AN ABSTRACT OF THE THESIS OF

MARSHALL TATE for the degree of Master of Science in Pharmacy presented on December 14, 1982

Title: AMINOPHYLLINE DOSING IN CONGESTIVE HEART FAILURE

Abstract approved: Redacted for Privacy

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A study was designed to examine the pharmacokinetics of theophylline in a well defined group of congestive heart failure (CHF) patients, without liver disease, and to evaluate the validity of the dosage guidelines recommended by the FDA. A total of five CHF patients and seven non-CHF patients were entered and studied. There was no significant difference between the mean theophylline clearance of the CHF group, 37.4 ml/kg/hr, and the non-CHF group, 36.3 ml/kg/hr ($p > 0.05$). The number of patients in the therapeutic range, 9/11, was compared to the number predicted to be in the therapeutic range following FDA guidelines, 0/11. This difference was highly significant ($p = 0.002$). The current FDA dosage guidelines may produce inadequate, subtherapeutic serum levels in patients requiring theophylline. Further study of dosages designed to achieve therapeutic serum concentrations is suggested.

AMINOPHYLLINE DOSING IN CONGESTIVE HEART FAILURE

by

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A THESIS

submitted to

Oregon State University

in partial fulfillment of

the requirements for the

degree of

Master of Science

Completed December 14, 1982

Commencement June 1983

APPROVED:

Redacted for Privacy

Professor of Pharmacy in charge of major

Redacted for Privacy

Head of Department (Pharmacy)

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Dean of Graduate School

Date thesis is presented December 14, 1982

Typed by (Elaine Plaggert) for Marshall Tate

ACKNOWLEDGEMENTS

I would like to thank the members of my graduate committee, especially my major professor, Lee Wanke, for their continued support, encouragement and advice. Many faculty members of the School of Pharmacy offered valuable contributions. A special thanks to Dr. J.W. Ayres for his pharmacokinetic questions and comments.

I would also like to thank Jim Sanger and the staff of Good Samaritan Hospital & Medical Center for their support and assistance. I could not have completed this project without them. My co-inventigators, Dr. Mark Hattenhauer and Dr. Arthur Zbinden willingly shared their clinical expertise. Geoff Carons provided technical assistance in the lab.

This project was supported by funds from the Neuroscience Institute, GSH&MC and from Abbott Laboratories. Immunoassay equipment was provided by Syva Company.

The encouraging stimuli of H.W.S. are acknowledged.

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AMINOPHYLLINE DOSING IN CONGESTIVE HEART FAILURE

I. INTRODUCTION

Theophylline has been recognized as an effective bronchodilator since its introduction more than 45 years ago.[1] Used intravenously as the ethylenediamine salt aminophylline, it has become well established in the management of chronic obstructive pulmonary diseases.

The use of aminophylline has been associated with clinical difficulties ranging from inadequate responses to serious adverse reactions. Dosage regimens have evolved from being strictly empirical to those based on pharmacokinetic principles. Mitenko and Ogilvie[2] were the first to propose an intravenous dosage regimen based on pharmacokinetic considerations. This regimen produced therapeutic, nontoxic serum concentrations in 95% of their patients. This dosage regimen was enthusiastically endorsed by editorials in both The New England Journal of Medicine[3] and The Lancet.[4]

Subsequent studies have demonstrated however, that there are patient populations where the recommended maintenance intravenous infusion rate of 0.9 mg/kg/hr ami-

nophylline, based on actual body mass (ABM), was in excess and resulted in toxicity and death.[5-10] Hughey et al.,[11] in a recent investigation of dosage regimens for intravenous theophylline, reported that 29 - 34% of patients dosed according to Mitenko and Ogilvie's guidelines became toxic.

In an effort to improve safety the Food and Drug Administration (FDA) recently issued a bulletin[12] recommending guidelines for reduced aminophylline infusion dosage rates in certain clinical conditions. In this bulletin, the FDA reminded physicians that the intravenous infusion rate commonly used previously was dangerous in some patients and could result in life-threatening cardiac arrhythmias and seizures. The dosage guidelines were advocated to permit safe intravenous administration of theophylline in differing patient populations.

In the FDA guidelines the smallest infusion dosage rates were recommended to achieve a steady state serum level of 10 mcg/ml in patients with congestive heart failure (CHF) and liver disease. The question of whether this guideline will produce therapeutic serum levels in a strictly defined population of patients with CHF has not been examined.

The CHF patient population has been described in general, in a number of studies, as having a decreased

clearance of theophylline and an increased serum half-life.[5-8,13] However, the pharmacokinetics of theophylline in CHF patients have not been adequately described. Many of the theophylline dosage guidelines have been based upon studies limited in their validity by small sample size, undefined or loosely defined patient characteristics, and ambiguous or unclear recommendations to calculate dosages. While these studies have used pharmacokinetic principles to increase the rational use of theophylline, many have been extrapolated and applied incorrectly by subsequent authors. The present study was initiated to investigate the pharmacokinetics of theophylline and to determine the appropriateness of the FDA guidelines in a group of patients with a standard and clinically useful definition of CHF, without evidence of liver disease.

II. BACKGROUND

Pharmacokinetic studies of theophylline and the evolution of theophylline dosage guidelines closely parallels the development of the science of pharmacokinetics. Many of these early studies can be faulted because of lack of proper controls-- small sample size, undefined or loosely defined patient characteristics, incorrect conversion of theophylline content of aminophylline, and ambiguous guidelines in regards to dose, product, and patient weight. In addition, some investigators have incorrectly extrapolated data in previous studies.

A review of studies discussing the pharmacokinetics of theophylline reveals three categories of investigations. The first, theophylline dosage guidelines in the general population,[2,14] is not pertinent to the present study. The second and third categories are pharmacokinetic studies in patients with cardiopulmonary disease (CPD) and theophylline dosage guidelines for CHF patients, respectively. These categories of studies are pertinent to the present study and will be discussed in further detail.

Pharmacokinetic Studies in CPD Patients: Jenne et al.,[15,16] reported a case history of a 63 year old man admitted to the hospital with an acute exacerbation of bronchitis and heart failure. Calculated theophylline half-life seemed to vary directly with increased left ventricular failure and acute exacerbation of chronic bronchitis. The authors felt that decreased theophylline metabolism might be due to decreased liver perfusion and/or hypoxic liver dysfunction. They stated that this twice published case report illustrated the exquisite dependence of theophylline clearance on dynamic circulation factors and demonstrated the need for maintenance dose reduction and frequent serum theophylline monitoring in this group of patients.

Weinberger et al.,[5] studied the incidence of toxicity with continuous intravenous aminophylline in 15 adults with acute airway obstruction. Seven patients were diagnosed as having cor pulmonale (CP); of these, three had left-side heart failure (LHF), and one had both. Further criteria for diagnosis or definition were not described. The authors commented that isolated observations of individual patients with severely decreased clearances in association with heart failure had been previously described but that in only one of their patients was the presence of cardiac decompensation associated with

a low clearance value. This value rose with clinical evidence of improvement of the heart failure.

Vicuna et al.,[17] studied theophylline clearance in patients receiving intravenous aminophylline. Eight of 36 patients had CP based on inclusion in the problem list in the patients' hospital charts. Total body clearance of theophylline estimated from data obtained during constant intravenous infusion was significantly lower in patients with CP. The authors concluded that in these patients reduced maintenance doses of theophylline were indicated.

Pancorbo et al.,[18] studied 55 patients in respiratory distress or failure, receiving intravenous aminophylline. Thirty-two of these had evidence of CHF or undefined liver disease. Patients with congestive heart failure or liver disease had significantly longer half-lives and significantly lower clearances.

Bauer and Blouin[19] examined the influence of age on theophylline clearance in 59 adult patients with chronic obstructive pulmonary disease (COPD) requiring intravenous aminophylline. Thirty-six COPD patients were compared to 23 patients with COPD and CHF. Patients with a history of liver disease were excluded. The authors found there was a significant difference in theophylline clearance between the groups with and without congestive heart failure.

Dosage Guidelines for CHF Patients: Table 1 lists nine

different published reports where theophylline dosage guidelines were recommended. This table shows a wide variation in recommendation for theophylline dosing in patients with CHF.

Piafsky et al.,[13,20,21] published dosage guidelines for theophylline use in CHF patients based on two studies. The first had three patients with acute pulmonary edema and five control subjects; the second had nine patients with acute cardiogenic pulmonary edema and 19 control subjects. Based on these studies, the authors stated that in patients with CHF and severe liver disease, the disposition of theophylline changed. The half-life increased and the clearance and elimination decreased. Their recommendation was to follow Mitenko and Ogilvie's loading dose of 6 mg/kg ABM aminophylline with a maintenance infusion reduced by one third of the usual dose in the presence of CHF and reduced by half in patients with severe liver impairment.

Koup et al.,[22] and Jusko et al.,[23] presented a system for clinical pharmacokinetic monitoring of theophylline therapy and dosage guidelines. The guidelines were generated from a study of five hospitalized, moderately ill patients who were receiving theophylline for therapeutic purposes. Three patients had some degree of CHF. The authors concluded that many older or acutely ill

patients required smaller maintenance infusion rates of aminophylline than had been recommended previously. From this preliminary study a dosage nomogram was generated which recommended a 50% reduction in the normal intravenous aminophylline rate so that patients with CHF and liver disease would receive 0.45 mg/kg/hr ABM. Seventy-two patients were then dosed via the nomogram. Fourteen of 72 (19.4%) patients were classified in nomogram category G "CHF, Liver Disease" and eight of these (57.1%) were in the therapeutic range after 24 hours.

Hendeles et al.,[8-10,24] reported toxicities frequently resulting from the widespread use of Mitenko and Ogilvie's guidelines. Population demographics of the 50 patients in the first study were not fully described but 27 patients were characterized as having risk factors such as cardiac decompensation, liver dysfunction or acute respiratory failure, either alone or in combination. This subpopulation with risk factors was not described in any further detail. The authors stated that the relationship between cardiac decompensation and plasma clearance was less clear in these data, possibly because of the method of reporting cardiac decompensation. It may be that some patients with mild or compensated congestive heart failure were included in this group. While not clearly defining this group with risk factors, Hendeles et al., concluded

that dosing regimens should be individualized with respect to differences in age, disease and concurrent functional abnormalities and recommended an intravenous aminophylline infusion rate of 0.6 (females) and 0.4 (males) mg/kg/hr, based on ideal body mass IBM. In subsequent reports, this guideline and categorization was modified.

Powell et al.,[25] examined theophylline disposition in acutely ill hospitalized patients. Three of 26 patients, without evidence of liver disease, had chronic bronchitis and CHF. CHF was defined as the presence of peripheral edema with radiologic evidence of cardiac enlargement and prominence of blood vessels in the upper lung zone on chest roentgenogram. There were also 31 healthy volunteers who served as control subjects. By calculating clearances for subgroups, Powell et al., were able to generate dosage recommendations for patients with uncomplicated asthma or chronic bronchitis depending upon concurrent clinical conditions. Their guideline for acutely ill patients to obtain a target theophylline concentration of 10 mcg/ml was a loading dose of 6 mg/kg ABM intravenous aminophylline and an initial maintenance infusion of 0.5 mg/kg/hr ABM. This initial dose was to be modified by a factor of 1.6 (smokers), 0.4 (CHF), 0.4 (pneumonia) and 0.8 (severe obstruction). This study was the first to suggest a method of dosing patients with more

than one predisposing clinical condition, so that when more than one condition were present, all modifications would be used simultaneously. The recommended maintenance aminophylline infusion rate for CHF in smokers and non-smokers was 0.32 and 0.2 mg/kg/hr ABM respectively.

Jusko et al.,[26] comprehensively examined factors affecting theophylline clearances in a group of 100 adult hospitalized patients combined with additional clinical and pharmacokinetic data obtained from the literature. They reported that a variety of factors significantly affected theophylline clearance such as age, liver disease, smoking status and CHF. Fifty-one patients were classified as having CHF using the criteria of Peck et al.[27] Based on pharmacokinetic parameters and using computer programs, a cascade of factors determining theophylline clearance was generated. According to this cascade, the mean($\pm$ SD) total body clearance of theophylline (Cl_t) in ml/hr/kg IBM for 61 subjects with none or mild CHF was 54.3(23.4). Of these, 14 subjects were classified as light cigarette smokers (less than one pack per day) with a mean ($\pm$ SD) Cl_t of 64.0(26.5) and 47 were grouped together as non- or heavy (equal to or greater than one pack per day) cigarette smokers with a mean ($\pm$ SD) Cl_t of 51.4(21.9). Twenty-two subjects with moderate or severe CHF had a mean ($\pm$ SD) Cl_t of 33.8

(15.2). Of these, 14 subjects were classed as non- or light cigarette smokers with a mean (± SD) Cl_t of 27.9 (13.3) and 8 subjects were heavy cigarette smokers with a mean (± SD) Cl_t of 44.2(13.2). The theophylline infusion recommendations for these last two subgroups were 0.28 and 0.44 mg/kg/hr IBM respectively, to achieve a steady state theophylline serum level of 10 mcg/ml.

In February, 1980, after vigorous encouragement, the FDA published dosage guidelines for intravenous theophylline products, upon recommendation of the FDA Pulmonary-Allergy Advisory Committee (see Table 2). The FDA recommended for "patients with congestive heart failure, liver disease" an aminophylline maintenance dose of 0.5 mg/kg/hr IBM for the first 12 hours following a loading dose and 0.1-0.2 mg/kg/hr IBM for a maintenance dose beyond 12 hours.

These dosing guidelines have several inherent difficulties. First there is not an adequate description of the disease states. Second the double maintenance dose schedules have been criticized because they have no rational pharmacokinetic basis[28] and because they could lead to increased toxic serum levels in cirrhotic patients.[29] Third, the recommendation to use IBM for both the loading and maintenance dose is not consistent with most previous recommendations.[30,31]

Finally, while the title of the FDA table of guidelines is "Aminophylline Dosage for Patient Population", a footnote reveals that the equivalent anhydrous theophylline dose has been indicated in parentheses. Not only is the incorrect conversion factor of aminophylline to anhydrous theophylline used, but this factor appears to vary in the table from 0.5 to 1.0. It was reported by Hilibrand and subsequently acknowledged[32] that although theophylline is equivalent to 85% anhydrous aminophylline, the USP monograph for aminophylline injection specifies the assay as aminophylline dihydrate (2 H_2O). Therefore, when calculating the dosage of the injection equivalent to theophylline, the correct factor to use is 78.9% not 85%. The existence of this discrepancy had been previously identified by Chiou.[33] In a limited survey of the literature the conversion factor of 0.85 was found to be used in a number of publications but in at least three previously published studies, including Mitenko's and Ogilvie, a factor of 0.8 was used. Chiou stated that the correct conversion factor for the official intravenous aminophylline injection dosage form should be 0.7894 but the approximation of 0.8 should be clinically acceptable.

Several of the studies and dosage guidelines discussed above have reported reduced theophylline clearance and increased toxicity rates in patients with CHF. Other stu-

dies and case reports confirmed the decrease in theophylline clearance observed in seriously ill patients with cardiac decompensation. The idea of reduced dosage requirements for critical patients with CHF has been well established in the literature and in the medical community.

However, in many of these studies, CHF was undefined, loosely defined, or based on inappropriate criteria. None of the previous dosage guidelines have strictly defined, clinically useful criteria for dosing patients with CHF, and often, only one category for "congestive heart failure, liver disease" is present. It is ironic that the patients at greatest risk have such inexact dosage guidelines. Clear and concise dosage guidelines for specific patient populations, based upon well controlled studies, are needed.

The purpose of this present study was to define the pharmacokinetics of theophylline in a group of patients with a strictly defined, clinically useful diagnosis of CHF but without evidence of liver disease; and to determine if the current FDA guidelines would have produced a therapeutic serum level in this group.

III. METHODOLOGY

The 11 subjects included in this study were patients at Good Samaritan Hospital and Medical Center, Portland, Oregon. Patients were admitted in the study if they fulfilled the following criteria:

(1) the patient's diagnosis included CHF and/or COPD;

(2) the patient's physician decided independently that intravenous administration of aminophylline was necessary and would be required for at least 48 hours;

(3) there was no clinical or laboratory evidence of liver disease;

(4) admission into the study was approved by the patient's physician;

(5) the patient signed an informed consent form.

This study was approved by the Good Samaritan Hospital & Medical Center Institutional Review Board and by the Human Subjects Committee, Oregon State University.

After informed consent was obtained, the patient's

clinical condition, pulmonary and cardiac status and type of cardiovascular disease were assessed by the physician co-investigators of this research project. One physician was a board certified cardiologist; the other a board certified pulmonologist.

Patients were divided into 3 groups based upon diagnosis. Group I consisted of 5 adult patients who fit the criteria for congestive heart failure used in the Framingham study as described by McKee et al.,[34] (see Table 3). These criteria were chosen because of their standard definition and clinical utility. Group II consisted of 3 adult patients who did not fit the criteria for CHF although they had a history of CHF or the diagnosis of CHF in their hospital chart. Group III consisted of 3 patients with a diagnosis of COPD, without CHF.

All patients received a loading dose and maintenance dose of intravenous aminophylline (80% theophylline; Abbott Laboratories) via constant infusion pump. Dosages were ordered by a physician according to clinical judgement. The loading dose of intravenous aminophylline was given over 30 minutes. Immediately after this the maintenance infusion was begun. Infusions were maintained at a constant rate by use of an Abbott Lifecare Pump, Model III. The maintenance infusion was continued for 36 hours except in the event of any clinical problems such as

theophylline toxicity, increased respiratory difficulties or changing medical condition.

Serum samples were taken immediately before the loading dose and 12, 24, and 36 hours after the subjects were started on the maintenance infusion. Samples were assayed for theophylline concentration within 6 hours using an enzyme immunoassay (EMIT^{r}; Syva, Palo Alto, CA) in the hospital's laboratory with the results immediately available to the physician. Assays were run in duplicate with a coefficient of variation less than 10%.

Steady state theophylline serum concentrations (Cp_{SS}) were considered to be reached 24 hours after a loading dose. Mean patient calculated theophylline clearance (Cl) was compared among groups and measured Cp_{SS} was compared with values predicted using the FDA guidelines.

Statistical analysis was performed using the Student's and paired t test, and analysis of variance. A p value of less than 0.05 was considered acceptable.

Total body theophylline clearance (Cl) in ml/kg/hr was determined using the equation:

$$Cl = \frac{R_O}{Cp_{SS}} \qquad \text{Eq. 1}$$

where R_O is the theophylline infusion rate in mcg/kg/hr and Cp_{SS} is the theophylline steady state serum con-

centration in mcg/ml. Predicted theophylline steady state serum concentration (Cp_{ss}) in mcg/ml was calculated using the equation:

$$Cp_{ss} = \frac{R_o}{Cl} \qquad \text{Eq. 2}$$

IBM was used for all calculations following Devine's method[35] where IBM (male) = 50 kg + 2.3 kg/in > 5 ft, and IBM (female) = 45 kg + 2.3 kg/in > 5 ft, except ABM was used when it was less than IBM.

IV. RESULTS

Patient characteristics including demographic and social data are summarized in Table 4. Seven females and four males took part in the study. The mean ($\pm$ S.D.) age of the group was 67.5(14.9) years, and the range was 34-87 years. Five patients (B,E,G,J, and K) fit the criteria for congestive heart failure and were placed in Class I. Three patients (A,D, and I) were in Class II, and three patients (C,D, and H) were in Class III. In four of the patients (D,F,I,J) ABM was less than IBM and thus ABM was used for calculations.

A summary of pertinent medications the patients were taking prior to admission into the study (PTA) and during the study (DS), up to achieving theophylline steady state, is presented in Table 5. Six patients were receiving digoxin, five were receiving a diuretic and seven were receiving theophylline or another pulmonary medication PTA. This information was obtained by chart review and by pharmacist medication history interviews. Patients A and E stated that they had taken no medications for two weeks PTA. Patient K stated that he was not taking any prescription or nonprescription medications PTA.

Patients were also screened for possible theophylline-drug interactions. None of the patients received any drugs previously reported to interact with theophylline clearance[36-38] except patient K who received two oral doses of cimetidine 300 mg, two and six hours prior to achieving theophylline steady state and patient J who was taking propranolol 20 mg orally four times daily (last dose 12 hours) prior to admission.

Patients' pharmacokinetic data including theophylline dose (Ro), calculated total body clearance (Cl), plasma level at steady state (Cp_{SS}), and half-life ($T_{\frac{1}{2}}$) based on IBM are summarized in Table 6. The mean clearance for all 11 patients was 36.8($\pm$ 7.3) ml/kg/hr, and the mean half-life was 9.8 ($\pm$ 2.0) hours. There was no significant difference among the mean clearance values of Groups I, II, and III (F test, $p > 0.05$).

Patients' calculated Cl was used to predict Cp_{SS} based upon FDA dosage recommendations. Table 7 compares the actual theophylline doses given and measured Cp_{SS} achieved compared to the FDA recommended doses and predicted Cp_{SS} for Class I patients with CHF. The actual mean Cp_{SS} achieved was 11.5($\pm$ 2.6) mcg/ml while the predicted mean Cp_{SS} was 2.76($\pm$ 0.64) mcg/ml; this difference was significant (Paired t test, $p=0.0009$). At steady state, 4/5 (80%) patients were in the therapeutic range of 10-20 mcg/ml.

However, when Cp_{SS} was predicted using FDA dosage guidelines 0/5 (0%) patients were predicted to be in the therapeutic range; this difference was significant (McNemar's exact test, $p = 0.03$). The data for Class II patients are shown in Table 8. Again, there was a significant difference between the actual and predicted mean Cp_{SS} values of 12.4($\pm$ 3.9) and 3.18($\pm$ 0.45) mcg/ml (Paired t test, $p=0.0429$). Table 9 shows the data for the Class III patients. In this class, there was insufficient evidence to conclude a difference between the actual mean Cp_{SS} value of 15.7($\pm$ 3.1) mcg/ml and the predicted mean value of 7.78($\pm$ 1.2) (Paired t test, $p=0.0683$).

The actual mean Cp_{SS} for all patients of 12.9($\pm$ 3.3) mcg/ml was significantly different from the predicted mean Cp_{SS} for all patients of 4.3($\pm$ 2.4) mcg/ml (Paired t test, $p < 0.0001$).

V. DISCUSSION

Theophylline is a drug with a narrow therapeutic index in which selection of the correct dose is essential to achieve therapeutic serum concentrations and to avoid toxicities. The influence of CHF on the clearance of theophylline has been assumed to be a dramatic reduction necessitating a much reduced dosage.

A decreased clearance of theophylline in patients with CHF has been reported in a limited number of single case reports and studies with small patient populations. Based on these, a variety of authors have proposed dosage guidelines as presented in Table 1. These guidelines have loosely defined the criteria for the diagnosis of CHF, and often this patient set has been grouped with patients having hepatic cirrhosis. In the present study, there was no significant difference in theophylline clearance at steady state in patients with strict criteria for the diagnosis of congestive heart failure, without hepatic dysfunction, and those patients who did not fit the criteria (Student's t-test, $p > 0.05$).

This finding is consistent with other authors who

noted a difference between initial and final theophylline clearance in patients with compromised versus compensated cardiovascular status. Weinberger et al.,[5] reported that in one patient where the presence of cardiac decompensation was associated with a low theophylline clearance, there was a 70% increase in clearance values associated with improvement of heart failure. Jenne et al.,[17] reported an abrupt decline in theophylline half-life from 64.9 to 8.6 hours with cardiac compensation in one patient with acute left ventricular failure. Powell et al.,[25] reported an increase in mean theophylline clearance values from an initial mean clearance of 26.5 ml/kg/hr to a final clearance of 66.4 ml/kg/hr for three patients with uncompensated versus compensated CHF and chronic bronchitis. This increase in theophylline clearance may be a direct result of improved cardiovascular function.[37] Improved hemodynamic effects resulting from intravenous theophylline therapy have long been noted in patients with both left ventricular failure[38] and cor pulmonale.[39] This may have been a factor contributing to the high Cl values at steady state, reported for the CHF patients in the present study.

The high Cl values at steady state in the present study may also be due to excluding patients with liver disease. Piafsky et al.,[40] reported that mean

theophylline clearance was significantly reduced in cirrhotic patients, 42 ml/kg/hr, compared to normal subjects, 62 ml/kg/hr. Mangione et al.,[41] reported a markedly decreased mean clearance in cirrhotic patients, 18.8 ml/kg/hr, compared to aged matched controls, 53.7 ml/kg/hr, and young normal patients, 63 ml/kg/hr. Hendeles et al.,[8] reported that patients with undefined "liver dysfunction" had a lower theophylline clearance compared to other patients in their study. It appears that hepatic cirrhosis plays a dramatic role in decreasing theophylline clearance; however, it is difficult to assess and quantify. Nevertheless, some authors who have published dosage guidelines for theophylline have suggested the most reduced dosages for patients with the two factors which have been reported to decrease theophylline clearance the most: congestive heart failure and hepatic dysfunction. Unfortunately, most of the guidelines make no attempt to define or separate these two distinct factors. From our data, it would appear to make a dramatic difference if dosage recommendations were based on formal criteria for congestive heart failure excluding hepatic dysfunction.

Other factors are known to alter theophylline clearance. Two of these factors are smoking and concurrent drug administration. Numerous studies have

reported that smoking increases the theophylline elimination rate from 50-100%.[5,25,26,42-46] In the present study, the four patients who were cigarette smokers had a 16.5% increase in clearance over nonsmokers. This difference was not significant (Student's t test, $p > 0.05$); but the small patient population must be taken into consideration.

Two patients in this study received drugs which have been reported to affect theophylline clearance.[36-38] Patient J's propranolol dose was lower than that reported to significantly decrease theophylline clearance.[49] This patient's clearance of 41.5 ml/kg/hr was above the mean value and does not appear to have been reduced due to propranolol.

Patient K received cimetidine prior to achieving theophylline steady state. Cimetidine has been reported to decrease theophylline clearance.[50-53] However conflicting data have also been reported.[54] It is impossible to ascertain whether this patient's low clearance value was the result of two doses of cimetidine or more related to age and disease factors.

The recent FDA recommendations for dosing theophylline have been based upon IBM. Data from Gal et al.,[30] indicated that mean theophylline clearances in the obese approached that of a normal population when IBM was used

to calculate clearance. They recommended basing the theophylline loading dose on ABM and the maintenance dose on IBM. Blouin et al.,[31] found a strong correlation in markedly obese patients with CHF when theophylline clearance was compared to ABM. But they stated that the mean theophylline clearance data more closely approximated a normal weight population when corrected with IBM. In the present study, mean theophylline clearance based on IBM was significantly different from that based on ABM (paired t test, $p = 0.013$) but had a smaller variation around the mean, 36.8($\pm$ 7.3) ml/kg/hr (IBM) compared to 29.5($\pm$ 8.6) ml/kg/hr (ABM). The data showed a higher correlation coefficient relating theophylline clearance with IBM ($r = 0.675$) than with ABM ($r = 0.315$). Because of this it was felt that patients should be dosed with theophylline using a clearance based on IBM, which better approximates a normal weight population with smaller individual error.

The tremendous variation in clearance values has caused a lack of success placing patients in the therapeutic range following any of the theophylline dosage guidelines discussed above. Table 10 shows the predicted Cp_{ss} for the CHF patients in Class I following various guidelines. The large standard deviations around the mean values for each author's recommendations and around the

mean values for each patient give testimony to the large intra- and interpatient variability in clearance. Data from the present study indicate that for patients fitting the Framingham criteria for CHF, without liver dysfunction, a theophylline maintenance infusion of 0.34 mg/kg/hr IBM for nonsmokers and 0.40 mg/kg/hr IBM for smokers was needed to achieve a Cp_{SS} of 10 mcg/ml.

Table 11 summarizes these data into the number of predicted patients in the therapeutic range following each set of guidelines. Again the large standard deviation around the means indicates the tremendous variability in patient clearances. The dosage guidelines proposed by Jusko et al.,[31] agree closest with the results obtained in the present study.

While no method can be expected to place 100% of patients in the therapeutic range, it is of great concern that the current FDA guidelines have failed to produce therapeutic serum levels. Table 12 shows the number of patients in the therapeutic range of 10-20 mcg/ml after the actual dosages given and predicted to be in the therapeutic range following FDA dosage guidelines. For the CHF patients in Class I, there was a significant difference in the number of patients in the therapeutic range after the actual dose given, 4/5 (80%) patients compared to the number predicted when following the FDA dosage guidelines,

0/5 (0%) patients (McNemar's exact test, p = 0.03). The difference in the total number of patients in the therapeutic ranges after the actual dosage given, 9/11 (82%) patients, compared to the number predicted to be following FDA dosages, 0/11 (0%) patients, was also highly significant (McNemar's exact test, p = 0.002). Based on the results of the present study, the use of the FDA theophylline dosage guidelines in this group of patients would be inappropriate.

VI. CONCLUSION

The use of pharmacokinetics to help achieve a therapeutic theophylline serum level in patients with congestive heart failure is critically important. A variety of dosage guidelines have been published to help the clinician achieve this goal, but they contradict each other and confuse the issue. The recent FDA guidelines appear not able to produce therapeutic theophylline concentrations.

In a well defined population of patients with congestive heart failure, without hepatic dysfunction, these guidelines are inadequate and may have produced subtherapeutic serum levels in all patients. It appears from the present data that the theophylline clearance at steady state may be higher than previously reported and that higher doses, based on IBM, may be needed to achieve therapeutic serum levels in this patient population. Subsequent work is needed to elucidate all the factors affecting theophylline clearance. Because of the wide variation in theophylline clearances frequent serum levels and pharmacokinetic monitoring are advised to avoid toxicity.

TABLE 1

THEOPHYLLINE DOSAGE RECOMMENDATIONS

STUDY	STUDY'S CATEGORIZATION TERM	THEOPHYLLINE DOSE (mg/kg/hr)	CHF PTS IN STUDY
Piafsky, 1975	Presence of CHF	0.48 ABM	0
Koup, 1976	CHF, liver disease	0.36 ABM	2
Hendeles, 1977	Cardiac decompensation	0.48 IBM Females 0.32 IBM Males	N/A
Powell, 1978	CHF with moderate COPD	0.20 ABM NS 0.32 ABM S	6
Hendeles, 1979	Cardiac decompensation or liver disfunction	0.20 ABM	0
Jusko, 1979	Moderate to severe CHF w/o cirrhosis	0.28 IBM NS 0.44 IBM S	51
FDA, 1980	CHF, liver disease	0.10 IBM	0
Hendeles, 1980	Cardiac decompensation, cor pulmonale and liver dysfunction	0.20 ABM 0.20 IBM if obese	0
Present study	CHF by Framingham criteria	0.34 IBM NS 0.40 IBM S	5

ABM = actual body mass
IBM = ideal body mass
NS = nonsmokers
S = smokers

TABLE 2

Aminophylline Dosage for Patient Population
I. Not currently receiving theophylline products:

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

* Equivalent anhydrous theophylline dose indicated in parentheses

\+ Based on estimated lean (ideal) body weight.

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TABLE 3

CRITERIA FOR DIAGNOSIS OF CONGESTIVE HEART FAILURE

adopted from McKee et al.[a]

MAJOR CRITERIA

Paroxysmal noctural dyspnea or orthopnea
Neck vein distension
Rales
Cardiomegaly
Acute pulmonary edema
S3 Gallop
Increased venous pressure (greater than 16 cm of water)
Circulation time greater than or equal to 25 seconds
Hepatojugular reflux

MINOR CRITERIA

Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity decreased 1/3 from maximum
Tachycardia (greater than 120/minute)

MAJOR OR MINOR CRITERIA

Weight loss greater than 4.5 kg in five days

For establishing a definite diagnosis of CHF two major or one major and two minor criteria must be present concurrently

[a] see reference 34

TABLE 4

PATIENT CHARACTERISTICS

PATIENT/ AGE/ GENDER			WEIGHT IN Kg[a] ABM	IBM	SMOKING HISTORY PACK-YEARS[b]	ADMITTING Dx[c]	FUNCTIONAL CLASS[d]
A	75	F	112.6	58.8	0	Hx CHF, PE	II
B	70	F	74.5	58.8	40	CHF, COPD, HT	I
C	57	F	60.0	45.0	0	COPD	III
D	76	F	31.8	45.0	75	Hx CHF, COPD, CA	II
E	66	M	97.7	75.3	40	CHF, COPD	I
F	61	M	68.6	75.3	0	COPD, IDDM	III
G	57	F	122.3	45.0	0	CHF, HT, IDDM	I
H	34	F	73.9	54.2	0	COPD	III
I	79	F	45.6	50.8	50	Hx CHF, COPD	II
J	87	M	57.3	67.3	0	CAD, CHF, PE	I
K	81	M	75.0	74.2	0	CAD, CHF, PE	I
MEAN	67.5		74.5	59.1	18.6		
S.D.	14.9		27.3	12.3	27.4		

a ABM = actual body mass on day of admittance, IBM = ideal body mass

b One pack per day per year = one pack-year of cigarette smoking.

c Admitting Diagnosis: Hx CHF = history of congestive heart failure, PE = pulmonary edema, COPD = chronic obstructive pulmonary disease, HT = hypertension, CA = cancer, IDDM = insulin dependent diabetes mellitus, CAD = coronory artery disease.

d Functional class I = patients fitting criteria for congestive heart failure; II = patients with history or diagnosis of CHF but not fitting criteria; III = patients having COPD, not fitting criteria and without history of CHF.

TABLE 5

SUMMARY OF PERTINENT PATIENT MEDICATIONS
PRIOR TO ADMISSION (PTA) INTO STUDY
AND DURING STUDY(DS)[a]

PATIENT	PTA	DS
A	digoxin, furosemide, metaproterenol, spironolactone, theophylline[b]	digoxin, furosemide, spironolactone w/hydrochlorthiazide, terbutaline, theophylline
B	digoxin, furosemide	digoxin, furosemide, theophylline
C	beclomethasone, metaproterenol, terbutaline, theophylline	beclomethasone, metaproterenol, terbutaline, theophylline
D	beclomethasone, digoxin, furosemide	digoxin, furosemide, theophylline
E	chlorthalidone, digoxin, metaproterenol, theophylline[c]	digoxin, furosemide metaproterenol, theophylline
F	dyphylline, metaproterenol	metaproterenol, theophylline
G	digoxin, spironolactone	digoxin, spironolactone, theophylline
H	beclomethasone, theophylline	albuterol, theophylline
I	digoxin, hydrochlorothiazide, terbutaline, theophylline	theophylline
J	propranolol	digoxin, furosemide, theophylline
K	cimetidine[d]	cimetidine, digoxin, theophylline[e]

a during study, up to achieving theophylline steady state

b patient stated she took no medications 2 weeks PTA

c patient stated she took no medications 2 weeks PTA

d patient stated he was not taking any medications PTA

e patient received 2 oral doses of cimetidine 300 mg prior to achieving theophylline steady state

TABLE 6

THEOPHYLLINE DOSE (R_o), CALCULATED CLEARANCE (Cl), PLASMA LEVEL AT STEADY STATE (Cp_{ss}) AND HALF-LIFE ($T_{\frac{1}{2}}$) BASED ON IBM

	PATIENT	R_o mcg/kg/hr	Cl ml/kg/hr	Cp_{ss} mcg/ml	$T_{\frac{1}{2}}$ HR
GROUP I	B	408.2	40.4	10.1	8.6
	E	340.0	42.0	8.6	8.3
	G	533.3	37.6	14.2	9.2
	J	418.8	41.5	10.1	8.3
	K	366.8	25.7	14.3	13.5
	MEAN	413.4	37.4[a]	11.5	9.6[b]
	±SD	74.1	6.8	2.6	2.2
GROUP II	A	408.2	30.4	13.4	11.4
	D	301.9	37.3	8.1	9.3
	I	438.6	28.1	15.6	12.3
	MEAN	382.9	31.9[a]	12.4	11.0[b]
	±SD	71.8	4.8	3.9	1.5
GROUP III	C	711.1	40.9	17.4	8.5
	F	373.2	30.8	12.1	11.3
	H	885.6	50.3	17.6	6.9
	MEAN	656.6	40.7[a]	15.7	8.9[b]
	±SD	260.5	9.8	3.1	2.2
TOTAL	MEAN	471.4	36.8	12.9	9.8
	±SD	176.4	7.3	3.3	2.0

[a] F test revealed insufficient evidence to conclude a difference ($p = 0.3668$, calculated $F = 1.140$).

[b] F test revealed insufficient evidence to conclude a difference ($p = 0.4775$, calculated $F = 0.812$).

TABLE 7

ACTUAL Cp_{ss} ACHIEVED IN CLASS I CHF PATIENTS COMPARED TO CALCULATED Cp_{ss} BASED ON FDA DOSAGE RECOMMENDATIONS

PATIENT	ACTUAL		FDA DOSE	CALCULATED
	R_o[a] (mcg/kg/hr)	Cp_{ss} (mcg/ml)	R_o[b] (mcg/kg/hr)	Cp_{ss}[c] (mcg/ml)
B	408.2	10.1	100	2.48
E	340.0	8.6	100	2.38
G	533.3	14.2	100	2.66
J	418.8	10.1	100	2.40
K	366.8	14.3	100	3.89
MEAN (±SD)	413.4 (74.1)	11.5[d] (2.6)	100(0)	2.76[d] (0.64)

[a] Actual theophylline intravenous dose given to patients in study, based on ideal body weight.

[b] FDA recommended theophylline intravenous dose based on ideal body mass (see reference 12).

[c] Predicted Cp_{ss} using equation 2 and patients calculated Cl.

[d] Paired t test revealed a significant difference ($p = 0.0009$, calculated $t = 8.8617$).

TABLE 8

ACTUAL Cp_{ss} ACHIEVED IN CLASS II PATIENTS COMPARED TO CALCULATED Cp_{ss} BASED ON FDA DOSAGE RECOMMENDATIONS

PATIENT	ACTUAL R_o[a] (mcg/kg/hr)	ACTUAL Cp_{ss} (mcg/ml)	FDA DOSE R_o[b] (mcg/kg/hr)	PREDICTED Cp_{ss}[c] (mcg/ml)
A	408.2	13.4	100	3.29
D	301.9	8.1	100	2.68
I	438.6	15.6	100	3.56
MEAN (±SD)	382.9 (71.8)	12.4[d] (3.9)	100 (0)	3.18[d] (.45)

[a] Actual theophylline intravenous dose given patients in study, based on ideal body mass.

[b] FDA recommended theophylline intravenous dose based on ideal body mass (see reference 12).

[c] Predicted Cp_{ss} using equation 2 and patient's calculated Cl.

[d] Paired t test revealed a significant difference ($p = 0.0429$, calculated $t = 4.6731$).

TABLE 9

ACTUAL Cp_{ss} ACHIEVED IN CLASS III PATIENTS COMPARED TO CALCULATED Cp_{ss} BASED ON FDA DOSAGE RECOMMENDATIONS

PATIENT	ACTUAL R_o[a] (mcg/kg/hr)	ACTUAL Cp_{ss} (mcg/ml)	FDA DOSE R_o[b] (mcg/kg/hr)	PREDICTED Cp_{ss}[c] (mcg/ml)
C	711.1	17.4	260	6.36
D	373.2	12.1	260	8.44
H	885.6	17.6	430	8.55
MEAN (±SD)	656.6 (260.5)	15.7[d] (3.1)	316.7 (98.1)	7.78[d] (1.2)

[a] Actual theophylline intravenous dose given patients in study, based on ideal body mass.

[b] FDA recommended theophylline intravenous dose based on ideal body mass (see reference 12).

[c] Predicted Cp_{ss} using equation 2 and patient's calculated Cl.

[d] Paired t test revealed insufficient evidence to conclude a difference ($p = 0.0683$, calculated $t = 3.6273$).

TABLE 10

CLASS I CHF PATIENTS
PREDICTED THEOPHYLLINE SERUM LEVELS
AT STEADY STATE BASED ON PUBLISHED
THEOPHYLLINE DOSING GUIDELINES

AUTHOR	PATIENTS'S PREDICTED Cp_{ss}[a]					MEAN(S.D.)
	B	E	G	J	K	
Mitenko, 1973	22.6	22.3	54.1	17.3	28.3	28.9(14.6)
Piafsky, 1975	15.0	14.9	36.1	11.6	18.9	19.3(9.7)
Koup, 1976 Jusko, 1977	11.3	11.1	27.1	8.7	14.2	14.5(7.3)
Hendeles, 1977	11.9	7.6	12.8	7.7	12.5	10.5(2.6)
Gal, 1978	17.8	8.1	19.1	17.3	28.0	18.1(7.1)
Powell, 1978	10.0	9.9	15.0	4.8	7.9	9.5(3.7)
Hendeles, 1979	6.3	6.2	15.0	4.8	7.9	8.0(4.0)
Jusko, 1979	10.9	10.5	7.4	6.7	10.9	9.3(2.1)
FDA, 1980	2.5	2.4	2.7	2.4	3.9	2.8(0.6)
Hendeles, 1980	6.3	4.8	5.3	4.8	7.9	5.8(1.3)
Present Study, 1982	10.1	8.6	14.2	10.1	14.3	11.5(2.6)
MEAN (S.D.)	15.0 (13.7)	9.3 (5.3)	18.4 (14.5)	8.3 (5.0)	13.4 (8.0)	

[a] predicted using equation 2. See text for explanation.

TABLE 11

NUMBER OF CLASS I CHF PATIENTS IN THERAPEUTIC RANGE BASED ON DOSING GUIDELINES

	NUMBER OF PATIENTS		
AUTHOR	SUBTHERAPEUTIC	THERAPEUTIC	TOXIC
Mitenko, 1973	0	1	4
Piafsky, 1975	0	4	1
Koup, 1976 Jusko, 1977	1	3	1
Hendeles, 1977	2	3	0
Gal, 1978	1	3	1
Powell, 1978	3	2	0
Hendeles, 1979	4	1	0
Jusko, 1979	2	3	0
FDA, 1980	5	0	0
Hendeles, 1980	5	0	0
Present Study, 1982	1	4	0
MEAN	2.2	2.2	0.6
(S.D.)	(1.8)	(1.5)	(1.2)

TABLE 12

NUMBER OF PATIENTS IN THERAPEUTIC RANGE[a]
AFTER ACTUAL DOSAGES GIVEN VS PREDICTED
AFTER FOLLOWING FDA GUIDELINES

CLASS	AFTER ACTUAL DOSE GIVEN		PREDICTED AFTER FDA DOSE	
	#	%	#	%
1	4/5	80	0/5	0
2	2/3	67	0/3	0
3	3/3	100	0/3	0
TOTAL	9/11[b]	82	0/11[b]	0

[a] accepted therapeutic range for theophylline serum concentrations = 10-20 mcg/ml (see reference 12).

[b] McNemar's exact test revealed a significant difference ($p = 0.002$, calculated chi-square = 9.00).

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