Estimation of Theophylline Clearance During Intravenous Aminophylline Infusions

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Abstract □ The utility of predicting theophylline clearance (*CL*) from two serum concentrations obtained during continuous intravenous aminophylline infusion was examined in 16 stable, adult patients. Blood for theophylline measurement was obtained 0, 6, and 12 h after starting infusions and, thereafter, at 12-h intervals. EMIT was used to assay samples in multiple runs as they were obtained. Later, each sample was reassayed by EMIT within a single run. Bayesian least-squares regression and the algebraic method of Chiou were used to predict *CL* using the 0,6 and 0,12 h concentrations. "Actual" *CL* was measured by nonlinear least-squares regression of all concentrations obtained during prolonged infusions. Prediction bias and precision were assessed by calculating mean percent error (PCE) and mean absolute percent error (APCE), respectively. A three-way repeated-measures ANOVA was used to examine the effect of the method of *CL* prediction, assay procedure, and time interval between samples on PCE and APCE. Bayesian predictions were less biased and slightly more precise than Chiou predictions. The assay procedure had no effect on bias but precision was improved using a single-assay run. Predictions were less biased and more precise with 0,12 h versus 0,6 h data. Serum samples for theophylline measurement should be obtained after initiating constant intravenous aminophylline and again 8–12 h later in stable, adult patients. Prediction of *CL* with either of the concentration-based methods studied will then allow safe and rapid adjustment of dosage to achieve therapeutic serum concentrations.

Aminophylline is frequently administered by constant intravenous infusion to treat hospitalized patients with respiratory impairment due to bronchospasm. Serum concentrations from 5 to 20 mg/L are associated with efficacious response[1] and minimal toxicity.[2] Serum concentrations above 20 mg/L are commonly associated with adverse reactions.[2,3] Seizures or other serious toxic manifestations may or may not be preceded by the development or recognition of less serious toxic effects such as sinus tachycardia, nausea, vomiting, tremors, headache, nervousness, and agitation.[4] Consequently, the FDA has issued dosing guidelines for intravenous aminophylline designed to minimize the occurrence of adverse reactions.[5] In addition, routine monitoring of serum theophylline concentrations in patients being treated with intravenous aminophylline has been recommended in order to avoid subtherapeutic or toxic concentrations[6-9] and to help determine chronic oral dosage needs.[10]

Several "population average" or "prior" models have been suggested for predicting individual patient dosage requirements in order to maintain serum theophylline concentrations within the therapeutic range.[1,9,11,12] Prior approaches are based on expectations for the total body clearance (*CL*) and apparent volume of distribution (*Vd*) of theophylline. They incorporate known interrelationships between these pharmacokinetic parameters and patient variables such as age, weight, smoking history, and clinical status.

Powell et al.[9] after studying 26 hospitalized patients and 31 healthy volunteers, suggested a prior model for predicting theophylline *CL*. This model is based on an estimated standard *CL* of 40 mL/h/kg of body weight for nonsmoking, otherwise healthy adults. Multiplicative factors are then applied to adjust this estimate of *CL* for the significant effects of certain patient characteristics. These factors are 1.6 for smoking, 0.8 for severe airway obstruction, 0.4 for congestive heart failure, and 0.4 for pneumonia. Powell measured a mean *Vd* of 0.49 L/kg with a coefficient of variation (CV) of 23%.

Jusko et al.[11] suggested a more comprehensive prior model for predicting theophylline *CL* based on data collected from 200 patient and volunteer subjects. The influence of patient factors (discontinuous, independent variables) on *CL* (continuous, dependent variable) was examined using "variance analysis" techniques. The result was a cascade of *mutually* exclusive subgroups. Classification of a particular patient into one of these subgroups allows the prediction of theophylline *CL* and its variance for that individual. The most significant factors were age, smoking, liver disease, and congestive heart failure. The uncertainty in predicted *CL* expressed as a CV averaged 36.0% and ranged from 21.5 to 47.7% in the 16 terminal cells of the cascade.

The large residual, interindividual variability in theophylline *CL*[8,9,11] makes prior approaches to dosage selection less than ideal. Chiou et al.[13] proposed an algebraic method for estimating theophylline *CL* whenever two serum theophylline concentrations are obtained during continuous intravenous aminophylline infusion therapy. They noted that the estimate of *Vd*, the accuracy of serum concentration assay, and the interval of time between blood samples were critical factors which could effect the estimation of *CL*.

Bayesian approaches have also been developed for predicting individual drug dosage needs.[14-18] A prior model is used to generate expectations for pharmacokinetic parameters and their associated variances for individual patients. These initial parameter estimates are then revised using measured serum concentrations. Bayesian approaches are appealing since they incorporate prior information and measured serum concentrations. However, they have not yet been fully evaluated in the clinical setting. The purpose of this study was to compare a Bayesian weighted least-squares method for estimating theophylline *CL* from two serum concentrations obtained during a constant intravenous aminophylline infusion with the algebraic method of Chiou. The effects of the time interval between blood samples and assaying serum specimens within the same run or in different runs were examined since these can be readily controlled in the clinical setting. In addition, the two concentration based methods were compared with prior approaches suggested by Powell[9] and Jusko[11] for predicting theophylline dosage and with the FDA guidelines.[5]

Experimental Section

Patients—Sixteen adult patients being treated with intravenous aminophylline for airway obstruction were studied. They met the following criteria: (*a*) no oral theophylline had been taken within the previous 12 h, (*b*) intravenous amino-

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phylline treatment had been initiated <24 h prior to beginning the study, and (c) informed consent could be obtained. All pertinent patient characteristics necessary for predicting theophylline *CL* by the Jusko[11] and Powell[9] methods were obtained from the clinical database and a thorough patient interview.

Patients were not studied if they had clinical or laboratory evidence of acute congestive heart failure, liver cirrhosis, pneumonia, sepsis, or severe malnutrition. Patients treated with erythromycin or cimetidine during the study or within the previous week were likewise excluded. Twelve patients were studied in the Los Angeles County/University of Southern California (LAC/USC) Clinical Research Center. Eight patients were studied in the LAC/USC Respiratory Intensive Care Unit (RICU). Four of the RICU patients were withdrawn from the study before completing the protocol. One developed pneumonia with bacteremia, two received erythromycin, and one received cimetidine.

Dosage and Delivery—If clinically indicated, loading doses of aminophylline were given in the Emergency Room before admission. Initial infusion rates were chosen to maintain steady-state serum concentrations between 10 and 20 mg/L and were based on desirable body weight, smoking history, and clinical status using current LAC/USC guidelines[19] (Table I). The initial rates were held constant during the first 12 h of study. Thereafter, they were adjusted as necessary to maintain serum concentrations between 10 and 20 mg/L and minimize adverse effects. Aminophylline infusions were delivered using a Harvard model 2620 syringe pump. Syringes were prepared to deliver the hourly dose in 5 mL of 5% dextrose in water.

Serum Sampling and Analysis—Timed blood samples for assay of serum theophylline concentration were obtained by venipuncture at 0, 6, and 12 h after initiation of the study or following any adjustment of infusion rate and at 12-h intervals thereafter. Blood specimens were sent immediately to the LAC/USC Toxicology Laboratory for routine analysis by enzyme immunoassay (EMIT, Syva Co., Palo Alto, Ca). A single determination was made by the EMIT manual procedure. Each sample was assayed in a separate run and concentration data generated in this way will be referred to as EMIT multiple run (EMR) data. The manual EMIT assay between-run CV was 8.5% at a concentration of 15 mg/L (n = 139).

Study sera were saved and stored at −5°C. When all sera for an individual patient had been collected, the samples were reassayed by EMIT in duplicate and within a single run using an ABA-100 automated clinical chemistry system (Abbott Laboratories). This concentration data will be referred to as EMIT single run (ESR) data. The ESR results were reported as the means of the duplicate determinations. The between-run CV for the automated EMIT assay was 5.1% at a concentration of 15 mg/L (n = 17).

Pharmacokinetic Estimation of Clearance—The prior models of Jusko[11] and Powell[9] were used to predict *CL* for each subject. For predictions of *CL*, desirable body weight[20] was used for all subjects rather than actual body weight. Serum concentration data obtained during the first 12 h of continuous intravenous aminophylline infusion were used to predict *CL* under the assumption of a single-compartment model with first-order elimination. The assumption of linear theophylline elimination appears to be reasonable since several recent reports[21-23] failed to demonstrate clinically significant saturable theophylline elimination in adults.

Table I—Suggested Initial Intravenous Aminophylline Maintenance Infusion Rates to Sustain Serum Theophylline Concentrations of 10 mg/L in Adults

Patient Subgroup	Rate, mg/kg/h[a]
Young smokers	0.9
Smokers >40-years old	
Nonsmokers	0.6
Patients with acute congestive heart failure, liver cirrhosis, or cor pulmonale	0.3

[a] Desirable body weight rather than actual weight is used for calculating maintenance infusion rates in obese patients.

It was possible to generate eight different predictions of each *CL* level using serum concentration data from the first 12 h of study. This was done by completely crossing three grouping factors with two levels each. These grouping factors were denoted "assay," "interval," and "method." The levels of "assay" were the EMR and ESR assay procedures. The levels of "interval" were defined by the 0,6 and 0,12 h data pairs.

For the first level of "method," eq. 1 was used to estimate serum theophylline *CL* algebraically as suggested by Chiou et al.:[13]

$$CL_{chiou} = \frac{(2)(0.8)(R_i)}{(C_1 + C_2)} + \frac{(2)(Vd)(C_1 - C_2)}{(C_1 + C_2)(t_2 - t_1)} \quad (1)$$

R_i is the continuous infusion rate of intravenous aminophylline (mg/h), C_1 and C_2 are serum theophylline concentrations (mg/L) obtained at times t_1 and t_2, respectively, during the infusion, and *Vd* is the apparent volume of distribution for theophylline (0.5 L/kg total body weight[13]). The factor 0.8 adjusts the infusion rate of aminophylline to reflect content of theophylline.

For the second level of "method," estimates of *CL* and *Vd* were found by fitting eq. 2 to the paired concentration data using Bayesian-weighted nonlinear least-squares regression:

$$C_2 = C_1 e^{-(CL/Vd)(t_2 - t_1)} + (0.8R_i/CL)(1 - e^{-(CL/Vd)(t_2 - t_1)}) \quad (2)$$

Bayesian regressions were performed with an iterative program written in BASIC by the investigators and employing the Gauss–Newton algorithm with Hartley's modification. This program can fit multiple concentrations obtained during multiple constant or intermittent intravenous infusions using superposition and has been implemented on a DEC KL 10/90 mainframe and several microcomputers including an IBM PC, Osborne 01, and TRS-80 model 100. Bayesian predictions were produced by minimizing the weighted sum of squares (WSS) given in eq. 3 as suggested by Sheiner et al.:[16-18]

$$WSS = \sum_{i=1}^{m} \frac{(\ln \bar{\theta}_i - \ln \hat{\theta}_i)^2}{(CV\theta_i)^2} + \sum_{j=1}^{n} \frac{(C_j - \hat{C}_j)^2}{\sigma^2 C_j} \quad (3)$$

where m is the number of parameters (m = 2; *CL*, *Vd*), n is the number of measured serum concentrations (n = 2; C_1, C_2), $\bar{\theta}_i$ represents the population average or prior estimate for the *i*th parameter, $\hat{\theta}_i$ is the estimate of the *i*th parameter for each individual, $CV\theta_i$ is the coefficient of variation of the *i*th parameter (the square of the coefficient of variation of the *i*th parameter approximates the variance of the natural logarithm of that parameter[16]), C_j is the *j*th measured serum concentration, $\hat{C}_j$ is the model prediction of the *j*th serum concentration, and $\sigma^2 C_j$ is the variance of the *j*th serum concentration (set at 1.0 mg^2/L^2 for all concentrations). Prior estimates for each *Vd* and its uncertainty were calculated as 0.5 ± 0.1 L/kg actual weight (mean ± SD). The cascade of factors determining theophylline *CL* found by Jusko et al.[11] was used to generate the initial estimate of *CL* and its associated CV for the Bayesian approach.

Measurement of Actual Clearance—"Actual" theophylline *CL* was found by employing nonlinear least-squares regression using the packaged computer program BMDPAR.[24] The model was stated as an analytical expression allowing multiple constant-infusion rates of varying duration. Concentration was expressed as a function of infusion rates and time together with the fitted parameters *CL*, *Vd*, and initial amount in the body. The result was a sum of terms specified by the superposition principle under the assumption of a single-compartment model with first-order elimination. The particular equation used for each patient depended upon the number of

distinct infusion rates administered since each change in rate required an extra term. Since the initial amount of drug in the body was unknown, it was treated as a parameter to be estimated along with *CL* and *Vd*. The parameters were estimated using the combined EMR and ESR concentration data obtained over the total duration of the study for each patient. Therefore, these parameter values represent the best unbiased estimates available. An example of a concentration versus time plot together with the fitted residuals is given in Fig. 1.

Comparisons and Statistical Analysis—The prediction error inherent in the methods used to estimate theophylline *CL* was examined by calculating percent error (PCE, eq. 4) and absolute percent error (APCE, eq. 5) for each patient. Mean PCE and mean APCE were used to assess predictive bias and predictive precision respectively.[25] Results are reported as mean ± SD unless otherwise noted. Differences in means were evaluated using two-sided, paired *t* tests ($\alpha = 0.05$).

$$\text{PCE} = \frac{(\text{predicted } CL - \text{actual } CL) \times 100}{\text{actual } CL} \quad (4)$$

$$\text{APCE} = \text{absolute value of PCE} \quad (5)$$

Sources of variation in the bias and precision of approaches for predicting theophylline *CL* with paired serum concentration data were studied using a three-way analysis of variance (ANOVA) with repeated measures[26] ($\alpha = 0.05$). PCE and APCE were examined as dependent variables. Prior to performing the ANOVA, Levene's test for equal variances was used to ensure homogeneity of variances. The main effects for the ANOVA model were "method," "assay," and "interval." Subject was treated as a fixed effect with 16 levels.

Results

Patients—Nine of the 16 patients studied were males. Mean age was 43.5 ± 15.8 years and mean weight was 75.7 ± 12.5 kg. Six subjects were cigarette smokers and one subject admitted to smoking two to three marijuana "joints" daily. Five subjects weighed at least 140% of their desirable weight and were considered obese. Median peak expiratory flow rate (PEF), excluding three patients receiving mechanical ventilation, was 180 and 370 L/min at the initiation and the end of the study, respectively. No patient had a PEF below 100 L/min at any time. Patient characteristics are summarized in Table II.

Dosage and Delivery—The mean initial intravenous aminophylline infusion rate was 50.6 ± 15.3 mg/h. Average duration of study was 63.8 ± 13.3 h and ranged from 38.0 to 83.9 h.

Serum Concentrations—The number of measured serum concentrations obtained in each subject averaged 9.1 and ranged from 6 to 14. The mean initial concentration was 11.3 ± 5.1 mg/L and ranged from 2.5 to 20.3 mg/L (EMR assay). Correlation between EMR and ESR assay results was good ($r = 0.95$, $n = 146$). The mean difference between the two assays was 0.02 ± 1.61 mg/L (EMR minus ESR) and the mean concentration was 13.3 mg/L.

Estimation of "Actual" Clearance—The asymptotic standard deviations of the regression estimates averaged <6% of "actual" *CL* (Table II), indicating that *CL* was well measured. Examination of computer-fitted residual versus concentration plots was done and there were no systematic deviations consistent with nonlinear theophylline elimination in any of these patients. Representative scatterplots of "actual" *CL* versus estimated *CL* for the prior methods of Jusko[11] and Powell,[9] for the method of Chiou with EMR 0,6 h data (least precise concentration based estimate), and for the Bayesian method with ESR 0,12 h data (most precise concentration based estimate) are shown in Fig. 2.

Examination of Bias and Precision—The mean PCE and mean APCE for the predictive methods of Powell and Jusko and for the eight predictions of *CL* using paired serum concentrations are shown in Table III. The coefficient of determination between actual and estimated *CL* is also given for each method. However, this is a measure of association only and is an unreliable index of predictive capability.[25]

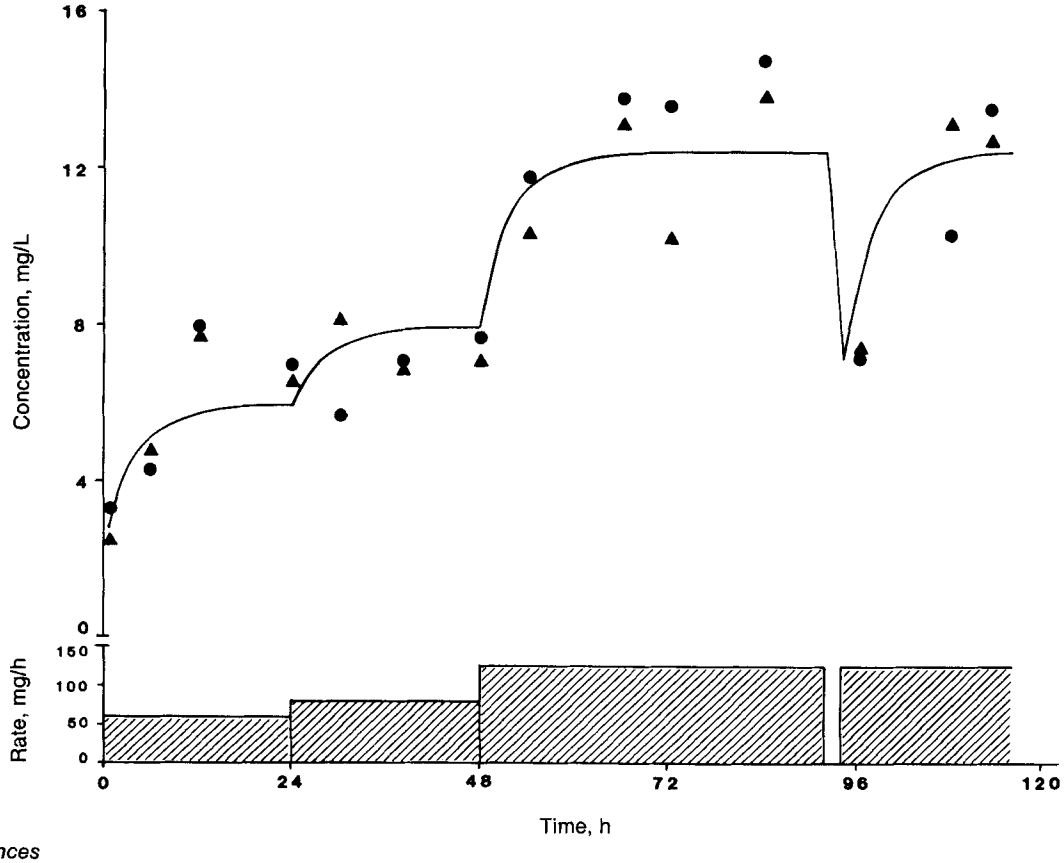

Figure 1—*Serum theophylline concentrations and intravenous aminophylline infusion rates for patient 8. The EMR (▲) and ESR (●) data are shown together with the least-squares regression line.*

Table II—Patient Data

Patient	Age[a]	Sex	ABW, kg[b]	DBW, kg[c]	Smoker	Indication[d]	Actual *CL*, L/h[e]	Initial Infusion, mg/h	Study Duration, h
1	19	M	80.9	73.5	NO	A	6.43 (0.16)	70	67.2
2	70	M	61.4	69.4	YES	CB, RF	2.79 (0.11)	35	60.3
3	56	M	79.0	65.7	YES	CB, CP	3.46 (0.45)	30	40.6
4	46	M	80.0	63.7	NO	A	2.32 (0.06)	75	63.0
5	37	F	83.4	56.9	NO	A	2.28 (0.07)	55	55.2
6	72	F	53.0	48.5	NO	A	3.79 (0.12)	30	73.3
7	36	F	104.3	53.5	NO	A	2.82 (0.15)	40	72.0
8	37	M	75.0	73.5	YES	SI, RF	7.93 (0.26)	60	83.9
9	58	F	75.2	55.9	YES	CB, CP, RF	3.13 (0.17)	40	72.5
10	31	M	74.3	69.4	YES	A	2.49 (0.14)	70	71.9
11	53	M	66.7	58.9	NO	A	1.53 (0.04)	45	72.2
12	20	F	57.3	49.9	NO	A	2.17 (0.09)	40	72.0
13	46	F	90.2	52.5	NO	A	3.15 (0.18)	50	60.1
14	41	F	71.8	48.5	NO	A	3.52 (0.24)	40	44.2
15	27	M	76.4	70.4	MJ	A	5.27 (0.54)	70	75.3
16	47	M	81.8	57.6	YES	A	1.57 (0.33)	60	38.0
Mean	43.5		75.7	60.5			3.41	50.6	63.8
SD	15.8		12.5	8.9			1.75	15.3	13.3

[a] In years. [b] Actual body weight. [c] Desirable body weight. [d] A asthma, CB chronic bronchitis, CP cor pulmonale, MJ marijuana smoker, RF respiratory failure requiring mechanical ventilation, SI smoke inhalation. [e] Numbers in parentheses are the asymptotic standard deviations found by regression analysis.

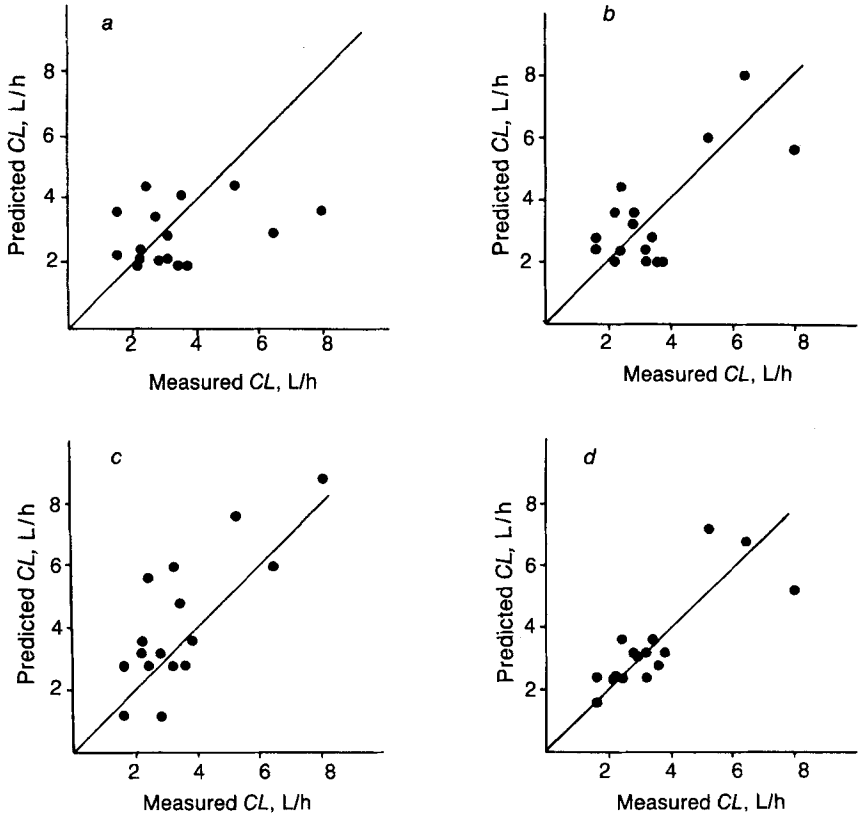

Figure 2—*Measured theophylline* CL *plotted against* (a) *predicted* CL *from the Powell prior model,* (b) *predicted* CL *from the Jusko prior model,* (c) *predicted* CL *from the method of Chiou using EMR 0,6 h data, and* (d) *predicted* CL *from the Bayesian method using ESR 0,12 h data. The solid lines are the lines of identity.*

The bias (PCE) was different from zero ($p < 0.05$, Table III) for three of the four estimates produced by the method of Chiou (C6M, C6S, C12S) but not for any of the Bayesian or prior methods. The precision (APCE) of the methods using paired concentration data was compared with the precision of each of the prior models. Three of four methods using the 0,12 h data (B12M, C12S, B12S) and one method using the 0,6 h data (B6S) were more precise than the Powell approach for predicting *CL* ($p < 0.05$, Table III). Two of the four methods using the 0,12 h data (B12M, B12S) were more precise than the Jusko prior model ($p < 0.05$, Table III).

Repeated-Measures ANOVA—Table IV summarizes the results of the three-way ANOVA with repeated measures. The ANOVA model shows an effect of "interval" on both bias

($p < 0.05$) and precision ($p < 0.0005$). In addition, there was an effect of "method" on bias ($p < 0.05$) and of "assay" on precision ($p < 0.01$). There were no statistically significant interactions.

Discussion

This study was designed to compare concentration based approaches for estimating theophylline *CL* using two measured serum concentrations. This is the minimum number of observations necessary to estimate theophylline *CL* before steady state has been reached in hospitalized patients taking some form of theophylline before admission. The ability to accurately predict theophylline *CL* before steady state is reached has obvious advantages for patients where achieving and maintaining maximum yet safe serum concentrations is desirable.

We specifically selected patients likely to be clinically stable and likely to have stable theophylline *CL* so that both concentration based methods could be tested under meaningful conditions. Patients similar to these account for the vast majority of patients who receive intravenous aminophylline. Patients with acute heart failure, those receiving drugs known to acutely alter theophylline clearance (erythromycin, cimetidine), and septic or severely malnourished patients were excluded because their *CL* could have been unstable during the period of study.[9,27] This would have invalidated the measurement of "actual" *CL*. For the same reason, reliance on the estimation of theophylline *CL* from early serum concentration data is inappropriate in such patients. Patients with liver cirrhosis are likely to have prolonged elimination half-lives.[8,27] They were excluded because we felt that an interval substantially longer than 12 h would be necessary to assure reasonably safe predictions of *CL* with the concentration-based methods.

Predicted Steady-State Concentration—Mean predicted steady-state serum concentrations (mean $\hat{C}_{ss}$), which would have been achieved using continuous intravenous aminophylline infusions suggested by various methods for predicting dosage, are given in Table V. Each $\hat{C}_{ss}$ was found by dividing the suggested aminophylline infusion rate (adjusted for theophylline content) by the "actual" *CL*. A target of 12.5 mg/L was used for all methods except the FDA and LAC/USC guidelines (where no target concentration is specified). Desirable body weight was used with the FDA and LAC/USC guidelines to estimate dosage needs. This allows comparison of these guidelines with the other approaches. The number of subjects whose $\hat{C}_{ss}$ would have been <7.5, 7.5–20.0, 20.0–25.0, and >25.0 mg/L are also depicted. The Jusko model was associated with $\hat{C}_{ss}$ between 7.5 and 20.0 mg/L more often than any of the other prior methods. The concentration-based methods using 0,12 h data similarly appeared superior to prior methods and to methods using the 0,6 h data.

Mean $\hat{C}_{ss}$ for the FDA guideline dosage was somewhat lower than for the other prior methods. Dosage needs were particularly underestimated with the FDA guidelines in four patients, two older than 70 and two with cor pulmonale, who were assigned final aminophylline infusion rates of 0.3 mg/kg/h. Using the FDA dosage guidelines, $\hat{C}_{ss}$ ranged from 3.0 to 5.9

Table III—Comparison of Approaches to Predict Theophylline Clearance Using Mean Percent Error (PCE) as a Measure of Bias and Mean Absolute Percent Error (APCE) as a Measure of Precision

Method[a]	r^2	Mean	
		PCE[b]	APCE[c]
Powell	0.09	1.0	38.3
Jusko	0.50	10.0	33.5
C6M	0.63	25.9*	39.7
B6M	0.60	15.9	32.8
C6S	0.84	24.1**	27.8
B6S	0.82	13.4	24.3*
C12M	0.67	12.1	24.5
B12M	0.66	8.7	20.7*,‡
C12S	0.68	13.2*	18.6*
B12S	0.70	8.9	17.4**,‡

[a] C, algebraic method of Chiou; B, Bayesian least squares; 6, 0,6 h concentration pair; 12, 0,12 h concentration pair; M, EMR assay; S, ESR assay. [b] Paired *t* test; H_0: mean PCE = 0 (* $p < 0.05$, ** $p < 0.01$). [c] Paired *t* test; H_0: mean APCE = mean APCE for the Powell method (* $p < 0.05$, ** $p < 0.01$) and H_0: mean APCE = mean APCE for the Jusko method (‡ $p < 0.05$).

Table IV—Effect of "Method", "Assay", and "Interval" on Bias (PCE) and Precision (APCE) of *CL* Pediction Using a Completely Crossed Three-Way ANOVA with Repeated Measures[a]

Sources of Variation	Dependent Variables	
	PCE	APCE
Method (M)	0.0472	0.1471
Assay (A)	0.8320	0.0064
Interval (I)	0.0111	0.0001
M × A	0.9101	0.5686
M × I	0.3598	0.6042
A × I	0.6988	0.2976
M × A × I	0.9956	0.9557

[a] Probabilities (p values) associated with F values for testing the significance of each main effect and interaction term in the model (sources of variation) are given. The null hypothesis for each F test is no effect or no interaction.

Table V—Comparison of Estimated Steady-State Concentrations ($\hat{C}_{ss}$) Using Continuous Intravenous Aminophylline Infusions[a]

	Mean (CV%)	Range	Number of Patients Having $\hat{C}_{ss}$ (mg/L) of			
			<7.5	7.5–20.0	20.0–25.0	>25.0
Prior methods						
FDA	8.3 (51.9)	3.0–17.6	9	7	0	0
LAC/USC	10.2 (48.5)	4.2–19.8	6	10	0	0
Powell	12.6 (50.9)	5.6–29.0	4	10	1	1
Jusko	13.7 (39.3)	6.4–26.5	2	13	0	1
Concentration-based methods						
C6M	15.7 (37.8)	4.8–28.2	1	11	3	1
B6M	14.2 (39.1)	7.0–28.3	1	12	2	1
C6S	15.5 (23.1)	11.5–23.4	0	14	2	0
B6S	13.9 (27.5)	8.6–21.4	0	14	2	0
C12M	14.0 (26.4)	9.4–21.2	0	15	1	0
B12M	13.2 (26.8)	8.5–21.9	0	15	1	0
C12S	14.1 (21.0)	9.1–19.5	0	16	0	0
B12S	13.3 (21.4)	8.4–18.8	0	16	0	0

[a] Suggested by the various methods for predicting theophylline clearance and dosage. Target $\hat{C}_{ss}$ was 12.5 mg/L except for the FDA and LAC/USC methods which have no stated target.

mg/L for these four patients. The LAC/USC guidelines similarly underestimated dosage needs in the two patients with cor pulmonale.

Bias—All mean PCEs were positive, indicating a tendency to overpredict *CL* within the subjects studied (Table III). Mean PCE (bias) was statistically significantly different from zero for three of the four estimates produced by the method of Chiou but not for any of the other estimates. Each estimate of *CL* by the method of Chiou appeared more biased than its Bayesian counterpart. Estimates produced by the 0,6 h data likewise appeared more biased than corresponding 0,12 h data estimates. The prior models for predicting *CL* were noticably less biased than the method of Chiou using 0,6 h data. Only the Bayesian predictions using 0,12 h data had mean PCE closer to zero than the Jusko prior method.

Precision—Precision, measured by mean APCE, ranged from 17.4% for the Bayesian approach utilizing 0,12 h ESR data to 39.7% for the method of Chiou with 0,6 h EMR data (Table III). The Jusko approach, with a mean APCE of 33.5%, outperformed the Powell method in the subjects studied. None of the Chiou predictions had a mean APCE which was statistically significantly different from the Jusko predictions. Indeed, when the Chiou approach was evaluated with the 0,6 h EMR data, mean APCE was greater than for the Jusko method. On the other hand, two of the four Bayesian methods (B12M, B12S) had lower and statistically significantly different mean APCE than the Jusko method.

Repeated-Measures ANOVA—Subject was treated as a fixed effect in the repeated measures ANOVA. This was considered appropriate since the small group of patients studied were not randomly selected from all patients treated with continuous intravenous aminophylline. Generalization of results should therefore be done with caution.[28] Since the study group was selected to be representative of stable patients receiving such treatment, statistically significant effects within the group are still of interest.

Bayesian predictions of *CL* were less biased ($p < 0.05$, Table IV) but no more precise ($p = 0.15$, Table IV) than Chiou predictions. Although no statistically significant effect on precision was evident, APCE was always less for Bayesian predictions compared to their Chiou counterparts. It is possible that the effect of method of *CL* prediction would have reached statistical significance for precision had a larger number of subjects been studied.

Assay procedure had no effect on bias ($p = 0.83$, Table IV), but the precision of *CL* prediction was improved using ESR data ($p < 0.01$), Table IV). APCE was always smaller for predictions based on ESR data compared to their EMR data analogues.

Predictions of *CL* were less biased ($p < 0.05$, Table IV) and more precise ($p < 0.0005$, Table IV) with 0,12 h data compared to 0,6 h data. The impact of interval on predictive precision appeared greater than either method of *CL* prediction or assay procedure. Chiou et al.[13] suggested an interval between samples of at least 3–5 h. D'Argenio and Khakmahd[29] demonstrated that the theoretical variance of an estimate of *CL* using an interval of 0.3–0.5 half-lives is about fourfold greater than with an interval of 1.0–1.5 half-lives. Since nonsmoking adults and obese, smoking adults have an average theophylline half-life of ~8 h,[8] the shortest practical interval in adult patients similar to those studied here is probably ~8 h. In more severely ill patients with sepsis, severe malnutrition, untreated congestive heart failure, or liver disease, and in patients receiving drugs known to impair theophylline clearance, the interval may need to be longer.

Prior Methods—The Jusko prior model appeared superior to the Powell model for predicting *CL* in this study. Gotz et al.,[30] using the Powell method, found no correlation between predicted and measured *CL* in 22 hospitalized patients of whom 6 had CHF, 3 had pneumonia, 6 were markedly underweight, 3 received cimetidine, and 1 received erythromycin. The present study excluded patients with these characteristics, since it was felt they might display unstable theophylline *CL* during the study period. Nevertheless, a similar lack of predictive capability was still evident. Despite the relatively good performance of the Jusko model, it would be premature to consider it adequately evaluated since the small number of patients studied fell into only 7 of 16 possible terminal cells of the cascade.

Concentration-Based Methods—Vozeh et al.[31] and Anderson et al.[32] have previously evaluated the method of Chiou. The former studied 15 acutely ill asthmatics, used an interval of 4 h, and assayed samples within the same run using an HPLC assay with an intrarun CV of <2%. They claimed the 95% confidence interval (CI) for predicted C_{ss} would range from 13.0 to 19.8 mg/L when 15.0 mg/L was selected as a target. This is equivalent to a 95% CI of 10.8 to 16.5 mg/L for a target of 12.5 mg/L.

Anderson et al.[32] studied 19 patients using an interval of 4–15 h and an EMIT or HPLC assay each having an intrarun CV of <5.7%. Whether samples were assayed within the same run was not stated. They estimated that C_{ss} would have ranged from ~4 to 20 mg/L in their patients if 14 mg/L had been chosen as the target. This is equivalent to a range of 3.3 to 16.7 mg/L with a target of 12.5 mg/L. Their data demonstrated a tendency to overpredict high values of *CL* and to underpredict low values of *CL*.

In the present study, the algebraic approach of Chiou did not perform as well as Vozeh et al.[31] suggested even with the 0,12 h ESR data (Table V). This may be related to the assay since Vozeh et al.[31] showed that prediction of C_{ss} was better with a highly reproducible HPLC assay compared to EMIT. Since EMIT has become the most prevalent clinical assay for measuring serum theophylline in the U.S.,[33] our findings may better reflect the current clinical situation. We conclude that a 3–5 h interval between samples is not sufficiently long for general application of the Chiou equation.

Our results for the method of Chiou were similar to those of Anderson et al.[32] when a 6-h interval was used and somewhat better when a 12-h interval was considered. We did not, however, observe any association between overestimation or underestimation of *CL* and the magnitude of *CL*.

The Bayesian method appeared to perform slightly better than the method of Chiou in the stable patients we studied. However, since the choice of a prior model is crucial to the performance of the Bayesian method, caution should be duly exercised when using such approaches in patient populations for whom prior models have not been developed or fully evaluated.

Certain crucial recommendations regarding the successful implementation of either concentration based method should be emphasized:

1. An accurate assay method must be employed in a competent laboratory.
2. A constant infusion for Chiou or an accurate infusion record for Bayesian least squares must be ensured throughout the period of serum concentration sampling.
3. A longer interval between the two samples is better than a shorter interval where other factors are equivalent. Based on the work of D'Argenio and Khakmahd,[29] the interval should be at least 1–1.5 theophylline half-lives long. Incorporating their results with our own, we recommend an interval of 8–12 h in stable, adult patients. In children a shorter interval may be feasible.
4. Caution should be exercised if these methods are used in patients likely to exhibit changes in their theophylline *CL* during acute treatment. This includes patients in whom erythromycin, cimetidine, or phenytoin have recently been initiated[27] and patients with certain disease states such as acute congestive heart failure or pneumonia.[9] Sepsis and severe malnutrition may also be conditions where *CL*s are likely to be unstable.
5. Caution should likewide be observed in patients whose

half-lives are expected to be prolonged beyond 12 h since a longer interval may be necessary. This includes patients with liver cirrhosis and acute congestive heart failure.

6. Measurement of both concentrations should be done within a single assay run whenever possible, although this appears less critical than using an adequate interval length.

In stable, uncomplicated, adult patients, we recommend that serum samples for theophylline measurement be obtained soon after initiating intravenous aminophylline and 8–12 h later. If the result of the first sample is not immediately needed, it may be submitted to the laboratory with the second to ensure that both specimens are assayed within the same run. In addition, an assay with accuracy comparable to or better than EMIT should be available. Constant infusion of intravenous aminophylline between the two samples is essential to the utilization of the Chiou method. However, this is not necessary when using Bayesian nonlinear regression.[15,16] Subsequent evaluation of such data with either of the concentration-based approaches will allow safer and more rapid adjustment of dosage to attain therapeutic serum concentrations.

References and Notes

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