rates, considerable investment of nursing time, and likelihood of GI toxicity when levels are rapidly raised (60) all make this form of therapy considerably more cumbersome than beta-agonist treatment.

Is intravenous aminophylline effective in the management of acute asthma? Several recent studies demonstrate that it may add little or nothing in the first few hours of therapy. Josephson (61) compared the response of 44 patients with acute asthma to randomized administration of subcutaneous epinephrine or epinephrine plus aminophylline (the dose being that recommended by Mitenko and Ogilvie (62)). As Figure 30 illustrates, there was no difference in improvement in PEFR between the two groups, though measurements were made for only 90 minutes. Rossing (63) carried out a similar study in which 48 patients with acute asthma were randomized to treatment with subcutaneous epinephrine, aerosolized isoproterenol or IV aminophylline. The study revealed that the two beta-agonists produced equal responses, while aminophylline was distinctly inferior in the first hour (Figure 31). The duration of ER stay was almost twice as long for those patients treated with aminophylline as for those treated with aerosol isoproterenol.

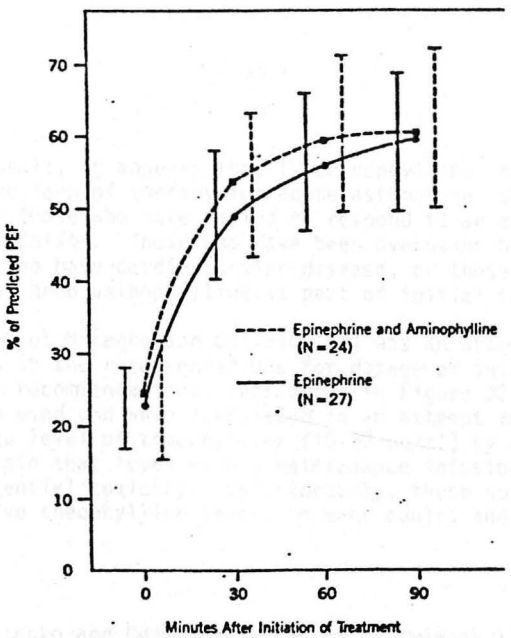


Figure 30. Aminophylline plus epinephrine vs epinephrine alone as initial therapy. (Ref. 61)

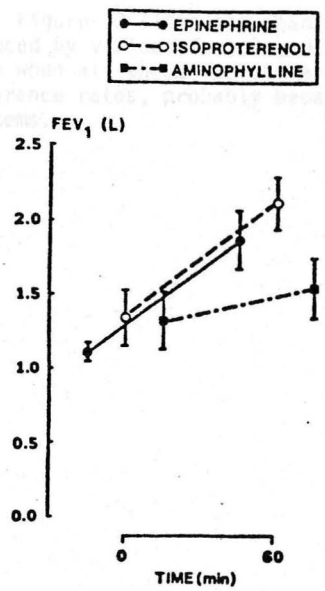


Figure 31. β-agonists or IV aminophylline as initial therapy. (Ref. 63)

As a result, it appears that IV aminophylline should be considered a second line form of therapy for acute asthma, and should generally be reserved for those who have failed to respond to an adequate trial of adrenergic agonists. Those who have been overusing beta-agonists at home, those who have cardiovascular disease, or those clearly requiring admission may need aminophylline as part of initial therapy.

The work of Mitenko and Ogilvie (62) was an attempt to bring order out of chaos in the recommendations for dosage of intravenous aminophylline. Their recommendations, reproduced in Figure 32, have been widely accepted and used and were formulated in an attempt to rapidly establish a therapeutic level of theophylline (10-20 µg/ml) by a loading dose and then to sustain that level with a maintenance infusion, all the while avoiding potential toxicity. Unfortunately, these guidelines will produce excessive theophylline levels in many adults and should be revised.

Figure 32

Mitenko and Ogilvie - Doses of IV Aminophylline

	Loading	Maintenance
Initial Therapy	5.6 mg/kg over 20 min.	0.9 mg/kg/hr

Figure 33 lists the changes in theophylline clearance known to be induced by various factors, usually beyond the control of the physician. Even when all these factors are similar, patients vary markedly in clearance rates, probably because of genetic differences in metabolic systems.

Figure 33

Factors Affecting Theophylline Pharmacokinetics

Factor	Change in Theophylline Metabolism	Comments
Patient Factors:		
-Age < 10 years[64]	↑ rate of elimination	Greater maintenance rates needed.
-Obesity (65)	↑ volume of distribution	Use ideal body weight to calculate dose.
-Smoker[66,67]	↑ rate of elimination	Greater maintenance rates needed.
Disease Factors:		
-CHF, cor pulmonale[68-70]	↓ rate of elimination	Elimination rates may fluctuate with severity of disease.
-Liver disease[71]	" " " "	
-Pneumonia(70)	" " " "	
-Severe obstruction[70]	" " " "	
-Acidosis (72)	↑ volume of distribution	
Other Factors:		
-High protein diet[73]	↑ rate rate of elimination	Probably not clinically important.
-Charcoal broiled meats[74]	" " " "	
-Macrolide antibiotic(75)	↓ rate of elimination	Erythromycin and Troleandomycin
-Heavy caffeine intake[76]	" " " "	

The wide variation in clearance rates, especially as underlying diseases such as pulmonary edema are resolving, makes it difficult to suggest guidelines for intravenous therapy without support from rapidly available serum theophylline levels. If guidelines are to be used, those recommended by the FDA, reproduced in Figure 34 below, should be used (77). These new guidelines make adjustments for disease states and age, as well as for the accumulation of theophylline which may occur after 10-12 hours of parenteral therapy.

Rectal administration of theophylline will only rarely be used in adults, though it is used with some frequency in children. One should realize that theophylline suppositories are often erratically and incompletely absorbed and should be discarded in favor of enemas of theophylline solutions (78).

In summary, intravenous aminophylline may be given as initial therapy to those with indicators of need for hospitalization or those in whom beta-agonists are contraindicated. When no contraindication to therapy with beta-agonists exist, they should be considered the first line of pharmacotherapy for the acute attack of asthma.

Aminophylline Dosage for Patient Population

I. Not currently receiving theophylline products:

Group	Loading Dose +	Maintenance Dose + For Next 12 Hours	Maintenance Dose + Beyond 12 Hours
Children 6 months to 9 yrs	6 mg/kg *(5)	1.2 mg/kg/hr *(1.0)	1.0 mg/kg/hr *(0.85)
Children age 9-16 and young adult smokers	6 mg/kg *(5)	1.0 mg/kg/hr *(0.85)	0.8 mg/kg/hr *(0.7)
Otherwise healthy nonsmoking adults	6 mg/kg *(5)	0.7 mg/kg/hr *(0.6)	0.5 mg/kg/hr *(0.43)
Older patients and patients with cor pulmonale	6 mg/kg *(5)	0.6 mg/kg/hr *(0.5)	0.3 mg/kg/hr *(0.26)
Patients with congestive heart failure, liver disease	6 mg/kg *(5)	0.5 mg/kg/hr *(0.4)	0.1-.2 mg/kg/hr *(0.1)

* *Equivalent anhydrous theophylline dose indicated in parentheses*
\+ *Based on estimated lean (ideal) body weight*

II. Currently receiving theophylline products:

Determine, where possible, the time, amount, route of administration, and form of the patient's last dose. The dosage should be based on theophylline equivalence (1.2 mg of aminophylline is equivalent to 1.0 mg of theophylline).

The loading dose for theophylline should be based on the general expectation that each 0.5 mg/kg (of lean or ideal body weight) of theophylline administered as a loading dose will result in a 1 mcg/ml increase in serum theophylline concentration. Ideally, then, the loading dose should be deferred until a serum theophylline concentration can be rapidly obtained. If this is not possible, the clinician must exercise judgment in selecting a dose that has a potential for benefit with minimum additional risk. When there is sufficient respiratory distress to warrant a small risk, 2.5 mg/kg of intravenous theophylline (2.9 mg/kg aminophylline) is likely to increase further the serum concentration by only about 5 mcg/ml. If the patient is not already experiencing theophylline toxicity, the risk of dangerous adverse effects from this dose is low.

After this modified loading dose, the maintenance dosage recommendations, in this group of patients,are the same as those described above.

Figure 34. FDA recommendations for IV aminophylline dose. (Ref. 77)

Future Pharmacologic Developments

A number of potentially useful therapeutic agents are now being investigated, including newer β_2 selective agonists. It is hoped that further study may illuminate what role, if any, corticosteroids play in the ER management of asthma. For the time being, the most promising investigational agent appears to be atropine and its derivatives.

Anticholinergic agents in one form or another have been used for the management of asthma for a number of years, and the effectiveness of atropine as a bronchodilator is well documented. Most physicians have been reluctant to use atropine because of possible cardiac side effects and the theoretic possibility of drying of secretions and production of inspissated mucus. In spite of these potential objections, small doses of nebulized atropine (.8 mg in adult) have been shown to be effective in both childhood and adult asthma (79,80). The synthesis of atropine derivatives which lack its cardiovascular effects has been enthusiastically pursued.

Ipratropium bromide (SCH 1000) is an atropine derivative which is an effective bronchodilator. Inhaled doses in the therapeutic range have only very infrequent side effects (81) and ciliary velocity and mucus secretion rates do not change (82,83). When compared to isoproterenol, the peak effect on FEV_1 and PEFR is somewhat delayed but comparable and the duration of action of ipratropium is at least 3-4 hours (84). Its effects have been shown to be additive with beta-agonists and steroids (85). Long term studies indicate that the drug is safe and effective.

It will be interesting to see if ipratropium has a role in the emergency room. It is hoped that it may prove useful to those who fail to respond to beta-agonists, as an adjunct to theophylline and/or steroids.

Therapeutic Plan for ER Management of Acute Asthma

Given the knowledge we now have of prediction of outcome, rates of resolution and drug treatment of the acute attack of asthma, conventional approaches to ER management are inadequate. A recent study at the University of Pennsylvania demonstrated the importance of monitoring improvement in pulmonary function (86). When decisions to discharge or hospitalize were made solely on historical and physical data, the relapse rate was 25%; 6% of those discharged required hospitalization in the next ten days.

The availability of simple devices to monitor therapy in the ER makes significant differences in type of therapy given, use of invasive monitoring, duration of ER stay and ultimate outcome. Management of acute asthma in our ER was monitored prior to and after instillation of a simple spirometer in the ER and institution of a one page flow sheet for asthma management. The following figure documents changes in practice and outcome as a result, primarily, of availability of spirometry:

PMH Emergency Room Asthma Audit

	Pre-Audit	Post-Audit
No. of patients	75	50
Average duration ER stay	> 5 hrs	3.4 hrs
% stays > 6 hours	-	4%
Relapse within 7 days	17%	2%
ABG's drawn	44%	16%
IV aminophylline as first therapy	75%	27%
Recording of pulsus paradoxus	16%	73%
Recording of SCM retraction	43%	76%

Duration of ER stay dropped, frequency of arterial puncture fell, and relapse rate was lower.

The following summarizes what I feel to be a reasonable approach to the ER management of asthma. The guidelines will be changed somewhat by each physician depending on his experience and most importantly, his prior experience with a particular patient. It should be emphasized that even patients who do not have strict indicators for admission by spirometric or clinical criteria may do better with hospitalization. This is particularly the case for those who respond well in the ER but are returning frequently or those who respond well, but are already on maximal home therapy.

1. The patient should be placed in a quiet room and reassured that his or her discomfort is understood and that help is forthcoming. A brief history and physical exam, with special attention to those features known to reflect severe disease should be done. This should be followed by expiratory spirogram or PEFR.

2. Those who have predictors of poor outcome in physical or spirometry should be admitted without undue delay in the ER. Therapy with beta-agonists, theophylline and corticosteroids will probably be necessary. Those with initial FEV_1 < 35% predicted should have arterial blood gases drawn. Those with initial FEV_1 > 35% predicted should be placed on nasal O_2, 2-4 L/min.

3. Those without predictors of necessity of admission should receive beta-adrenergic therapy for one hour, after which physical and spirometry should be repeated. Those who have contraindications to beta-agonists should receive IV aminophylline initially.

4. If response to beta-agonists is good, this therapy may be continued up to a maximum of 4-6 hours. If no response to beta-agonists (admission probably necessary) or only partial response, begin IV aminophylline.

5. Above therapy may be continued for a total of 4-6 hours. At the end of this time, all of those not ready for ER discharge should be admitted, and probably will require steroids.

6. Remember that those discharged from the ER will probably have significant residual disease and should be sent home on intensified therapy (not their usual maintenance regimen). In some cases, a short course of corticosteroids at home may be required.

References

1. American Thoracic Society Committee on Diagnostic Standards for Nontuberculous Diseases. Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. Am Rev Respir Dis 85:762, 1962.

2. McFadden ER Jr: Respiratory mechanics in asthma, in Weiss and Segal, ed. Bronchial Asthma. Boston, Little, Brown, 1976. p. 260.

3. Dick EC, TE Minor, JA Peterson, et al: Viruses as precipitants of asthmatic attacks. Clin Res 20:799, 1972.

4. Hudgel DW, Lelon Langston Jr, JC Selner, et al: Viral and bacterial infections in adults with chronic asthma. Am Rev Res Dis 120:393, 1979.

5. Clarke CW: Relationship of bacterial and viral infections to exacerbations of asthma. Thorax 34:344, 1979.

6. Osler W: The Principles and Practice of Medicine. (4th ed.) Edinburgh:Pentland, 1901.

7. Clark TJH: Acute severe asthma, in Clark & Godfrey, Eds. Asthma, Philadelphia, WB Saunders, 1977, pg. 306.

8. Hetzel MR, TJH Clarke and MA Branthwaite: Asthma: analysis of sudden deaths and ventilatory arrests in hospital. Br Med J 1: 808, 1977.

9. Crompton GK, IWB Grant and P Bloomfield. Edinburgh emergency asthma admission service: Report on 10 year's experience. Br Med J 2:1199, 1979.

10. Iisalo EI, EVM Iisalo and EJ Tala: Deaths from asthma, with special reference to the last drug treatment. Acta Med Scand 185:45, 1969.

11. Karetzky MS: Asthma mortality: an analysis of one years experience, review of the literature and assessment of current modes of therapy. Medicine 54:471, 1975.

12. Cooke NJ, GK Crompton and IWB Grant: Observations on the management of acute bronchial asthma. Br J Dis Chest 73:157, 1979.

13. Walton CHA, DW Penner and JC Wilt: Sudden death from asthma. Can Med Assoc J 64:95, 1951.

14. Shapiro JB and CF Tate: Death in status asthmaticus: A clinical analysis of eighteen cases. Dis Chest 48:484, 1965.

15. Richards W and JR Patrick: Death from asthma in children. Am J Dis Child 110:4, 1965.

16. Houston JC, S DeNavasquez and JR Trounce. A clinical and pathological study of fatal cases of status asthmaticus. Thorax 8:207, 1953.

17. Editorial: Increasing deaths from asthma. Br Med J 1:329, 1968.

18. Speizer FE and R Doll: Observations on recent increase in mortality from asthma. Br Med J 1:335, 1968.

19. Fraser P and R Doll: Geographical variations in the epidemic of asthma deaths. Brit J Prev Soc Med 25:34, 1971.

20. Gandevia B: The changing pattern of mortality from asthma in Australia. Med J Aust 1:747, 1968.

21. Inman WHW and AM Adelstein: Rise and fall of asthma mortality in England and Wales in relation to use of pressurized aerosols. Lancet 2:279, 1969.

22. Stolley PD: Why the United States was spared an epidemic of deaths due to asthma. Amer Rev Resp Dis 105:883, 1972.

23. Palmer KNU and ML Diament: Effect of aerosol isoprenaline on blood gas tensions in severe bronchiol asthma. Lancet 2:1232, 1967.

24. Chervinsky P and S Belinkoff: Comparison of metaproterenol and isoproterenol aerosols: spirometric evaluation after two months therapy. Ann Allergy 27:611, 1969.

25. Rhoades RB, Leifer KN, Bloom FL, et al: Spirometric comparison of carbuterol and isoproterenol aerosol therapy in bronchial asthma. Amer Rev Resp Dis 114:79, 1976.

26. Stain M and S Spector: Isoproterenol, asthma and the heart. Ann Int Med 83:408, 1975.

27. Stolley PD and R Sckinnor: Association between asthma mortality and isoproterenol aerosols: a review. Prev Med 7:519, 1978.

28. McFadden ER Jr and RH Ingram: Sprometry, lung volumes, and distribution of ventilation in asthma, in Weiss and Segal, eds. Bronchial Asthma, Boston, Little Brown, 1976, pg 280.

29. Pride NB: Physiology, in Clark and Godfrey, eds. Asthma, Philadelphia, W.B. Saunders, 1977, pg. 20.

30. Martin J, E Powell, S Shore, et al: The role of respiratory muscles in the hyperinflation of bronchial asthma. Am Rev Resp Dis 121:441, 1980.

31. Woolcock AJ and J Read: Improvement in bronchial asthma not reflected in forced expiratory volume. Lancet 1:1323, 1965.

32. Woolcock AJ and J Read: Lung volumes in exacerbations of asthma. Am J Med 41:259, 1966.

33. McFadden ER, Jr and HA Lyons: Airway resistance and uneven ventilation in bronchial asthma. J Appl Phys 25:365, 1968.

34. McFadden ER and HA Lyons: Arterial blood gas tension in asthma. N Engl J Med 278:1027, 1968.

35. Field GB: The effects of posture, oxygen, isoproterenol and atropine on ventilation-perfusion relationships in the lung in asthma. Clin Sci 32:279, 1967.

36. Wagner PD, RB Laravuso, RR Uhl, et al: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest 54:54, 1974.

37. Palmer KNU, JS Legge, WFD Hamilton, et al: Comparison of effect of salbutamol and isoprenaline on spirometry and blood gas tensions in bronchial asthma. Br Med J 2:23, 1970.

38. Legge JS, J Gaddie and KNU Palmer: Comparison of two oral selective β_2 adrenergic stimulant drugs in bronchial asthma. Br Med J 1:637, 1971.

39. Tai E and J Read: Response of blood gas tensions to aminophylline and isoprenaline in patients with asthma. Thorax 22:543, 1967.

40. Rebuck AS and J Read: Assessment and management of severe asthma. Am J Med 68:11, 1971.

41. Shim CS and MH Williams: Evaluation of the severity of asthma: patients versus physicians. Am J Med 68:11, 1980.

42. McFadden ER Jr, R Kiser, and WJ deGroot: Acute bronchial asthma: relations between clinical and physiologic manifestations. N Engl J Med 288:221, 1973.

43. Banner AS, RS Shook and WW Addington: Rapid prediction of need for hospitalization in acute asthma. JAMA 235:1337, 1976.

44. Nowak RM, KR Gordon, DA Wroblewski, et al: Spirometric evaluation of acute bronchial asthma. JACEP 8:9, 1979.

45. Tashkin DP, E Trevor, SK Chopra, et al: Sites of airway dilatation in asthma following inhaled versus subcutaneous terbutaline. Am J Med 68:14, 1980.

46. Holten K: Bronchodilator effect and effect on blood gases after subcutaneous injection and inhalation of terbutaline. Brit J Dis Chest 68:111, 1974.

47. Amory DW and SC Burnham: Comparison of the cardiopulmonary effects of subcutaneously administered epinephrine and terbutaline in patients with reversible airway obstruction. Chest 67:3, 1975.

48. Sackner MA, R Dougherty, H Watson, et al: Hemodynamic effects of epinephrine and terbutaline in normal man. Chest 68:5, 1975.

49. Bloomfield P, J Carmichael, GR Petrie, et al: Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma. Br Med J 1: 848, 1979.

50. Schwartz AL, JM Lipton, D Warburton, et al. Management of acute asthma in childhood-a randomized evaluation of β-adrenergic agents. Am J Dis Child 134:474, 1980.

51. Shim C and MH Williams: The adequacy of inhalation of aerosol from canister nebulizers. Am J Med 69:891, 1980.

52. Taylor WF, EM Heimlich, L Strick, et al: Intermittent positive pressure breathing versus Freon-unit nebulized isoproterenol in asthmatic children. J Allergy 38:257, 1966.

53. Chang N and H Levison: The effect of a nebulized bronchodilator administered with or without IPPB on ventilatory function in children with cystic fibrosis and asthma. Am Rev Resp Dis 106:867, 1972.

54. Weber BA, GM Shenfield and JW Paterson: A comparison of three different techniques for giving nebulized albuterol to asthmatic patients. Am Rev Resp Dis 109:293, 1974.

55. Loren M, H Chai, D Miklich, et al: Comparison between simple nebulization and IPPB in asthmatic children with severe bronchospasm. Chest 72:145, 1977.

56. Freedman BJ and GB Hill: Comparative study of duration of action and cardiovascular effects of bronchodilator aerosols. Thorax 26:46-50, 1971.

57. Pierson RN Jr. and MH Grieco: Isoproterenol aerosol in normal and asthmatic subjects. Am Rev Resp Dis 100:533, 1969.

58. Heimer D, C Shine and MH Williams Jr: The effect of sequential inhalations of metaproterenol aerosol in asthma. J Allergy Clin Immunol 66:75, 1980.

59. Williams MH Jr and C Shine: Asthma: Discussions in patient management. Flushing, NY, 1976, Medical Examination Publishing Co., Inc., pg 46.

60. Weinberger M and L Hendeles: Experience with theophylline for the management of chronic asthma. Eur J Resp Dis Suppl 109, 61:120, 1980.

61. Josephson GW, EJ Mackenzie, PS Hetmon, et al: Emergency treatment of asthma - a comparison of two treatment regimens. JAMA 242:639, 1979.

62. Mitenko PA and RI Ogilvie: Rational intravenous doses of theophylline. N Engl J Med 289:600, 1973.

63. Rossing TH, CH Fanta, DH Goldskin, et al: Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Resp Dis 122:365, 1980.

64. Ellis EF, R Koysooko and G Levy: Pharmacokinetics of theophylline in children with asthma. Pediatrics 58:542, 1976.

65. Gal P, WJ Jusko, AM Yurchak, et al: Theophylline disposition in obesity. Clin Pharmacol Ther 23:438, 1978.

66. Jenne J, H Nagasawa, R McHugh, et al: Decreased theophylline half-life in cigarette smokers. Life Sci 17:195, 1975.

67. Powell JR, JF Thiercelin, S Vozeh, et al: The influence of cigarette smoking and sex on theophylline disposition. Am Rev Resp Dis 116:17, 1977.

68. Jenne J, TW Chick, BA Miller, et al: Apparent theophylline half-life fluctuations during treatment of acute left ventricular failure. Am J Hosp Pharm 34:408, 1977.

69. Piafsky KM, DS Sitor, RE Rangno, et al: Theophylline kinetics in acute pulmonary edema. Clin Pharmacol Ther 21:310, 1977.

70. Powell JR, S Vozek, P Hopewell, et al: Theophylline disposition in acutely ill hospitalized patients. Am Rev Resp Dis 118:229, 1978.

71. Piafsky KM, DS Sitor, RE Rangno, et al. Theophylline disposition in patients with hepatic cirrhosis. N Engl J Med 296:1495, 1977.

72. Resor RK, PD Walson, WL Fritz, et al: Kinetics of theophylline-variability and effect of arterial pH in chronic obstructive lung disease. Chest 76:11, 1979.

73. Kappos A, KE Anderson, AH Corney, et al: Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther 20:643, 1976.

74. Kappos A, AP Alvares, KE Anderson, et al: Effect of charcoal-broiled beef on antipyrine and theophylline metabolism. Clin Pharmacol Ther 23:445, 1978.

75. Weinberger M, D Hudgel, S Spector, et al: Inhibition of theophylline clearance by troleandomycin. J Allergy Clin Immunol 59: 228, 1977.

76. Riegelman S, K Muir, and R Upton: Factors affecting the pharmacokinetics of theophylline. Eur J Resp Dis 61: Suppl 109, 67, 1980.

77. IV Dosage Guidelines for Theophylline Products. FDA Drug Bulletin,, Feb, 1980.

78. Bohme P, P-O Edlund, M Eriksson, et al: Pharmacokinetics of theophylline in young children with asthma: Comparison of rectal enemas and suppositories. Eur J Clin Pharmacol 16:133, 1979.

79. Hemstreet MPB: Atropine nebulization-simple and safe. Ann Allergy 44:138, 1980.

80. Snow RM, WC Miller, HT Blair, et al: Inhaled atropine in asthma. Ann Allergy 42:286, 1979.

81. Wieser O and and R. Konigshofer R: Dose-response study of SCH 1000 MDI on heart rate, ECG, and blood pressure in healthy volunteers. Postgrad Med J 51 (Suppl 7):125, 1975.

82. Francis RA, ML Thompson, D Pavia, et al: Ipratropium bromide: mucociliary clearance rate and airway resistance in normal subjects. Brit J Disease Chest 71:173, 1977.

83. Chervinsky P: Double-blind study of ipratropium bromide, a new anticholinergic bronchodilator. J Allergy Clin Immunol 59:22, 1977.

84. Gross NJ: SCH 1000: A new anticholinergic bronchodilator. Am Rev Resp Dis 112:823, 1975.

85. Lightbody IM, CG Ingram, JS Legge, et al: Ipratropium bromide, salbutamol and prednisolone in bronchial asthma and chronic bronchitis. Br J Disease Chest 72:181, 1978.

86. Kelsen SG, DP Kelsen BF Fleegler, et al: Emergency room assessment and treatment of patients with acute asthma: adequacy of the conventional approach. Am J Med 64:622, 1978.