Pharmacokinetics of theophylline in preterm neonates during the first month of life

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ABSTRACT

Objective: The present work aimed to estimate the theophylline pharmacokinetic parameters (TH-PKP) in preterm neonates with apnea during the first month of life in order to optimize its dosage regimen.

Methods: Fifty preterm neonates enrolled in the study with recurrent apnea were admitted during 1998-2000 to the Neonatal Intensive Care Unit of Maternity and Children's Hospital, Al-Mosaida, Jeddah, Kingdom of Saudi Arabia. Criteria for this study were preterm with gestational age (GA) of 26-33 weeks (mean $\pm$ SD 30 $\pm$ 3.9). They received TH of 3-6 mg/kg loading dose (LD) followed by maintenance dose (MD) of 0.5 - 3.0 mg/kg/12 hours. Eight of these patients received phenobarbital and 19 received cimetidine concomitantly for at least 7 days. Blood samples were taken one hour post LD and at steady state (Css). Theophylline levels were determined by fluorescence polarization immunoassay.

Results: Phenobarbital significantly enhanced TH clearance (CL) and reduced its half-life ($t_{0.5}$) but cimetidine had no significant effect. Excluding patients receiving phenobarbital. The mean $\pm$ SD TH-PKP were volume of distribution (Vd) = 0.77 $\pm$ 0.25 L/kg; elimination rate constant (Ke) = 0.027 $\pm$ 0.011 h^{-1}; CL = 0.019 $\pm$ 0.006 L/h/kg, $t_{0.5}$ = 30.7 $\pm$ 12.1. There was marked intra patient variability in all TH-PKP.

Conclusion: In view of the results and practical considerations, initial dosage regimen to attain a TH Css level within the therapeutic range (6-12 ug/ml) was suggested: LD 6-7 mg/kg, MD 1.5 - 2.0 mg/kg/12 hours. To compensate for maturation changes or drug interaction, a method, based on estimation of individual TH CL, was described for adjusting MD.

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Apnea is a cessation of respiration for 20 seconds or for a shorter period if accompanied by functional changes such as hypotonia, bradycardia (<80 beats/minute), cyanosis, or marked pallor.[1] Recurrent episodes of apnea are common in preterm neonates. Both the incidence and severity are inversely related to gestational age (GA).[2] The peak incidence occurs between 5-7 days after birth. Apnea of prematurity represents the most common cause of apnea in preterm neonates. It is a specific diagnosis and one of exclusion. However, it is necessary to identify and rule out other disorders associated with apnea (for example metabolic disturbances, anemia, sepsis, pneumonia, congestive heart failure, seizures, maternal drugs and so forth).[3] Theophylline (TH), a 1,3-dimethylxanthine has been used in clinical practice since the 1970's for treatment or prophylaxis of apnea[4,5] and as an aid to ventilator weaning.[6] The proposed mechanism by which TH exert its beneficial effect in apnea include stimulatory effect on the motor output to upper airway dilator muscles and enhanced diaphragmatic contractility.[7] Caffeine has demonstrated similar efficacy to TH and is currently more preferred, in developed countries as it has more reliable oral absorption, wider margin of safety and longer

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half-life that allows once daily administration.[8] A rapid highly sensitive high performance liquid chromatography method has been developed for the determination of TH in serum, which required no longer than 7 minutes to perform.[9] Comparing the fluorescence polarization immunoassay (FPIA) with high performance liquid chromatography (HPLC) methods, both demonstrate sufficient, accuracy and practicability for the therapeutic monitoring of TH levels in patients. However, the HPLC method offers an advantage over the FPIA method, for the measurement of both caffeine and TH and their metabolites in serum samples from neonates.[10] Theophylline clearance in severe asthmatic children is said to have a trend for decrease with an increase in age. However, TH is still the most commonly used drug for the management of apnea in the Kingdom of Saudi Arabia (KSA). Therapeutic drug monitoring of TH is highly relevant in neonates due to its narrow therapeutic range[3] and markedly reduced and highly variable metabolic and renal clearance.[11,12] The aim of the present study was to estimate the pharmacokinetic parameters (PKP) of TH in preterm neonates with apnea in the first month of birth in order to provide the optimal dosage regimen in view of these parameters.

Methods. Fifty preterm neonates enrolled in the study were admitted to Neonatal Intensive Care Unit at Maternity and Children Hospital Al-Mosaidia, Jeddah, KSA during the period 1998 to 2000. Criteria for entry into the study were preterm <34 weeks GA, receive TH for management of apnea of prematurity and TH was started within the first month after birth. The exclusion criteria were preterm with congenital abnormalities, cholestatic jaundice, and those who suffered birth asphyxia. Demographic and clinical characteristics of the patients are summarized in **Table 1**. Theophylline was given in the form of aminophylline (250 mg/10ml, Antigen Pharmaceuticals Ltd, Roscrea, Ireland) by slow intravenous (IV) over 10 minutes. The appropriate dose was drawn by a tuberculin syringe and transferred to a 5 mls syringe, then diluted to 5 mls with saline. Loading dose (LD) of 3-6 mg/kg was given followed by a maintenance dose (MD) of 0.5-3 mg/kg/12 hours. For the management of convulsion (8 patients), 20 mg/kg of phenobarbital was given IV then followed by 5mg/kg/day. For management of gastrointestinal bleeding (19 patients) cimetidine was given IV in a dose of 5mg/kg/12 hours. Both drugs were given at least for 7 days. Most patients received one or more of the following antibiotics IV in appropriate dose: gentamycin, vancomycin, amikacin or cefotaxime. All drugs and doses were determined by the physician in-charge and not due to any requirement of the study.

Sample collection and theophylline level determination. It has been reported that TH steady state (Css) level in preterm to be approximately attained after 5-6 days of repeated administration.[11] Two blood samples were collected from each patient for determination of TH level, the first sample was taken one hour post loading dose, and the second on the sixth day halfway between doses. In all cases, one ml was drawn into a plain tube, immediately centrifuged to separate the serum, and kept at 4°C until analysis within 2 days. Serum samples were analyzed by FPIA method, using Abbott TDx analyzer. The coefficient of variation for within day and between days runs were < ± 5% for concentration range (1-20 mg/ml). No interference from any of the concomitantly taken drugs or TH metabolites has been reported.

Estimation of pharmacokinetic parameters of theophylline. The 50 preterm neonates who received TH were subdivided into 3 groups according to the concomitantly taken drugs, group 1 comprised 8 patients who received phenobarbital, group 2 comprised 19 patients who received cimetidine and group 3 comprised 23 patients who received neither of these drugs. Pharmacokinetic (PK) analysis was performed using conventional PK equations.[6]

Apparent volume of distribution (Vd) was determined by:

Equation 1:

$$Vd\ (L/kg) = (LD \times 0.8)/C1$$

C1 is the TH level (mg/L) determined in the sample taken one hour post LD, 0.8 is factor to convert aminophylline dose to TH equivalent. The clearance (CL) was estimated by:

Equation 2:

$$CL\ (L/kg/h) = (MD \times 0.8)/(Css \times \tau)$$

Css is the TH level (mg/L) determined halfway between doses at steady state, τ is the dosing interval (h). Elimination rate constant (Ke) was determined by:

Equation 3:

$$Ke\ (h^{-1}) = CL/Vd$$

Half-life ($t_{0.5}$) was determined by:

Equation 4:

$$t_{0.5}\ (h) = 0.693/Ke$$

Statistical analysis. Analysis of variance was used to determine significant differences between means. Chi Square was used for comparison of ratios. Regression analysis was used to investigate correlation between demographic variables and PKP. Value of $p<0.05$ was considered significant. Statistics were performed using Excel 7, and Sigma Stat version 2.

Results. ***Theophylline pharmacokinetic parameters.*** The mean values of PKP of TH in preterm neonates subdivided into three groups according to the concomitantly administered drugs are presented in **Table 2** Patients that received Phenobarbital showed significantly lower mean TH $t_{0.5}$ ($p<.01$), significantly higher mean TH CL ($p=0.02$). Mean GA, birth weight (BWT) and Apgar score of patients of these groups were significantly different ($p<0.05$) (**Table 1).** In view of this finding, all patients excluding those that received phenobarbital were re-categorized in one group (group 4), which present the subject of all further analysis (**Table 3**). Mean ± SD values for TH-PKP were as follows Vd=0.77 ± 0.25 L/kg, Ke=0.026 ± 0.011 h^{-1}, CL=0.019 ± 0.006 L/kg/h, and $t_{0.5}$=30.7 ± 12.1. High interpatient variability was observed concerning all TH-PKP. The coefficient of variations in Vd and CL is 30%, and 40% in Ke and t0.5. **Table 4** shows the PKP of TH in preterms subdivided according to their GA or BWT. Theophylline PK in all subgroups shows no significant difference in mean values. However, there was a trend for decrease in both mean Vd and CL values with decrease of mean BWT. Poor correlation was observed between TH PKP and GA or BWT ($r^2<0.1$).

Therapeutic drug monitoring and theophylline level distribution. **Figure 1** shows the TH level distribution in samples taken at Css from preterm neonates. Thirty-six percent of samples were within therapeutic range (6-12 ug/ml), 57% were sub-therapeutic, and 7% were potentially toxic. However, patients' files were reviewed and no signs of toxicity due to TH were reported. **Table 5** shows the relationship between the MD of TH and Css level distribution. Patients that received MD of 1.6-2 mg/kg showed significantly higher ($p<0.05$) percentage of samples (80%) within therapeutic range compared to those who received higher or lower doses. Out of the 5 patients who received MD >2mg, 3 showed a potentially toxic level.

Discussion. ***Pharmacokinetic of theophylline in preterm neonates.*** Metabolic and renal clearance of TH are markedly reduced in neonates,[13] prolonged half life showed variable absorption after oral administration.[14] Furthermore, these properties may frequently change, often unpredictably, depending on the degree of prematurity, postnatal age, food intake, rate of development, and other illnesses.[15-18] For these reasons, therapeutic drug monitoring and clinical PK seemed essential to optimize TH use in preterm neonates. The PK of TH in neonates has been the subject of numerous studies which adopt either conventional PK analysis.[11,14,16-28] or population PK approach for example non-effect mixed effect method.[29-32] Of these studies, few have been concerned with PK of TH in neonates during the first few days[26,32] or few weeks after birth.[14] Our study is characterized by focusing not only on investigations of PK of TH in preterm neonates during the first month of life but also studying the effect of concomitantly taken drugs that are known to alter PK of TH in children and adults. Theophylline metabolism in adults and children involves C-8 hydroxylation to form 1,3-dimethyl uric acid and N-demethylation at one and 3 position to yield 3-methylxanthin and 1-methylxanthin.[33,34] The demethylation pathways are catalyzed primarily by cytochrome (CYP) 1A2 isozyme whereas C8 hydroxylation is mediated by multiple CYP isozymes including CYP 1A2 and CYP 2E1.[35] In premature neonates, only unchanged TH and caffeine were found in urine, indicating the absence of oxidative pathways. The demethylation pathway was substituted by N-methylation to caffeine, which is mediated by a different subfamily of CYP 450. The other major metabolic pathway of TH, C-8 hydroxylation was slightly diminished.[36] Phenobarbitone is a well-known enzyme inducer. It has been reported to significantly enhance TH CL in adults. However, Kandrotas et al[37] reported that TH CL in neonates receiving phenobarbital was not significantly different from the neonates receiving aminophylline alone. In our study, phenobarbital had been found to significantly increase TH CL, and reduce TH $t_{0.5}$ (**Table 2**). Studies in adults have shown that cimetidine significantly decrease TH CL and TH Ke and consequently increase TH $t_{0.5}$.[38] The mechanism of this interaction is thought to be the inhibitory effect of cimetidine on hepatic microsomal mixed function oxidase for example CYP 450 and CYP 448.[38] In the present study, patients that received cimetidine did not show any significant change in any of the TH PKP. The observed significant induction of TH metabolism by concomitant administration of Phenobarbital while it was not significantly affected by Cimetidine could be explained in view of the altered metabolic pathway of TH in preterm, which is mediated through CYP subfamily different from those in children and adults. In view of our findings, all patients excluding those that received phenobarbital were combined in one group that represents the subject of all coming discussions. The mean values ± SD of TH PKP were as follows: (Vd) = 0.77 ± 0.25 L/kg; Ke = 0.027 ± 0.011 h^{-1}; CL = 0.019 ± 0.006 L/kg/h; $t_{0.5}$ = 30.7 ± 12.1. Our results are comparable with some reported values. The following values for Vd were reported: 0.77,[16] 0.91,[23] 0.86,[27] 0.71.[21] The reported values for TH CL were 0.024,[13] 0.0188,[15] 0.028.[23]

Table 1 - Characteristics of preterm neonates classified according to concomitantly administered drugs.

Parameters	Concomitantly administered drugs			
	Phenobarbital N=8 group 1	**Cimetidine N=19 group 2**	**Other patients* N=23 group 3**	**Group 2 + Group 3 N=42**
Gender				
Male	3	12	13	25
Female	5	7	10	17
Ethnic origin				
African	2	3	5	8
Asian	6	16	18	34
Gestational age (week)				
Range	27-33	28 - 33	27 - 33	27 - 33
Mean ± SD	29.25 ± 2.43	30.79 ± 1.27	29.65 ± 1.70	30.17 ± 1.60
p value	0.043	0.043	0.043	
Birth weight (kg)				
Range	0.7 - 1.93	1 - 2.3	0.88 -1.64	0.88 - 2.3
Mean ± SD	1.19 ± 0.41	1.40 ± 0.32	1.29 ± 0.21	1.34 ± 0.26
p value	0.207	0.207	0.207	
Apgar Score				
1 minute=Mean ± SD	5.56 ± 2.23	6.20 ± 2.05	6.45 ± 2.30	6.00 ± 2.15
p value	0.617	0.617	0.617	8.21 ± 1.08
5 minutes= Mean ± SD	6.65 ± 2.17	7.45 ± 2.22	7.85 ± 2.13	
p value	0.407	0.407	0.407	
Antibiotics (n)				
Gentamicin	6	13	14	27
Vancomycin	3	3	8	11
Amikacin	2	3	10	13
Claforan	8	11	8	19

*Received neither phenobarbital nor cimetidine. Tukey test showed no significant difference among means of all parameters.

Table 2 - Effect of concomitantly administered drugs on pharmacokinetic parameters of theophylline preterm neonates.

Pharmacokinetic parameters	Concomitantly administered drugs			
	Phenobarbital N=8	**Cimetidine N=19**	**No interfering drugs N=23**	***p* value**
Volume of distribution				
Mean ± SD	0.884 ± 0.173	0.733 ± 0.194	0.793 ± 0.295	*p*>0.05
Range	0.675 - 1.179	0.427 - 1.030	0.306 - 1.395	
95% confidence interval	0.764 - 1.004	0.646 - 0.820	0.672 - 0.914	
Coefficient of variation %	19.570	24.467	37.200	
Clearance				
Mean ± SD	0.036 ± 0.017	0.019 ± 0.007	0.018 ± 0.005	*p*= 0.02
Range	0.017 - 0.067	0.010 - 0.035	0.008 - 0.026	
95% confidence interval	0.024 - 0.048	0.016 - 0.022	0.016 - 0.020	
Coefficient of variation %	47.222	36.842	27.778	
Elimination rate constant				
Mean ± SD	0.042 ± 0.023	0.027 ± 0.012	0.026 ± 0.012	*p*>0.05
Range	0.023 - 0.092	0.013 - 0.062	0.012 - 0.055	
95% confidence interval	0.026 - 0.058	0.022 - 0.032	0.021 - 0.031	
Coefficient of variation %	54.762	44.444	46.154	
$T_{0.5}$				
Mean ± SD	20.076 ± 8.180	29.591 ± 11.300	31.623 ± 12.890	*p*=0.01
Range	7.567 - 30.603	11.139 - 52.321	12.603 - 59.945	
95 % confidence interval	14.408 - 25.745	24.488 - 34.610	26.355 - 36.891	
Coefficient of variation %	40.745	38.187	40.761	

Table 3 - Mean pharmacokinetic parameters of theophylline in preterm neonates excluding patients that received Phenobarbital (N=42).*

Parameters	Mean ± SD	Range (lower-upper)	Coefficient of variation%	95% confidence interval
Volume of distribution	0.766 ± 0.253	0.306 - 1.395	33.029	0.843 - 0.690
Clearance	0.019 ± 0.006	0.008 - 0.035	31.597	0.021 - 0.017
Elimination rate constant	0.026 ± 0.011	0.012 - 0.062	42.308	0.029 - 0.023
$T_{0.5}$	30.676 ± 12.097	11.14 - 59.95	39.435	34.355 - 27.017

*gestational age range = 27-33 weeks. Mean ± SD = 31.2 ± 1.6, birth weight range = 0.88 - 2.3kg, Mean ± SD =1.34 ± 0.27, $T_{0.5}$ - half life

Table 4 - Pharmacokinetic parameters of theophylline in preterm neonates (N=42) classified according to their gestational age and birth weight.

Parameters	Pharmacokinetic values (Mean ± SD)					
	Range	Mean ± SD	Volume of distribution	Clearance	Elimination rate constant	$T_{0.5}$
Gestational age*						
Group 1 (n=12)	27 - 29	28 ± 0.426	0.801 ± 0.288	0.018 ± 0.001	0.026 ± 0.010	31.625 ± 13.56
Group 2 (n=30)	30 - 33	31.033 ± 0.927	0.751 ± 0.241	0.019 ± 0.007	0.027 ± 0.012	30.296 ± 11.687
Birth weight†						
Group 1 (n=5)			0.688 ± 0.303	0.016 ± 0.0056	0.026 ± 0.10105	31.437 ± 14.23
Group 2 (n=31)			0.767 ± 0.269	0.019 ± 00069	0.028 ± 0.016	31.02 ± 14.62
Group 3 (n=6)			0.818 ± 0.244	0.019 ± 0.006	0.025 ± 0.009	33.919 ± 17.75

*p>0.05 for all parameters using t-test assuming unequal variance, †p>0.05 for all parameters using one way analysis of variance, $T_{0.5}$ - half life

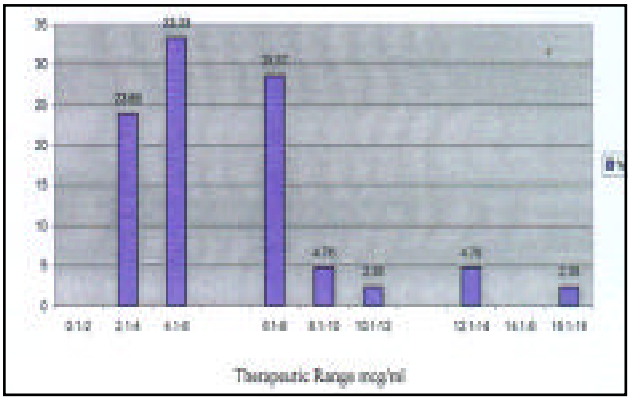

Figure 1 - Theophylline level distribution of Css in preterm neonates. Css - theophylline steady state

Table 5 - Relationship between amionophylline maintenance dose (MD) mg/kg/12hours and theophylline level distribution at Css (N=42)

MD	Total samples*	Theophylline level (ug/ml)					
		<6		6-12		>12-15	
		n	(%)†	n	(%)	n	(%)
>.5-1.0	**14**	12	(85.7)	2	(4.3)	-	-
1.1-1.5	**18**	11	(61.1)	7	(38.9)	-	-
1.6-2.0	**5**	1	(20)	4	(80)‡	-	-
2.1-3.0	**4**	-	-	2	(50)	2	(60)
3.1-3.5	**1**	-	-	-	-	1	(100)
Total	**42**	**24**	**(57.1)**	**15**	**(35.7)**	**3**	**(7.1)**

*one sample per patient.
†Relative to the total number of samples within each patient group received certain MD. ‡Significantly high (p<0.01)

Correlation between pharmacokinetic parameters and demographic variables. The influence of several demographic and clinical variables on TH PKP in preterm neonates was the subjects of several studies, which disagreed on the level of contribution of these factors on the PKP. Neese and Soyka[19] showed lack of correlation between TH PKP and GA, PNA, or duration of treatment. Latini et al[20] also reported absence of correlation between TH $t_{0.5}$ and GA during the first 25 days of life. Jones and Baillie[21] found no correlation between CL and PNA or GA. Hilligoss et al[18] found a limited correlation between CL/body surface and duration of therapy (r=0.53) and no correlation with maturation factors. In contrast, Giacoia et al[22] observed that TH CL increased with PNA in 8 patients, Gilman et al[16] described a weak correlation between TH CL and PNA (r=0.23; $p<0.01$) as well as post conceptional age (r=0.20; $p<0.01$). In the present study, poor correlation between TH PKP and GA, BWT, were observed ($r<0.1$)

Therapeutic drug monitoring and theophylline level distribution. The majority of Css TH levels were subtherapeutic (**Figure 1**). Subtherapeutic levels were predominant in samples of patients that received low TH doses. Thus, it was concluded that the main reason for attaining subtherapeutic Css TH is sub-optional dosing.

Suggested optimal initial theophylline dosing. The estimated mean TH CL and Vd were utilized to provide the theoretical optimal initial TH dosing to attain a desired TH target level within the therapeutic range (6-12 ug/ml). Optimal LD to attain a TH level of 6ug/ml was estimated using Equation 1 by substituting C1 by 6 and Vd by 0.77. Similarly the optimal MD to attain any desired TH Css level was estimated using Equation 2 by substituting CL by 0.019 and Css by a value of 6-12. It is worthy to note that this dosing regimen is valid only in case of absence of significant drug interaction. For practical consideration, and due to great intraindividual variations, maturational changes, possibility of drug interaction, we suggest starting TH-MD as 1.5-2.0 mg/kg/12 hours. Theophylline level must be checked at the sixth or seventh days after starting administration (at Css) then every week. In view of determined TH levels, *TH MD could be adjusted appropriately as follows:*

Adjustment of theophylline in view of individual theophylline clearance. Individual TH CL could be calculated using Equation 1. Calculate the MD (mg/12 h) required to attain a desired Css TH (10 ug/ml) level as follows

$$MD = TH\ CL\ individual \times (desired\ TH\ Css\ level) \times (\tau) / 0.8$$

Desired TH level is 10 ug/ml, or other levels within the therapeutic range (6-12 ug/ml) and τ is the time interval which is usually 12 hours.

In conclusion, the suggested optimal aminophylline maintenance dose is mg.kg/12 hours to attain certain targeted TH level ug/ml are as follows: Target 6ug/ml MD=1.7, 8ug/ml MD=2.0, 10ug/ml MD=2.9, 11ug/ml MD=3.1 and 12ug/ml MD=3.4 namely the MD range between 1.5-3.0 to attain the lower or upper sides of the reference range. The higher side is considered when phenobarbital is given concomitantly. Since these values are empirical in nature, clinical judgment is essential before any decision.

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