$$C_{ij} = C'_{ij}(1 + \varepsilon_{ij}) \quad (2)$$

where C_{ij} is the ith observed serum concentration for the jth patient; C'_{ij} is the serum theophylline concentration predicted by the pharmacokinetic model, and ε_{ij} is the residual variability term, representing independent identically distributed statistical error with mean zero and variance σ^2_E for the serum concentrations.

A preliminary analysis was conducted by permitting NONMEM to estimate the parameters of the basic model (i.e. no covariates). Each candidate covariate was added, in turn, to the base model and the change in the objective function noted. Covariates screened were body weight (BW), GA, PNA, post-conceptional age (PCA = GA + PNA), gender and the presence of oxygen support.

To test the significance of various factors that influence pharmacokinetic parameters the value of the objective function determined in the NONMEM fitting routine was used. The difference in objective function values obtained by comparing each model is asymptotically distributed as chi-square with degree of freedom equal to the difference in the number of parameters between the two models. In order to identify potentially significant factors, the difference in the objective function associated with a P-value of <0·05 was required.

RESULTS

NONMEM estimates

In the preliminary analyses, the modelling of clearance with BW, PCA and the presence of oxygen support improved the estimate of theophylline clearance (Table 2). Gender did not significantly improve the estimate of theophylline clearance. PCA was superior to GA and PNA for the estimate of clearance.

The full regressions for the fundamental pharmacokinetic structural parameters may be described by the following models: CL (mL/h) = $(\theta_1 \cdot BW^{\theta 4} + \theta_5 \cdot PCA) \cdot \theta_6^{\text{oxygen support}}$, Vd (L) = $\theta_2 \cdot BW$, $F = \theta_3$. The results of the hypothesis testing are summarized in Table 3.

The final pharmacokinetic parameters were CL (mL/h) = [6·98 · BW (kg)$^{2·17}$ + 0·244·PCA (weeks)] · 1·24$^{\text{oxygen support}}$, Vd (L) = 0·492 · BW (kg) and F = 0·660, respectively. The minimum value of the objective function in the NONMEM run was 428·412, and the objective function difference from the value of the basic model was 139·070. The parameter estimates of the final model are shown in Table 4. The interindividual variabilities in clearance and apparent volume of distribution were 15·6% and 80·4%, respectively, and the residual variability was 34·2% as a coefficient of variation. A plot of observed serum concentration vs. final model-predicted concentration is shown in Fig. 1. A plot of weighted residual vs. final model-predicted concentration confirmed that the weighted residuals were normally distributed around the zero ordinate (Fig. 2).

Table 2. Summary of the NONMEM analysis

No.	Model equation	OBJ
1	CL (mL/h) = θ_1, Vd (L) = θ_2	567·482
2	CL (mL/h) = $\theta_1 \cdot$ BW, Vd (L) = $\theta_2 \cdot$ BW	477·634
3	CL (mL/h) = $\theta_1 \cdot$ BW, Vd (L) = θ_2·BW F = θ_3	439·139
4	CL (mL/h) = θ_1·BW$^{\theta 4}$ + θ_5·PCA Vd (L) = θ_2·BW F = θ_3	433·282
5	CL (mL/h) = $(\theta_1 \cdot BW^{\theta 4} + \theta_5 \cdot PCA) \cdot \theta_6^{\text{oxygen support}}$ Vd (L) = $\theta_2 \cdot$ BW F = θ_3	428·412

OBJ, the minimum value of objective function (−2 log likelihood) in each NONMEM run; BW, body weight; PCA, post-conceptional age.

Validation

If the mathematical approach to determining theophylline doses were accurate and practical, the use of calculated doses could reduce the potential for toxicity and decrease the need for repetitious theophylline assays. In the validation group of 12 patients, predictions of the theophylline serum concentrations were made with the final regression model using the dosing history and demographic characteristics (Table 1). The predictive performance of regression models were evaluated using the mean prediction error (ME) and mean absolute

Table 3. Hypothesis testing using restricted models of full model

Hypothesis	Reduced model	LLD	*P*-value	Conclusion
Did body weight influence CL?	$BW^{\theta 4 = 0}$	72·728	<0·001	Yes
Did body weight influence CL in exponential power relationship?	$BW^{\theta 4 = 1}$	7·317	<0·01	Yes
Did post-conceptional age influence CL?	$\theta_5 \cdot PCA = 0$	5·681	<0·025	Yes
Did oxygen support influence CL?	$\theta_6^{\text{oxygen support} = 0}$	4·870	<0·05	Yes

Full model; CL (mL/h) = $[\theta_1 \cdot BW\ (kg)^{\theta 4} + \theta_5 \cdot PCA\ (weeks)] \cdot \theta_6^{\text{oxygen support}}$.
Vd (L) = $\theta_2 \cdot BW$ (kg), $F = \theta_3$.
LLD, −2 log likelihood difference from the value for full model equation.

Table 4. Final parameter estimates

Parameter	Estimate	Standard error
θ_1	6·98	2·89
θ_2	0·492	0·059
θ_3	0·660	0·0488
θ_4	2·17	0·515
θ_5	0·244	0·0703
θ_6	1·24	0·207
Interindividual variability		
CL	0·0244 (15·6%)	0·0256
Vd	0·647 (80·4%)	0·513
Residual variability	0·117 (34·2%)	0·0344

CL (mL/h) = $[\theta_1 \cdot BW\ (kg)^{\theta 4} + \theta_5 \cdot PCA\ (weeks)] \cdot \theta_6^{\text{oxygen support}}$.
Vd (L) = $\theta_2 \cdot BW$ (kg), $F = \theta_3$.
Oxygen support = 0 for without oxygen support.
Oxygen support = 1 for with oxygen support.
BW, body weight; PCA, post-conceptional age.

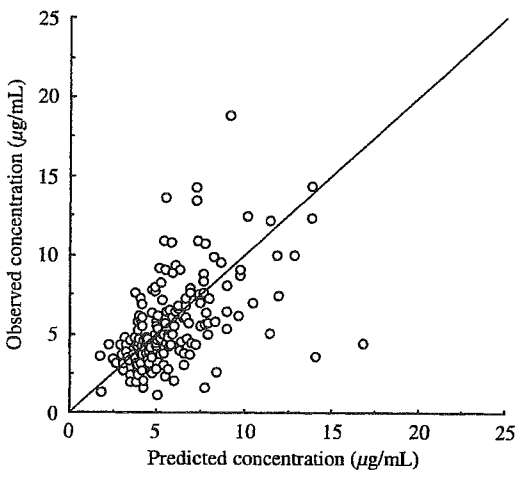

Fig. 1. Plot of observed serum concentration vs. final model-predicted concentration.

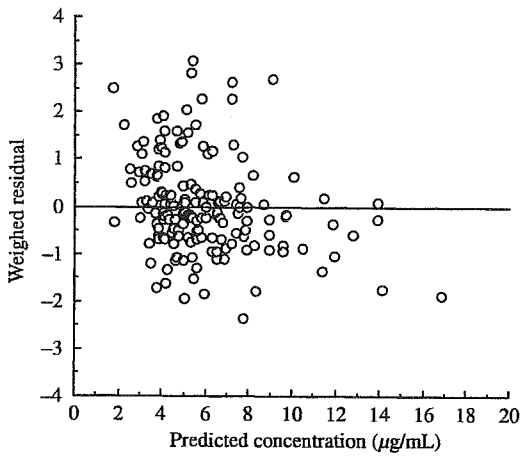

Fig. 2. Plot of weighted residual vs. final model-predicted concentration.

prediction error (MAE) according to methods outlined by Sheiner and Beal (13). The MAE and standard deviation for our derived population model was 1·73 ± 1·35 μg/mL (Table 5). The predictive performance of our model was superior to the models of Moore *et al.* and Lee *et al.*

DISCUSSION

In this study, the pharmacokinetics of intravenously and orally administered theophylline was studied in 107 neonates and young infants using routine data. The parameter estimates obtained from the analysis may be used (a) in developing guidelines for initial loading doses and maintenance therapy, (b) in assessing the optimal time to sample for therapeutic monitoring and (c) as *a priori* parameters estimates for Bayesian analysis.

Table 5. Predictive abilities of each method

Method	Mean prediction error (μg/mL)	Mean absolute prediction error (μg/mL)
Moore *et al.*		
Mean ± standard deviation	−0·57 ± 2·11	1·86 ± 1·09
Range	−4·0–3·5	0·2–4·0
Lee *et al.*		
Mean ± standard deviation	−0·51 ± 2·35	2·01 ± 1·25
Range	−4·4–4·9	0·2–4·9
Present study		
Mean ± standard deviation	−1·39 ± 1·71	1·73 ± 1·35
Range	−4·5–1·3	0·2–4·5

The final regression model for clearance suggests that theophylline clearance increases disproportionately with increasing weight. Moreover, there was further improvement in fit obtained upon the inclusion of PCA in the model for theophylline clearance. Each of these factors is related to the stage of development of the newborn. PCA was superior to GA and PNA for the estimate of clearance. Other investigators have shown an influence of PNA on theophylline clearance (8, 9). We had supposed that the PCA would add to the influence of PNA on the clearance, as our patients were more younger than those of Lee *et al.* (9) and Preez *et al.* (11).

Preez *et al.* (11) reported a 47% higher clearance in premature neonates with oxygen support. In our study, neonates and young infants who received oxygen support had a 24% higher clearance than those who did not. The patients studied by Preez *et al.* were neonates within 2 days of birth, whereas our patients were postnatal 2–104 days. So that the effects of oxygen supply on the clearances of theophylline would be expected to be different.

Moore *et al.* (8) reported that bioavailability of orally administered theophylline was not significantly less than unity. Lee *et al.* (9) also reported that oral bioavailability from liquid preparations was 91·8%. The bioavailability of theophylline following oral administration of a suspension in milk was 66% in our population. Therefore, suspension of aminophylline powder in milk was stopped, and injection solutions were diluted and administered as oral solutions in order to improve bioavailability.

The weight-normalized value of Vd of 0·492 L/kg is lower than that found in other population studies that reported a range from 0·63 to 0·937 L/kg (8, 9, 11). However, this lower value is within the range (0·18 to 0·95 L/kg) recorded in some other analyses (14–16).

A method that would provide correct predictions about whether a drug concentration is subtherapeutic, therapeutic or toxic from a given dosage regimen would be valuable in the clinical setting. In the validation set of 12 patients, the performance of the final population model was good. Clinical application of these findings to patient care may allow for a more accurate initial estimate of theophylline clearance and for the selection of an appropriate initial maintenance dose, thus enabling the clinician to achieve desired serum concentration and therapeutic effect.

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Autonomic Modulation of Sinus and Atrioventricular Nodes in Premature Low-Birth-Weight Infants

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HATA, T., ET AL.: Autonomic Modulation of Sinus and Atrioventricular Nodes in Premature Low-Birth-Weight Infants. *Respiratory vagal activity is expressed by heart rate variability (HRV) at approximately 1 month of age in premature low-birth-weight infants (PLBWI). However, the autonomic inputs into the sinus node (SAN) and atrioventricular node (AVN) in PLBWI are unclear. We evaluated the variability in PP and PR intervals at day zero (day 0) and 1 month (1 month) after birth in 16 PLBWI (gestation 32.3 ± 1.3 weeks, birth weight 1.578 ± 257 g). The polygraph was recorded during sleep on day 0 and at 1 month. PP and PR intervals and the number of respiratory cycles were measured, and frequency analysis was performed by auto-correlation fast Fourier transforms. Power spectral density (PSD: ms^2) was calculated for the low frequency domain (LF: 0.036~0.146 Hz), high frequency domain (HF: 0.146~0.390 Hz), total frequency (TF: 0.036~2.000 Hz), and respiratory sinus arrhythmia (RSA: frequency bandwidth of 0.3 Hz with peak respiratory frequency as median), and the PSD ratio in the PP and PR intervals (LF/HF, RSA/TF) were compared. Compared with day 0, a decrease in the LF/HF ratio and an increase in the RSA/TF ratio in PP intervals were observed at 1 month, consistent with expression of respiratory vagal activity. For PR intervals, on the other hand, the LF/HF ratio increased, indicative of accentuated sympathetic activity. However, the respiratory vagal input was weak, and the RSA/TF ratio remained unchanged. These observations suggest that, in PLBWI at 1 month, AVN conduction was not predominatly influenced by respiratory-related vagal activity, but was controlled by autonomic regulation, independent of the SAN. (PACE 2005; 28:S288–S291)*

atrioventricular node, sinus node, heart rate variability, respiratory vagal activity

Introduction

Frequency analyses of heart rate variability (HRV) and respiratory movements were performed to clarify the postnatal development of respiratory and circulatory dynamics in premature low-birth-weight infants (PLBWI). Previous studies have shown that, in PLBWI, respiratory vagal activity comparable to that in mature infants is expressed in heart rate control due to postnatal development.[1] This respiratory vagal activity has a strong chronotropic effect on the conduction system of the heart. While the sinus node (SAN) cycle (PP interval), which determines the ventricular cycle, is physiologically positively correlated with the atrioventricular node (AVN) conduction time (PR interval), these two measures exhibit different frequency variations.[2] This is attributable to separate autonomic conduction pathways in mammalian SAN and AVN, and an indirect effect of autonomic activity on the AVN during the cardiac cycle.[3,4] We studied the development of autonomic input into the SAN and AVN in PLBWI, and the respiratory vagal activity, which develops after birth and affects the autonomic inputs during the cardiac cycle.

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Methods

We studied 16 PLBWI (gestation 32.3 ± 1.3 weeks, birth weight 1.578 ± 257 g, Apgar score [1 minute] 8.1 ± 1.1, [5 minute] 8.9 ± 0.6) without underlying disease, admitted to our neonatal intensive care unit. Electroencephalogram, electrooculogram, electrocardiogram, and respiratory cycles were recorded on an MP150 polygraph recorder (Biopack Systems, Santa Barbara, CA) during quiet sleep at day 0 and 1 month after birth. Continuous PP and PR recordings during 60 seconds of normal sinus rhythm were obtained. Frequency analysis was performed for PP and PR intervals using the analytical program Acknowledge ver. 3.5 (Biopack Systems) by auto-correlation fast Fourier transforms. From the frequency components obtained, power spectral density (PSD: ms^2) was calculated for low frequency domain (LF: 0.036~0.146 Hz), high frequency domain (HF: 0.146~0.390 Hz), total frequency (TF: 0.036~2.000 Hz), and respiratory sinus arrhythmia (RSA: frequency bandwidth of 0.3 Hz with peak respiratory

Table I.

PP and PR Intervals, on Day 0 and at 1 Month

	Day 0	1 Month	P
PP (ms)	437.9 ± 36.5	403.5 ± 39.1	0.0007
PR (ms)	95.9 ± 11.8	97.3 ± 10.9	0.0004

n = 16 in each comparison.

frequency as median in each infant), and the characteristic ratios of PSD (LF/HF, RSA/TF) were compared.

Between-groups comparisons were made by paired Student's *t*-test, with a significance level of $P < 0.05$.

Results

Postnatal Changes in PP and PR Intervals

Table I shows the mean and standard deviation of PP and PR intervals at day 0 and 1 month. The mean PP interval shortened significantly between day 0 and 1 month (437.9 ± 36.5 vs 403.5 ± 39.1 ms, $P < 0.05$) consistent with an increase in heart rate. In contrast, the mean PR interval lengthened (95.9 ± 11.8 vs 97.3 ± 10.9 ms, $P < 0.05$), consistent with a prolongation of the AVN conduction time.

Frequency Analysis of PP and PR Intervals

Figure 1 shows postnatal changes in frequency characteristics of PP and PR in case 1. The power spectral density of PR >0.1 Hz on day 0 was smaller than that of PP. The components which were synchronized for RSA in both PR and PP spectra were not clear on day 0, as indicated by the ranges (arrows). The RSA component in both PR and PP spectra increased at 1 month after birth (right panels), as well as the frequency components lower than RSA. The respiratory synchronized components in 1 month appeared in both the PR and PP RSA regions, though were not single peaks.

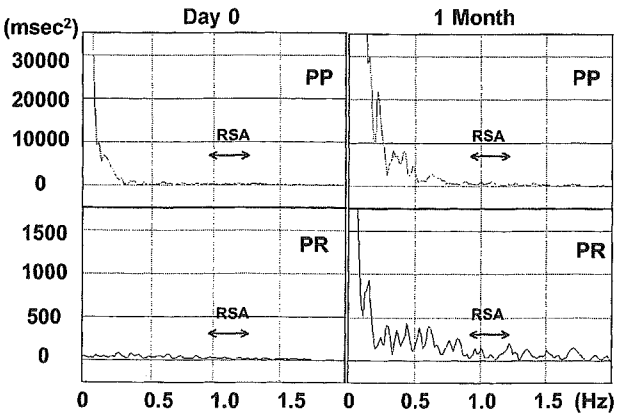

Figure 1. *Representative power spectral comparison derived from PP (upper panels) and PR (lower panels) intervals between day 0 (left panels) and 1 month (right panels). See text for further explanations. PP = spontaneous sinus node cycle. PR = atrioventricular node conduction time. RSA = frequency bandwidth of 0.3 Hz with peak respiratory frequency as median.*

In the frequency analysis of PP intervals, the LF/HF ratio decreased from 8.231 ± 4.428 at day 0 to 4.414 ± 2.375 at 1 month ($P < 0.05$). On the other hand, the RSA/TF ratio increased from 0.015 ± 0.020 at day 0 to 0.048 ± 0.059 at 1 month ($P < 0.001$, Table II). In the frequency analysis of PR intervals, the LF/HF ratio increased from 0.864 ± 0.336 at day 0 to 1.372 ± 0.961 at 1 month ($P < 0.001$). On the other hand, the RSA/TF ratio was 0.138 ± 0.113 at day 0 and 0.125 ± 0.058 (ns) at 1 month (Table I).

Figure 2 shows the LF/HF ratio, which represents autonomic balance, and the RSA/TF ratio, which represents the ratio of respiratory-related vagal activity to the total frequency component. The LF/HF ratio decreased significantly in PP, but increased significantly in PR. The RSA/TF ratio significantly increased in PP, but remained constant in PR between day 0 and 1 month.

Discussion

Commonly performed analysis of HRV involves the analysis of electrical signals of ventricular activation transmitted through AVN conduction. However, since the RR interval includes AVN conduction time, it not represent a pure SAN excitation cycle. Therefore, we evaluated the autonomic input in a pure SAN excitation cycle by determining the PP interval from ECG using an algorithm.

In frequency analysis of HRV, the frequency band is divided into the LF and HF domains.[5] The LF component is believed to include a sympathetic activity component and a parasympathetic component.[6] The HF component includes the etiology of RSA, and is mainly influenced by the parasympathetic nervous system through the respiratory vagal nerve. Consequently, the LF/HF ratio is an indicator of sympathetic tone.[7] HRV in children and neonates has thus far been analyzed using the RR interval as an indicator of autonomic function, and the development of the autonomic nervous system was observable in HRV.[8–10]

We studied whether respiratory vagal activity influences the variability of AVN conduction time. In the PP interval variability, the power of TF increased from day 0 through 1 month after birth, suggesting the development of autonomic

Table II.

LF/HF and RSA/TF Ratios on Day 0 and at 1 Month

	LF/HF			RSA/TF		
	Day 0	1 Month	P	Day 0	1 Month	P
PP	8.231 ± 4.428	4.414 ± 2.375	0.0384	0.015 ± 0.020	0.048 ± 0.059	0.0008
PR	0.864 ± 0.336	1.372 ± 0.961	0.0007	0.138 ± 0.113	0.125 ± 0.058	0.8812

n = 16 in each comparison.

cardiopulmonary regulation. The LF/HF ratio decreased from day 0 through 1 month, indicating the development from sympathetic dominance to parasympathetic dominance, as shown by previous studies.[1,9,10] The RSA/TF ratio significantly increased, which indicated that the development of respiratory function contributed to the vagal input in the SAN.

In the PR interval variability, the power of TF increased from day 0 through 1 month, indicative of and increase in the input of nerve activity on AVN conduction. In contrast, the LF/HF ratio significantly increased, consistent with a further increase in sympathetic. In addition, the RSA/TF ratio did not increase, suggesting that the respiratory vagal activity on AVN conduction remained weak at 1 month. Our study showed that the variability in PR interval dependent on respiration was smaller than the absolute value of PP interval variability, demonstrating that respiratory vagal activity accounted for only a small percentage of total PSD. The AVN abounds in sympathetic and parasympathetic fibers as compared with the SAN, and is strongly controlled by the autonomic system. In fact, PP interval variability was shown by its total PSD to have a stronger autonomic input compared with PR interval variability in 1-month-old PLBWI. From day 0 through 1 month, no changes occurred in the respiratory vagal activity on AVN conduction, and the conduction time was prolonged in contrast to the increase in the LF/HF ratio, indicating an increase in sympathetic tone. Therefore, vagal nerve activity seemed to predominantly control AVN conduction over respiratory vagal activity in PLBWI.

Conclusions

In 1-month-old PLBWI, compared with day 0, a decrease in the LF/HF ratio and an increase in the RSA/TF ratio in PP intervals were observed, indicating increased autonomic activities and the expression of respiratory vagal activity in the physiological cardiac cycle. An increase in the LF/HF ratio was observed in the frequency characteristic of PR intervals, which showed accelerated sympathetic activity for AVN conduction. However, respiratory vagal input was weak, and the RSA/TF ratio remained unchanged. This indicates that, in the 1-month-old PLBWI, AVN conduction was dominated by non-respiratory-related vagal activity, and controlled by autonomic regulation independent of the SAN.

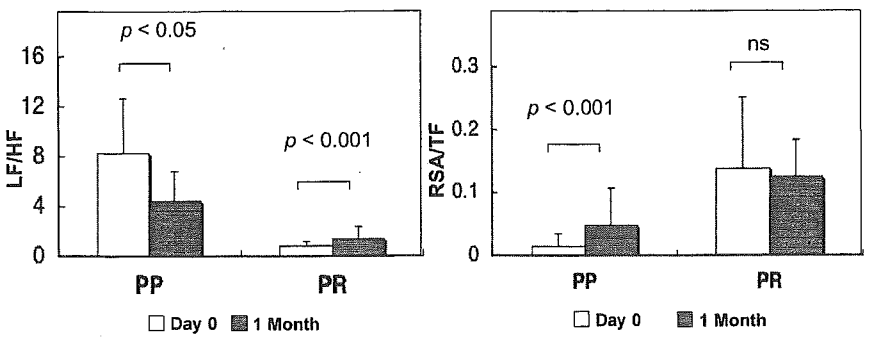

Figure 2. *Significant decrease in LF/HF ratio derived from PP intervals and significant increases in the LF/HF ratio derived from PR intervals and the RSA/TF ratio derived from PP intervals between day 0 and 1 month after birth. See text for further explanations. Values are means ± SD. n = 16 in each comparisons. LF = low frequency. HF = high frequency. TF = total frequency. RSA = frequency bandwidth of 0.3 Hz with peak respiratory frequency.*

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