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The Population Pharmacokinetics of Theophylline in Neonates and Young Infants

Emory S. Moore,[1] Roger G. Faix,[2] Raul C. Banagale,[3] and Thaddeus H. Grasela[4,5]

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The population pharmacokinetics of theophylline were evaluated using 391 theophylline serum concentration measurements from 108 neonates and young infants (postnatal age 0–26 weeks), who received theophylline for the treatment of neonatal apnea. A one-compartment pharmacokinetic model with first-order elimination was used, with intravenous aminophylline and oral theophylline administration modeled as zero-order infusions. The effect of a variety of developmental and demographic factors on clearance (CL) and volume (V) were investigated. Hypothesis testing to evaluate potentially significant factors produced a final model in which clearance was based on weight (kg) raised to an exponential power and postnatal age (weeks), with CL (ml/hr) = 17.5 (weight)$^{1.28}$ + 1.17 (postnatal age). Clearance was reduced by 12% for patients receiving parenteral nutrition. Volume of distribution in this population was adequately described using only weight, with V (L) = 0.858 L/kg. Bioavailability of orally administered drug was not significantly less than unity. Interindividual variability in clearance was modest, with a coefficient of variation for clearance of 16%. An estimate of interindividual variability in volume could not be obtained. As a measure of residual variability in theophylline serum concentrations, the coefficients of variation for theophylline serum concentrations of 5.0, 10.0, and 13.0 mg/L were found to be approximately, 25, 12, and 9%, respectively. The identification of influential patient factors and the quantification of their influence on theophylline disposition allow for a priori *estimates of theophylline pharmacokinetic parameters in these patients.*

KEY WORDS: theophylline; population analysis; methylxanthines; neonatal apnea; kinetics; NONMEM.

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[1]College of Pharmacy, The University of Texas at Austin, Austin, Texas 78712.
[2]Department of Pediatrics-Newborn Services, The University of Michigan Medical Center, Ann Arbor, Michigan 48109.
[3]Apnea and SIDS Program, Emanuel Hospital and Health Center, Portland, Oregon 97227.
[4]Pharmacoepidemiology Research Center, State University of New York at Buffalo, Schools of Pharmacy and Medicine, Amherst, New York.
[5]To whom correspondence should be addressed.

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INTRODUCTION

Neonatal apnea is observed in approximately 25% of newborns with birth weights less than 2.5 kg (1). Apneic episodes are often associated with hypoxia and bradycardia, and are considered a significant factor for morbidity and mortality in this patient population (2). Current approaches to management of neonatal apnea include appropriate treatment of predisposing conditions and administration of theophylline or caffeine (3-5).

The range of effective theophylline serum concentrations for the treatment of neonatal apnea is relatively narrow and generally accepted to be between 5 and 15 μg/mL (6). Signs and symptoms of minor theophylline toxicity have been observed at the higher concentrations with more serious central nervous system and cardiac toxicity appearing as serum concentrations exceed 20 μg/mL (7,8). The relatively narrow therapeutic window for theophylline in the treatment of neonatal apnea and the serious side effects associated with elevated theophylline serum concentrations in this population have prompted interest in designing dosing regimens to achieve optimal therapeutic serum concentrations.

Several studies have been performed to determine the pharmacokinetics of theophylline in the neonate and young infant for use in dosing regimen design. However, ethical issues of drug research in this group, e.g., risks associated with multiple phlebotomies and problems concerning informed consent, have limited the scope of these studies. Table I lists the details of major pharmacokinetic studies of theophylline in the newborn (9-17). These studies suggest that clearance in the newborn is much lower than in adults, particularly in the very premature neonate, while the volume of distribution tends to be higher in neonates than in adults. These studies also suggest a substantial degree of unexplained interindividual variability in theophylline pharmacokinetics, particularly with regard to clearance.

Unfortunately, the large degree of variability in theophylline pharmacokinetics observed makes it difficult to predict *a priori* the optimal dosing regimen for an individual neonate. In particular, one would like to have an understanding of the influence of developmental factors (such as weight, postnatal age, etc.) and frequently observed patient variables on theophylline disposition (18,19). Sheiner *et al.* (20) have proposed a method for estimating pharmacokinetic parameters and the influence of patient variables on these parameters utilizing routinely available clinical data. The use of this approach in the neonatal population is particularly attractive since it does not require the patient to undergo the rigors of a traditional experimental protocol. This paper describes the results obtained by using this approach to analyze data collected from neonates and young infants receiving theophylline for the prevention or treatment of neonatal apnea.

Table I. Results of Traditional Theophylline Pharmacokinetic Studies in the Newborn and Young Infant

Author	Year	No. of subjects	Mean postnatal age in weeks (range)	Mean clearance in ml/hr per kg (range)	Mean volume of distribution in L/kg (range)
1. Aranda *et al.* (9)	1976	6	~1.0 {0.4–2.1}	17.6 {12.1–25.9}	0.7 {0.4–1.1}
2. Lattini *et al.* (11)	1978	7	1.0 {0.6–1.1}	12.9 {6.3–29.9}	0.4 {0.2–1.0}
3. Brazier *et al.* (12)	1979	20	2.6 {~1–5.5}	24.0 {SD = 5.1}	1.0 {SD = 0.2}
4. Jones and Baillie (13)	1979	11	~3.0 {0–5.6}	18.6 {12.3–27.9}	0.7 {0.4–1.2}
5. Giacoia *et al.* (10)	1976	8	5.9 {3.6–8.1}	39.0 {22.6–68.3}	1.1 {0.7–2.9}
6. Hilligoss *et al.* (14)	1980	17	7.1 {~3–10}	22.9 {15.5–29.5}	0.6 {0.4–0.9}
7. Nassif *et al.* (15)	1981	4	~15.0 {10–20}	26.4 {17.4–34}	0.5
8. Lonnerholm *et al.* (16)	1983	3	~1.2 {0.9–1.6}	16.8 {SD = 0.7}	—
			~5.0 {5–5.4}	22.9 {SD = 2.3}	—
			~9.5 {9.1–9.9}	30.9 {SD = 4.3}	—
9. Gilman *et al.* (17)	1986	73[a]	2.3 {SD = 1.9}	16.4 {SD = 5.3}	0.78 {SD = 0.16}
		106[b]	1.7 {SD = 1.3}	20.2 {SD = 5.4}	0.76 {SD = 0.17}

[a] Newborns with birth asphyxia.
[b] Newborns without birth asphyxia.

METHODS

Patients

Between 1982 and 1985, routine clinical data from 108 neonates and young infants receiving theophylline in the University of Michigan Hospital's Holden Neonatal Intensive Care Unit, and subsequently seen as outpatients in the Pediatric Clinic, were collected by a clinical pharmacokineticist providing a pharmacokinetic consult service. All patients less than 6 months of age who received theophylline for the prevention or treatment of neonatal apnea and had theophylline serum concentrations measured were eligible for inclusion in this study.

Table II. Patient Demographic Data

Theophylline serum concentrations measurements	
Total no.	391
Mean concentration (range)	7.0 (0.7-16.3)
No. of patients	108
No. of levels per patient	
Mean (range)	3.6 (1-12)
Birth weight (kg)	
Mean (range)	1.5 (0.6-4.2)
Gestational age (weeks)[a]	
Mean (range)	31 (24-42)
Weight at last theophylline level (kg)	
Mean (range)	3.8 (0.8-7.6)
Postnatal age at last theophylline level (weeks)	
Mean (range)	8.4 (0.5-26)

Incidence of patient variables	*n*	% patients	% TCM's[b]
Gender			
Male	58	54	53
Female	50	46	47
Maternal smoking history			
Positive	35	33	33
Negative	36	33	35
Indeterminate	37	34	32
Incidence of birth asphyxia	54	50	54
Incidence of phenobarbital administration during study period	29	27	14
Nutrition source[c]			
Parenteral nutrition	43	40	25
Breast milk	32	30	20
Formula	67	62	55

[a] As determined by the Ballard *et al.* method (21).
[b] Percentage of total number of theophylline serum concentration measurements available where a particular variable was present.
[c] Patients may have received multiple sources of nutrition during the study. Nutrition source dictated by major source of nutrition at each theophylline dose.

The data collected for this study included the theophylline dosing history as recorded in the nursing drug administration record for inpatients or as recorded by the patient's parent on a outpatient basis, the time of blood sampling for theophylline concentrations, and measured theophylline serum concentrations. Daily weights were recorded, but because of the difficulty encountered in obtaining accurate and reproducible heights in these patients, height data were not included. Table II describes the demographic characteristics of the patient population studied.

All blood samples for determination of serum theophylline concentrations were obtained as part of routine monitoring of theophylline therapy, and were not dictated by study protocol. Blood samples were typically obtained shortly before a dose, and the method of sampling (umbilical catheter, heel stick, or venipuncture) was determined by the nurse at the time of phlebotomy. No record of sampling method was maintained. Theophylline serum concentrations were determined by the hospital's Drug Analysis Laboratory using HPLC (22). The coefficient of variation associated with this assay was approximately 4% over the range of theophylline concentrations observed in this study. The study protocol was approved by the Human Use Committee of the University of Michigan Hospitals.

Pharmacokinetic Model

The concentration time course of theophylline was described using a one-compartment model with first-order elimination. Previous studies of theophylline disposition have shown that theophylline pharmacokinetics are adequately described using this model when serum concentrations are below 20 μg/ml (6,23). Oral administration of theophylline syrup and intravenous infusions of aminophylline were modeled as zero-order input. Drug absorption following oral administration was assumed to peak at 1 hr postdose. Explicit modeling of the absorption process following oral administration was not possible due to a lack of theophylline serum concentrations obtained during the absorption phase. Intravenous doses were administered by a retrograde technique, and drug delivery was assumed to be constant over a 20-min period (24).

The pharmacokinetic model was written in a recursive form as described previously (20). The recursive model for non-steady-state dosing is

$$\hat{C}_{ij} = \frac{F_{ij} \cdot S_{ij} \cdot Dose_{ij}/TP_{ij}}{CL_{ij}} \cdot [1 - \exp\{-(CL_{ij}/V_{ij}) \cdot TP_{ij}\}] \times \exp[-(CL_{ij}/V_{ij}) \cdot (\Delta t - TP_{ij})] + \hat{C}_{i-1,j} \times \exp[-(CL_{ij}/V_{ij}) \cdot \Delta t] \quad (1)$$

where $\hat{C}_{ij}$ is the i^{th} serum concentration of theophylline predicted in the

j^{th} individual at time t_i, $\hat{C}_{i-1,j}$ is the previously predicted serum concentration at time $t_{i-1}(t_i > t_{i-1})$, and Δt is equal to $t_i - t_{i-1}$. F_{ij} is bioavailability for the i^{th} dosage form administered to the j^{th} patient, equalling unity for parenteral doses and calculated as a regression parameter for oral doses. S_{ij} is the salt factor for the i^{th} dosage form in the j^{th} patient, equalling 0.85 for aminophylline doses and unity for theophylline doses. $Dose_{ij}$ is the amount of the i^{th} dose (mg) in the j^{th} patient, TP_{ij} is the time to peak following the i^{th} oral dose or the duration of the infusion for the i^{th} intravenous dose in the j^{th} patient, with a value of 1.0 and 0.33 hr, respectively. Individuals may have received oral and/or intravenous dosing during the course of theophylline therapy. CL_{ij} and V_{ij} are the i^{th} total clearance and volume of distribution for theophylline in the j^{th} individual. Using the recursive form of the model, the solution is updated for each successive event (dose or calculation of theophylline serum concentration) in chronological order using the currently predicted values for $\widehat{CL}_{ij}$ and $\hat{V}_{ij}$.

Patients receiving a constant dosing regimen (dosage and dosing interval) for 4 days or longer were assumed to be at a steady state condition, and the pharmacokinetic model was modified so that the serum concentration of theophylline ($\hat{C}ss_{ij}$) obtained at time t_i during a steady state dosing regimen was calculated as

$$\hat{C}ss_{ij} = \frac{[F_{ij} \cdot S_{ij} \cdot (Dose_{ij}/TP_{ij})/CL_{ij}] \cdot [1 - \exp\{-(CL_{ij}/V_{ij}) \cdot TP_{ij}\}]}{[1 - \exp\{-(\widehat{CL}_{ij}/\hat{V}_{ij}) \cdot \tau_{ij}\}]} \times \exp[-(CL_{ij}/V_{ij}) \cdot (t_{ij} - TP_{ij})] \quad (2)$$

where F_{ij}, $S_{ij}Dose_{ij}$, TP_{ij}, CL_{ij}, V_{ij}, and t_{ij} are as defined above, and τ_{ij} is the steady state dosing interval (hr) for the i^{th} steady-state dose in the j^{th} patient.

Initial Regression Models for Clearance and Volume

In the initial regression model, clearance was based on the patient's weight raised to an exponential factor, and was modeled to increase in an additive fashion with increasing postnatal age, as suggested by Lonnerham *et al.* (16). The effects of other patient variables on clearance were also included in the model as seen in Eq. (3). Because the data were composed of primarily steady state concentrations, with relatively little information regarding volume of distribution, only the effect of patient weight and postnatal age on volume were explored as seen in Eq. (4).

$$\widehat{CL}_{ij} = (\theta^{cl}_{w,1} \cdot WT_{ij}^{\theta^{cl}_{w,2}} + \theta^{cl}_{a} \cdot AGE_{ij}) \cdot \theta_{\text{parenteral nutrition}} \times \theta_{\text{breast milk}} \cdot \theta_{\text{phenobarbital}} \cdot \theta_{\text{female gender}} \cdot \theta_{\text{low gestational age}} \times \theta_{\text{asphyxia}} \cdot \theta_{\text{maternal smoking}} \cdot \theta_{\text{compliance}} \quad (3)$$

Table III. Criteria for Regression Formula Factors

Factor	Criteria
$\theta_{\text{parenteral nutrition}}$	Current primary source of patient's nutrition is parenteral nutrition.
$\theta_{\text{breast milk}}$	Current primary source of patient's nutrition is breast milk.
$\theta_{\text{phenobarbital}}$	Patient must be currently receiving phenobarbital, or have received phenobarbital in the past 5 days.
$\theta_{\text{female gender}}$	Patient must be female.
$\theta_{\text{low gestational age}}$	Patient must have a gestational age of $\leq$30 weeks.
θ_{asphyxia}	Patient must have at least one of the following: (i) Frank cyanosis at birth requiring emergent intubation; (ii) first arterial blood *p*H of $\leq$7.2; (iii) a 1- or 5-minute Apgar score of $\leq$3.
$\theta_{\text{maternal smoking}}$	Patient is born to mother with a documented positive smoking history.
$\theta_{\text{compliance}}$	Patient must currently be an outpatient.

$$\hat{V}_{ij} = \theta^{v}_{w,1} \cdot WT_{ij}^{\theta^{v}_{w,2}} + \theta^{v}_{a} \cdot AGE_{ij} \tag{4}$$

where $\widehat{CL}_{ij}$ and $\hat{V}_{ij}$ represent the i^{th} predicted theophylline clearance (mL/hr) and volume of distribution (L) for the j^{th} individual. The θ^{cl}'s and θ^{v}'s are computed regression parameters relating the j^{th} patient's weight in kilograms (WT_{ij}) and postnatal age in weeks (AGE_{ij}) at the time of a theophylline dose or sampling for a theophylline serum concentration to the predicted theophylline clearance and volume, respectively. The remaining θ's represent the fractional increase or decrease in theophylline clearance associated with the presence of various patient variables. When a variable is absent in an individual, the θ is assigned a value of 1. In 34% of patients, the maternal smoking history could not be ascertained. In these cases the data were fit twice: once by assuming the patients were born to nonsmoking mothers and once by including only those patients with a known positive or negative exposure. The criteria for these variables are given in Table III.

Statistical Model

The persistent random individual deviations in clearance and volume from the values predicted by the regression formulas were modeled using Eqs. (5) and (6), respectively.

$$\ln CL_{ij} = \ln \widehat{CL}_{ij} + \eta^{cl}_{j} \tag{5}$$

$$\ln V_{ij} = \ln \hat{V}_{ij} + \eta^{v}_{j} \tag{6}$$

where $\ln \widehat{CL}_{ij}$ and $\ln \hat{V}_{ij}$ are the natural logarithm of the values of clearance and volume predicted for the j^{th} individual by Eqs. (3) and (4), $\ln CL_{ij}$ and $\ln V_{ij}$ are the natural logarithms of the j^{th} individual's (unknown) true pharmacokinetic parameters, the ones used in equations (1) and (2), and η^{cl}_{j} and η^{v}_{j} are normally distributed random errors that represent the

difference between the j^{th} patient's true parameters and the values predicted by the regression models. The η_j^{cl} and η_j^{v} are assumed to be independent, identically distributed statistical errors with mean zero and variances ω_{cl}^2 and ω_v^2, respectively. The variances of η_j^{cl} and η_j^{v} across the patient population are the population variances of the "true" clearance and volume about their respective predicted values (20). The use of Eqs. (5) and (6) to model the variance of clearance and volume implies that the interindividual variability increases with increasing clearance and volume. Also, when ω^2 is small, the square root of the variance of clearance and volume approximates the coefficients of variation of the respective parameter (25).

Residual variability, describing the random deviation of the i^{th} observed theophylline concentration in the j^{th} individual from the "true" concentration given by Eq. (1) or (2), was modeled as

$$C_{ij} = \hat{C}_{ij} + \varepsilon_{ij}, \tag{7}$$

where C_{ij} is the i^{th} measured theophylline concentration in the j^{th} patient and $\hat{C}_{ij}$ is the corresponding theophylline serum concentration from Eq. (1) or (2), as appropriate. The ε_{ij} are assumed to be independent, identically distributed statistical errors with mean of zero. The variance for ε_{ij}, σ_{ij}^2, was modeled as

$$\sigma_{ij}^2 = \theta_{\varepsilon 1}^2 + \theta_{\varepsilon 2}^2 \cdot \hat{C}_{ij}^2 \tag{8}$$

where $\theta_{\varepsilon 1}$ and $\theta_{\varepsilon 2}$ are freely estimated variables relating the variance of ε_{ij}, σ_{ij}^2, to the squared predicted theophylline serum concentration, $\hat{C}_{ij}^2$. The use of this model for σ_{ij}^2 allowed for hypothesis testing regarding the nature of this error. In this way, a proportional error model ($\theta_{\varepsilon 1}$ fixed to 0) could be compared to an additive error model ($\theta_{\varepsilon 2}$ fixed to 0). In the evaluation of the initial regression models for clearance and volume, the general form of the model for σ_{ij}^2, as described by Eq. (8) was employed.

Data Analysis

Data analysis was performed using version II, level I of the NONMEM program and the PREDPP package (ADVAN 1, TRANS 2, SS 1) (25,26). Estimates of the coefficients (θ) of the regression formulas, the components of σ^2 ($\theta_{\varepsilon 1}^2$ and $\theta_{\varepsilon 2}^2$), ω_{cl}^2, ω_v^2, and their 95% confidence intervals were sought.

Evaluating Improvement in Fit

In fitting the data, NONMEM computes the value of a statistic, the minimum value of the objective function, which is proportional to minus

twice the log likelihood of the data. In preliminary evaluations of various demographic factors and patient variables in the initial regression model, objective function values were used to evaluate the increase in goodness of fit upon inclusion of each parameter. The difference in objective function values obtained by comparing a restricted model in which a parameter's value is fixed to the null hypothesis value, and a nonrestricted model in which the parameter's value is freely estimated, is asymptotically distributed as chi-square with 1 degree of freedom (27). In order to identify potentially significant factors, a change in objective function of >3.8, associated with a p value of ≤ 0.05 was required. Factors that were determined to have a potentially significant effect were then included in an intermediate model for further hypothesis testing.

In the evaluation of the intermediate regression model, the objective function values were used to evaluate the decrease in goodness of fit obtained upon independent deletion of each parameter. This was achieved by alternately fixing (restricting) each parameter value to the null hypothesis value. Because of the multiple tests performed in this analysis, we required a change in objective function of >7.9, associated with a p value of ≤ 0.005, to indicate statistical significance. The final model included only those parameters that proved significant using this more rigorous criterion. An overall test of the candidate for the final model was then made by comparing its objective function value with that of the intermediate model in which all parameters were freely estimated. The difference in the objective function values is approximately distributed as chi-square with degrees of freedom equal to the difference in the number of parameters between the two models.

In testing models where one model was not merely a subset of the other, e.g., a comparison of the effect of modeling volume with or without weight, strict application of the likelihood ratio test was deemed inappropriate. In this case, the difference in objective functions was evaluated and it was assumed that a difference, similar in magnitude to that observed during testing of highly significant factors in restricted models, i.e., >7.9, indicated that one model was potentially superior to another.

RESULTS

The preliminary analyses using the initial regression models for clearance indicated that gender, low gestational age, birth asphyxia, and maternal smoking were not associated with a significant effect on clearance ($p > 0.05$). Moreover, patient compliance in the outpatient setting appears equivalent to compliance during inpatient care, given the lack of difference in clearance between the two settings in neonates of equivalent age and size. With regard to the apparent volume of distribution of theophylline, neither postnatal

age nor the exponential function for volume were associated with a significant effect ($p > 0.05$). The bioavailability of orally administered theophylline was not significantly less than unity ($p > 0.05$). All of these evaluations were associated with a log likelihood difference of <3.8.

As a result of the preliminary analyses, the intermediate model for theophylline clearance was based on patient weight raised to a power, with factors for patients receiving parenteral nutrition, breast milk feedings, and phenobarbital administration retained. The intermediate model for volume of distribution was based only on patient weight. As seen from Tables IV and V, hypothesis testing of these intermediate models supported a final model in which theophylline clearance is based on patient weight raised to a power, with a factor for patients receiving parenteral nutrition; volume of distribution is adequately modeled using a linear function of patient weight. The final regression formulas for clearance (ml/hr) and volume of

Table IV. Results of Hypotheses Testing of Intermediate Model

Question addressed	Hypothesized value of parameter	Log likelihood difference	p	Conclusion
Clearance				
Does the use of a linear relationship between weight and clearance influence clearance?	$\theta^{cl}_{w,1} = 0$	276.9	$\ll 0.0005$	Yes
Does the use of an exponential relationship between weight and clearance influence clearance?	$\theta^{cl}_{w,2} = 0$	40.1	<0.0005	Yes
Does postnatal age influence clearance?	$\theta^{cl}_{a} = 0$	30.9	<0.0005	Yes
Do parenteral nutrition feedings influence clearance?	$\theta_{\text{parenteral nutrition}} = 1$	21.4	<0.0005	Yes
Do breast milk feedings influence clearance?	$\theta_{\text{breast milk}} = 1$	6.3	>0.01	No
Does short-term phenobarbital administration influence clearance?	$\theta_{\text{phenobarbital}} = 1$	5.5	>0.01	No
Residual variability				
Is the intercept term important in modeling residual variability?	$\theta_{\varepsilon_1} = 0$	16.3	<0.0005	Yes
Is the slope term important in modeling residual variability?	$\theta_{\varepsilon_2} = 0$	<1	>0.30	No

Table V. Results of Hypotheses Testing for Nonrestricted Models

Question addressed	Log likelihood difference	Answer
Is a model without an effect of weight on volume as good as a model which uses weight?	74.2	Probably not
Is a model that uses postconceptional age as an age-related factor influencing CL as good as the intermediate model in which postnatal age is used?	24.3	Probably not

distribution (L) are giving by Eqs. (10) and (11).

$$\widehat{CL}_{ij} = (\theta^{cl}_{w,1} \cdot WT_{ij}^{\theta^{cl}_{w,2}} + \theta^{cl}_{a} \cdot AGE_{ij}) \cdot \theta_{\text{parenteral nutrition}} \tag{10}$$

$$\hat{V}_{ij} = \theta^{v}_{w,1} \cdot WT_{ij} \tag{11}$$

The final estimates (with 95% confidence intervals shown in parentheses) of the regression coefficients provided by the NONMEM analysis were:

$$\theta^{cl}_{w,1} = 17.5 \quad (15.5\text{–}19.5) \quad \text{ml/hr per kg}$$

$$\theta^{cl}_{w,2} = 1.28 \quad (1.18\text{–}1.38) \quad \text{(an exponential term)}$$

$$\theta^{cl}_{a} = 1.17 \quad (0.643\text{–}1.70) \quad \text{ml/hr per week}$$

$$\theta_{\text{parenteral nutrition}} = 0.879 \quad (0.816\text{–}0.942) \quad \text{(fractional decrease)}$$

$$\theta^{v}_{w,1} = 0.858 \quad (0.793\text{–}0.923) \quad \text{L/kg}$$

Under the final regression formula and parameter estimates described above, the estimate of the coefficient of variation for interindividual variability in clearance was 16%, with a 95% confidence interval of 10.4–20.1%. The estimate of the coefficient of variation for volume was insignificantly small suggesting that all observed interindividual variability is adequately explained by the model for interindividual variability in clearance.

An evaluation of the model for residual variability [see Eq. (8)], performed once the final regression models were determined, suggested that residual variability was adequately described with a simple additive error model. This additive error model for residual variability yields a standard deviation of 1.24 μg/ml, with a 95% confidence interval of 1.16–1.31 μg/ml. Thus, the coefficient of variation for residual variability in theophylline serum concentrations of 5.0, 10.0, and 13.0 μg/ml would be approximately 25, 12, and 9%, respectively.

In a final check of the overall acceptability of the final regression model described in Eqs. (9) and (10), these formulas were compared with the

initial fully defined models for clearance, volume, and residual variability. In performing this hypothesis test, all parameters in the initial models were freely estimated and the following factors were then fixed to their null hypothesis values: θ_{gender}, $\theta_{\text{low gestational age}}$, θ_{asphyxia}, $\theta_{\text{maternal smoking}}$, $\theta_{\text{breast milk}}$, $\theta_{\text{phenobarbital}}$, $\theta_{\text{compliance}}$ from the equation for clearance [Eq. (3)]; θ_a^v and $\theta_{w,2}^v$ from the equation for volume [Eq. (4)]; and $\theta_{\varepsilon 2}$ from the equation for residual variability [Eq. (8)]. The log likelihood difference for these two fits was 12.7, $p > 0.2$, χ^2 distribution with 10 degrees of freedom.

DISCUSSION

It is not surprising that the most important variables for predicting theophylline clearance in this patient population are weight and postnatal age. Each of these factors is related to the stage of development of the newborn and thus, the degree of functional activity of drug-eliminating organ systems (9). The final regression model for clearance suggests that the rate of theophylline clearance increases disproportionately with increasing weight. Moreover, the further improvement in fit obtained upon the inclusion of postnatal age in the model for theophylline clearance indicates that an older newborn is expected to have a higher rate of clearance than a younger newborn of equal weight.

Other researchers have attempted to provide insight into predicting theophylline clearances in this population by investigating the correlation of various developmental factors with clearance. The majority of published studies appear to support the results reported herein. Nassif *et al.* (15) showed good correlation between increasing postnatal age and increasing theophylline dosage requirement. Lonnerholm *et al.* (16) showed that theophylline clearance (ml/hr per kg) appeared to increase linearly with postnatal age. Gilman *et al.* (17) found that among body weight, postnatal age, postconceptional age, and duration of theophylline therapy, postnatal age was the most important determinant in theophylline clearance. Bada *et al.* (28) documented higher theophylline concentrations in newborns with gestational ages less than 30 weeks relative to more mature babies on equivalent mg/kg theophylline doses.

The strong relationship observed between indices of maturation (such as weight and postnatal age) and clearance suggest that similar factors such as gestational age should also be important predictors of theophylline clearance. The results of this analysis suggest that theophylline clearance is adequately described using weight to an exponential power and postnatal age, regardless of gestational age. Other investigators have also failed to show an influence of gestational age on theophylline clearance (16,19). It

should be pointed out, however, that there is a high degree of linear correlation between gestational age and birth weight in the neonate (Pearson's correlation coefficient equals 0.72 in our population). Thus, the inclusion of weight in our final clearance model captured any differences in theophylline clearance in the low gestational age neonate. Finally, though postconceptional age has been used to estimate clearance in other studies (29), it did not perform as well as postnatal age in our model for theophylline clearance.

In addition to the factors of weight and postnatal age, the only factor having a statistically significant influence on the rate of theophylline clearance in our population was concomitant parenteral nutrition (PN) administration. Patients receiving PN had a mean theophylline clearance that was 12% lower than those receiving breast milk or oral formula. This decrease in theophylline clearance might be expected since high glucose intake has been noted to inhibit drug metabolism in animals (30) and the administration of PN has been associated with hepatic dysfunction in the newborn (31). In a study of the effects of PN on theophylline disposition in a group of 17 premature infants, Hilligoss *et al.* (14) found that the rates of theophylline clearance in five patients receiving PN (~17–25 ml/hr per kg) were generally similar to clearance rates observed in 12 young infants not receiving PN (~16–30 ml/hr per kg). Interestingly, the gestational age and birth weight were significantly lower in the group receiving PN, but additional demographic information for the two groups (e.g., postnatal age and current weight) was not reported. A graph of individually determined theophylline clearance values (ml/hr per m^2) versus duration of therapy included in the publication suggests that among patients who received theophylline for a similar duration, those who received PN tended to have lower rates of clearance.

In our study population, PN was typically administered in the early weeks of life to the more premature newborns. Because the clinical course of such patients is often more complicated than that of more mature newborns, it is unclear whether the administration of PN itself or the typical clinical status of study patients receiving PN resulted in the observed decreased rate of theophylline clearance. In order to explore this further, we compared theophylline clearance in patients who had previously received PN, but who were currently receiving enteral feedings, with patients who had never received PN. Interestingly, once PN administration was discontinued, the estimated theophylline clearance in these patients when adjusted for age and weight did not differ from the estimated clearance for patients who had never received PN. These findings imply that it is only during the time of PN administration, or concurrent with the clinical situation common to patients receiving PN, that theophylline clearance is altered. It should

be noted that all of our PN patients were less than 16 weeks postnatal age. As such, the impact of PN on theophylline clearance in patients beyond this age could not be assessed.

Oral formula was the primary source of nutrition in the majority of these patients. However, for 30% of the study patients, breast milk (typically supplemented with oral formula) was the major source of nutrition at some time during the study period. Although extreme variations in diet protein content have been reported to alter theophylline clearance (32), the change in theophylline clearance in patients who received low-protein breast milk feedings (with or without formula supplementation) did not differ significantly ($p > 0.01$) from the estimate of clearance in patients who received only oral formula.

One of the unique aspects of this analysis was our ability to investigate the effects of two known inducers of drug metabolism, cigarette smoking and phenobarbital, on theophylline metabolism in a neonatal population. Although maternal cigarette smoking during pregnancy has been associated with placental changes and adverse fetal effects, there is no information concerning the distribution of polyaromatic hydrocarbons or other substances from cigarette smoking into animal or human fetal circulation and their subsequent effect on fetal drug metabolism. Although smoking can markedly increase theophylline clearance in adults (18,33–35), it appears that neonates whose mothers smoked during pregnancy do not have theophylline clearances significantly different than the values for neonates born to nonsmokers. This effect was further evaluated by performing an analysis that limited the effect of smoking on theophylline clearance to the first 2 or first 4 weeks of life. In both cases there did not appear to be a difference in the estimated theophylline clearance between neonates born to smokers or non smokers. As stated above, the maternal smoking history could not be ascertained for 34% of the study population. The lack of an effect of smoking on clearance was upheld in an analysis that assumed these patients were born to nonsmoking mothers and in an analysis that excluded these patients from the study population.

Another possible inducer of theophylline clearance frequently used in this population is phenobarbital. Phenobarbital has been documented to induce theophylline metabolism in the adult after administration for at least a month, increasing theophylline clearances by 11 to 60% (36). Several researchers have been unable to show an effect of phenobarbital on theophylline clearance in children (37,38). However, possible induction of bilirubin glucuronidation in premature neonates has been achieved with only 3 to 5 days of phenobarbital administration (39,40). During the study period, 27% of the patients received phenobarbital for approximately 5 days (shortly after birth) as prophylaxis against intraventricular hemorrhage (41).

Phenobarbital serum concentrations at the end of therapy were typically 20 μg/ml. Because the half-life of phenobarbital in this group is prolonged (5 to 6 days) (41), the neonate would have been exposed to significant serum concentrations of phenobarbital for at least a week following the cessation of drug therapy, and the potential effect of phenobarbital was allowed to be present during phenobarbital administration and for a period of 5 days following cessation of phenobarbital therapy. Fourteen percent of the theophylline serum concentrations available for analysis were obtained during this period. The estimated theophylline clearance in this group was slightly increased (12%), and although this increase was not statistically significant ($p > 0.01$), this finding may warrant further study. In order to pursue this further, we allowed an effect for phenobarbital in only those patients who received phenobarbital for more than 2 weeks. The estimated theophylline clearance in this small group of patients ($N = 7$) was also higher (10%) but not significantly different than that of similar patients who never received phenobarbital ($p > 0.20$). The small number of patients precludes any definitive conclusions concerning the effect of long-term phenobarbital administration on theophylline clearance in this newborn population.

In considering the induction of theophylline clearance in neonates, it is important to note that the primary elimination pathways for theophylline in the early postnatal period include renal elimination of unchanged drug, hepatic microsomal methylation to caffeine, and oxidation to 1,3-dimethyl-uric acid probably via the cytochrome P450 system (6). Cytochrome P450 monoxygenase, responsible for the demethylation of theophylline (a major route of metabolism in the adult), appears to be almost absent in the newborn (42). Although phenobarbital is believed to be a nonspecific inducer of the entire P450 system as well as other microsomal enzymes in the adult (41), the results of this analysis were not able to show conclusively that the P450 pathways responsible for theophylline metabolism in the newborn are significantly induced by short-term phenobarbital administration.

One of the patient variables we examined, birth asphyxia, has been previously reported to result in a marked decrease in theophylline clearance. Gal *et al.* (43) originally reported a considerable decrease in theophylline clearance in 15 newborns (with a mean postnatal age of 10 days), in whom the mean theophylline clearance was 46% lower than that observed in nonasphyxiated newborns (10.8 vs. 20.1 ml/hr per kg). In a subsequent multicenter study using similar criteria, Gilman *et al* (17) reported a lesser influence of asphyxia on clearance. Newborns who had experienced birth asphyxia had a mean theophylline clearance that was 19% lower than nonasphyxiated newborns at a mean postnatal age of 14 days (16.4 vs. 20.2 ml/hr per kg). Based on these two studies, it appears that the degree

to which birth asphyxia affects theophylline clearance can be very significant in some groups of patients but may also be quite variable. Despite the use of criteria for defining birth asphyxia that were similar to those of Gal (28) and Gilman (17), we found no significant influence of birth asphyxia on theophylline clearance. It may be important to note, however, that less than 10% of our serum concentration measurements were collected within the first postnatal week, and any short-term change in theophylline disposition in subjects with birth asphyxia may not have been detected.

Although the literature suggests that other patient factors and exposure to interacting medications (either *in utero* or postnatally) may affect theophylline clearance (44), the low incidence of occurrence in our study population precluded a study of their influence. These included *in utero* exposure to maternal medications such as cimetidine, erythromycin, allopurinol, phenytoin, phenobarbital, and ritodrine, postnatal exposure to cimetidine, erythromycin, phenytoin, and furosemide, and renal or hepatic dysfunction in the neonate.

As seen in Fig. 1, theophylline clearances calculated from this study's results [Eq. (9)] for typical patients with postnatal ages of 1-24 weeks appear compatible with the mean clearances reported in traditional pharmacokinetic studies by other researchers for patients of similar age. With theophylline clearances of approximately 30 ml/hr per kg at 24 weeks postnatal age, it appears that the patients in our population (premature with neonatal apnea) have not yet achieved the theophylline clearance values of 75-100 ml/hr per kg observed in asthmatic infants and young children (45).

Compared with other drugs and other patient populations, it is surprising that the estimate of the coefficient of variation for interindividual variability in theophylline clearance expressed as the coefficient of variation of clearance was only 16%, with a 95% confidence interval of 10.4 to 20.1%. These findings suggest that our final model was able to account for the majority of sources of interindividual variability in theophylline clearance in neonates and young infants. This is a much smaller degree of variability than observed in other newborn studies, and markedly different than the amount of variability observed in populations of older children and adults.

It should be noted that because of logistical difficulties, many of the previously published studies in newborn patients have employed a traditional approach to pharmacokinetic analysis to obtain individual estimates of pharmacokinetic parameters from limited theophylline serum concentration determinations. The error that arises in estimating these parameters will add to the biologic variability and result in an inflated estimate of the magnitude of interindividual variability. With respect to older children and adults our findings underscore the importance of dietary, environmental,

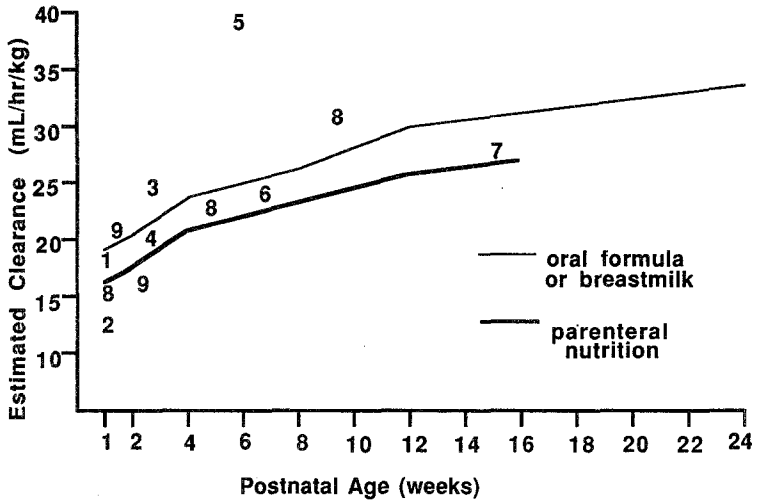

Fig. 1. This graph depicts predicted theophylline clearances for typical patients receiving formula and/or breast milk feedings, or receiving parenteral nutrition. It illustrates the relationship between theophylline clearance (ml/hr per kg) and increasing postnatal age in our study population. The curves were constructed from estimates of theophylline clearance (ml/hr per kg) based on weight and age as modeled by the final clearance regression formulas. At postnatal ages of 1, 2, 4, 8, 12, 16, 20, and 24 weeks, hypothetical patients (representative of our study population) were assigned body weights of 1.0, 1.0, 1.5, 2.0, 3.5, 4.0, 4.5, and 5.0 kg, respectively. Mean clearance values for theophylline from several traditional pharmacokinetic studies are similarly plotted (numbers correspond to 1-9 listing of refs. 9-17 in Table I) for comparison.

and genetic factors in generating the large degree of variability in theophylline disposition observed across these patient populations.

The estimate of the population mean volume of distribution of theophylline (0.856 L/kg) is similar to the range of values found by others (see Table I). As with previous analyses of predominantly steady state serum concentrations, we were unable to obtain an estimate of the magnitude of interindividual variability in volume of distribution (46). Much of the data for this analysis consist of trough theophylline levels at steady state and contains little information regarding volume of distribution. A more diverse data set with additional non-steady-state theophylline concentrations, concentrations following loading doses, and peak concentrations would have permitted differentiation between these two sources of variability.

Seventy-two percent of this study's theophylline serum concentration measurements were collected during oral dosing regimens. Although oral theophylline solution is reported to be highly bioavailable in adults (47), very little is known regarding the oral absorption of theophylline in this

population. In this analysis, bioavailability of oral drug was not significantly different than parenteral drug, although further study may be warranted.

At a mean theophylline serum concentration of 7 μg/ml observed in this study, the estimate of the coefficient of variation for residual variability is approximately 17%. This suggests a relatively low amount of intra-individual variability in clearance. This is particularly noteworthy since the typical patient in this study was followed for almost 4 weeks and had approximately four theophylline serum concentrations measured.

CONCLUSION

Although the variability of theophylline pharmacokinetics in neonates and young infants is small relative to that seen in children and adults, it appears that some of the observed variability in clearance can be accounted for by the consideration of other patient factors beyond simply patient weight. By modeling clearance with weight (exponentially) and postnatal age, and including a factor for patients receiving parenteral nutrition, reasonable *a priori* estimates of theophylline clearance may be obtained. Clinical application of these findings to patient care may allow for a more accurate initial estimate of a neonate's theophylline clearance and for the selection of an appropriate initial maintenance dose, thus enabling the clinician to achieve a desired serum concentration and a desired therapeutic effect.

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