A COMPARISON OF TWO AMINOPHYLLINE DOSING REGIMENS:

LOADING DOSE AND MAINTENANCE INFUSION
versus
INTERMITTENT BOLUS DOSING

A THESIS

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ABSTRACT

Intermittent and continuous infusion dosing of aminophylline were compared in a randomized, double-blind study of twenty-four asthmatic patients. Thirteen patients received an intermittent regimen of 500 mg every 6 hours and eleven received a loading dose of 5.6 mg/kg and a continuous infusion of 0.9 mg/kg/hour thereafter. Spirometric measurements, vital signs, serum theophylline levels, and subjective effects were compared at regular intervals during a 7 hour study period. The results indicate that the continous infusion regimen had significantly less potential for toxicity according to serum theophylline levels. Number of complaints with the intermittent regimen exceeded that of the continuous infusion regimen by a factor of three. A trend toward greater efficacy with the continuous infusion was detected but this was statistically insignificant with the number of patients studied.

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LIST OF ABBREVIATIONS

hr	- hour
rpm	- revolutions per minute
UV	- ultra-violet
id	- internal diameter
$FEV_{1.0}$	- forced expiratory volume in one second
FVC	- forced vital capacity
MMFR	- maximum mid-expiratory flow rate
AMP	- adenosine monophosphate
ADP	- adenosine diphosphate
ATP	- adenosine triphosphate
GMP	- guanosine monophosphate
HPL	- high pressure liquid
Vd	- volume of distribution
T½	- half-life
Ig	- immunoglobulin
PDE	- phosphodiesterase
SRS-A	- slow reacting substance of anaphylaxis
ECF-A	- eosinophil chemotaxic factor of anaphylaxis
PG	- prostaglandin

psi - pounds per square inch

CI - loading dose followed by continuous infusion

ID - intermittent dosing

T - one dosage unit

TT - two dosage units

Bid - twice daily

Tid - thrice daily

Qid - four times daily

Q12h - every twelve hours

Q4h - every four hours

SC - subcutaneous

S - systolic

D - diastolic

S.E.M. - standard error of the mean

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1. INTRODUCTION

Asthma is a disease characterized by an increased responsiveness of the airways to various stimuli and manifested by slowing of forced expiration which changes in severity either spontaneously or as a result of therapy.[1] About 400,000 Canadians suffer from asthma. During a year, 16,000 or more of them need hospital care. About 500 die of this condition.[2] That asthma is a potentially lethal condition, is now well known. Attention has been drawn to the alarming mortality statistics which occur when the gravity of asthma is underestimated or an attack inappropriately managed. That acute asthma may be misassessed and undertreated, has become recognized only in the past ten years,[3,4,5] hence the recent increase in interest towards providing more rational therapy.

Aminophylline is well established in the management of acute bronchospasm[6,8,9,13] since its first intravenous use more than forty years ago.[7] It has been stated that aminophylline intravenously is the most effective agent available for prompt relief of severe asthma[10] and that it is the bronchodilator of first choice.[11,12] Epinephrine hydrochloride (1:1,000), given subcutaneously in a dose of 0.2 to 0.3 ml (adults), has been widely used for the treatment of an acute attack of asthma, as have the adrenergic aerosol bronchodilators. Inadequate response to the adrenergic drugs is an indication for use of intravenous aminophylline.[14]

Studies correlating serum theophylline levels with clinical relief from bronchospasm, have confirmed that serum levels of 10 to 20 µg per ml are desirable in the treatment of the adult asthmatic patient.[13,15,17,18,19,20] However, until 1973, when Mitenko and Ogilvie suggested rational intravenous doses of theophylline, there was no clear-cut definition of dose schedules for this agent.[19] Based on a pharmacokinetic study, these researchers recommended a loading dose of aminophylline, 5.6 mg per kg given intravenously over 15 to 30 minutes, followed by a maintenance infusion of 0.9 mg per kg per hour, to give a serum theophylline concentration of 10 µg per ml. This regimen has been revised more recently by the same group to: 6 mg per kg over 20 minutes intravenously followed by a maintenance infusion of 0.9 mg per kg each hour, with a further loading dose of 3.0 mg/kg over 20 minutes and the maintenance increased to 1.35 mg per kg per hour if the patient is unimproved and free of toxic signs.[21]

This dosing concept has achieved some support;[11] however, Jenne et al,[15] who suggested a similar dosing regimen of a 500 mg loading dose followed by 50 mg per hour maintenance infusion, state that, based on average theophylline clearances, a few patients will reach toxic levels at this dose. Also the investigations of Weinberger

et al[6] do not support the dosage recommendation by Mitenko and Ogilvie. Wide individual variations in the serum half-life of theophylline have been reported [15,19,22,20] with recommendations that serum theophylline levels be used as therapeutic guides.[6,15,20,22] Such recommendations have received little attention in medical practice,[23] possibly for the practical reason that the theophylline assay has not been economically and rapidly available.

It is obvious from the previous discussion that the safety of such regimens has not been confirmed and that confusion still exists about the dosing of theophylline. Confusion is even more evident when dosage recommendations from recent review articles are considered:

1. Intravenously until side effects occur.[10]
2. 250-500 mg per 6-8 hr., diluted and cautiously.[8]
3. a) 250 mg in 10 ml fluid over a period of 5 minutes, or
   b) 500 mg in 500 ml physiological saline by continuous infusion over each 8 hours.[5]
4. a) 250-500 mg intravenously ever 4 hours run in over 20 minutes, not to exceed 1.5 - 2.0 g per 24 hours, or
   b) loading dose of 5.6 mg per kg run in over 20 minutes followed by continuous intravenous drip of 0.5 - 0.9 mg per kg per hour.[24]

5. a) 4-5 mg per kg diluted 1:1 with intravenous fluids over 10 to 20 minutes, repeated every 6 hours; or

   b) 3.6 mg per kg over 10 minutes, followed by a constant infusion dose of 0.9 mg per kg per hour.[14]

"Is it better to use intravenous aminophylline as intermittent bolus therapy or a loading dose followed by a continuous infusion in a hospitalized asthmatic patient?"[25,26] This unanswered question deserves an immediate answer if improvement in the rational therapy of acute asthmatic attacks is to continue.

This dissertation is concerned primarily with the evaluation of bronchodilation, produced by the intermittent bolus dosing versus the loading dose followed by maintenance infusion, as measured by pulmonary function studies. Evaluation of the toxicity potential for each regimen as measured by serum theophylline levels and comprehensive observation of side-effects is also presented.

2. LITERATURE REVIEW

A. ASTHMA: DESCRIPTION RATHER THAN DEFINITION

Asthma has been defined as "recurrent generalized airway obstruction which, in the early stages, is paroxysmal and reversible and is accompanied by eosinophilia of the blood and sputum;"[27] or as a "hypersensitivity reaction of the bronchial tree producing bronchoconstriction, mucosal edema and excess mucus in predisposed people."[28] These definitions and others, for example, "wheezing dyspnea"[29] have failed to convey a distinct clinical description of asthma based on current knowledge.[30] This is re-inforced by the fact that a symposium of experts came to the conclusion that asthma could not be defined.[31] Recent articles [1,24] tend to characterize the disease with statements similar to the introduction (1.) statement.

In a recent monograph, Farr and Spector [32] centre a description of asthma around the heterogeneity among asthmatic patients. For the purpose of characterizing this disease more fully, the following discussion will focus on their five categories of heterogeneity:

i) Factors Responsible for Precipitating Attacks

Asthmatics are heterogeneous with respect to factors

responsible for precipitating attacks. Allergy and respiratory infections are the commonest factors which precipitate acute asthma but their relative importance varies in different individuals and in different countries. In the majority of patients, an asthma attack may be triggered by one of a number of factors, and often it is impossible to determine the factor responsible for a particular attack.[33]

a) Inhalants

The commonest allergens which cause asthma are house dust, flower and grass pollens, dander from cats, dogs and horses, and feathers.[33] Smoke, strong odours and irritant fumes may also be implicated in asthmatic attacks.[14] Inhaled medications such as acetylcysteine or sodium chromoglycate may also precipitate bronchospasm.

b) Ingestants

According to Speer,[34] nine out of ten common food allergens are important in asthma. These are milk, chocolate and cola, egg, peanuts, citrus fruits, tomatoes, wheat, cinnamon, and food colours such as amaranth and

tartrazine. Fish have also been mentioned.[33]

Acetylsalicylic acid has been reported to precipitate asthma attacks in 4.2 per cent of asthmatic patients.[35] Most reports conclude that this intolerance is not immunologically mediated.[32,35,36] Similar asthmatic reactions may occur after other analgesics such as indomethacin, mefenamic acid, flufenamic acid, antipyrine, aminopyrine, phenylbutazone, oxyphenbutazone, naproxen, and ibuprofen.[35,52] A recent review[52] has classified this reaction as an idiosyncrasy, as its inhibitory effect on prostaglandin synthesis is still being debated. This review has broken drug-induced bronchospasm into four categories: allergic reaction, idiosyncrasy, pharmacological action, and local irritation. Examples of drugs inducing bronchospasm by allergic reaction include penicillin, sulfonamides, nitrofurantoin, contrast media, and protein substances found in vaccines and antisera. Idiosyncrastic reactions, other than those induced by analgesic-antiinflammatory drugs, include those induced by drugs such as isoproterenol, diuretics, some intravenous anesthetics, and methyldopa. Drugs

inducing pharmacological bronchospasm include propranolol and other beta-blockers, antihistamines, and cholinergic drugs such as carbachol. Local irritants have already been mentioned.

c) Infection

Respiratory infection commonly exacerbates asthma.[33] The principal infectious agents responsible for exacerbations of asthma are viral agents, mainly respiratory syncytial virus - particularly in young children, parainfluenza virus, rhinovirus, and in older patients, influenza virus.[40]

d) Exercise

Exercise is a well-recognized provoking factor which produces acute airway obstruction. In most asthmatic patients, the maximum result comes shortly after stopping the exercise. Severity depends on the type of exercise, with running being the most asthmogenic and swimming or walking the least.[44]

e) Psychological Factors

Asthma has been reported to be non-psychogenic;[30] however, it has been stated also that emotional stress

may precipitate acute asthma.[27,33] Undoubtedly certain situations can lead to decreases in airway calibre in individuals with previously established asthma. Patients can make their condition worse if they panic, hyperventilate, or derive secondary gain.[30]

f) Non-Specific Stimuli

Non-specific stimuli such as change in temperature and humidity have also been associated with attacks of bronchospasm.[27,33]

Asthma is sometimes divided into extrinsic and intrinsic types on the basis of the immunological status of the patient and the factors which precipitate acute attacks. "Extrinsic" refers to the allergic form in which an exogenous allergen can be identified, whereas "Intrinsic" refers to the idiopathic form in which no offending antigen can be recognized. Because many patients show features of both extrinsic and intrinsic types (approximately eighty per cent have been termed "mixed"[47]). It is no longer considered meaningful to use these terms.[30,33,41]

ii) Location and Degree of Obstruction

Functionally, the main feature in asthma is airway obstruction or flow limitation.[5,10] Asthmatic patients are heterogeneous with respect to the location and extent of airways obstruction.[32]

Pulmonary function measurements such as $FEV_{1.0}$ (forced expiratory volume in one second), FVC (forced vital capacity), and MMFR (maximum mid-expiratory flow rate) indicate the severity of airways obstruction.[4,33] Between attacks, pulmonary function tests may be near normal.[39] Obstruction may be so mild that only sensitive tests can demonstrate it,[10,37] or obstruction may be so severe that pulmonary function testing is impossible. Pulmonary function test values for asthmatic patients in severe distress have been reported at less than ten per cent of predicted normal (discussed under section 3.D.ii).[38]

The entire extent of the airways, from the large central bronchi to the peripheral bronchioles is involved in asthma. The part of the airways involved varies not only between individuals but may vary greatly in the same individual at different times and phases of his/her disease.[42]

Researchers have found that some patients have primarily large airways obstruction, as revealed by increased airways resistance, and other patients have primarily small airways obstruction, as revealed by measurements such as MMFR, while still other patients have both large and small airways obstruction.[32,39] Hyperinflation due to air trapping also may be present in asthma.[32,43]

iii) Degree of Reversibility of Airway Obstruction

Those patients with obstructive airways disease who fail to show evidence of reversibility, even after the most rigorous therapy program, by definition do not have asthma.[32]

Researchers report that spirometric measurements ($FEV_{1.0}$, FVC, and MMFR) are extremely useful in quantifying the response of the asthmatic to therapeutic regimens.[37,43] Investigators have found that some patients with severely decreased spirometric measurements before adequate therapy can normalize after a few inhalations of standard aerosolized bronchodilators, whereas others require prolonged, intensive therapy, before they can achieve significant improvement.[32,45,43,46] Some patients may have complete reversibility as evidenced by functions returning to normal following

therapy;[45] however, many patients with asthma have a significant degree of irreversibility despite maximum medication and during clinical remission.[47]

iv) Response to Medications

Asthmatic patients are heterogeneous in their response to various forms of medications. Patients vary in their response to medications because of differences in severity, acuity or chronicity of attack, however, over and above these variances, others exist.

Many patients respond to beta-sympathomimetic stimulators such as salbutamol. Patients claim preference to particular sympathomimetics because of differing relief-to-side-effect ratios. Certain rare patients may have paradoxic bronchoconstrictor effects after initial bronchodilation.[47] Some respond to cholinergic inhibitors such as atropine while a very small number respond to alpha-blocking agents.[32] Other patients may require corticosteroids to adequately control this condition.

v) Differences in Drug Dosage Requirements

It has been demonstrated that the serum half-life of theophylline varies as much as eightfold among different

patients,[15] indicating that the therapeutic dose of theophylline should also vary from patient to patient. This phenomenon has been observed with other medication as well.[47]

B. AMINOPHYLLINE

The history of the use of intravenous aminophylline in the treatment of asthma goes back some 40 years.[7] Its clinical use has waxed and waned in the intervening years as a result of clinical difficulties ranging from inadequate response to serious adverse reactions caused by overdosage. Administration of aminophylline is presently regarded as a cornerstone in the treatment of pulmonary disease involving reversible bronchoconstriction,[9] because theophylline is potentially the most potent non-steroid agent available.[85]

Aminophylline is the ethylenediamine salt of theophylline, the active portion of the molecule (Figure 2). Like caffeine and theobromine, theophylline is structurally classified as a xanthine derivative but therapeutically it is classified as a bronchodilator.[65]

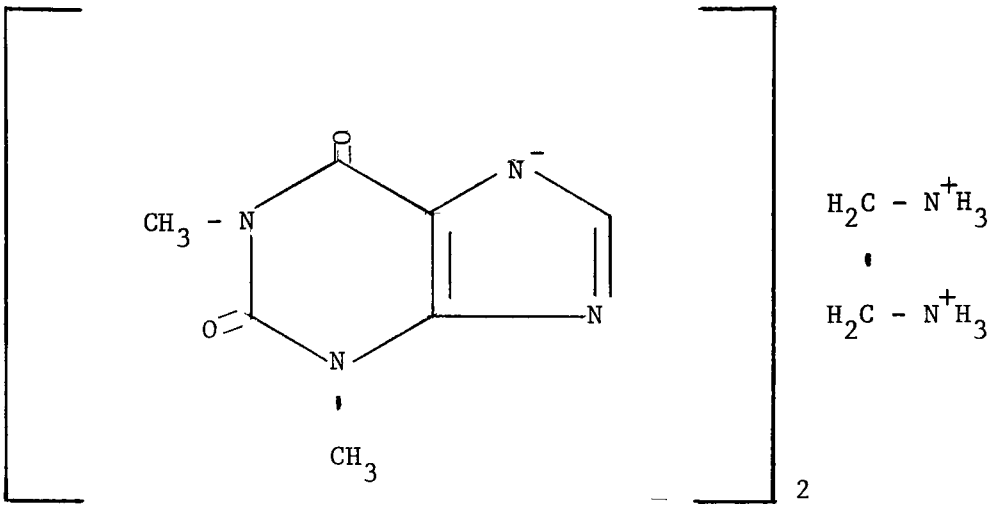


Figure 1. Aminophylline

i) Pharmacology

Theophylline competitively inhibits phosphodiesterase, the enzyme that catalyzes the degradation of cyclic AMP into 5'-AMP (Figure 3). The increased levels of intracellular cyclic AMP are believed to mediate most of the drug's pharmacologic effects, however, the details of this action remain to be elucidated. A recent hypothesis centres on the fact that theophylline antagonizes the action of prostaglandins, and proposes that prostaglandins may control the activity of phosphodiesterase.[66] Another hypothesis suggests that purinergic receptors, that mediate the bronchoconstrictive responses of adenosine and adenosine triphosphate, are present in the airways. Theophyllines,

which are structurally related to the purines, block this action.[67] Intracellular translocations of calcium may play a more important role in the action on the myocardium and on neurotransmission.

The most important effect of theophylline is its relaxation of smooth muscle. Included is smooth muscle of the bronchioles, the pulmonary arterioles, and the biliary and gastrointestinal tract. Stimulation of the vasomotor and vagal centres promotes vasoconstriction and bradycardia respectively. In the medulla, theophylline lowers the threshold of the respiratory centre to carbon dioxide or direct stimulation of the medullary respiratory centre may occur. Therapeutic doses may stimulate the vomiting centre and toxic doses may activate all levels of the cortex and spinal cord. In high doses theophylline produces a positive inotropic effect on the myocardium and a chronotropic effect at the sino-atrial node. The ethylenediamine component of aminophylline may contribute to the positive inotropic and respiratory stimulant actions of theophylline. The theophyllines directly dilate coronary, pulmonary, renal and general

systemic arterioles and veins, decreasing peripheral vascular resistance and venous pressure. Any effect on blood pressure is the result of previously mentioned opposing central and peripheral effects. In contrast to peripheral vasodilation, theophylline contracts cerebral vasculature. The decrease in cerebral blood flow and increase in carbon dioxide tension may result in respiratory centre stimulation. Mild diuresis is produced by the combined effect of theophylline on increasing glomerular filtration rate and decreasing sodium and chloride reabsorption at the proximal tubule. Release of catecholamines from the adrenal medulla may be stimulated by theophylline, hence the adrenergic effects exhibited; hyperglycemia, cardiac affects, and lipolysis. The theophyllines may potentiate the calcemic response to parathyroid hormone and inhibit that of calcitonin. It may also increase basal metabolic rate.[65]

ii) Pharmacokinetics

Absorption will not be considered in the discussion of theophylline kinetics because the aminophylline administered in this study was given intravenously.

a) Theophylline Assay

Any discussion of kinetics and investigation of serum levels requires some mention of the theophylline assay method. In this investigation a high-pressure liquid (HPL) chromatographic analysis was performed. An ultraviolet spectrophotometric method has been frequently employed for theophylline determination in serum. However, other xanthines such as caffeine, theobromine and theophylline metabolites, and barbiturates interfere in the absorption measurements.[86] Other paper, column, thin-layer, and gas chromatographic assays have been used, however they required higher concentrations of theophylline than normally found in human serum.[87] The HPL chromatographic assay was selected for its specificity*, sensitivity**, rapidity (approximately 30 determinations in 8 hours), simplicity to perform, smallness of serum sample required, and availability.[48,88,89]

* Not interfered with by theophylline metabolites, other xanthines, or other commonly used drugs.

** Sensitive to 0.1 µg/ml with a coefficient of variation of less than 3 per cent on duplicate samples.

b) Distribution

Theophylline is readily distributed throughout extra cellular fluids and body tissues. Apparent volume of distribution (Vd) has been estimated at approximately 0.50 litre/kg.[9,69,90] This was based on data taken from different studies[15,68] with a range from 0.12 litre/kg to 0.76 litre/kg. This estimated distribution volume, being less than total body water (50-70% of body weight) and more than extracellular fluid volume, suggests that theophylline is transferred from the plasma to tissues.[68] Smoking is one factor reported to increase distribution volume[70] and may be partly responsible for the variation. Volume of distribution may be slightly increased in patients with hepatic cirrhosis.[90] Theophylline is about 55 to 63 per cent bound to plasma proteins in the therapeutic concentration range,[71] and either enters or binds to erythrocytes.[68] Theophylline readily crosses the placenta and also distributes well into breast milk.[72] Saliva concentration of theophylline have been reported to be approximately one-half (52%,[71] 58%[72]) of plasma concentra-

tions but have ranged from less than 50 to over 100 per cent.[9]

c) Metabolism

Theophylline is readily and almost completely metabolized as presented in Figure 2. It is generally accepted that this metabolism takes place in the liver by oxidative mechanisms[65,70,73,74] and that individual differences in metabolism are responsible for the wide range of plasma half-life ($T\frac{1}{2}$).[9,15,19,75] Plasma $T\frac{1}{2}$ has been reported to vary from 3.0 to 12.0 hours in adults.[15,90] A recent article criticizes previous kinetic data for reasons of: lack of specificity in assay method, number of subjects, number and frequency of serum samples, and length of time during which serum samples were obtained.[91] It estimates $T\frac{1}{2}$ as 11.0 hours with a range of 8.6 to 20.7 hours on data taken from six subjects.[91] Age, genetic factors, weight, other drugs, disease state and smoking are all believed to play a part in explaining the variation.[9] Decreased liver perfusion or hypoxic liver dysfunction with decreased theophylline metabolism is favoured as

the reason for toxic theophylline levels in patients with liver dysfunction often associated with congestive heart failure.[78] The decrease in plasma theophylline clearance in patients with cirrhosis is probably due to a combination of disordered hepatocyte function, shunting of blood away from the liver because of portasystemic anastomoses and decreased hepatic blood flow.[90] The half-life of theophylline in cigarette smokers has been found to be almost one-half that in non-smokers and this is consistent with the induction of microsomal enzymes by polycyclic hydrocarbons found in cigarette smoke.[70,76]

The metabolites of theophylline as shown in Figure 2 are 1,3-dimethyluric acid, 3-methylxanthine, and 1-methyluric acid.[73,77] The 1-demethylation of theophylline to 3-methylxanthine has been suggested to be the dominant reaction determining serum theophylline.[77] Caffeine is metabolized to theophylline and for this reason xanthine-containing preparations (such as tea, coffee or cola) other than aminophylline were forbidden during the study, although abnormally

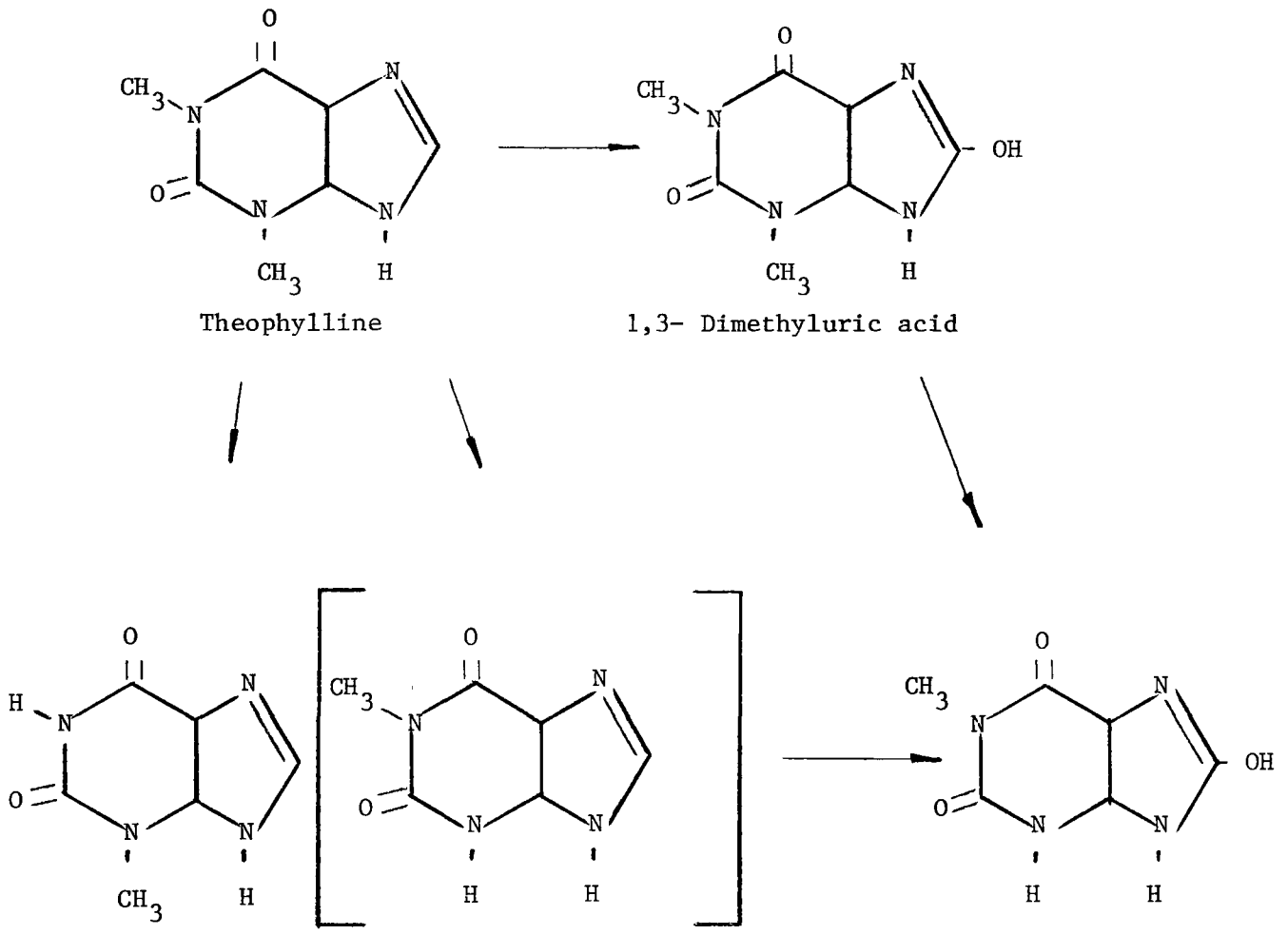


Figure 2. Metabolism of Theophylline

large caffeine consumption would be required to produce any clinical effect.[79]

d) Excretion

Theophylline and its metabolites are excreted primarily by the kidneys. From a recent study[77] mean values expressed as fraction of total in urine (plus or minus standard deviation) were as follows: unchanged theophylline 7.7 ± 6.1%; 1,3-dimethyluric acid 39.6 ± 4.5%; 1-methyluric acid 16.5 ± 3.3; and 3-methylxanthine 36.2 ± 7.3%. The first three values are consistent with those obtained in an earlier study using different methodology: 10%, 35%, and 19%.[73] The fourth value, 36.2 ± 7.3% for 3-methylxanthine, does not agree with the earlier value of 13%. This difference may be the result of different assay procedures or may be the result of a different formation rate of 3-methylxanthine as this has been suggested as the rate determining reaction in the degradation of theophylline.[77]

iii) Therapeutic Use

Present indications for the clinical use of aminophylline include the symptomatic treatment of reversible bronchoconstriction associated with chronic obstructive pulmonary emphysema, chronic bronchitis,

bronchial asthma and related bronchospastic disorders.[81] Other uses have included relieving dyspnea associated with left heart failure, abolishing apnea associated with Cheyne-Stokes, and relieving acute episodes of pulmonary edema.[8]

Theophylline relieves the primary manifestations of asthma, including dyspnea and wheezing, and improves pulmonary function as measured by increased $FEV_{1.0}$ and FVC.[65] Acutely distressed asthmatic patients were chosen as subjects in which to measure the improvement in pulmonary function because they have the widest possible range of measurements (near normal -100% to less than 10% of predicted normal).

iv) Adverse Effects

The many possible adverse effects attributed to theophylline have been extensively reviewed elsewhere.[8,65] Undesirable effects include anorexia, nausea, vomiting, increased restlessness and irritability, anxiety, delirium, tachycardia, dehydration accompanied by severe thirst, fever and diaphoresis, hematemesis, stupor, convulsions, coma and death. Other allergic reactions such as skin

eruptions may also occur. However, it should be noted that the ethylenediamine component of aminophylline may be responsible.

For the purposes of this study the relationship between toxicity and serum theophylline concentration will be examined more closely. There is general agreement that serum theophylline levels should be maintained at less than 20 µg/ml because toxicity becomes a problem at this level.[15,21,23,74] The main and most persistent side effects are gastrointestinal and are most common starting at serum levels of about 15 µg/ml.[15,21,75] When the drug concentration progressively exceeds 20 µg/ml, atrial tachycardia and then ventricular arrhythmias are more likely to be observed.[21] The incidence of adverse effects almost doubles at serum concentrations over 25 µg/ml as compared to 15-25 µg/ml.[75] Seizures have been reported associated with levels of 25 µg/ml.[74,82] Serious toxicity (cerebral seizures, cardiac arrhythmias, or respiratory or cardiac arrest) is infrequent and occurs most commonly with rapid intravenous injection.[21] For this reason large doses in this study were administered

by slow infusion over 30 minutes. Another comment worth making at this time concerns any suggestion of using toxicity as a valid end point for dosage titration. This assumes that gastrointestinal symptoms will invariably precede more serious signs of toxicity. Any such suggestion and/or assumption are invalidated when one considers the report of 8 patients experiencing seizures attributed to aminophylline in whom 7 patients had no recognized prior adverse effects.[74]

C. DIAGNOSIS AND TREATMENT

Diagnosis and treatment of asthma are discussed together with particular emphasis on the acutely distressed asthmatic patient which was the type of patient selected for this study.

The diagnosis of bronchial asthma is based on patient history, physical findings, and demonstration of reversible airway obstruction.[44] Presenting symptoms are likely to follow the classic pattern of periodic episodes of wheezing, cough, and shortness of breath that characterize asthma. The severity of the wheeze and breathlessness is variable. Severe distress is obvious if the patient is too dyspneic to speak. Monosyllable speech and frequent pauses in speech

are rough guides to establishing moderate or mild distress respectively. The cough may be dry or productive of sticky mucoid sputum. The sputum may be purulent if infection is present but occasionally yellow sputum is due to large numbers of eosinophils. The respiratory rate and the depth of breathing are increased and the patient sits up and leans forward using the accessory muscles of respiration. Audible expiratory wheeze is often the main physical finding. The pulse is rapid and the degree of tachycardia may be an index of the severity of the attack. The chest is hyperinflated. Auscultation reveals inspiratory and expiratory rhonchi heard over both lungs and expiration is prolonged. Further information about frequency and severity of attacks, details of precipitating factors, history of allergy, smoking history, family history and the details of previous treatment is required. Medication history is essential with special concern given to frequency of use of bronchodilator aerosols and corticosteroids, and previous intake of methyl-xanthines. Aside from routine blood work and urinalysis, arterial blood gases may be necessary to assess severity and any carbon dioxide retention associated with bronchitis. The chest radio-graph in asthma is frequently normal or may show hyperinflation,

but is essential for detection of complications such as pneumonitis, transient infiltrates, partial pneumothorax, atelectasis, or emphysema.

The diagnosis of asthma on physiologic grounds is established by demonstrating reversible airways obstruction.[44] Spirometry measures the volume of maximal fast, forceful expiration, starting in the full inspiratory position, and measured as a function of time and is the mainstay of diagnosis and management of reversible airway disease.[37] The $FEV_{1.0}$ is recorded by measuring the volume of expired air in the first full second after the start of expiration. The FVC is the maximum volume of air exhaled from the lung by a voluntary forceful effort following a maximal inspiration. The MMFR is the average rate of air flow during the middle half of the forced expiratory vital capacity. Spirometric measurement is carried out before and after bronchodilator therapy. A fifteen per cent rise in $FEV_{1.0}$ or FVC indicates significant reversibility.[33,84] In this study spirometry was chosen because of portability and ease of handling of the spirometer with the acutely distressed patient. Also, the previously discussed measurements were obtained on a permanent chart record (see Figure 4).

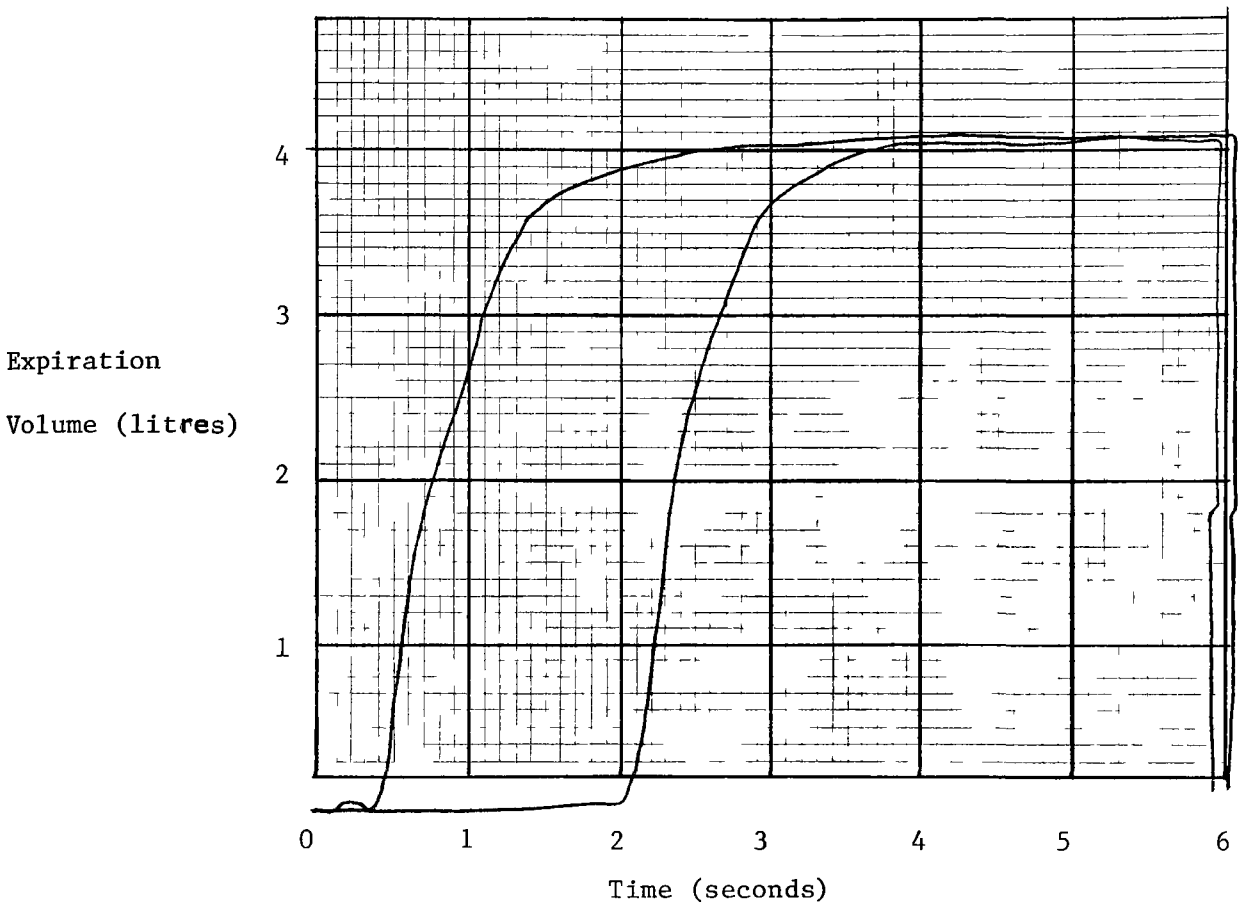


Fig.4: Copy of Permanent Chart Record Produced by Vitalor Spirometer

The effective management of asthma involves consideration of important general principles such as avoidance of precipitating factors and maintenance of adequate hydration. Therapeutic modalities include hyposensitization and pharmacologic intervention. Drugs used in the treatment of asthma may be categorized as follows:[14]

Adrenergic - epinephrine, isoproterenol, ephedrine, orciprenaline, salbutamol and terbutaline.

Methylxanthines - theophylline, aminophylline, and oxtriphylline.

Sodium cromoglycate

Corticosteroids - Systemic such as prednisone.
- Aerosol such as beclomethasone diproprionate.

Atropine and related anticholinergics.

Miscellaneous drugs of questionable or unproved efficacy.

Since the patients selected for this study were acutely distressed and required admission to the emergency unit for treatment, only the treatment of the emergency will be considered. There is agreement[14,57,58] that the pharmacologic approach to therapy should include injectible epinephrine, intravenous aminophylline and intravenous corticosteroids. (Figure 3)

Epinephrine, a time-tested remedy for temporary relief of acute asthma,[57] has been widely used.[14] The beta-adrenergic receptor stimulation, and consequent elevation in intracellular cyclic AMP result in bronchial smooth muscle relaxation and inhibition of mediator release. Other cardiovascular effects of epinephrine may limit its usefulness. Tachycardia resulting from the beta-adrenergic stimulation of the heart may be a limiting consideration. Life-threatening cardiac arrhythmias are more common because of hypoxemia stemming from ventilation-perfusion mismatching. Also many patients in difficulty have already been using considerable amounts of sympathomimetics and may have some toxicity signs or may be refractory to further dosage.

The methylxanthines are also time-tested drugs useful in maintenance and emergency management.[57] Next to the adrenergic drugs theophylline compounds are the most effective bronchodilator drugs available for the treatment of bronchial asthma.[14,59] Because they act at least in part by elevating cyclic AMP in the smooth muscle of the airway by a different mechanism than the adrenergic drugs, they are useful in conjunction with and in cases refractory to the adrenergic drugs. Aminophylline as representative of this category and as the drug under question in this study, has been considered in detail in section 2.B.

Corticosteroids have been cited as the single-most valuable drugs for stopping prolonged asthmatic attacks.[57] The mechanism of action of the antiasthmatic effect is still unknown. Possibilities include the facilitation of catecholamine responsiveness at the level of the beta adrenergic recepter, decreased alpha receptor-mediated bronchoconstriction, decreased production of cyclic GMP, inhibition of certain catecholamine-metabolizing enzymes, and inhibition of histamine production.[60,61] The inhibition of antigen processing by macrophages, cell-mediated immunity, and the

inflammatory response following antigen-antibody union have also been discussed.[62]

Controversy exists concerning the use of corticosteroids in the acute asthma attack. Some authors suggest hydrocortisone sodium succinate 200 mg or more intravenously after intensive treatment with bronchodicators has failed.[5,14,63] Other authors indicate that hydrocortisone sodium succinate (or equivalent) 100 mg or more is essential in the initial treatment of severe acute asthma.[10,58] Controversy also exists concerning the onset of action of the corticosteroids. One author states that even large doses are not effective for 6 hours.[10] In another study most patients reported subjective improvement by about 4 hours after starting treatment but objective evidence did not appear until about 6 hours from the start.[38] Another study demonstrated an increase in peak expiratory flow rate at one hour after injection of corticosteroid.[64] Because studies cannot ethically be done in severe asthma that omit this therapy,[10] all patients in the present study received hydrocortisone sodium succinate 100 mg intravenously at the initiation of therapy with aminophylline.

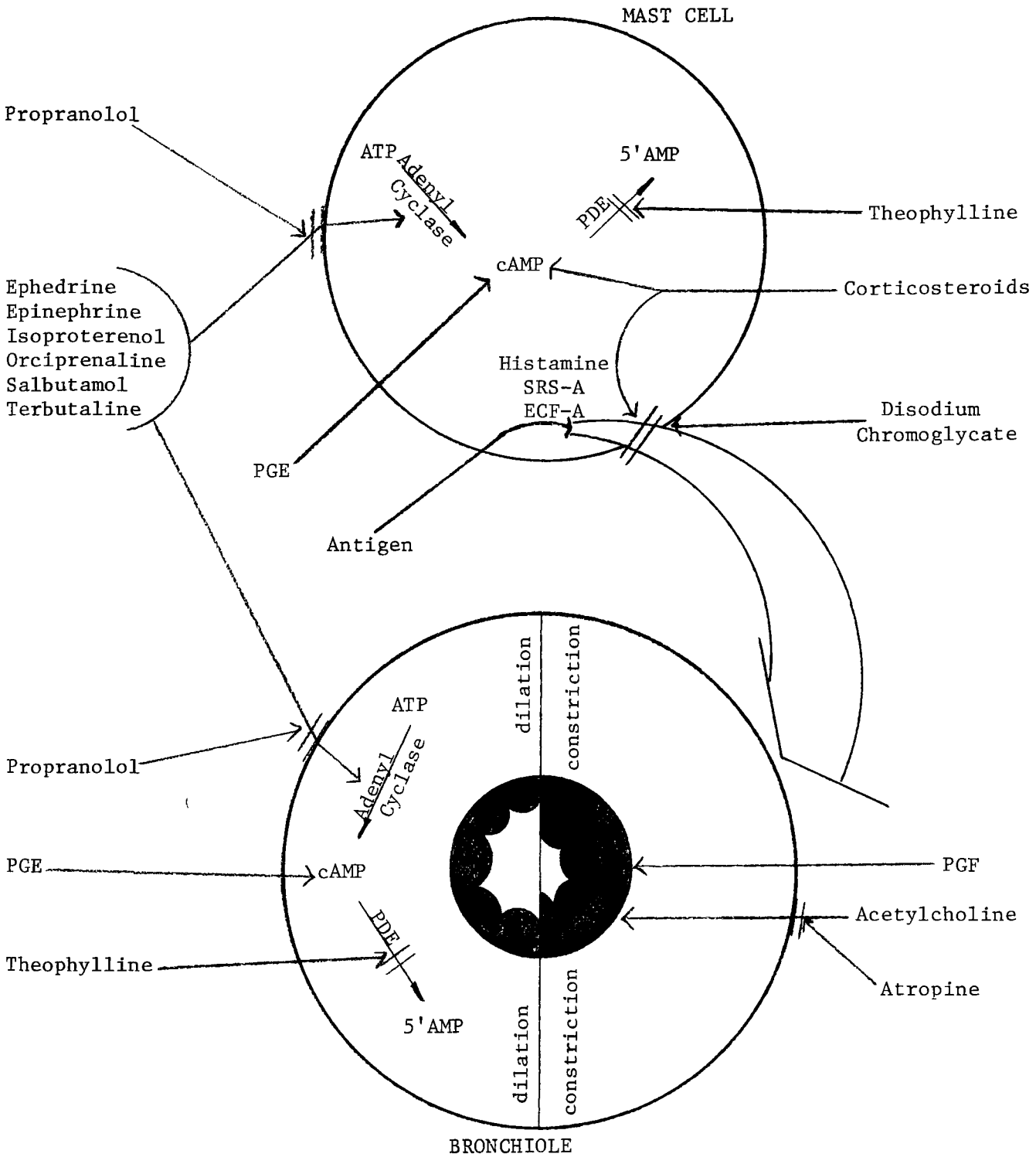


Figure 3: Schematic Diagram for Sites of Drug Action in Asthma

D. PATHOPHYSIOLOGY

Airway obstruction is caused by excessive bronchial secretions, edema of the bronchial mucosa and contraction of bronchial muscle. In fatal asthma tenacious secretions may form viscous casts in the smaller bronchi. There is increase in the number of goblet cells and mucous glands. The bronchial wall is infiltrated with eosinophils and the bronchial muscle is hypertrophied.[5,33,44]

These pathological findings are the end-result of a disease process or processes which may be characterized mainly as hyperreactivity of the airways. The cause of this hyperreactivity has not been clearly elucidated. A variety of abnormalities have been implicated. Included in these are immunological, hypersensitivity and deranged autonomic nervous control such as excessive cholinergic responses and/or subnormal beta-adrenergic effects.[53]

Detailed considerations of the contributing mechanisms have been compiled in a recent book by Weiss and Segal.[53] Only a synopsis of salient factors will be discussed hereinafter.

The immunological basis of asthma is well established in many cases, although the reasons for the unusual immunological picture are far from clear. Basic knowledge relates to the extrinsic type of asthma in which an antigen has been identified. In extrinsic asthma, tissue-sensitizing antibody of the IgE type is present in abnormally large amounts and includes a significant quantity of antibody specific for the allergens to which the subject reacts. Most of the IgE fixed in the lung is on the mast cells, which are thus the principal sites of challenge and are regarded as the major source of bronchoreactive mediators. The pathological stigmata have been attributed to the biologic activity of these mediators.[44] The mast cells are located close to the bronchial vascular system and thus the vessels, the smooth muscle, and the glands of the airways are passive recipients of the mediators. The immunological mechanism does not exclude other factors nor does it account for intrinsic asthma.

The autonomic nervous system exercises control on airways, distribution of blood in the lung, and release of mediators from mast cells. The parasympathetic (vagus) has the predominant influence over bronchomotor tone and

is also able to enhance the release of mediators in the immune response. It has been postulated that a low threshold for vagal responses is a feature of asthma. The vagus may be important in the early stages of an attack or when the asthma is not severe, but becomes less so in the more serious stage when the lung is burdened with secretions and edema, and contains high levels of directly acting mediators.

The sympathetic nervous system is poorly represented in the lung by direct innervation, but appears to have marked influence by way of circulating catecholamines. Both alpha and beta adrenergic receptors are present in the lungs, but beta receptors are dominant. Speculation exists about alpha adrenergic activity inducing bronchospasm. However, more attention has been given to Szentivanyi's proposal that the asthmatic condition was the consequence of insufficient response of tissues to beta-adrenergic stimuli.[54]

Beta-stimulating substances, such as isoproterenol or salbutamol catalyze the conversion of adenosine triphosphate (ATP) to cyclic 3', 5' adenosine monophosphate (cyclic AMP). The latter is degraded by the enzyme phosphodiesterase (PDE) to the inactive 5'-AMP. Accumulation of intracellular cyclic

AMP leads to bronchial smooth muscle relaxation and inhibition of mast cell generation and/or release of mediators. Alpha-stimulating agents such as norepinephrine and phenylephrine catalyze the conversion of ATP to adenosine diphosphate (ADP), with resultant decrease in intracellular cyclic AMP. Decrease in intracellular cyclic AMP facilitates mast cell release of mediators and bronchoconstriction. Cholinergic-stimulating agents such as acetylcholine and carbachol result in an increase of intracellular cyclic 3', 5'-guanosine monophosphate (cyclic GMP). Accumulation of cyclic GMP leads to enhancement of mediator release and bronchoconstriction.

The previous mention of mediators at various points deserves more attention. Among these are histamine, slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor of anaphylaxis (ECF-A), and prostaglandins. Detailed discussions of these and others are found elsewhere.[53,55,56] A brief resume follows.

Histamine is found in high concentrations in tissue mast cells located in the perivascular connective tissue of human lung. It has the ability to increase venular permeability, induce constriction of bronchiolar and other smooth muscle, and

stimulate irritant receptors. Mast cell histamine can be liberated at a wide variety of physical, chemical and immunological stimuli. As previously inferred, an inverse relationship exists between cyclic AMP levels and histamine release.

SRS-A is a low molecular weight acidic lipid that has not been completely characterized and that has biologic activity at low levels. It is not stored in the human lung but is produced and released with the appropriate stimuli. The mast cell has been presumed to be the cell source. SRS-A increases vascular permeability and has a contractile effect to which bronchial smooth muscle is exquisitely sensitive. It appears after immunologic activation.

Local eosinophil infiltration is common in asthmatic lungs and may contribute substances to eliminate products of the mast cell allergic response. ECF-A is a low molecular weight, acidic peptide stored in lung tissue. It selectively attracts eosinophils to sites of tissue that are injured.

Prostaglandins (PG) are synthesized from arachidonic acid by the prostagandin synthetase system. These are normal constituents of lung tissue and are released from sensitized, challenged lung preparations. Inhibition of the formation of

the prostaglandins results in an accumulation of the unsaturated acids and of the peroxides which they readily form. These peroxides are very reactive chemically and may cause tissue damage. The paradoxical bronchoconstrictive response of certain asthmatic patients exposed to acetylsalicylic acid has been speculatively related to its inhibitory effect on prostaglandin synthetase. The prostaglandins are active on the smooth muscle of the bronchial tree. The important actions are the broncho-constrictive effect of $PGF_{2\alpha}$ and the bronchodilating effect of PGE_1 and PGE_2. An imbalance in the ratio of these opposite-acting prostaglandins has been suggested to play a role in the etiology of asthma. It is interesting that anoxia in the tissues favours the production of $PGF_{2\alpha}$ over the production of PGE. It is also interesting that the sympathetic and cholinergic branches of the autonomic nervous system have been implicated in modulating reciprically the release of prostaglandins. As well, PGE_1 and PGE_2 increase intracellular cyclic AMP levels, whereas $PGF_{2\alpha}$ decreases cyclic AMP levels.

The pathogenesis and clinical manifestations of bronchial asthma may be involved with multiple pathophysiological factors. This discussion has only touched upon some considerations

involved in attempts to establish a cause or causes for asthma.

3. METHODOLOGY

A. PATIENTS

All patients had an admitting diagnosis of asthma, based on clinical observations of dyspnea and wheezing and a history of reversible airway obstruction, episodes of dyspnea with wheezing, symptomatic response to bronchodilators, intervals with complete remission of abnormal clinical features, or hyper-reactivity of airways. Patients with a history or evidence of renal, hepatic, or cardiac disease were excluded. Only patients between the ages of 16 and 65 years of age were included. Medication histories were documented with particular emphasis on methylxanthine intake during the preceding 24 hours. Smoking histories, allergies, age, sex, height, and weight were recorded.

Twenty-eight patients, diagnosed as asthmatics at the emergency departments between March 22nd, 1976 and December 31, 1976 during the hours 0800 to 2400, were accepted sequentially into the study protocol (see Demographic Data, Tables I and II). The first two patients were studied at the Ottawa General Hospital and the subsequent twenty-six patients were studied at the Ottawa Civic Hospital emergency

departments. In all cases, the emergency resident on duty made the final decision about inclusion of any patient into the study.

The first three patients were subsequently excluded from the study for technical reasons and patient number eight, was excluded as a result of change in diagnosis from exacerbation of asthma to congestive heart failure and cor pulmonale. These exclusions were made prior to the breaking of the blinding code.

B. MEDICATION DOSING REGIMENS

Patients were randomly assigned to one of two possible dosing regimens for aminophylline. The first was a loading dose of 5.6 mg per kg of body weight given over 30 minutes intravenously followed by a maintenance infusion of 0.9 mg per kg per hour thereafter. The second was an intermittent regimen of 500 mg given intravenously over 30 minutes every 6 hours.

All patients were given 100 mg of hydrocortisone sodium succinate* intravenously over 30 minutes via drip chamber, starting at the initiation of the aminophylline infusion.

* Solu-Cortef by the Upjohn Company of Canada Limited

These medications were administered through an intravenous line established by a nurse technician prior to therapy. The infusion solution was 5% dextrose in water running slowly to keep the vein open.

Oral fluids, water and juice, were encouraged throughout. Tea, coffee, cola and xanthines from any other source were forbidden. Any other medications deemed necessary by the medical resident were recorded (see Table III).

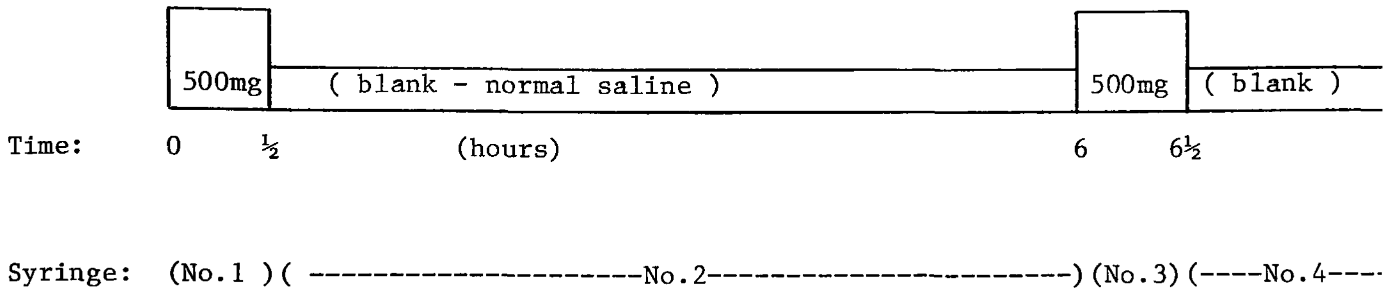
C. BLINDING PROCEDURE

Aminophylline was administered in a double-blind manner such that the resident physician, nurses, patient, and investigator were unaware of which regimen the patient was receiving.

The sequence number and weight of each asthmatic patient was relayed to the hospital pharmacy by telephone.

According to a randomization list previously prepared by a non-participating supervisor, the pharmacist would complete preparation and deliver four syringes labelled respectively No. 1, No. 2, No. 3 and No. 4 according to the appropriate sequence of administration of aminophylline and/or normal saline (see Figure 5). In all cases, delivery

<u>Intermittent Regimen</u>: 500 mg dose every 6 hours each given over 30 minutes.



<u>Continuous Regimen</u>: loading dose followed by maintenance infusion.

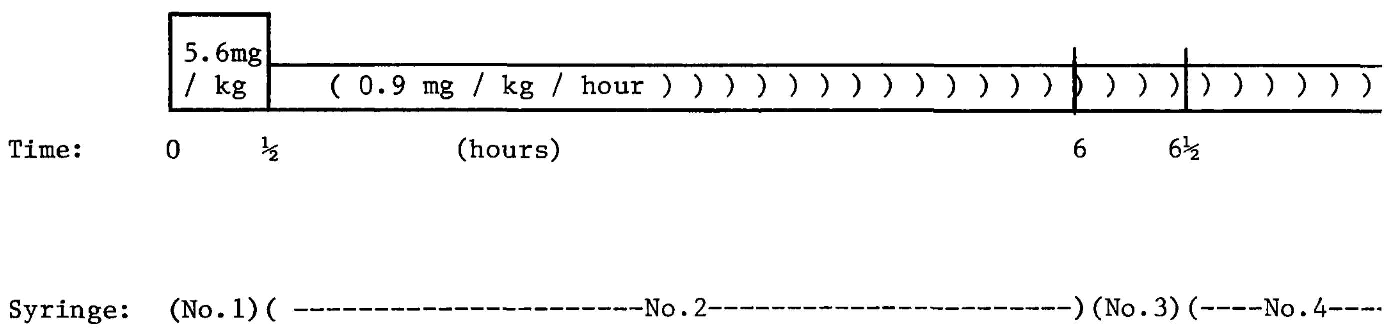


Fig.5: Illustration of Blinding Procedure for Dosing Regimen Syringes

Aminophylline administered by continuous infusion via a Harvard infusion pump.

All syringes were brought up to a volume of 30 ml by adding sterile normal saline to facilitate the blinding procedure.

of the four syringes was made to the investigator in the emergency department at one-half hour after the original telephone call to pharmacy.

Syringes* were prepared and labelled previously as far as possible by the investigator and stored in a refrigerator in pharmacy to facilitate careful completion and consistent delivery at 30 minutes. Calculation sheets and charts (see Appendix I) were provided as a further dosage check.

D. STUDY PARAMETERS

Each patient's distress was staged initially by the investigator as mild (frequent pauses in speech), moderate (monosyllable speech) and severe (too dyspneic to speak). (See Demographic Data - Table II .)

After preliminary patient evaluation by the medical resident and subsequent satisfying of entrance requirements, the patient was informed about test procedures by the investigator. Initiation of study and further observations and tests were co-ordinated by the investigator.

* Syringes were disposable 30 ml Plastipak Luer-Lok Tip made by Becton, Dickinson and Co. Canada Ltd.

Aminophylline was Aminophylline Injection Sterilab Ltd. 500 mg in 10 ml ampoules Lot: 7554-12 made by Sterilab Corporation Ltd.

Normal saline was Sodium Chloride Injection B.P. 0.9% w/v 30 ml vials Lot: 7453-12 made by Sterilab Corporation Ltd.

i) Vital Signs

Radial pulse and respiratory rate were taken and recorded by the investigator. Blood pressure was taken by the attending nurse with a mercury sphygomanometer and recorded by the investigator. Vital signs were taken prior to the initiation of the aminophylline dosing and at hourly intervals thereafter, always before pulmonary function studies were started. Patients were lying in bed with the head of the bed elevated. All readings were taken within the 10 minutes previous to the hour. (See Tables IV, V and VI.)

ii) Pulmonary Function Studies

Spirometric study was performed with the patient in the sitting position, using the McKesson Vitalor Model 44-030 spirometer. Patients were tested immediately prior to the initiation of the aminophylline infusion and at hourly intervals thereafter. At each test time, patients were instructed to complete two forced expiratory spirograms. Measurements of forced vital capacity (FVC), forced expiratory volume in one second ($FEV_{1.0}$), and maximal midexpiratory flow rate (MMFR) were obtained from the

best attempt. Instruction, supervision and encouragement for every pulmonary function test were provided by the investigator. In all pulmonary function studies, after the initial (0000 hour) studies, except two (noted in Tables), the tests were completed within 10 minutes after the hour. (See Tables VII, VIII and IX.) Predicted normal values for FVC and $FEV_{1.0}$ were based on nomograms by Kory et al[49,50] and normal values for MMFR were based on extrapolations from Bates et al.[51]

iii) Plasma Theophylline Levels

Blood samples were drawn from an intravenous heparin-lock* established in the arm contralateral to the one with the running intravenous infusion. The heparin-lock was maintained patent throughout with heparin solution 25 units/ml. At each sampling time 0.5 ml (enough to clear heparin solution from tubing-preventing dilution of the blood samples and erroneous theophylline levels) was drawn from the heparin-lock and discarded.

* Butterfly-21, INT, intermittent infusion set with reseal injection site; No. 4721 made by Abbott Laboratories.

Blood samples of 3 ml were then drawn and injected into labelled heparinized tubes which were kept in ice-water. The injection part of the heparin-lock was then re-injected with 0.5 ml of heparin solution 25 units/ml. All blood samples were centrifuged at 2400 rpm for 10 minutes. The plasma was decanted off by micropipette, and frozen for subsequent analysis.

Sampling times were at 0 hour (immediately prior to aminophylline administration), 15, 30 and 45 minutes, 1, 1.5, 2, 3, 4, 5, 6, 6.25, 6.5 and 7 hours after start of aminophylline infusion. (See Table XIII.) All samples were collected by the investigator.

Serum theophylline levels were operationally defined as subtherapeutic - less than 10 µg/ml, therapeutic - 10-20 µg/ml, and toxic - greater than 20 µg/ml.

iv) Adverse Effects

The investigator questioned the patients at least hourly during study period to encourage reporting of any adverse effects. The time and nature of adverse effects, as described by the patient were recorded (see Table XVI).

In addition, each patient was asked by the investigator to complete a questionnaire (see Appendix II) at the end of his/her treatment period. The questionnaire was designed to determine the presence or absence of

specific subjective effects experienced by the patient. (See Table XV.)

v) Subjective Improvement

At the end of the treatment period, patients were asked to indicate how much they had improved since the beginning of therapy by making two marks on a 100 mm line analogy representing, at one end, no difficulty in breathing or no chest tightness and, at the other, very much breathing difficulty or very much chest tightness (see Appendix III). One mark was to indicate difficulty in breathing at the beginning of treatment. The other mark was to indicate difficulty in breathing at the end of study treatment. Explanation was provided by the investigator (see Table XVII).

E. ANALYSIS OF PLASMA SAMPLES FOR THEOPHYLLINE

Plasma was analysed for theophylline content at the Health Protection Branch Pharmaceutical Chemistry Laboratories* by a slightly modified extraction and assay method of Sitar et al.[48]

* Tunney's Pasture, Ottawa, Ontario.

To 0.25 ml of plasma and 0.25 ml of water in a screw-capped centrifuge tube (18 ml) with a teflon liner, were added 0.2 g of ammonium sulfate, 10 ml of a mixture of chloroform-isopropanol (95:5) and 1 ml of prednisolone* solution (5 µg/ml in chloroform-isopropanol 95:5) as internal standard. The mixture was extracted on a Roto-Rack (Fisher Scientific Company, Ottawa, Ontario) at 75 rpm for 30 minutes. After centrifugation at 2000 rpm for 10 minutes, the aqueous layer and interface were removed by suction and the organic layer was evaporated to dryness at 70°C under a gentle stream of dry filtered nitrogen. The dried residue was redissolved in 25 µl of chromatographic mobile phase (chloroform-isopropanol-acetic acid, 94.5: 4.5: 1.0) and chromatographed.

Chromatographic separation was carried out on a Waters Model 440 - Waters High Pressure Liquid Chromatograph equipped with a Model L440 UV absorbance detector at 280 nm. The chromatographic column (stainless steel tubing 3.2 id x 250 mm) was packed with silica gel (Lichrosorb Si-60, 5 µm nominal particle size) using a balanced density slurry method with 35 per cent dibromomethane in chloroform. Lichrosorb was heated for 2 hours at 200°C and slurry contained 2 g Lichrosorb per 12 ml of liquid. The flow rate was 2.0 ml per minute and the back pressure approximately 4400 psi. Chart

* Sigma Chemical Company.

speed at all times was 5 mm per minute.

Theophylline** standards were made up in plasma taken from a male volunteer who denied methylxanthine intake over previous 48 hours. Standard concentrations included 0.5, 1.0, 5.0, 10.0 and 20.0 µg per ml.

** Anhydrous Theophylline N.F. by British Drug Houses.

4. RESULTS

A. PATIENTS

Twenty-four patients were included in the study analysis. Of these, eleven had received the loading dose followed by continuous infusion (CI) and thirteen had received the intermittent dosing (ID) regimen. Demographic data for the patients are presented in Tables I and II. The continuous infusion group consisted of 5 females and 5 males. One of the females was studied twice. The intermittent dosing group consisted of 7 females and 6 males. No significant difference was found between the two groups with respect to age, weight, height, and history of asthma when compared by unpaired T-test. All patients except two were assessed as having mild acute distress. Patient #4 in the CI group was moderately distressed and patient #20 in the ID group was severely distressed. Inspection of Table II revealed no obvious differences between groups with respect to smoking, medication or allergy history. Patients #4, #5, #16 and #17 from the CI group were queried by attending medical resident and/or investigator as having some bronchitis based on histories of cough and sputum production. Patients #21 and #27 from ID group were queried

similarly. Patients #12, #13, #16, #17, #22, #23 and #28 were believed to have had their asthmatic attacks as a consequence of upper respiratory tract infections. Patients #4 and #7 (CI) claimed that they had hypertension and their medication histories coincided with this. Patients #10 and #25 (ID) complained of migraine headaches and narcolepsy respectively. Patient #28 (CI) had a history of seizures and was taking medication for same.

Patients #5, #10, #21, #23, #26, #27 did not display a 15 per cent improvement in any pulmonary function parameter. Clinical evidence such as a history of tolerance to physical exertion during remissions was used to confirm reversibility of lung disease.

B. TIME OF TREATMENT

Times of patient entry into the hospital emergency department varied from 0555 to 2320 with times for both groups sprinkled in between. The delay from entry time to start of treatment was approximately equal for each group, being 78.5 ± 22.3 (CI) and 75.7 ± 6.5 (ID) minutes.

Duration of treatment varied from 3 hours to the full 7 hour study period. Eight patients, four from each group, were admitted into regular hospital beds for continuation of treatment. The other 16 patients were assessed by the medical resident as sufficiently improved to be discharged from the hospital. Seven patients, five from LD and CI group and two from the ID group, were discharged before 7 hours. Two CI patients and one ID patient were discharged after 4 hours and two patients from LD and CI group were discharged after 5 hours. One patient from the CI group was admitted to a regular hospital bed after 6 hours because of a bed crisis in the emergency department. This patient was considered as requiring the full 7 hours of treatment. Although the average study time for CI group (5.6 hours) was shorter than the average for ID group (6.5 hours), there was no significant difference between durations of stay when compared by a Wilcoxon's Rank Sum test.

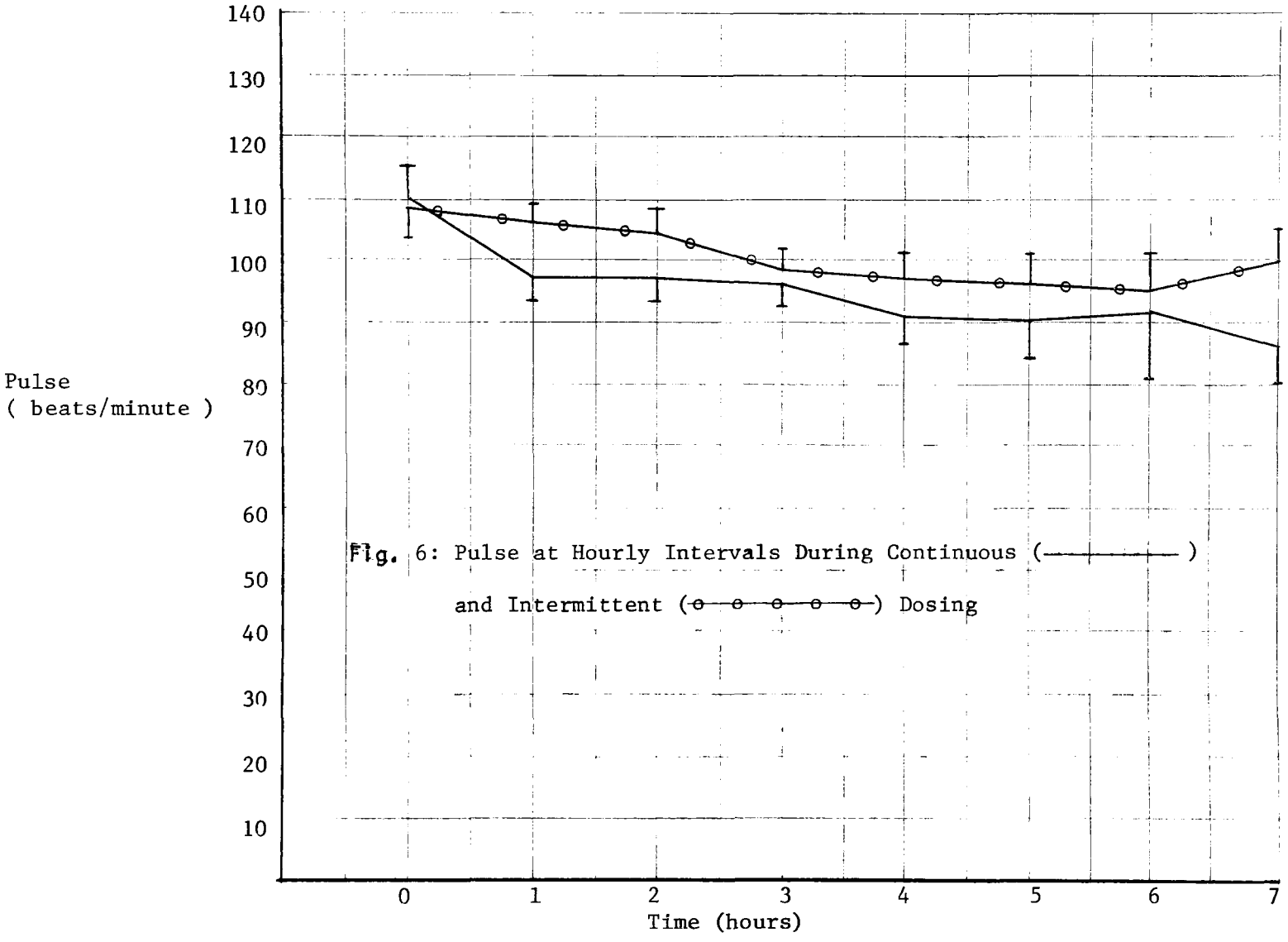


Fig. 6: Pulse at Hourly Intervals During Continuous (———) and Intermittent (—o—o—o—o—) Dosing

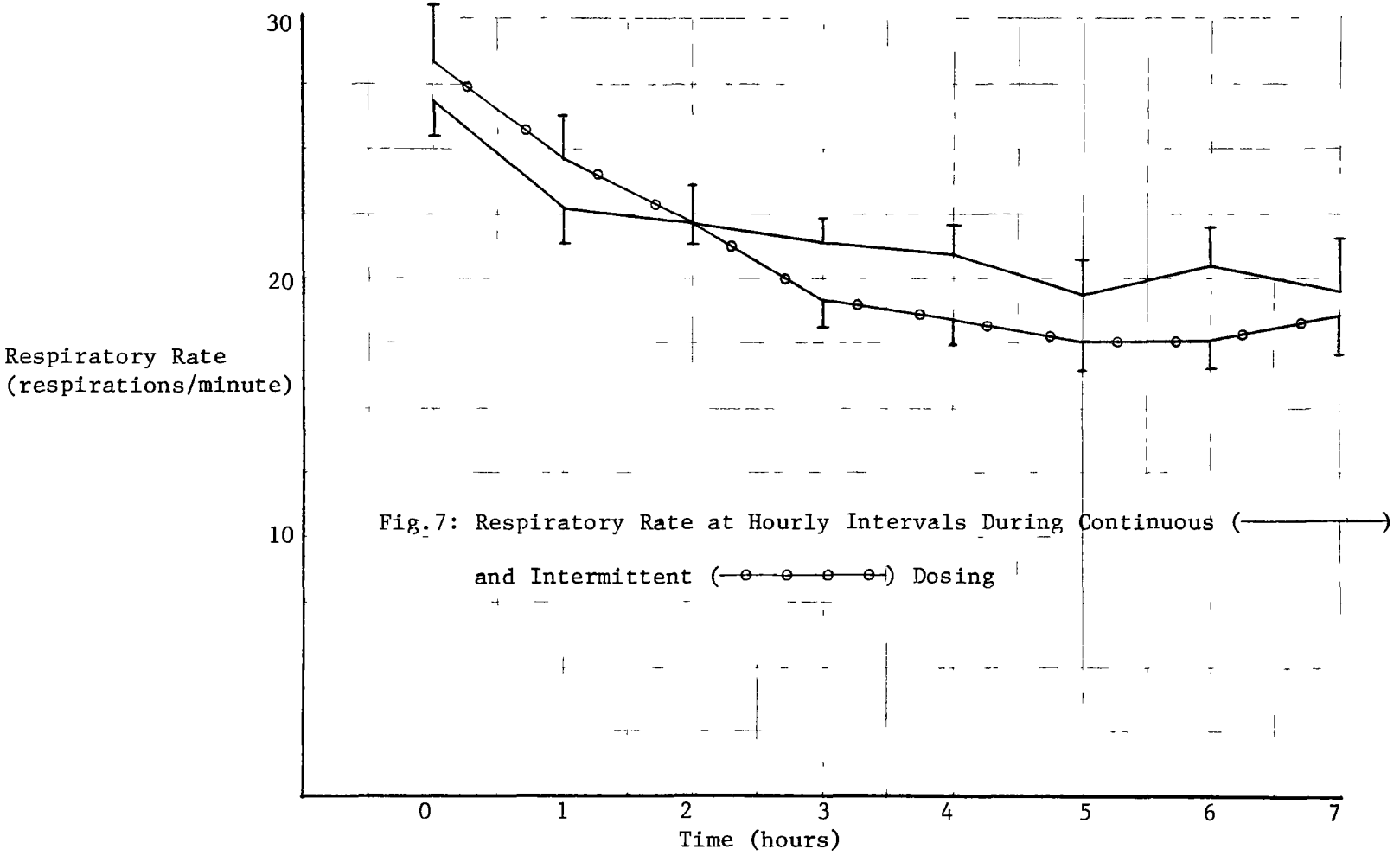


Fig. 7: Respiratory Rate at Hourly Intervals During Continuous (———) and Intermittent (—o—o—o—o—) Dosing

C. VITAL SIGNS

i) Pulse

As seen in Figure 6 the mean pretreatment heart rate was almost equal for the two groups at 110.7 $\pm$ 4.9 for CI and 108.8 $\pm$ 4.5 for ID. A decrease in heart rate was noted during the study period. The decrease was significant for the CI group ($p < 0.01$ as compared by paired T-test). The decrease in pulse rate was not significant for the ID group (as compared by paired T-test). There was no significant difference between mean heart rates for the two groups at any pulse time during the study as compared by unpaired T-test.

ii) Respiratory Rate

Mean respiratory rates are presented graphically in Figure 7. Pretreatment rates were not significantly different at 26.9 $\pm$ 1.5 respirations per minute and 28.5 $\pm$ 2.1 respirations per minute for CI and ID groups respectively. In both groups the respiratory rate decreased during the study period. This decrease was significant; $p < 0.02$ by paired T-test for the CI group and $p < 0.01$ by paired T-test for the ID group. There was no significant difference in respiratory rate at any measurement time throughout the 7 hours between the two groups as compared by unpaired T-test.

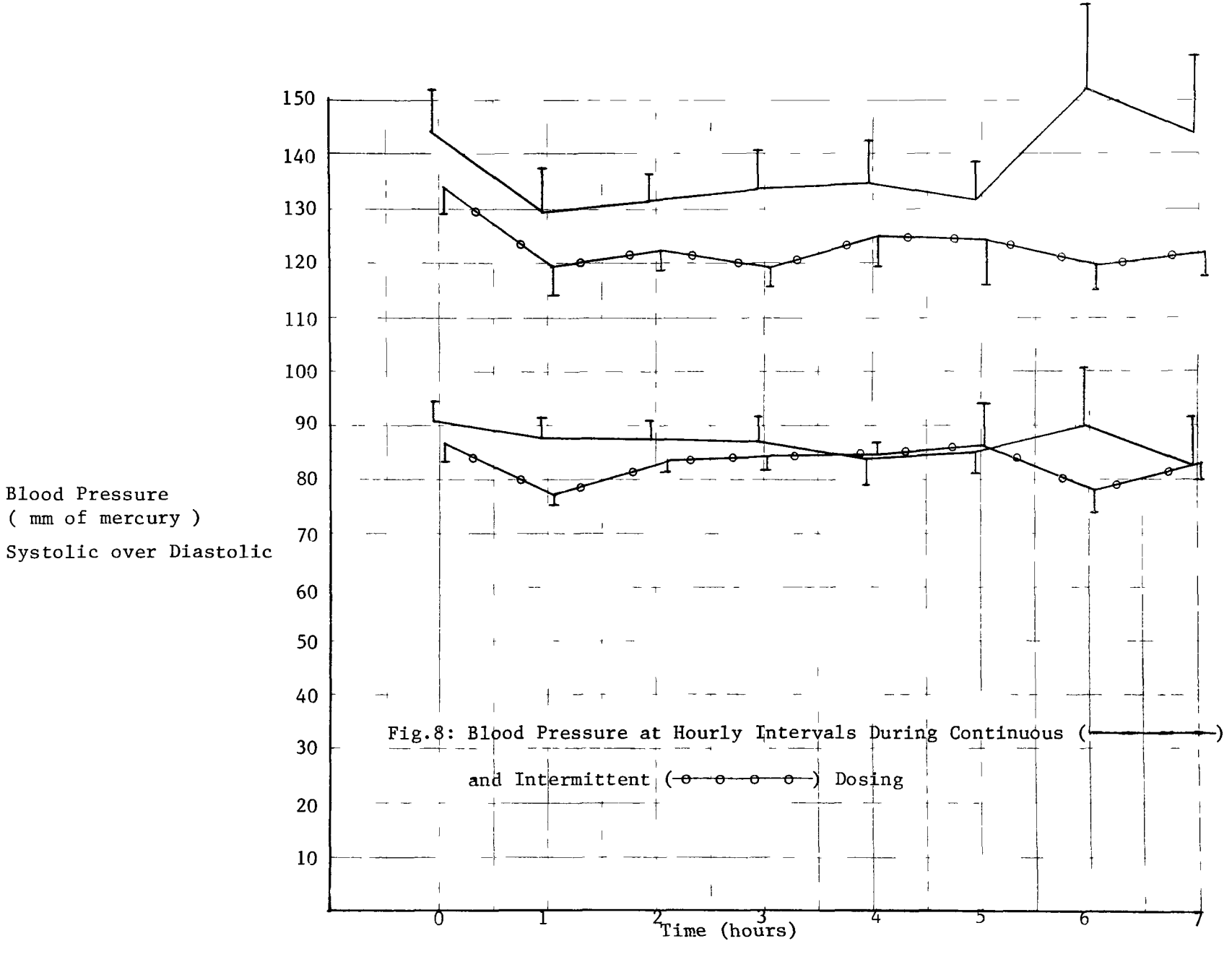


Fig.8: Blood Pressure at Hourly Intervals During Continuous (——) and Intermittent (—o—o—o—o—) Dosing

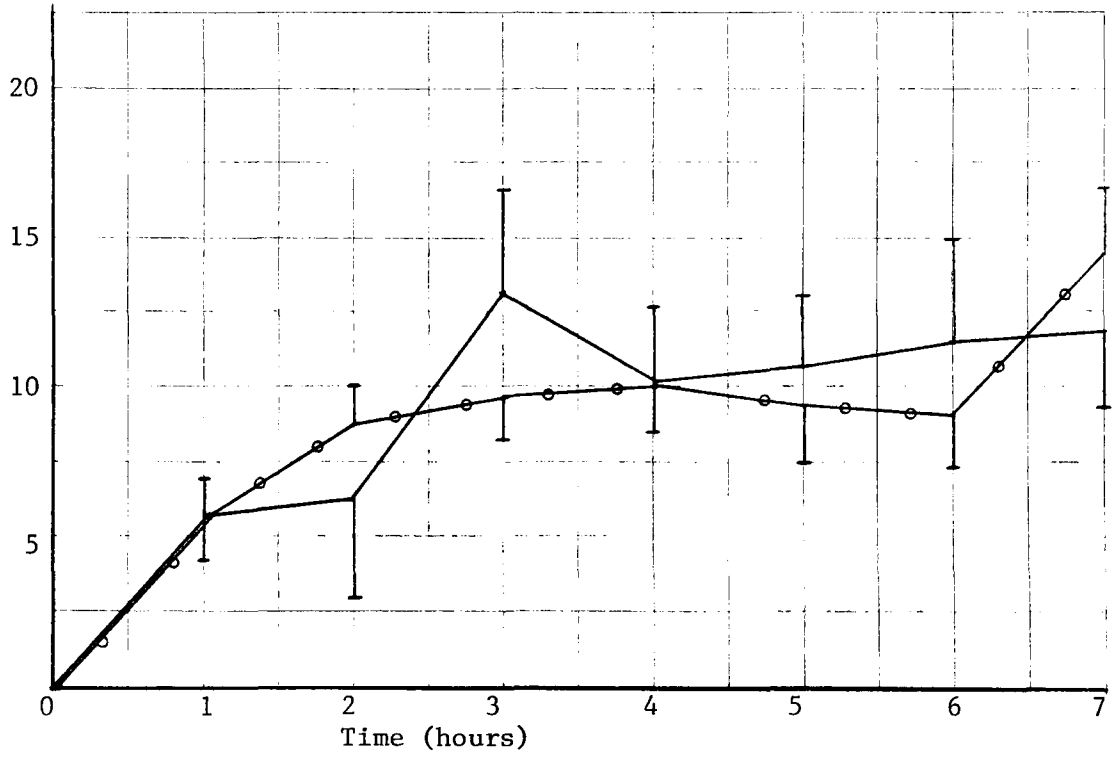
iii) Blood Pressure

Blood pressure, both systolic and diastolic, was higher in the CI group pretreatment but not significantly as seen in Figure 8. Systolic pressure remained consistently higher throughout the study period and at the 6 hour time was significantly higher than that for the ID group ($p. < 0.05$ by unpaired T-test).

D. PULMONARY FUNCTION STUDIES

Pulmonary function values are presented in Table VII - $FEV_{1.0}$, Table VIII - FVC, and Table IX - MMFR. Actual values obtained from spirograms and the same values expressed as percentage of predicted normal values (to eliminate age, sex, and size variation) are presented. To facilitate expression of values in terms of improvement in pulmonary function the pretreatment percentage value for each patient was subtracted from each subsequent percentage value to obtain the difference in pulmonary function as a percentage of predicted normal. These values are found in Table X - $FEV_{1.0}$, Table XI - FVC, and Table XII - MMFR.

Fig.9: Improvement in $FEV_{1.0}$ as a Percentage of Predicted Normal at Hourly Intervals During Continuous (————————) and Intermittent (—o—o—o—o—) Dosing



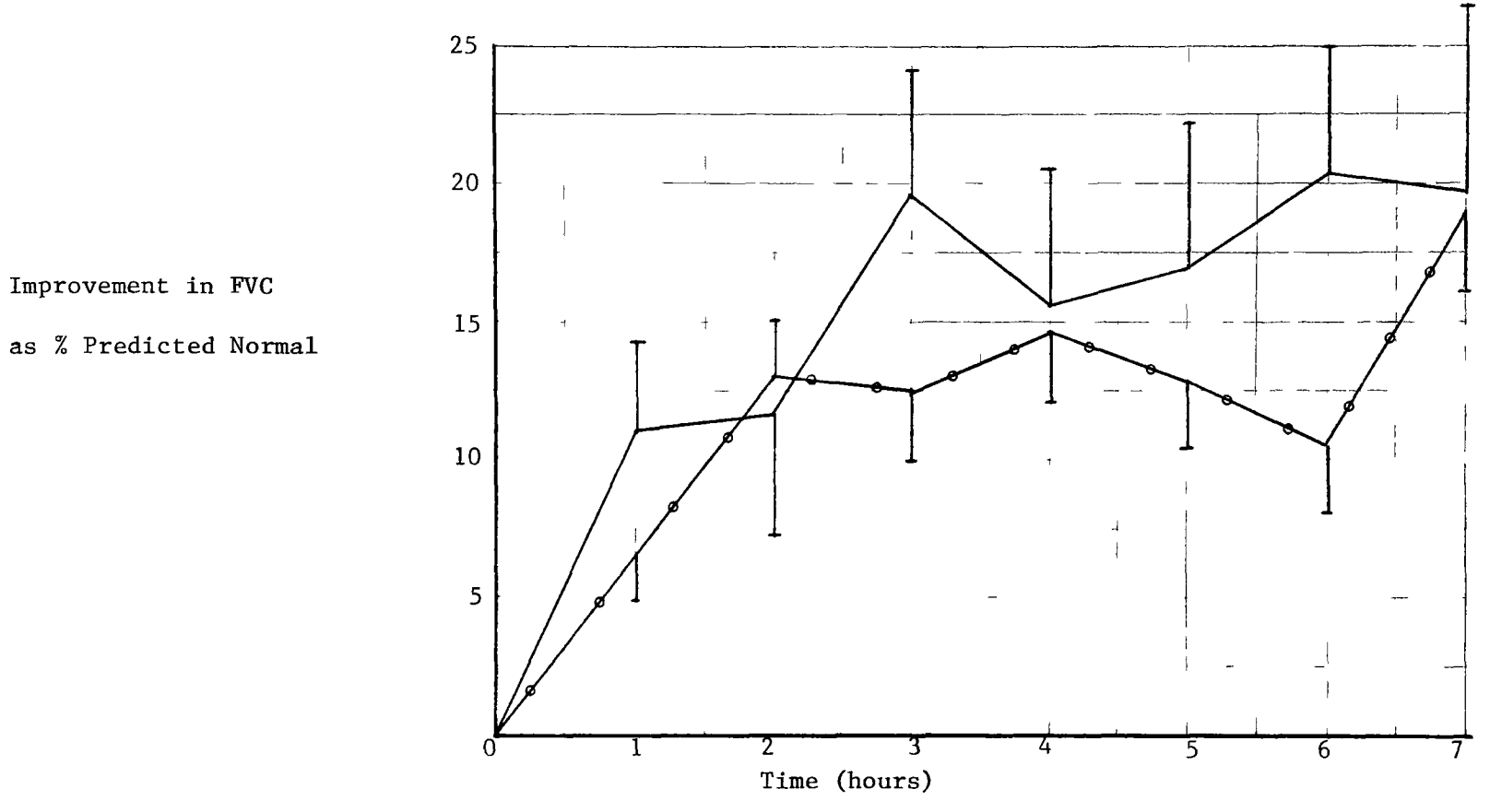
i) Forced Expiratory Volume in One Second

As seen in Table X the mean pretreatment values for $FEV_{1.0}$ as percentage of predicted normal, 18.1 $\pm$ 2.7 for CI group and 22.3 $\pm$ 3.7 for ID group, were not significantly different. Inspection of Figure 9 reveals the $FEV_{1.0}$ improvement pattern. At 2 hours and 7 hours after the start of therapy there was a trend for greater improvement with the ID regimen. At 3 hours, 5 hours and 6 hours, there was a trend for greater improvement with the CI regimen. There was no significant difference between the two dosing regimens at any time during the study period as compared by unpaired T-test.

ii) Forced Vital Capacity

As seen in Table XI the mean values for pretreatment FVC as percentage of predicted normal, 27.5 $\pm$ 4.0 for the CI group and 34.7 $\pm$ 3.9 for the ID group, were not significantly different. Inspection of Figure 10 reveals the improvement pattern. At 2 hours after the beginning of treatment the intermittent dosing ID regimen had a trend toward greater improvement. At the other times, 1, 3, 4, 5, 6 and 7 hours, a trend toward greater improvement occurred with the

Fig.10: Improvement in FVC as a Percentage of Predicted Normal at Hourly Intervals During Continuous (————————) and Intermittent (—o—o—o—o—) Dosing



continuous infusion. There was no significant difference between the two dosing regimens at any time during the study period as compared by unpaired T-test at the 0.05 level. There was, however, a significant difference at the 0.07 level* at 6 hours.

iii) Maximum Mid-Expiratory Flow Rate

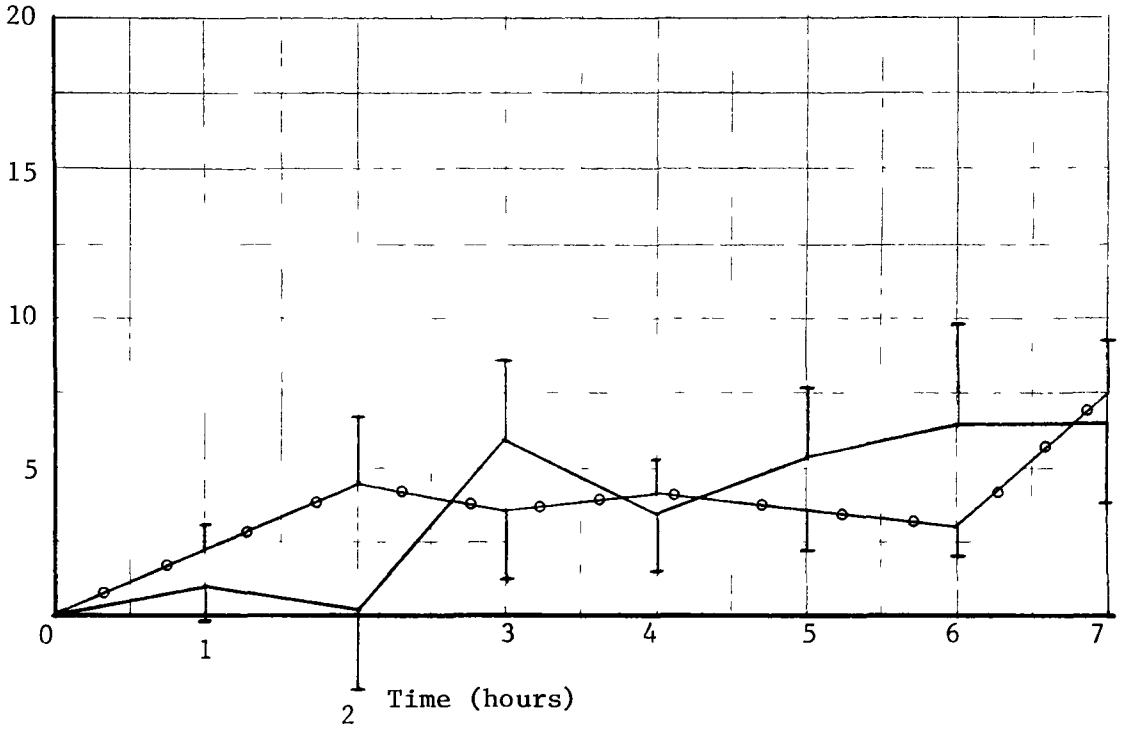
As seen in Table XII the mean values for MMFR as percentage of predicted normal, 12.6 $\pm$ 2.6 for CI group and 15.4 $\pm$ 3.6 for ID group, were not significantly different. Inspection of Figure II reveals the MMFR improvement pattern. At 1, 2, 4 and 7 hours a trend for more improvement was associated with the ID regimen, whereas at 3, 5 and 6 hours a trend for more improvement was associated with the CI regimen. At no time during the study period was there any significant difference between the two dosing regimens as compared by unpaired T-test.

E. PLASMA THEOPHYLLINE LEVELS

Plasma theophylline concentrations for the two groups are presented in Table XIII. Pretreatment mean plasma theophylline concentration was similar for the two groups,

* Extrapolated from T-distribution tables.

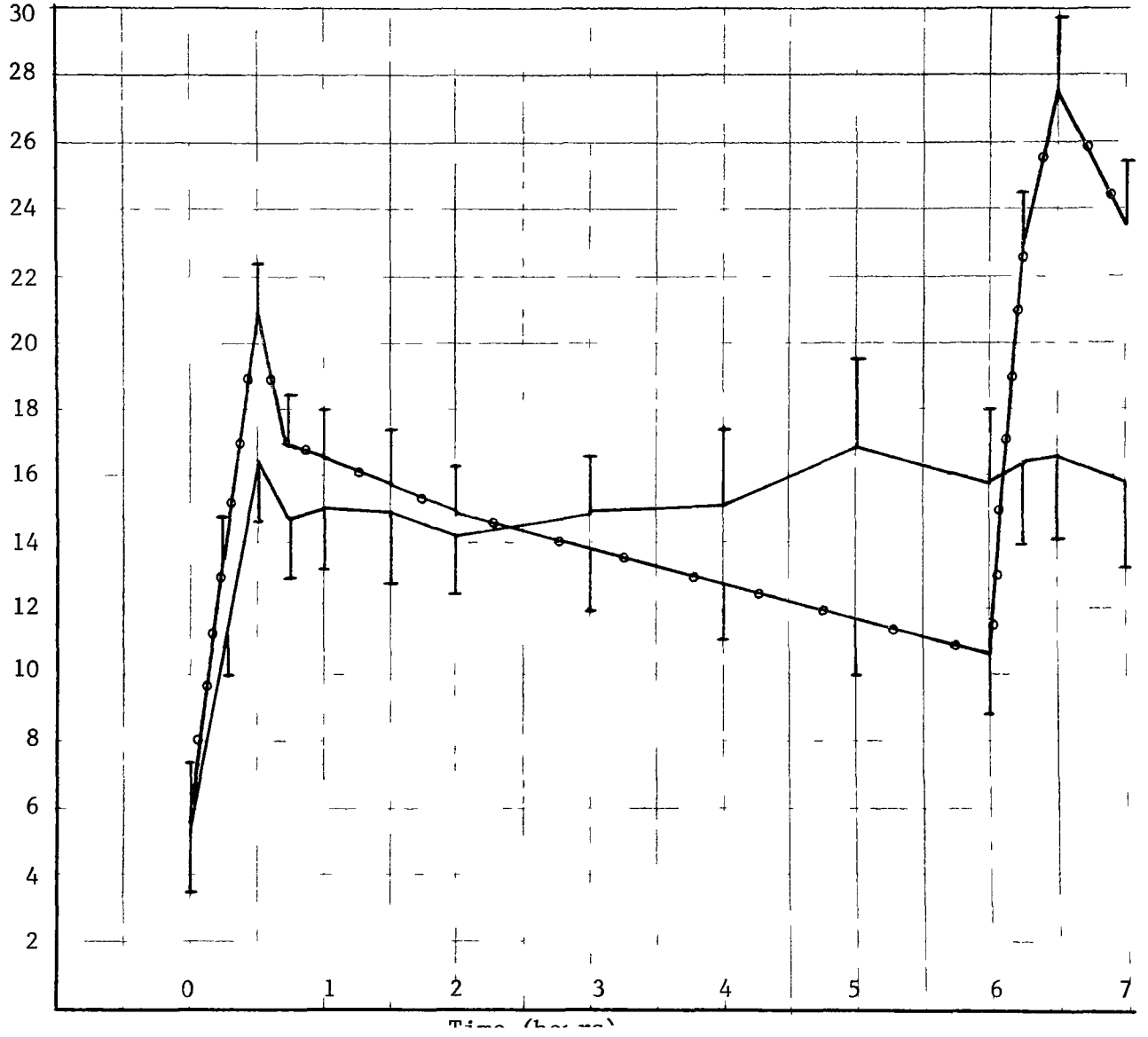
Fig.11: Improvement in MMFR as a Percentage of Predicted Normal at Hourly Intervals During Continuous (—————) and Intermittent (—o—o—o—o—o—) Dosing



5.5 ± 2.1 µg/ml for CI group and 5.6 ± 1.8 µg/ml for ID group, as seen in Table XIII and Figure 10. Inspection of Table II reveals that previous self-administration of oxtriphylline and 'Tedral' tablets and aminophylline suppositories was the cause of the initial levels of theophylline.

As seen in Figure 12 the mean plasma level of theophylline reaches a therapeutic level in 15 minutes, increases to above mid-therapeutic concentration by 30 minutes, and remains in approximately mid-therapeutic range throughout the study period with the continuous infusion. With the intermittent dosing regimen the theophylline level reached a therapeutic level in 15 minutes also, but increased to a toxic level at 30 minutes, decreased progressively to a low therapeutic level at 6 hours, and then increased to toxic levels for the remaining measurement times. The mean level at 0630 and 0700 was significantly higher than that for the CI regimen ($p < 0.01$ and $p < 0.05$ respectively by unpaired T-test). The level at 0630 was highly significantly above 20 µg/ml ($p < 0.01$ by one-tailed T-test). The number of patients' theophylline levels found in subtherapeutic, therapeutic and toxic ranges is presented in Table XIV for each group. Inspection of Tables XIII and XIV immediately reveals that one patient in the CI group was already in toxic range at the onset of treatment and remained so throughout. One other patient in this group and three more from the ID group were already

Fig.12: Serum Theophylline Levels at Intervals During Continuous (————————)
and Intermittent (—o—o—o—o—) Dosing



in therapeutic range. Other points to be noted are: at 0030 all patients are out of the subtherapeutic range and 6 out of the 13 patients from the ID group are in the toxic range compared to 3 out of 11 patients from the CI group; there is a progressive increase in the number of patients dropping into subtherapeutic range in the ID group; and the dramatic increase in the number of patients from the ID group in the toxic range at 0630 time (10 out of 11 patients) compared to 1 out of 5 patients in the CI regimen.

F. ADVERSE EFFECTS

Adverse effects, as indicated by affirmative answers on the questionnaire are shown in Table XV. More patients receiving the intermittent dosing regimen answered affirmatively to the eight questions, except to the question concerning irregular heartbeat or palpitations. Considering the lesser number of patients and decreased overall time of study, no difference in the numbers was apparent.

Complaints related to the drugs, as volunteered by the patient during the study period, are presented in Table XVI. In brackets beside the numbers are the plasma theophylline levels or range of levels most closely associated temporally with the complaint. In some instances a patient suffered an

adverse effect more than once. The plasma theophylline level at each time is shown, thus explaining the greater number of theophylline levels than numbers of patients with complaints. With the exception of headache and rash the number of complaints was greater with the intermittent dosing regimen. Of particular interest were two reports of tasting the drug and one complaint of "passing out" by patient #27. In each instance of tasting, the theophylline level was greater than 30.0 µg/ml. To this author's knowledge, this side effect has not previously been reported. The "passing out" episode occurred at a theophylline level of 13.7 µg/ml. None of the adverse effects was deemed serious and none required discontinuation of therapy.

Contemplation of the theophylline levels associated with the complaints of adverse effects reveals considerable variation. Headache was associated with theophylline levels between 3.6 to 33.2 µg/ml; vomiting 15.4 to 41.9 µg/ml; nausea 9.9 to 41.9 µg/ml; and dizziness 9.9 to 29.0 µg/ml. Persual of Table XVI reveals that most adverse effects were seen at therapeutic and even subtherapeutic concentrations of theophylline.

G. SUBJECTIVE EFFECTS

Some difficulty was encountered in determining subjective impression of improvement in breathing. Many patients required explanation and even demonstration of using the line analogy. Two patients did not comply with instructions. Patients #9 and #12 did not make any marks on the line. Patient #9 wrote in the figures, 15 to 20 per cent, to indicate improvement. The mean of this range was accepted as percentage improvement. At the end of the study period patients may have had difficulty in evaluating or remembering their status before the start of therapy.

As seen in Table XVII there was no significant difference between the two groups at the beginning of therapy. At the end of the study period the ID group indicated that its status was closer to normal as indicated by the mean of 75.4 ± 3.8 as compared to 70.9 ± 4.6 for the CI group. Subjective improvement, 61.2 ± 5.6 per cent for the ID group, tended to be greater than that for the CI group 51.4 ± 4.8. This difference was not significant as determined by unpaired T-test.

TABLE I: DEMOGRAPHIC DATA

Information obtained from patients.

Patient Number	Sex	Age (Years)	Weight (kg)	Height (cm)	History of Asthma (Yrs)	Date and Time of Hospital Entry
	Continuous Infusion					
4	F	63	43	155	2	9/9/76-0555
5	M	57	106	170	4	13/9/76-0845
7	F	41	52	160	10	20/9/76-2320
9	M	28	108	191	25	26/9/76-1919
14	M	46	65	174	3	9/10/76-1010
15	M	20	52	170	19	14/10/76-1910
16*	F	53	54	157	5	14/10/76-2305
17*	F	53	54	157	5	17/10/76-1304
19	F	27	50	163	25	2/11/76-1415
23	M	21	73	179	5	15/11/76-1410
28	F	27	54	170	25	15/12/76-1420
Mean		39.6	64.6	167.8	11.6	
± S.E.M.		±4.7	±6.7	±3.3	±2.9	
	Intermittent Dosing					
6	F	53	68	155	25	17/9/76-2300
10	M	32	63	157	25	30/9/76-2205
11	F	47	82	169	10	1/10/76-2230
12	F	17	53	160	14	2/10/76-1320
13	F	19	66	165	9	5/10/76-2230
18	F	24	52	163	3	20/10/76-1120
20	F	30	61	170	27	2/11/76-2215
21	F	40	73	157	25	8/11/76-1510
22	M	33	80	175	24	12/11/76-2025
24	M	31	100	179	5	16/11/76-1140
25	M	22	66	175	20	19/11/76-2218
26	M	34	85	173	17	30/11/76-1425
27	M	46	83	168	1	8/12/76-1503
Mean		32.9	71.7	166.6	15.8	
± S.E.M.		±3.1	±3.8	±2.2	±2.6	

* The same patient returned three days later.

TAPLE II DEMOGRAPHIC DATA

Information obtained from patients, except degree of severity which was assessed by investigator.

Patient Number	Medication History: Past	Medication History: Hours Prior to Treatment	Allergies	Other Methylxanthine Intake	Smoking History (cigarettes)	Degree of Distress	Delay from Hospital Entry Until Treatment	Other Problems
4	Hydrochlorothiazide 50 mg daily** Oxtriphylline 200 mg Qid -- T* Co-Trimoxazole TT Bid Salbutamol Inhaler ** Tedral, Methyldopa	16	'has had allergy shots'	½ cup of tea 17 hrs before		Moderate	285 min.	Hypertension ? Some Bronchitis
5					40/day for 20 years	Mild	45 min.	? Some Bronchitis
6	Salbutamol Inhaler ---------- TT Salbutamol 2 mg Qid -- T Oxtriphylline 200 mg Bid -- Aminophylline Supp. 500 mg ----- T Prednisone	5 min. 18 14	dogs, cats peanuts chocolate			Mild	48 min.	
7	Oxtriphylline 200 mg Qid T Aldactazide TT daily Ampicillin 500 mg Qid Chlordiazepoxide 25 mg Tid Prednisone 10 mg daily Salbutamol Inhaler and Tablets	13	adrenaline wool feathers			Mild	40 min.	Hypertension
9	Prednisone 5 mg daily Salbutamol 4 mg ----- T Isoproterenol-Phenylephrine Inhaler -- T Orciprenaline, Hydroxyzine Sodium Cromoglycate Spinhaler	10 0.25	ragweed pollen cats dust	1 cup of coffee 6 hours before 1 cola drink 3 hours before		Mild	71 min.	

Patient Number	Medication History: Past		Hours Prior to Treatment	Allergies	Other Methylxanthine Intake	Smoking History (cigarettes)	Degree of Distress	Delay from Hospital Entry Until Treatment	Other Problems
10	Tedral ---------- T Adrenaline 1:1000	0.3 ml SC	6 2	feathers dust	2 cups of tea in previous 6 hours	25/day for 15 years	Mild	127 min.	Migraine Headaches
11	Tedral ---------- T Epinephrine Inhaler – TT		2 1	sulfa drugs, dust feathers	1 cup of tea 3 hours before		Mild	60 min.	
12	Salbutamol 4 mg Tid T Salbutamol Inhaler TT Adrenaline 1:1000	0.3 ml SC	5 5 1				Mild	85 min.	? Infectious Exacerbation
13	Orciprenaline Inhaler -------- $\dot{T}$		2	penicillin cats adhesive tape			Mild	90 min.	? Infectious Exacerbation
14	Orciprenaline Inhaler ------- – $\dot{T}$ Actifed Adrenaline Injectible		2	dogs, cats feathers dust ragweed	1 cup of tea 2 hours before	20/day for 15 years. Quit 4 years ago	Mild	50 min.	
15	Tedral S.A. ---------- TT Diazepam		3	dust, fruit, feathers, milk			Mild	35 min.	
16	Salbutamol 4 mg ---------- T Orciprenaline Inhaler		2	'hay fever'	2 cups of tea 5 hours before	20/day for 25 years	Mild	85 min.	? Some Bronchitis ? Infectious Exacerbation
17	Amoxicillin 250 mg Qid Oxtriphylline 200 mg Qid ---- $\dot{T}$ Salbutamol 4 mg Orciprenaline Inhaler		3	'hay fever'	2 cups of tea 3 hours before	20/day for 25 years	Mild	36 min.	? Some Bronchitis ? Infectious Exacerbation

Table II continued

Patient Number	Medication History: Past	Hours Prior to Treatment	Allergies	Other Methylxanthine Intake	Smoking History (cigarettes)	Degree of Distress	Delay from Hospital Entry Until Treatment	Other Problems
18	Isoproterenol Inhaler ------ XV Actifed, Cortisone, Tetracycline, Ephedrine, Aminophylline, Orciprenaline, Salbutamol, Sodium Cromoglycate, Spinhaler, Beclomethasone Inhaler.	during6	dust cats dogs feathers		20/day for 4 years. Quit 3 years ago.	Mild	60 min.	
19	Isoproterenol ---------- T Salbutamol Inhaler 6 puffs/day Cortisone, Neo-Citran	5				Mild	45 min.	
20	Tedral ---------- T Orciprenaline 20 mg. Qid Orciprenaline Inhaler ------- T Sodium Cromoglycate Spinhaler Adrenaline 1 1000 0.3 ml SC T Adrenaline 1 1000 0.3 ml SC T	5 1 50 min. 35 min.		½ cup of coffee, 2 hours before	Occasional, less than 25 per month.	Severe	55 min.	
21	Salbutamol Inhaler, Tetracycline, Beclomethasone Inhaler, Adrenaline 1 1000 0.3 ml SC	6		1 cup of coffee 8 hours before	15/day for 23 years	Mild	65 min.	? Some Bronchitis
22	Beclomethasone Inhaler, Aminophylline Supp. 500 mg. T Ephedrine Inhaler ---------- T	5 30 min.				Mild	95 min.	? Infectious Exacerbation
23	Tedral T Q4h ---------- T Tedral SA T Q12h T Dimetane Expectorant	4 14	cats, dust feathers weeds	1 cup of coffee 5 hours before		Mild	115 min.	? Infectious Exacerbation

Table II continued

Patient Number	Medication History: Past	Hours Prior to Treatment	Allergies	Other Methylxanthine Intake	Smoking History (cigarettes)	Degree of Distress	Delay from Hospital Entry Until Treatment	Other Problems
24	Tedral SA Tid -------- T Isoproterenol Inhaler -- 3 puffs during Dimetane Expectorant DC, Tetracycline, Isoproterenol Inhaler, Diazepam	7 6	milk, dust, gas fumes, cats, dogs.	1 cup of tea 2 hours before	Light for 6 years Quit 5 years ago	Mild	80 min.	
25	Imipramine, Tedral, Tedral SA, Asthmanephrin, Neo-Citran		feathers, elm tree sap.		8/day for 2 years	Mild	47 min.	Narcolepsy
26	Beclomethasone Inhaler, Salbutamol Inhaler, Erythromycin, Co-Trimoxazole, Trisulfaminic Prednisone 20 mg------ T Adrenaline 1 1000 0.2 ml SC	 5 1	dust, feathers, mold, penicillin, cats, horse dander, sawdust.	1 cup of chocolate tea, 4 hours before.		Mild	100 min.	Infectious ? Exacerbation
27	Oxtriphylline 200 mg Tid -- T Prednisone 5 mg daily Tetracycline, Trimipramine, Butabarbital, Maalox, Rolaids	3	dust, smoke, exhaust fumes, some deodorants.	1 cup of coffee 6, 4 and 2 hours before.	100/day for 20 yrs. Quit 1 year ago.	Mild	72 min.	Some ? Bronchitis
28	Orciprenaline 20 mg Qid --- T Phenytoin 100 mg Bid Phenobarbital 30 mg Bid Penicillin	4	'49 allergies' dust, feathers, pine trees.	1 cup of tea 5 hours before	?0/day for 12 yrs.	Mild	56 min.	Seizures Infectious ? Exacerbation

*T------- One Dosage Unit
** ------- Unless specified otherwise refers to oral dosage.
*** ------ Unspecified dosage schedule may refer to dosage when required, medication not being taken at the time, or forgotten schedule.

TABLE III: MEDICATIONS RECEIVED DURING THERAPY WITH INTRAVENOUS AMINOPHYLLINE AND HYDROCORTISONE.

Patient Number	Medication Administered	Dosage, Route and Time in Hours After Therapy Started
4	--	--
5	--	--
7	Chlordiazepoxide	10 mg orally at 0420
	Aldactazide	1 orally at 0600
	Ampicillin	250 mg orally at 0600
9	Salbutamol	100 µg by inhalation at 0410
	Hydrocortisone	250 mg intravenously at 0630
14	--	--
15	--	--
16	--	--
17	Salbutamol	100 µg by inhalation at 0215
	Oxygen	By face mask inhalation intermittently throughout.
19	--	--
23	--	--
28	--	--
6	Prochlorperazine	10 mg intramuscularly at 0105
10	--	--
11	--	--
12	Ampicillin	500 mg orally at 0615
13	--	--
18	--	--
20	Dimenhydrinate	50 mg intramuscularly at 0030
	Oxygen	By face mask inhalation intermittently during first hour.
21	--	--
22	--	--
23	--	--
24	--	--
25	--	--
26	--	--
27	--	--

TABLE IV: HEART RATE AS MEASURED BY RADIAL PULSE

Patient Number	Hour 0	1	2	3	4	5	6	7
	Continuous Infusion							
4	110	104	104	104	100	76	64	72
5	90	80	96	94	92	96		
7	112	88	84	84	84	88	88	84
9	116	88	96	96	92	-- *	--	
14	120	84	80	84	80	76	116	100
15	148	116	112	108				
16	100	100	100	92	92	92	100	90
17	120	112	104	--	--	--	--	--
19	92	112	104	100				
23	110	116	116	116	116	114		
28	100	76	80	84	76			
Mean	110.7	97.8	97.8	96.2	91.5	90.3	92.0	86.5
± S.E.M.	±4.9	±4.6	±3.7	±3.5	±4.4	±5.8	±11.0	±5.9
	Intermittent Dosing							
6	132	124	112	104	100	96	100	96
10	88	88	80	76	72	72	74	76
11	126	104	96	98	100	104	104	110
12	120	112	130	120	112	116	108	116
13	108	126	112	104	92	100	100	120
18	116	100	120	120	116	116	116	116
20	120	110	112	88	80	68	56	80
21	92	100	96	84	96	94	88	98
22	100	98	96	92	92			
24	120	110	116	112	116	108	118	112
25	120	120	96	104				
26	88	104	100	96	104	84	96	96
27	84	86	96	86	92	100	92	88
Mean	108.8	106.3	104.8	98.8	97.7	96.2	95.6	100.7
±S.E.M.	±4.5	±3.4	±3.7	±3.8	±3.9	±4.8	± 5.5	±4.6

* Value not included because patient received another interfering drug.

TABLE V: RESPIRATORY RATE

Patient Number	Hour 0	1	2	3	4	5	6	7
	Continuous Infusion							
4	24	24	24	22	26	20	24	24
5	32	20	20	24	22	20		
7	18	18	22	24	20	20	18	20
9	28	24	24	24	22	--	--	
14	32	16	20	16	16	14	22	14
15	32	30	24	20				
16	32	26	22	22	20	18	18	20
17	28	28	28	--	--	--	--	--
19	24	16	16	16				
23	22	24	20	24	24	24		
28	24	24	24	22	18			
Mean	26.9	22.7	22.2	21.4	21.0	19.3	20.5	19.5
±S.E.M.	± 1.5	±1.4	±1.0	±1.0	±1.1	±1.3	±1.5	±2.1
	Intermittent Dosing							
6	22	20	20	14	16	16	14	20
10	30	30	22	20	20	20	18	22
11	36	22	18	16	16	16	16	18
12	32	18	18	20	20	18	16	16
13	28	24	24	22	16	12	14	14
18	20	24	22	20	18	18	20	20
20	44	36	24	18	18	16	16	18
21	26	36	36	28	28	26	28	32
22	22	22	20	18	16			
24	24	18	16	14	16	14	12	12
25	40	28	26	18				
26	22	20	20	20	18	16	16	16
27	24	22	24	22	20	20	24	18
Mean	28.5	24.6	22.3	19.2	18.5	17.5	17.6	18.7
±S.E.M.	±2.1	±1.7	±1.4	±1.0	±1.0	±1.1	±1.4	±1.6

TABLE VI: BLOOD PRESSURE

Patient Number	Hour 0 S	0 D	1 S	1 D	2 S	2 D	3 S	3 D	4 S	4 D	5 S	5 D	6 S	6 D	7 S	7 D
	Continuous Infusion															
4	192	90	200	80	152	90	182	76	162	70	150	84	180	90	172	84
5	150	100	118	76	146	80	154	84	140	80	150	86				
7	172	116	134	116	156	98	140	116	154	100	138	100	160	110	158	105
9	160	100	140	94	134	100	135	90	150	100	--	--	--	--		
14	160	90	120	92	130	98	142	92	126	96	110	80	160	100	140	80
15	114	90	110	70	115	80	130	90								
16	110	70	110	80	110	80	108	70	100	60	116	70	108	60	106	60
17	130	92	150	80	122	76	--	--	--	--	--	--	--	--	--	--
19	142	80	100	98	122	88	116	80								
23	140	100	130	95	142	100	120	95	134	88	124	90				
28	110	70	108	80	118	72	112	74	108	76						
Mean	143.6	90.7	129.1	87.4	131.5	87.5	133.9	86.7	134.3	83.8	131.3	85.0	152.0	90.0	144.0	82.3
±S.E.M.	±8.0	±3.3	±8.4	±3.9	±4.7	±3.1	±7.1	±4.2	±7.8	±5.2	±7.8	±4.1	±15.4	±10.8	±14.3	±9.2
	Intermittent Dosing															
6	150	86	136	90	138	80	122	80	124	86	126	80	128	82	130	86
10	142	90	122	70	128	78	120	82	118	78	120	90	120	80	124	86
11	140	100	110	60	114	72	144	80	140	74	140	80	130	70	132	78
12	120	80	100	78	100	80	100	76	100	80	96	72	96	70	108	86
13	140	90	132	80	150	90	124	84	140	90	128	80	130	80	132	88
18	110	70	118	90	122	90	114	88	110	86	110	100	112	78	100	90
20	150	100	99	70	110	80	104	82	110	70	94	50	100	50	104	70
21	90	70	102	70	128	90	122	90	120	90	120	90	120	90	122	80
22	130	70	144	84	118	88	116	80	100	70						
24	140	110	110	82	118	94	140	106	160	110	198	150	132	100	150	100
25	140	90	125	80	130	80	110	80								
26	140	80	150	86	128	80	124	95	158	90	130	90	145	95	122	76
27	150	90	110	70	110	80	110	76	122	80	106	70	100	66	120	70
Mean	134.0	86.6	119.8	77.7	122.6	83.2	119.2	84.5	125.2	83.7	124.4	86.5	119.4	78.3	122.2	82.7
± S.E.M.	±4.9	±3.5	±4.7	±2.5	±3.6	±1.8	± 3.5	±2.3	±5.9	±3.2	±8.5	±7.5	±4.7	±4.3	±4.3	±2.7

S - Systolic D - Dystolic

TABLE VII: PULMONARY FUNCTION STUDIES

Part 1. Forced Expiratory Volume in One Second (litres)

Patient Number	Predicted Normal Value°	Hour 0 A+	% P++	1 A	% P	2 A	% P	3 A	% P	4 A	% P	5 A	% P	6 A	% P	7 A	% P
4	2.14	--#	--	.30	14.0	.24	11.2	.36	16.8	.37	17.3	.40	18.7	.30	14.0	.37	17.3
5	3.08	.56	18.2	.72	23.4	.64	20.8	.80	26.0	.84	27.3						
6	2.35	.44	18.7	.66	28.1	.62	26.4	.66	28.1	.52	22.1	.48	20.4	.60	25.5	.58	24.7
7	2.78	.72	25.9	.80	28.8	1.06	38.1	1.15	41.4	1.26	45.3	1.30	46.8	1.32	47.5	1.22	43.9
9	4.20	.84	20.0	1.22	29.0	1.00	23.8	1.06	25.2	1.10	26.2	--¢	--	--	--		
10	3.32	1.23	37.0	1.18	35.5	1.46	44.0	1.55	46.7	1.46	44.0	1.28	38.6	1.44	43.4	1.64	49.4
11	2.90	.28	9.7	.30	10.3	.58	20.0	.58	20.0	.60	20.7	.54	18.6	.52	17.9	.78	26.9
12	3.26	.62	19.0	.94	28.8	1.20	36.8	1.28	39.3	1.11	34.0	1.16	35.6	1.18	36.2	1.40	43.0
13	3.36	.65	19.3	.93	27.7	1.10	32.7	1.02	30.4	.98	29.2	1.20	35.7	.80	23.8	1.06	31.5
14	3.56	.64	18.0	.82	23.0	.84	23.6	.90	25.3	1.00	28.1	1.05	29.5	1.02	28.7	1.12	31.5
15	4.14	.36	8.7	.78	18.8	1.48	35.7	1.80	43.5								
16	2.40	.32	13.3	.32	13.3	.36	15.0	.44	18.3	.42	17.5	.52	21.7	.52	21.7	.48	20.0
17	2.40	.10	4.2	.34	14.2	.20	8.3	--	--	--	--	--	--	--	--	--	--
18	3.20	.30	9.4	.56	17.5	.52	16.3	.44	13.8	.62	19.4	.56	17.5	.46	14.4	.88	27.5
19	3.14	.80	25.5	1.16	36.9	1.50	47.8	1.60	51.0								
20	3.26	--#	--	.64*	19.6	.80	24.5	.66	20.2	.76	23.3	.94	28.8	1.00	30.7	1.30	39.9
21	2.68	1.26	47.0	1.36	50.7	1.40	52.2	1.30	48.5	1.36	50.7	1.42	53.0	1.40	52.2	1.36	50.7
22	3.96	.42	10.6	.58	14.6	.80	20.2	1.04	26.3	1.24	31.3						
23	4.44	.64	14.4	.62	14.0	.66	14.9	.64	14.4	.68	15.3	.78	17.6				
24	4.16	.84	20.2	.96	23.1	.94	22.6	1.04	25.0	1.50	36.1	1.54	37.0	1.58	38.0	1.54	37.0
25	4.28	1.82	42.5	2.40	56.1	2.36	55.1	2.50	58.4								
26	3.86	.56	14.5	.84**	21.8	.74	19.2	.84	21.8	.76	19.7	.70	18.1	.68	17.6	1.00	25.9
27	3.62	.70	19.3	.74	20.4	.88	24.3	1.04	28.7	1.02	28.2	1.00	27.6	.96	26.5	1.12	30.9
28	3.33	1.08	32.4	1.20	36.0	.64	19.2	1.78	53.5	1.80	54.1						

o Based on sex, age and height.
\+ Actual Value
++ Percentage of Predicted Normal.

\# Patient unable to comply.
* Pulmonary Function Test not completed until 0115 for technical reasons.
** Pulmonary Function Test not completed until 0115 for technical reasons.
¢ Value not included because patient received another interfering drug.

TABLE VIII: PULMONARY FUNCTION STUDIES

Part 2. Forced Vital Capacity (litres)

Patient Number	Predicted Normal Values Based On Sex, Age, and Height	Hour 0 A+	% P++	1 A	% P	2 A	% P	3 A	% P	4 A	% P	5 A	% P	6 A	% P	7 A	% P
4	2.54	.10	3.9	.98	38.6	.80	31.5	.94	37.0	1.20	47.2	1.12	44.1	.96	37.8	1.10	43.3
5	4.04	.86	21.3	1.02	25.2	1.04	25.7	1.30	32.2	1.40	34.7	1.40	34.7				
6	2.73	.68	24.9	1.10	40.3	1.40	51.3	1.38	50.5	1.24	45.4	1.10	40.3	1.20	44.0	1.64	60.1
7	3.16	1.44	45.6	1.46	46.2	1.75	55.4	1.88	59.5	1.88	59.5	1.92	60.8	2.02	63.9	1.88	59.5
9	5.78	1.72	29.8	1.96	33.9	2.04	35.3	2.16	37.4	1.94	33.6	--	--	--	--	--	--
10	3.91	1.70	43.5	1.72	44.0	2.12	54.2	1.88	48.1	2.06	52.7	2.12	54.2	2.06	52.7	2.16	55.2
11	3.44	.86	25.0	.90	26.2	1.28	37.2	1.48	43.0	1.52	44.2	1.44	41.2	1.22	35.5	1.68	48.8
12	3.60	.94	26.1	1.40	38.9	1.70	47.2	1.67	46.4	1.68	46.7	1.78	49.4	1.67	46.4	1.82	50.6
13	3.77	1.46	38.7	1.96	52.0	2.21	58.6	2.08	55.2	2.08	55.2	2.18	57.8	1.78	47.2	2.08	55.2
14	4.50	1.46	32.4	1.70	37.8	1.78	39.6	1.92	42.7	2.18	48.4	2.16	48.0	2.02	44.9	2.16	48.0
15	4.86	.53	10.9	1.46	30.0	2.30	47.3	2.72	56.0								
16	2.82	.82	29.1	.96	34.0	1.02	36.2	1.18	41.8	1.08	38.3	1.28	45.4	1.28	45.4	1.10	39.0
17	2.82	.40	14.2	.92	32.6	.58	20.6	--	--	--	--	--	--	--	--	--	--
18	3.60	.52	14.4	.94	26.1	.96	26.7	.94	26.1	1.08	30.0	.98	27.2	.78	21.7	1.44	40.0
19	3.55	1.52	42.8	2.24	63.1	2.66	74.9	2.82	79.4								
20	3.77	--	--	1.94	51.5	2.34	62.1	1.78	47.2	2.08	55.2	2.36	62.6	2.38	63.1	2.80	74.3
21	3.05	1.92	63.0	1.94	63.6	2.02	66.2	1.86	61.0	1.98	64.9	1.96	64.3	1.88	61.6	2.08	68.2
22	4.85	1.32	27.2	1.48	30.5	1.92	39.6	2.34	48.2	2.82	58.1						
23	5.33	1.98	37.1	1.90	35.6	1.98	37.1	2.00	37.5	1.94	36.4	2.02	37.9				
24	5.12	1.70	33.2	1.94	37.9	1.98	38.7	2.14	41.8	2.74	53.5	2.66	52.0	2.72	53.1	2.68	52.3
25	5.10	2.60	51.0	2.92	57.3	3.58	70.2	3.68	72.2								
26	4.72	1.30	27.5	1.66	35.2	1.60	33.9	1.58	33.5	1.54	32.6	1.20	25.4	1.30	27.5	1.70	36.0
27	4.18	1.74	41.6	1.78	42.6	1.94	46.4	2.04	48.8	1.98	47.4	2.06	49.3	1.90	45.4	2.07	49.5
28	3.82	1.34	35.1	1.73	45.1	.98	25.7	2.30	60.2	2.33	61.0						

\+ Actual

++ Percentage of Predicted Normal

TABLE IX PULMONARY FUNCTION STUDIES

Part 3. Maximal Mid-Expiratory Flow Rate (litres/second)

Patient Number	Predicted Normal Values Based On Sex, Age, and Height	Hour 0 A+	0 %P++	1 A	1 % P	2 A	2 % P	3 A	3 % P	4 A	4 % P	5 A	5 % P	6 A	6 % P	7 A	7 % P
4	2.2	--	--	.17	7.7	.15	6.8	.22	10.0	.23	10.5	.19	8.6	.18	8.2	.21	9.5
5	3.1	.32	10.3	.51	16.5	.34	11.0	.44	14.2	.50	16.1	.52	16.8				
6	2.6	.33	12.7	.43	16.5	.38	14.6	.38	14.6	.30	11.5	.25	9.6	.33	12.7	.37	14.2
7	3.2	.40	12.5	.43	13.4	.69	21.6	.72	22.5	.81	25.3	.91	28.4	.90	28.1	.84	26.3
9	4.6	.96	20.9	.59	12.8	.42	9.1	.52	11.3	.66	14.3	--	--	--	--		
10	3.4	1.20	35.3	1.02	30.0	1.13	33.2	1.02	30.0	1.32	38.8	1.15	33.8	1.26	37.1	1.35	39.7
11	3.1	.21	6.8	.22	7.1	.33	10.6	.33	10.6	.35	11.3	.31	10.0	.32	10.3	.43	13.9
12	4.0	.42	10.5	.76	19.0	1.57	39.3	1.50	37.5	.93	23.3	.85	21.3	.59	14.8	1.30	32.5
13	4.0	.36	9.0	.50	12.5	.57	14.3	.51	12.8	.52	13.0	.51	12.8	.42	10.5	.55	13.8
14	3.7	.32	8.6	.39	10.5	.42	11.4	.42	11.4	.42	11.4	.45	12.2	.52	14.1	.56	15.1
15	4.6	.27	5.9	.51	11.1	.82	17.8	1.28	27.8								
16	2.6	.20	7.7	.22	8.5	.22	8.5	.26	10.0	.24	9.2	.29	11.2	.27	10.4	.26	10.0
17	2.6	.13	5.0	.23	8.8	.13	5.0	--	--	--	--	--	--	--	--	--	--
18	3.8	.25	6.6	.37	9.7	.30	7.9	.25	6.6	.36	9.5	.31	8.2	.29	7.6	.59	15.5
19	3.6	.55	15.3	.63	17.5	.83	23.1	1.02	28.3								
20	3.7	--	--	.38	10.3	.42	11.4	.32	8.6	.40	10.8	.46	12.4	.44	11.9	.62	16.8
21	3.2	1.30	40.6	1.31	40.9	1.29	40.3	1.11	34.7	1.30	40.6	1.36	42.5	1.31	40.9	1.33	41.6
22	4.5	.27	6.0	.29	6.4	.40	8.9	.45	10.0	.53	11.8						
23	4.8	.38	7.9	.38	7.9	.32	6.7	.32	6.7	.36	7.5	.38	7.9				
24	4.4	.45	10.2	.48	10.9	.45	10.2	.35	8.0	.82	18.6	.84	19.1	.93	21.1	.87	19.8
25	4.6	1.35	29.3	1.62	35.2	1.69	36.7	1.88	40.9								
26	4.2	.27	6.4	.41	9.8	.30	7.1	.37	8.8	.35	8.3	.35	8.3	.33	7.9	.48	11.4
27	3.5	.38	10.9	.39	11.1	.54	15.4	.57	16.3	.58	16.6	.59	16.9	.53	15.1	.69	19.7
28	3.8	1.22	32.1	1.17	30.8	.51	13.4	1.64	43.2	1.53	40.3						

\+ Actual

++ Percentage of Predicted Normal

TABLE X: IMPROVEMENT IN $FEV_{1.0}$ AS PERCENTAGE OF PREDICTED NORMAL

	Patient Number	Hour 0 Pretreatment	1	2	3	4	5	6	
ontinuous	4	8.3*	5.7	2.9	8.5	9.0	10.4	5.7	
ıfusion	5	18.2	5.2	2.6	7.8	9.1	9.1		
	7	25.9	2.9	12.2	15.5	19.4	20.9	21.6	1
	9	20.0	9.0	3.8	5.2	6.2	--	--	
	14	18.0	5.0	5.6	7.3	10.1	11.5	10.7	1
	15	8.7	10.1	27.0	34.8				
	16	13.3	0.0	1.7	5.0	4.2	8.4	8.4	
	17	4.2	10.0	4.1	--	--	--	--	--
	19	25.5	11.4	22.3	25.5				
	23	14.4	- .4	.5	0.0	0.9	3.2		
	28	32.4	3.6	-13.2	21.1	21.7			
Mean		18.1	5.7	6.3	13.1	10.1	10.6	11.6	11.8
± S.E.M.		±2.7	±1.2	±3.3	±3.5	±2.5	±2.4	±3.5	±2.5
Intermittent	6	18.7	9.4	7.7	9.4	3.4	1.7	6.8	6.0
Dosing	10	37.0	-1.5	7.0	9.7	7.0	1.6	6.4	12.4
	11	9.7	0.6	10.3	10.3	11.0	8.9	8.2	17.2
	12	19.0	9.8	17.8	20.3	15.0	16.6	17.2	24.0
	13	19.3	8.4	13.4	11.1	9.9	16.4	4.5	12.2
	18	9.4	8.1	6.9	4.4	10.0	8.1	5.0	18.1
	20	14.0*	5.6	10.5	6.2	9.3	14.8	16.7	25.9
	21	47.0	3.7	5.2	1.5	3.7	6.0	5.2	3.7
	22	10.6	4.0	9.6	15.7	20.7			
	24	20.2	2.9	2.4	4.8	15.9	16.8	17.8	16.8
	25	42.5	13.6	13.0	15.9				
	26	14.5	7.3	4.7	7.3	5.2	3.6	3.1	11.4
	27	19.3	1.1	5.0	9.4	8.9	8.3	7.2	11.6
Mean		22.3	5.6	8.7	9.7	10.0	9.3	8.9	14.5
± S.E.M.		±3.7	±1.2	±1.2	±1.4	±1.5	±1.8	±1.7	±2.1

* Patient unable to give an actual reading at this time. This value was derived by subtracting the mean improvement percentage at Hour 1 from the percentage value for the patient at Hour 1

TABLE XI: IMPROVEMENT IN FVC AS PERCENTAGE OF PREDICTED NORMAL

	Patient Number	Hour 0 Pretreatment	1	2	3	4	5	6	7
:inuous	4	3.9	34.7	27.6	33.1	43.3	40.2	33.9	39.4
sion	5	21.3	3.9	4.4	10.9	13.4	13.4		
	7	45.6	0.4	9.8	13.9	13.9	15.2	18.3	13.9
	9	29.8	4.1	5.5	7.6	3.8	--	--	
	14	32.4	5.4	7.2	10.3	16.0	15.6	12.5	15.6
	15	10.9	19.1	36.4	45.1				
	16	29.1	4.9	7.1	12.7	9.2	16.3	16.3	9.9
	17	14.2	18.4	6.4	--	--	--	--	--
	19	42.8	20.3	32.1	36.6				
	23	37.1	-1.5	0.0	0.4	-0.7	0.8		
	28	35.1	10.0	-9.4	25.1	25.9			
lean		27.5	10.9	11.6	19.6	15.6	16.9	20.3	19.7
S.E.M.		±4.0	±3.3	±4.3	±4.6	±4.9	±5.2	±4.7	±6.7
ıtermittent	6	24.9	15.4	26.4	25.6	20.5	15.4	19.1	35.2
osing	10	43.5	0.5	10.7	4.6	9.2	10.7	9.2	11.7
	11	25.0	1.2	12.2	18.0	19.2	16.2	10.5	23.8
	12	26.1	12.8	21.1	20.3	20.6	23.3	20.3	24.5
	13	38.7	13.3	19.9	16.5	16.5	19.1	8.5	16.5
	18	14.4	11.7	12.3	11.7	15.6	12.8	7.3	25.6
	20	45.0*	6.5	17.1	2.2	10.2	17.6	18.1	29.3
	21	63.0	0.6	3.2	-2.0	1.9	1.3	-1.4	5.2
	22	27.2	3.3	12.4	21.0	30.9			
	24	33.2	4.7	5.5	8.6	20.3	18.8	19.9	19.1
	25	51.0	6.3	19.2	21.2				
	26	27.5	7.7	6.4	6.0	5.1	-2.1	0.0	8.5
	27	41.6	1.0	4.8	7.2	5.8	7.7	3.8	7.9
ean		34.7	6.5	13.2	12.4	14.7	12.8	10.5	18.8
S.E.M.		±3.9	±1.5	±2.0	±2.4	±2.4	±2.4	±2.4	±2.9

* Patient unable to give an actual reading at this time. The value was derived by subtracting the mean improvement percentage at Hour 1 from the percentage value for the patient at Hour 1.

TABLE XII: IMPROVEMENT IN MMFR AS PERCENTAGE OF PREDICTED NORMAL

	Patient Number	Hour 0 Pretreatment	1	2	3	4	5	6	7
tinuous	4	6.5*	1.2	0.3	3.5	4.0	2.1	1.7	3.0
sion	5	10.3	6.2	0.7	3.9	5.8	6.5		
	7	12.5	0.9	9.1	10.0	12.8	15.9	15.6	13.8
	9	20.9	-8.1	-11.8	-9.6	-6.6	--	--	
	14	8.6	1.9	2.8	2.8	2.8	3.6	5.5	6.5
	15	5.9	5.2	11.9	21.9				
	16	7.7	0.8	0.8	2.3	1.5	3.5	2.7	2.3
	17	5.0	3.8	0.0	--	--	--	--	--
	19	15.3	2.2	7.8	13.0				
	23	7.9	0.0	-1.2	-1.2	-0.4	0.0		
	28	32.1	-1.3	-18.7	11.1	8.2			
Mean		12.6	1.2	0.2	5.8	3.5	5.3	6.4	6.4
S.E.M.		±2.6	±1.1	±2.7	±2.7	±2.1	±2.3	±3.2	±2.6
termittent									
osing	6	12.7	3.8	1.9	1.9	-1.2	-3.1	0.0	1.5
	10	35.3	-5.3	-2.1	-5.3	3.5	-1.5	1.8	4.4
	11	6.8	0.3	3.8	3.8	4.5	3.2	3.5	7.1
	12	10.5	8.5	28.8	27.0	12.8	10.8	4.3	22.0
	13	9.0	3.5	5.3	3.8	4.0	3.8	1.5	4.8
	18	6.6	3.1	1.3	0.0	2.9	1.6	1.0	8.9
	20	8.2*	2.1	3.2	0.4	2.6	4.2	3.7	8.6
	21	40.6	0.3	-0.3	-5.9	0.0	1.9	0.3	1.0
	22	6.0	0.4	2.9	4.0	5.8			
	24	10.2	0.7	0.0	-2.2	8.4	8.9	10.9	9.6
	25	29.3	5.9	7.4	11.6				
	26	6.4	3.4	0.7	2.4	1.9	1.9	1.5	5.0
	27	10.9	0.2	4.5	5.4	5.7	6.0	4.2	8.8
ean		15.4	2.1	4.4	3.6	4.2	3.4	3.0	7.4
S.E.M.		±3.6	±0.9	±2.2	±2.3	±1.1	±1.2	±0.9	±1.7

* Patient unable to give an actual reading at this time. This value was derived by subtracting the mean improvement percentage at Hour 1 from the percentage value for the patient at Hour 1.

TABLE XIII: PLASMA THEOPHYLLINE CONCENTRATIONS (μg/ml)

	Patient Number	Time* 0000	0015	0030	0045	0100	0130	0200	0300	0400	0500	0600	0615	0630	0700	
Continuous Infusion	4	23.3	30.4	31.5	30.0	30.5	34.1	28.6	28.4	30.0	33.2	25.2	25.8	24.6	25.4	Continuous Infusion
	5	0.6	13.0	21.0	14.4	14.8	16.2	16.2	17.4	17.2	19.8					
	7	7.5	12.8	17.9	15.9	15.2	15.7	13.6	16.4	13.6	16.5	17.3	15.9	15.7	14.8	
	9	0.4	8.4	12.9	9.3	9.4	9.0	9.3	10.0	10.4	11.6	10.6				
	14	0.3	7.0	13.2	9.3	9.2	8.3	8.6	9.1	9.7	9.5	9.6	9.6	8.9	9.8	
	15	3.4	7.1	10.1	10.6	10.9	11.1	13.4	14.2							
	16	9.5	13.1	17.5	15.5	16.1	13.4	14.3	13.7	13.6	14.2	15.8	14.7	15.3	13.5	
	17	12.2	17.9	21.4	20.0	20.2	19.1	18.0	17.0	17.4	16.0	19.2	16.3	18.4	15.7	
	19	6.8	8.6	12.4	14.0	16.2	16.1	14.7	15.2							
	23	3.6	7.6	11.3	13.2	12.7	12.5	12.8	14.0	15.8	14.4					
	28	0.1	6.3	12.3	10.0	9.3	8.7	6.4	8.4	7.8						
Mean ± S.E.M.		5.5 ±2.1	12.0 ±2.1	16.5 ±1.9	14.7 ±1.8	15.0 ±1.9	14.9 ±2.2	14.2 ±1.8	14.9 ±1.6	15.1 ±2.2	16.9 ±2.6	15.7 ±2.3	16.5 ±2.6	16.6 ±2.5	15.8 ±2.6	Mean ± S.E.M.
Intermittent Dosing	6	16.4	23.2	31.4	27.8	29.0	27.8	28.3	28.3	25.9	24.9	24.7	33.9**	38.4	35.5	Intermittent Dosing
	10	0.4	6.8	15.7	11.3	10.9	9.5	9.0	7.8	6.9	5.5	4.7	16.6	17.5	13.9	
	11	14.3	-- #	27.7	12.8	12.1	11.3	11.7	12.2	12.1	11.4	8.9	22.4	26.1	25.1	
	12	0.2	8.5	17.4	14.9	15.4	13.7	12.3	10.5	10.4	9.3	7.9	18.1	26.9	23.6	
	13	0.1	10.6	17.9	14.4	12.8	10.2	9.9	8.8	7.8	6.5	6.3	16.5	22.4	17.6	
	18	3.7	10.2	19.9	-- #	18.5	19.4	19.9	16.3	14.8	13.8	13.1	33.6	41.9	33.1	
	20	4.5	15.4	21.4	17.8	18.5	18.6	16.8	13.4	12.8	11.9	8.3	20.9	25.2	23.6	
	21	0.3	12.0	17.3	14.7	15.2	15.3	12.4	11.8	10.3	9.5	10.3	19.4	28.2	23.6	
	22	17.5	21.4	23.2	23.4	23.4	23.9	23.5	23.5	15.5						
	24	7.2	17.4	24.7	19.3	17.8	16.5	15.8	14.9	14.8	14.3	14.0	27.1	29.6	24.3	
	25	1.2	15.1	20.0	14.5	11.8	10.5	9.2	9.0							
	26	0.7	7.2	11.3	12.7	10.9	11.1	10.2	7.8	7.1	7.6	6.0	17.9	23.1	18.2	
	27	5.7	9.9	22.8	18.9	17.9	16.4	13.7	12.9	12.0	12.1	9.8	22.5	23.5	19.6	
Mean ± S.E.M.		5.6 ±1.8	13.1 ±1.6	20.8 ±1.5	16.9 ±1.4	16.5 ±1.5	15.7 ±1.6	14.8 ±1.6	13.6 ±1.7	12.5 ±1.5	11.5 ±1.6	10.4 ±1.7	22.6 ±1.9	27.5 ±2.1	23.5 ±1.9	Mean ± S.E.M.

* Time as measured by 24 hour clock; for example; 0130 refers to 1 hour and 30 minutes.

** Blood sample drawn at 0620 rather than 0615 for technical reasons.

\# For technical reasons sample could not be obtained.

TABLE XIV: OPERATIONALLY DEFINED EFFICACY AND TOXICITY

Time 0000	0015	0030	0045	0100	0130	0200	0300	0400	0500	0600	0615	0630	0700	
Continuous Infusion														
9	6	0	2	3	3	3	2	2	1	1	1	1	1	Subtherapeutic (less than 10 μg/ml)
1	4	8	8	6	7	7	8	6	6	4	3	3	3	Therapeutic (10-20 μg/ml)
1	1	3	1	2	1	1	1	1	1	1	1	1	1	Toxic (over 20 μg/ml)
Intermittent Dosing														
10	4	0	0	0	1	3	4	3	5	7	0	0	0	Subtherapeutic (less than 10 μg/ml)
3	6	7	10	11	10	8	7	8	5	3	5	1	4	Therapeutic (10-20 μg/ml)
0	2	6	2	2	2	2	2	1	1	1	6	10	7	Toxic (over 20 μg/ml)

TABLE XV: SUBJECTIVE ADVERSE EFFECTS AS INDICATED BY QUESTIONNAIRE

Adverse Effect Felt by Patient	Number of Patients	
	Continuous Infusion	Intermittent Dosing
Nausea	4	7
Palpitations	4	3
Nervousness	5	6
Dizziness	4	7
Chest Pain	3	4
Cramps	0	3
Flushed	6	7
Diuresis	2	5

TABLE XVI: SUBJECTIVE ADVERSE EFFECTS AS VOLUNTEERED BY THE PATIENT

Complaint	Number of Patients (closest associated plasma theophylline level or range in µg/ml) Continuous Infusion	Intermittent Dosing
Headache	3 (3.6-15.8, 9.0-9.4, 10.0-11.6, 30.0-33.2)	2 (12.0-23.5, 13-7, 15.4-21.5)
Vomited		3 (15.4, 19.9, 23.6, 29.0, 31,4, 41.9)
Nauseated	2 (11.1, 15.8)	7 (9.9, 10.9, 12.8, 13.7, 17.6, 19.9, 23.6, 25.2, 41.9)
Dizzy	1 (11.1)	3 (9.9, 11,3, 29.0)
Flushed	1 (9.3)	2 (14.9, 27.7)
Hot		2 (9.0, 27.7)
Perspiring		2 (9.9, 13.7, 14.9)
Chest Pain		1 (9.5)
Faint, Lightheaded		2 (27.7, 41.9)
Trembly		3 (13.7, 14.9, 22.4)
IV arm sore		1
Taste Drug (cool)	1 (30.0-33.2)	1 (33.6)
Rash	1	
Pulse Racing		1 (19.9)
Anxious, Cold, Clammy, Congested)		1 (14.0)
Passed Out (cough syncope)		1 (13.7)

TABLE XVII: SUBJECTIVE IMPRESSION OF RESPIRATORY STATUS AS TAKEN FROM LINE ANALOGY

Patient Number	Percentage of Normal* At Beginning of Therapy	Percentage of Normal* At the End of Study Period	Impression of Improvement in Respiratory Status
Continuous Infusion			
4	10	51	41
5	17	71	54
7	18	81	63
9	--	--	17.5
14	18	69	51
15	37	95	58
16	12	77	65
17	6	50	44
19	6	79	73
23	21	57	36
28	16	79	63
Mean ± S.E.M.	16.1 ± 2.8	70.9 ± 4.6	51.4 ± 4.8
Intermittent Dosing			
6	7	91	84
10	10	75	65
11	5	82	77
12	--	--	--
13	9	86	77
18	19	81	62
20	3	91	88
21	29	75	46
22	16	78	62
24	15	61	46
25	17	77	60
26	27	47	20
27	14	61	47
Mean ± S.E.M.	14.3 ± 2.3	75.4 ± 3.8	61.2 ± 5.6

* Measured as distance in mm to end representing very much difficulty.

5. DISCUSSION

The present study was unique in that it compared an intermittent dosing and a continuous infusion regimen of intravenous aminophylline under a randomized, double-blind protocol. Also acutely distressed asthmatic patients were studied in the real emergency ward setting. Despite recent advances in analysing theophylline levels and studies defining the relationship between theophylline blood levels and improvements of pulmonary function, the question concerning which is better, intermittent bolus or loading dose followed by a continuous infusion, has not yet been answered. This unique study provides a preliminary indication of that answer.

The results from this study suggest that both intravenous aminophylline regimens are effective in the treatment of acute asthmatic attacks. This is in accord with the general belief that aminophylline is a cornerstone in the treatment of acute asthma.[10,11,12] The improvement is evidenced by the changes in the parameters measured.

Heart rate decreased in both groups during the period of study. This decrease was more prominent with the continuous infusion. In view of the high theophylline levels after the second

intermittent dose of aminophylline, the slight elevation in pulse at hour seven may have been due to a chronotropic effect of theophylline.[65] Any overall decrease in heart rate may have occurred as a result of decreasing patient anxiety with improvement in condition and exposure to the security of emergency treatment and professional help.

Mean respiratory rate decreases of 9.8 respirations per minute for the ID group and 7.4 respirations per minute for the CI group were not significantly different but indicate return to nearer normal for both groups. This may be attributed to the bronchodilating effect of the aminophylline with a resultant decrease in the patient's dyspnea.

Blood pressure, especially the systolic pressure showed a marked drop in both groups at the end of the first hour. Transient hypotension with large intravenous aminophylline doses is known.[8] However, this decrease may also have been a return to normal following high circulating levels of catecholamines from anxiety and previous medication. The systolic blood pressure in the continuous infusion group was consistently above that in the intermittent dosing group, and at 6 hours this difference became significant. The reason for this probably was that two of the patientsfrom the continuous infusion group

were known hypertensives and taking hypotensive medication. These two patients received therapy for the full seven hours hence their blood pressure data contributed significantly to this figure.

Some variation may have been introduced into the blood pressure readings because in each instance the reading was taken by the attending nurse. Many different nurses were involved with the patients. Also different sphygmomanometers were used for each patient. Although increasing the variation within groups, no particular bias should have been introduced to either group as the nurses were blinded to the regimen being administered to the patient.

Mean pretreatment spirometric data revealed that both groups had pulmonary function consistent with a severe clinical state.[83] This was not consistent with the general assessment made by the observer of mild acute distress. The mode of assessment, hesitancy in speech, is a crude one and may have consistently underestimated severity of situation after patients had rested in bed a period of time before being seen by the observer. The best preserved function was the FVC followed by $FEV_{1.0}$ and then MMFR. This is also consistent with data presented by McFadden and Ingram.[83] Improvement as seen in Figures7, 8 and 9 was highest with the FVC. There were lesser, but similar improvements in $FEV_{1.0}$, whereas MMFR

improved the least. These improvement patterns are compatible with the explanation[83] that when patients are symptomatic probably all regions of the tracheobronchial tree are involved so that the flow that could be achieved at any lung volume is low. With treatment, the flow that can be generated high in the lung volume tends to return to normal first because resistance within the larger bronchi is dropping. FVC and $FEV_{1.0}$ are determined to a large extent by the cross-sectional area of the large airways; these parameters improve together and more quickly than does the MMFR, which reflects peripheral airway resistance. From this discussion we conclude that in this study both groups had improvement that mainly involved the larger, more central airways and that longer treatment period would be required to perceive near normality in the peripheral airways.

Comparison of the pulmonary function values revealed a consistent trend of greater improvement with the continuous infusion regimen at 3, 5 and 6 hours. Especially at the 5 and 6 hours the decreasing pulmonary values seem to coincide with the decreasing serum theophylline levels. The significance of the difference at 6 hours is not sufficient to draw any conclusion but suggests that a larger study should be attempted. Also to be considered is the fact that the best responders were discharged before the end of the study

period. There were more patients discharged early in the continuous infusion group; thus those values are lost in the latter hour calculations.

It is well established that serum theophylline levels of 10 to 20 µg per ml are optimum in the treatment of the adult asthmatic patient.[15,17,18,19,20] Levels above 20 µg/ml are associated with an increased risk of toxicity. Seizures have been associated with such levels,[74,82] even as low as 25 µg/ml.[74] The most dramatic finding in this study was the potential for toxicity exhibited in the intermittent dosing regimen with 91 per cent (10 out of 11) of patients in toxic range compared to 20 per cent (1 out of 5) of patients in the continuous infusion regimen. The opposite end of the scale also requires consideration. Initially more patients receiving the CI regimen had subtherapeutic theophylline levels, however, by two hours a reverse of this trend is noticeable with more patients receiving the ID regimen dropping into subtherapeutic range. By six hours more than half of the patients receiving the ID regimen were at subtherapeutic level. This is reflected by the decreasing pulmonary function value.

Comparison of adverse effects as determined by questionnaire revealed little difference between the two regimens, when number

of patients and hours of exposure were considered. Comparison of subjective complaints, however, revealed more than three times as many complaints with the ID regimen (32) as the CI regimen (9). Application of statistics to this incidence of adverse effects with this number of patients would be impossible; however a much larger study might supply statistical significance.

Follow-up of the "passing out" complaint disclosed that it probably had little to do with drug therapy as the patient was later assessed neurologically as having cough syncope. This particular episode may have been precipitated by the exertion of pulmonary function testing.

No reliable correlation was apparent between serum theophylline levels and onset of adverse effects. Patient complaints of nausea were heard more at therapeutic and even subtherapeutic levels than at toxic levels. Two patients vomited at therapeutic levels. These data and those of others suggesting that serious adverse effects are not always preceded by gastrointestinal symptoms[74,82] would seem to preclude any suggestion that toxicity be used as a dosing guide.[10]

Subjective assessment of improvement did not reveal any significant difference between regimens. The greater improvement with the ID regimen did coincide with better average $FEV_{1.0}$ and MMFR values at the seventh hour of study. The greater number of patients remaining in the ID group and the sudden improvement between 0600 and 0700 may have biased these results. Suggestions for improvement in measuring this parameter include demonstrating the line analogy in advance to all patients and having all patients complete their analogy impression at each hour interval.

Limitations of this study include a number of control factors. Firstly the population of asthmatics is a heterogeneous one. The

number of patients in the sample for each group was not large enough to document a statistically significant difference between regimens with respect to efficacy. Lack of means of estimating the duration of acute distress before admission was a problem. This factor may have been an important consideration in the degree and onset of patient response. Ideally times of admission, evaluating physician, nurse, precipitating factors, and smoking history should be consistent throughout. In the interest of studying a heterogeneous population in the real emergency setting, these factors were not controllable.

Another factor that could have been made more equivalent between groups was the dosage of aminophylline. A 70 kg person would have received (5.6 mg/kg x 70 kg + 0.9 mg/kg/hour x 70 kg x 6.5 hour =) 801.5 mg of aminophylline in the continuous infusion regimen compared to 1000 mg of aminophylline in the intermittent regimen. To equate the absolute quantities of aminophylline received the intermittent dosage could have been based on weight as well; for example, 5.7 mg/kg every 6 hours gives an absolute value of (5.7 mg/kg x 70 kg x 2 doses) 798 mg. One may argue however that with elimination rate of theophylline depending on serum concentration (first order kinetics), a greater amount of active theophylline was lost to pharmacological activity during the administration peaks

and that the absolute amount of theophylline at receptor sites was closer to equal during the time period of study. In terms of amount of aminophylline administered the advantage was with the intermittent dosing regimen even though the results indicate the superiority of the continuous infusion regimen.

Medications taken by the patients previous to study period and concurrent to study therapy should have been more controlled under optimum clinical study conditions. Again the heterogeneity of the population and the setting made this difficult. Consideration of the individual situations in the study by the investigator and advisers resulted in elimination of any values from the results that were thought to influence efficacy or toxicity measures. It is noteworthy that two patients receiving the intermittent regimen received phenothiazine-type anti-emetic medication. These may actually have masked later signs of toxicity of the medication. Again the advantage would be in favour of the intermittent regimen whereas toxicity data indicate superiority of the continuous infusion.

6. SUMMARY

A randomized, double-blind study comparing two dosing regimens of intravenous aminophylline was completed in a sample population of asthmatic patients. Twenty-eight patients were studied according to a protocol established after a small pilot study. The data from four patients were not included for diagnostic or technical reasons. Of the twenty-four patients thirteen received an intermittment dosing regimen of 500 mg of aminophylline every six hours. Eleven patients received a loading dose of 5.6 mg/kg followed by a continous infusion of 0.9 mg/kg/hour.

The results clearly demonstrate the superiority of the continuous infusion regimen when potential for toxicity by means of serum theophylline levels and subjective complaints of adverse effects were compared. Theophylline levels with the second intermittent dose were highly significantly above the accepted maximum therapeutic level of 20 µ g/ml at six and one half-hours after the beginning of treatment and fell below the therapeutic (10 µg/ml) between doses with 64% of patients. Complaints of adverse effects with the intermittent regimen outnumbered the complaints with the continuous infusion by a factor of three.

Consideration of efficacy comparison as measured by pulmonary function studies revealed a tendency for more consistent continuous improvement with the continuous infusion regimen.

Also more patients were discharged sooner with this regimen. A greater number of patients need to be studied in a similar protocol to demonstrate statistically significant superiority of the continuous infusion regimen.

7. REFERENCES

1. American College of Chest Physicians - American Thoracic Society Joint Committee on Pulmonary Nomenclature, Pulmonary Terms and Symbols. Chest 67:583-593,1975.

2. Pamphlet Published in Canada by the Canadian Tuberculosis and Respiratory Disease Association, Asthma The Facts. 5, 1973.

3. Editorial, Assessment and Management of Severe Asthma. The Lancet 1:1055-1056, 1972.

4. Rebuck, A.S. and Read, J., Assessment and Management of Severe Asthma. The American Journal of Medicine 51:788-798, 1971.

5. Rebuck, A.S., Antiasthmatic Drugs. I: Pathophysiological and Clinical Pharmacological Aspects II: Therapeutic Aspects. Drugs 7: 344-390, 1974.

6. Weinberger, M.W., Matthay, R.A., Ginchansky, E.J., Chidsey, C.A., and Petty, T.L., Intravenous Aminophylline Dosage. Journal of the American Medical Association 235: 2110-2113, 1976.

7. May, C.D., History of the Introduction of Theophylline into the Treatment of Asthma. Clinical Allergy 4:211-217, 1974.

8. Tong, T.G., Aminophylline - Review of Clinical Use. Drug Intelligence and Clinical Pharmacy 7:156-167,1973.

9. Koup, J.R., Schentag, J.J., Vance, J.W., Kyritzky, P.M., Pyszczynski, D.R., and Jusko, W.J., System for Clinical Pharmacokinetic Monitoring of Theophylline Therapy. American Journal of Hospital Pharmacy 33:949-956, 1976.

10. Franklin, W., Treatment of Severe Asthma. The New England Journal of Medicine 290:1469-1472, 1974.

11. Editorial, Intravenous Aminophylline. The Lancet 2: 950, 1973.

12. Freitag, A., Letter: Intravenous Aminophylline Treatment for Acute Asthma. The Medical Journal of Australia. 2: 109, 1975.

13. Jackson, R.H., Garrido, R., Silverman, H.I., and Salem, H., Blood Levels Following Oral Administration of Theophylline Preparations. Annals of Allergy 31: 413-17, 1973.

14. Ellis, E.F., Pharmacologic Therapy of Asthma. Postgraduate Medicine 59: 127-133, 1976.

15. Jenne, J.W., Wyze, E., Rood, F.S. and MacDonald, F.M., Pharmacokinetics of Theophylline - Application to Adjustment of the Clinical Dose of Aminophylline. Clinical Pharmacology and Therapeutics. 13: 349-360, 1972.

16. Waxler, S.H. and Schack, J.A., Administration of Aminophylline (Theophylline Ethylene Diamine). Journal of the American Medical Association. 143: 736-740, 1950.

17. Turner-Warwick, M., Study of Theophylline Plasma Levels after Oral Administration of New Theophylline Compounds. British Medical Journal 2: 67-69, 1957.

18. Jackson, R.H., McHenry, J.I., Moreland, F.B., Raymer, W.J. and Etter, R.L., Clinical Evaluation of Elixophyllin with Correlation of Pulmonary Function Studies and Theophylline Serum Levels in Acute and Chronic Asthmatic Patients. Diseases of the Chest 45: 75-85, 1964.

19. Mitenko, P.A. and Ogilve, R.I., Rational Intravenous Doses of Theophylline. The New England Journal of Medicine 289: 600-603, 1973.

20. Nicholson, D.P. and Chick, T.W., A Re-Evaluation of Parenteral Aminophylline. American Review of Respiratory Disease 108: 241-247, 1973.

21. Piafsky, K.M. and Ogilvie, R.I., Dosage of Theophylline in Bronchial Asthma. The New England Journal of Medicine 292: 1218-1222, 1975.

22. Lampton, L., Manion, C., Azarnoff, D., and Ruth, W., Is a Dose Formula Adequate to Predict Physiologic Effects of Intravenous Theophylline? American Review of Respiratory Disease 109: 715, 1974.

23. Jacobs, M.H., Senior, R.M., and Kessler, G., Clinical Experience with Theophylline: Relationships Between Dosage, Serum Concentration, and Toxicity. American Review of Respiratory Disease 109: 715, 1974.

24. Hodgkin, J.E., Balchum, O.J., Kass, I., Glaser, E.M., Miller, W.F., Haas, A., Shaw, D.B., Kimbel, P. and Petty, T.L., Chronic Obstructive Airway Diseases - Current Concepts in Diagnosis and Comprehensive Care. Journal of the American Medical Association 232: 1243 - 1260, 1975.

25. Powell, J.R., A Rational Approach to Theophylline Use in Asthma, In Applied Therapeutics for Clinical Pharmacists edited by Young, L.Y. and Kimble, M.A., p.p. 525-535. California Syllabus, California (1976).

26. Koup, J.R., (Personal Communication), 1977.

27. Cherniack, R.M., Cherniack, L., and Naimark, A., Asthma, in Respiration in Health and Disease, Second Edition pp. 329-334, W.B. Saunders Company, Toronto (1972).

28. Penna, P.M., Chronic Obstructive Pulmonary Disease. Journal of the American Pharmaceutical Association NS13: 690-697, 1973.

29. Dworetzky, M., Immediate Assessment of Acute Respiratory Distress in Asthma; in The Asthmatic Patient in Trouble edited by Petty, T.L., pp. 11. The UpJohn Company, CPC Communications, Inc., Connecticut (1976).

30. Spector, S.L. and Farr, R.S., The Heterogeneity of Asthmatic Patients - An Individualized Approach to Diagnosis and Treatment. Journal of Allergy and Clinical Immunology 57: 499-511, 1976.

31. Report of the Working Group on Definition of Asthma, in Identification of Asthma Edited by Porter, R. and Birch, J. pp. 172-174 by Churchill Livingstone, London (1971).

32. Farr, R.S. and Spector, S.L., What is Asthma? in The Asthmatic Patient in Trouble edited by Petty, T.L., pp. 5-9. The UpJohn Company, CPC Communications, Inc., Connecticut (1976).

33. Schonell, M., Bronchial Asthma; in Respiratory Medicine pp. 122-136 by Churchill Livingstone, London (1974).

34. Speer, F., Food Allergy: The 10 Common Defenders. American Family Physician 13: 106-112, 1976.

35. Parker, W.A., A.S.A. - Induced Asthma. The Canadian Journal of Hospital Pharmacy 29:64-65, 1976.

36. Samter, M. and Beers, R.F., Intolerance to Aspirin. Annals of Internal Medicine 68:975-983, 1968.

37. Huber, G.L., Indications for Pulmonary Function Tests and Blood Gas Studies in Asthma. in The Asthmatic Patient in Trouble edited by Petty, T.L., pp. 21-29. The UpJohn Company, CPC Communications, Inc. Connecticut (1976).

38. Collins, J.V., Clark, T.J.H., Brown, D. and Townsend, J., The Use of Corticosteroids in the Treatment of Acute Asthma. Quarterly Journal of Medicine, New Series 44: 259-73, 1975.

39. Kopetzky, M.T., Pulmonary Function Tests in Asthma. The Medical Clinics of North America 58: 93-110, 1974.

40. Ellis, E., Asthma, Infection, Allergy Relationship; in Recent Advances in Asthma Therapy edited by Farr, R.S., Middleton, E., and Spector, S.L., pp. 87-94. Schering Corporation, Symposia Specialists, Florida (1976).

41. Bellanti, J.A. and Church, J.A., Natural History of Reversible Obstructive Airway Disease: IgE - Mediated and Non-IgE-mediated; in Recent Advances in Asthma Therapy edited by Farr, R.S., Middleton, E., and Spector, S.L., pp. 5-24. Schering Corporation, Symposia Specialists, Florida (1976).

42. Reed, C.E., Sites and Mechanisms of Airway Obstruction in Reversible Obstructive Airway Disease; in Recent Advances in Asthma Therapy edited by Farr, R.S., Middleton, E., and Spector, S.L., pp. 31-37.
Schering Corporation, Symposia Specialists, Florida (1976).

43. Petty, T.L., Pulmonary Function in Reversible Obstructive Airway Disease; in Recent Advances in Asthma Therapy edited by Farr, R.S., Middleton, E., and Spector, S.L., pp. 95-107. Schering Corporation, Symposia Specialists, Florida (1976).

44. Bardana, E.J. Jr., Modern Aspects in Diagnosis and Treatment of the Asthmatic Patient. Clinical Notes on Respiratory Diseases 15: 3-13, 1976.

45. Sobol, B.J. and Emirgil, C., Pulmonary Function in Ambulatory Asthmatics. Journal of Chronic Diseases 29: 233-242, 1976.

46. Report of the Committee on Emphysema, American College of Chest Physicians, Criteria for the Assessment of Reversibility in Airways Obstruction. Chest 65: 552-553, 1974.

47. Farr, R.S. and Spector, S.L., Medical Management of Reversible Obstructive Airway Disease; in Recent Advances in Asthma Therapy edited by Farr, R.S. Middleton, E., and Spector, S.L., pp. 39-53, Schering Corporation, Symposia Specialists, Florida (1976).

48. Sitar, D.S., Piafsky, K.M., Rangno, R.E., and Ogilvie, R.I., Plasma Theophylline Concentrations Measured by High-Pressure Liquid Chromatography, Clinical Chemistry 21:1774-1776, 1975.

49. Kory, R.C., Callahan, R., Boren, H.G., Syner, J.C., The Veterans Administration - Army Co-Operative Study of Pulmonary Function. I. Clinical Spirometry in Normal Men, American Journal of Medicine 30: 243-58, 1961.

50. Clinical Spirometry Nomograms presented by Warren E. Collins, Inc. Braintree, Mass. 02184 Cat. No. P-465.

51. Bates, D.V., Macklem, P.T., Christie, R.V., Respiratory Function in Disease edited by W.B. Saunders Company, Toronto, Ontario. pp. 93-94

52. Kounis, N.G., A Review: Drug-Induced Bronchospasm. Annals of Allergy 37:285-291, 1976.

53. Brocklehurst, W.E., Pharmacodynamics and Mechanisms of Asthma; in Bronchial Asthma - Mechanisms and Therapeutics edited by Weiss, E.B. and Segal, M.S. pp. 117-136. Little, Brown and Company, Boston. (1976).

54. Szentivanyi, A., The Beta Adrenergic Theory of Atopic Abnormality in Bronchial Asthma. Journal of Allergy and Clinical Immunology 42:203-232, 1968.

55. Austen, K.F. and Orange, R.P., Bronchial Asthma: The Possible Role of the Chemical Mediators of Immediate Hypersensitivity in the Pathogenesis of Subacute Chronic Disease. American Review of Respiratory Disease. 112: 423-436, 1975.

56. Valentine, M.D., Chemical Mediators in Asthma; in Bronchial Asthma - Mechanisms and Therapeutics Edited by Weiss, E.B. and Segal, M.S. pp. 181-190, Little, Brown and Company, Boston (1976).

57. Petty, T.L., Acute Bronchial Asthma - an Approach to Therapy. in The Asthmatic Patient in Trouble edited by Petty, T.L., pp. 16-20, The UpJohn Company, CPC Communication, Inc., Connecticut (1976).

58. Lowell, F.C., Therapeutic Schedules in Asthma, in Bronchial Asthma - Mechanisms and Therapeutics Edited By Weiss, E.B. and Segal, M.S. pp. 709-714, Little, Brown and Company, Boston (1976).

59. Williams, M.H. Jr. and Shim, C.S., Theophylline, in Bronchial Asthma - Mechanisms and Therapeutics, edited by Weiss, E.B. and Segal, M.S. pp. 749-757, Little, Brown and Company, Boston (1976).

60. Middleton, E. Jr., Summary, in Recent Advances in Asthma Therapy, Edited by Farr, R.S., Middleton, E., Jr., and Spector, S.L., pp. 159-162, Schering Corporation, Symposia Specialists, Florida (1976).

61. Knight, A., and Iazzetta, J., The Treatment of Bronchial Asthma. Part II, Modern Medicine of Canada 31:773-784, 1976.

62. Melby, J.C., Pituitary-Adrenal Function: Considerations in Asthma in Bronchial Asthma - Mechanisms and Therapeutics edited by Weiss, E.B. and Segal, M.S., pp. 759-771, Little, Brown and Company, Boston (1976).

63. Feldman, B.R. and Davis, W.J., Treatment of Asthma with Cromolyn and Corticosteroids, Cutaneous Medicine for the Practitioner 17: 1091-1098, 1976.

64. Ellul-Micallef, R. and Fenech, F.F., Intravenous Prednisolone in Chronic Bronchial Asthma, Thorax 30:312-315, 1975.

65. Monograph on Theophyllines, The American Hospital Formulary Service 86:00, by the American Society of Hospital Pharmacists, 1977.

66. Manku, M.S. and Horrobin, D.F., Chloroquine, Quinine, Procaine, Quinidine, Tricyclic Antidepressants, and Methylxanthines as Prostaglandin Agonists and Antagonists, The Lancet 2:1115-1117, 1976.

67. Aviado, D.M. and Salem, H., Bronchodilator and Anti-Asthmatic Drugs, in Bronchial Asthma - Mechanisms and Therapeutics, edited by Weiss, E.B. and Segal, M.S. pp. 715-725, Little, Brown and Company, Boston (1976).

68. Mitenko, P.A. and Ogilvie, R.I., Pharmacokinetics of Intravenous Theophylline, Clinical Pharmacology and Therapeutics 14: 509-513, 1973.

69. Levy, G., Pharmacokinetic Control of Theophylline Therapy, Clinical Pharmacokinetics edited by Levy G., pp. 103-110, American Pharmaceutical Association (1974).

70. Hunt, S.N., Jusko, W.J. and Yurchak, A.M., Effect of Smoking on Theophylline Disposition, Clinical Pharmacology and Therapeutics 19: 546-551, 1976.

71. Koysooko, R., Ellis, E.F., and Levy, G., Relationship Between Theophylline Concentration in Plasma and Saliva of Man, Clinical Pharmacology and Therapeutics 15: 454-460, 1974.

72. Yurchak, A.M. and Jusko, W.J., Theophylline Secretion into Breast Milk, Pediatrics 57:518-520, 1976.

73. Cornish, H.H. and Christman, A.A., Study of the Metabolism of Theobromine, Theophylline, and Caffeine in Man, Journal of Biological Chemistry 228: 315-323, 1957.

74. Zwillich, C.W., Sutton, F.D., Neff, T.A, Cohn, W.M. Matthay, R.A., and Weinberger, M.M., Theophylline-Induced Seizures in Adults, Annals of Internal Medicine 82: 784-787, 1975.

75. Jacobs, M.H., Senior, R.M., and Kessler, G., Clinical Experience with Theophylline, Journal of the American Medical Association 235: 1983-1986, 1976.

76. Jenne, J., Nagasawa, H., McHugh, R., MacDonald, F., and Wyse, E., Decreased Theophylline Half-Life in Cigarette Smokers, Life Sciences 17: 195-198, 1975.

77. Jenne, J.W., Nagasawa, H.T., and Thompson, R.D., Relationship of Urinary Metabolites of Theophylline to Serum Theophylline Levels, Clinical Pharmacology and Therapeutics 19: 375-381, 1976.

78. Jenne, J.W., Chick, T.W., Miller, B.A., and Strickland, R.D., Apparent Theophylline Half-Life Fluctuations During Treatment of Acute Left Ventricular Failure, American Journal of Hospital Pharmacy 34: 408-409, 1977.

79. Sved, S., Hossie, R.D., and McGilveray, I.J., The Human Metabolism of Caffeine to Theophylline, Research Communications in Chemical Pathology and Pharmacology 13:185-192, 1976.

80. Levy, G. and Koysooko, R., Renal Clearance of Theophylline in Man, The Journal of Clinical Pharmacology 16:329-332, 1976.

81. Monograph on Aminophylline in Compendium of Pharmaceuticals and Specialties, Twelfth Edition, Edited by Rotenberg, G.N., Canadian Pharmaceutical Association, Toronto (1977).

82. Yarnell, P.R. and Chu, N.S., Focal Seizures and Aminophylline, Neurology 25:819-822, 1975.

83. McFadden, E.R. Jr., and Ingram, R.H., Jr., Spirometry, Lung Volumes, and Distribution of Ventilation in Asthma, in Bronchial Asthma - Mechanisms and Therapeutics edited by Weiss, E.B. and Segal, M.S., pp. 279-294, Little, Brown and Company, Boston (1976).

84. McFadden, E.R. Jr., Respiratory Mechanics in Asthma, in Bronchial Asthma - Mechanisms and Therapeutics edited by Weiss, E.B. and Segal, M.S., pp. 259-278, Little, Brown, and Company, Boston (1976).

85. Weinberger, M. and Hendeles, L., Pharmacotherapy of Asthma, American Journal of Hospital Pharmacy 33: 1071-1080, 1976.

86. Shah, V.P. and Riegelman, S., GLC Determination of Theophylline in Biological Fluids, Journal of Pharmaceutical Sciences 63: 1283-1285, 1974.

87. Chrzanowski, F.A., Niebergall, P.J., Nikelly, J.G., Sugita, E.T., and Schnaare, R.L., Gas Chromatographic Analysis of Theophylline in Human Serum, Biochemical Medicine 11:26-31, 1974.

88. Midha, K.K., Sved, S., Hossie, R.D., and McGilveray, I.J., High Performance Liquid Chromatographic and Mass Spectrometry Identification of Demethyl-xanthine Metabolites of Caffeine in Human Plasma, Biomedical Mass Spectrometry 4: 172-177, 1977.

89. Sved, S., (Personal Communication), 1976.

90. Piafsky, K.M., Sitar, D.S., Rangno, R.E., and Ogilvie, R.I., Theophylline Disposition in Patients with Hepatic Cirrhosis, The New England Journal of Medicine 296: 1495-1497, 1977.

91. Chrzanowski, F.A., Niebergall, P.J., Mayock, R.L., and Taubin, J.M., Kinetics of Intravenous Theophylline, Clinical Pharmacology and Therapeutics 22:188-195, 1977.

APPENDIX 1: CALCULATIONS FOR CONTINUOUS INFUSION

Patient No. _____

Weight (kg) _____

Please display calculations and sign your name.

Syringe No. 1 - 5.6 mg/kg x ____kg=____mg/50 mg/ml=ml.

Syringe No. 2 - 0.9 mg/kg x ____kg x 5.5 hr = ____mg/50 mg/ml = ____ml.

Syringe No. 3 - 0.9 mg/kg x ____kg x 0.5 hr = ____mg/50 mg/ml = ____ml.

Syringe No. 4 - exactly the same as No. 2 syringe.

Please check calculations with the following chart:

Patient Weight (kg)	Amount of Aminophylline Required (Weight and Volume Given)			
	Syringe No. 1	Syringe No. 2	Syringe No. 3	Syringe No.
55	308 mg or 6.2 ml	272 mg or 5.5 ml	25 mg or 0.50 ml	similar to No. 2
60	336 mg or 6.7 ml	297 mg or 5.9 ml	27 mg or 0.54 ml	"
65	364 mg or 7.3 ml	322 mg or 6.4 ml	29 mg or 0.59 ml	"
70	392 mg or 7.8 ml	347 mg or 6.9 ml	32 mg or 0.63 ml	"
75	420 mg or 8.4 ml	371 mg or 7.4 ml	34 mg or 0.68 ml	"
80	448 mg or 9.0 ml	396 mg or 7.9 ml	36 mg or 0.72 ml	"
85	476 mg or 9.5 ml	421 mg or 8.4 ml	38 mg or 0.77 ml	"

Prepared by: _____

APPENDIX II: QUESTIONNAIRE

Please circle the appropriate answer.

1.	Have you had any nausea (felt sick to your stomach)?	No	Yes
2.	Has your pulse (heartbeat) been irregular (or have you had any heart palpitations)?	No.	Yes
3.	Have you been feeling nervous, irritable, or agitated (jumpy or trembling)?	No	Yes
4.	Have you felt dizzy or lightheaded?	No	Yes
5.	Have you had any chest pain?	No	Yes
6.	Have you had any pains or cramps in your stomach?	No	Yes
7.	Have you felt warm (flushed or sweating)?	No	Yes
8.	Have you been urinating more often in the last few hours?	No	Yes

(Pour completer le questionnaire en francais, veuillex tournez la page.)

QUESTIONNAIRE:

Veuillez encercler la response appropriée.

1.	Avez-vous eu des nausées (mal de coeur)?	Non	Oui
2.	Est-ce que votre poule a été irrégulier (ou avez-vous eu des palpitations du coeur)?	Non	Oui
3.	Est-ce que vous avez eu des sensations nerveuses, irritables, ou agitées (tremblant)?	Non	Oui
4.	Avez-vous eu des vertiges?	Non	Oui
5.	Avez-vous eu des sensations de douleur dans votre poitrine?	Non	Oui
6.	Avez-vous eu des douleurs ou des crampes dans l'estomac?	Non	Oui
7.	Avez-vous eu des sensations de chaleur (bouffé de chaleur ou transpiration)?	Non	Oui
8.	Avez-vous uriné plus souvent dans les dernières heures?	Non	Oui

(To complete the questionnaire in English, please turn the page.)

APPENDIX III: SUBJECTIVE IMPROVEMENT

Please indicate how much difficulty you have in breathing (or how much tightness you have in your chest), by making a mark (/) on the line. Please make another mark indicating the difficulty in breathing that you had just before the intravenous medication was started.

No Difficulty
or
No Tightness

Very Much Difficulty
or
Very Much Tightness

Pas de Difficulté
ou
Pas d'Oppression

Beaucoup de Difficulté
ou
Beaucoup d'Oppression

Veuillez indiquer combien de difficulté que vous avez à respirer (ou combien d'oppression que vous avez dans votre poitrine), en faisant une trace (/) sur la ligne. Veuillez en faisant une autre trace indiquer la difficulté à respirer juste avant le début de la medication intra-veineuse.