Original Article

A Randomized Controlled Trial Comparing Serum Theophylline Levels and Side Effects between Two Regimens of Aminophylline in Preterm Infants

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Background: Aminophylline is the medication use for treating apnea of prematurity and facilitating endotracheal extubation in preterm infants. The regimen of aminophylline therapy varies among institutions. However, the data on its safety are limited.

Objective: To compare rate of achieving theophylline therapeutic level and side effects between two regimens of aminophylline therapy in preterm infants.

Materials and Methods: Infants of gestational age less than 35 weeks and birthweight less than 2,000 grams who required aminophylline treatment or prophylaxis for apnea of prematurity were randomly allocated to one of two groups. Group 1 received an intravenous aminophylline loading dose at 5 mg/kg and then maintenance at 6 mg/kg/day. Group 2 received a loading dose at 8 mg/kg and maintenance at 4 mg/kg/day. Serum theophylline levels were measured at 2 to 3 hours after the loading dose and before the sixth maintenance dose. Apnea episodes, heart rate, and urine volume were closely monitored.

Results: Twenty-two infants were enrolled to each group. No differences of gestational age, birthweight, and indication were found among the two groups. At 2 to 3 hours after the loading dose, infants of group 2 had significantly higher rate of serum theophylline levels within the therapeutic range than group 1 (59.1% vs. 4.5%). This difference was not observed before the sixth maintenance dose. Frequency of apnea episodes was not different between the two groups. Only infants of group 2 had significant increases in heart rate after the loading dose. Both groups had significant increased in urine output volume after the loading dose.

Conclusion: The high loading-low maintenance regimen of aminophylline had advantage in achieving the therapeutic level more rapidly, whereas the low loading-high maintenance regimen had lower risk of tachycardia. Physicians should weigh between benefit and risk before choosing a regimen of aminophylline for preterm infants.

Keywords: Aminophylline, Theophylline, Apnea of prematurity

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Apnea of prematurity is a common problem in preterm infants, secondary to immaturity of respiratory control and instability of upper airway. Methylxanthine including caffeine and theophylline is the standard pharmacologic treatment of apnea of prematurity by stimulating respiratory center and improving respiratory muscle function[1,2]. Prophylactic methylxanthine has also been used for facilitating endotracheal extubation in preterm infants[3]. Since caffeine is not available in Thailand, aminophylline (theophylline ethylenediamine), which has bioavailability approximately 80% of theophylline[1,4], is widely used. The common side effects of aminophylline include tachycardia, diuresis, hyperglycemia, irritability, and feeding intolerance[5-8]. Cases of toxicity, seizure, and dysrhythmias were described[5]. The regimen of aminophylline treatment for apnea of prematurity is controversial[1,4]. Most neonatal intensive care units in Thailand use an aminophylline loading dose at 8 mg/kg and maintenance doses at 4 mg/kg/day[4]. The authors rather use lower loading and higher maintenance doses of aminophylline because of concern of the side effects. To date, there have been controlled trials to determine the pharmacokinetics and optimal aminophylline dosage in preterm infants but the data on its safety is limited[9-12]. Therefore, the authors conducted a study to compare the rate of achieving serum therapeutic level and side effects between two regimens of aminophylline therapy in preterm infants.

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Materials and Methods

A randomized controlled trial was conducted in

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the infants admitted to the neonatal intensive care unit at Phramongkutklao Hospital. The inclusion criteria were infants with gestational age less than 35 weeks and birthweight less than 2,000 grams who required aminophylline for treatment of apnea of prematurity or for prophylaxis before endotracheal extubation. The age at enrollment was less than one week. The infants were excluded if they had other identified causes of apnea, congenital anomalies of cardiorespiratory or genitourinary systems, or parental refusal to participate in the study.

After obtaining parental informed consent, the eligible infants were allocated by using opaque sealed envelopes and block of 4-randomization. Group 1 (low loading-high maintenance regimen) received an intravenous loading dose of aminophylline at 5 mg/kg and then maintenance doses at 2 mg/kg every 8 hours, beginning at 8 hours after the loading dose. Group 2 (high loading-low maintenance regimen) received an intravenous loading dose of aminophylline at 8 mg/kg and then maintenance doses at 2 mg/kg every 12 hours, beginning at 12 hours after the loading dose. Serum theophylline levels, using florescent polarization immunoassay technique, were measured at 2 to 3 hours after the loading dose, and at 30 minutes before the sixth maintenance dose. The target of serum theophylline level at therapeutic range was 7 to 12 mcg/mL.

Apnea of prematurity was defined as a respiratory pause longer than 15 seconds or accompanying bradycardia and desaturation[13,14]. Heart rate and oxygen saturation were monitored continuously by central monitor and database was recorded every 30 minutes. Clinical response as decreasing frequency of apnea episodes was monitored for 72 hours after initiation of treatment. Side effects of aminophylline after the loading dose as tachycardia, polyuria, and hyperglycemia were assessed by monitoring heart rate for 72 hours and urine output for eight hours and blood glucose levels for four hours. The monitoring of other side effects and occurrence of vomiting and seizure was continued for 72 hours after initiation of aminophylline treatment. Tachycardia was defined as heart rate above 180 beats/minute. A subsequent dose of aminophylline was withheld if the infant had tachycardia before the next scheduled dose. Aminophylline dosages were adjusted by physicians if a serum theophylline level was above 12 mcg/mL or below 7 mcg/mL without improvement of apnea episodes. The research protocol was approved by the Royal Thai Army Institutional Review Board.

Statistical analysis

Sample size was calculated based on the difference in rate of achieving the therapeutic range at 36%[9] with type I error of 0.05 and power of 0.80. The number of infants needed in each group was 22. Comparisons between groups were analysed by using Mann-Whitney U test for continuous data and Chi-square or Fisher's exact test for categorical data. Comparisons within group between before and after loading doses were analysed by using Wilcoxon signed ranks test. SPSS version 15.0 was used for performing statistical analysis. A p-value less than 0.05 was considered as statistically significant.

Results

Twenty-two infants were enrolled to each study group. No differences of gender, gestational age, birthweight, age at initiation of treatment and indication were found (Table 1). At 2 to 3 hours after a loading dose, serum theophylline levels of group 2 were significantly higher than group 1 (Table 2). Infants of group 2 had higher rate of achieving theophylline levels within the therapeutic range than group 1 (Table 2). However, serum theophylline levels and the rate of achieving therapeutic level were not different before the sixth maintenance dose. One infant of group 1 had serum theophylline level above 12 mcg/mL before the sixth maintenance dose.

There was no difference in the rate of apnea episodes after aminophylline treatment (Table 3). One infant of group 1 had frequent apnea episodes requiring endotracheal intubation at 60 hours of age. Dosages of aminophylline were adjusted in two infants of group 2 after the sixth maintenance dose due to no improvement in apnea with serum theophylline levels below the therapeutic range.

When compared the heart rate within eight hours after loading dose, only infants of group 2 had significant increases in heart rate from baseline (Table 4). Three (13.6%) infants of group 2 exhibited heart rate above 180 beats/minute (Table 4). After 24 hours of aminophylline treatment, both groups had significant increases in heart rate compared to baseline. However, there were no differences of heart rate and rate of tachycardia between the groups (Table 4). Aminophylline was temporarily withheld in two infants of group 1 due to tachycardia just before the sixth maintenance dose. No correlation between serum theophylline levels and the heart rate was demonstrated.

Within 8 hours after the loading dose, infants of both groups had significant increases in urine

volume compared to baseline (Table 4). There were no significant changes of blood glucose levels from baseline within each group (Table 4). When compared between the groups, no differences of urine volume and blood glucose levels were demonstrated (Table 4). No infants of both groups developed vomiting or seizure throughout 72 hours after initiation of aminophylline treatment.

Discussion

Pharmacokinetics and pharmacodynamics of theophylline in newborn infants are significantly different from those in older children and adults. In newborn infants, theophylline has prolonged half-life

Table 1. Baseline characteristics of the infants using low loading-high maintenance regimen (group 1) and high loading-low maintenance regimen (group 2)

Characteristics	Group 1 (n = 22)	Group 2 (n = 22)	*p*-value*
Male gender, n (%)	11 (50.0)	11 (50.0)	1.000
Gestational age (week)#	31 (26, 34)	31 (25, 34)	0.830
Birthweight (g)#	1,519 (1,175, 2,000)	1,400 (720, 2,000)	0.404
Weight for gestational age, n (%)			0.600
Appropriate for gestational age	20 (90.9)	19 (86.4)	
Small for gestational age	2 (9.1)	2 (9.1)	
Large for gestational age	0 (0.0)	1 (4.5)	
Delivery: caesarean section, n (%)	14 (63.6)	12 (54.5)	0.540
Apgar scores#			
At 1 minute	8 (1, 9)	8 (3, 10)	0.971
At 5 minute	9 (5, 9)	9 (5, 10)	0.569
Mode of ventilation support, n (%)			0.953
None	1 (4.5)	1 (4.5)	
NCPAP/nasal IMV	12 (54.5)	11 (50.0)	
Conventional/HFV	9 (40.9)	10 (45.5)	
Age at initiation of treatment (hour)#	10.8 (1.4, 81.2)	8.1 (0.4, 73.5)	0.360
Indication of treatment			1.000
Apnea/desaturation	13 (59.1)	13 (59.1)	
Prophylaxis before extubation	9 (40.9)	9 (40.9)	

g = gram; NCPAP = nasal continuous positive airway pressure; IMV = intermittent mandatory ventilation; HFV = high frequency ventilation

* Mann-Whitney U test

Data presented as median (min, max)

Table 2. Comparison of serum theophylline levels between the two groups

Data	Group 1 (n = 22)	Group 2 (n = 22)	*p*-value*
Time measuring serum theophylline level after a loading dose (hour)#			
The first specimen	2.00 (2.00, 3.50)	2.52 (2.00, 3.00)	0.215
The second specimen	48.00 (47.00, 75.00)	71.50 (67.00, 107.50)	<0.001
Serum theophylline levels (mcg/mL)#			
At 2 to 3 hours after a loading dose	5.00 (2.40, 9.50)	7.20 (2.50, 11.70)	0.001
Before the sixth maintenance dose	8.95 (5.40, 12.80)	8.10 (4.30, 11.40)	0.086
Range of serum theophylline levels, n (%)			
At 2 to 3 hours after a loading dose			<0.001
• <7 mcg/mL	21 (95.5)	9 (40.9)	
• 7 to 12 mcg/mL	1 (4.5)	13 (59.1)	
• >12 mcg/mL	0 (0.0)	0 (0.0)	
Before the sixth maintenance dose			0.150
• <7 mcg/mL	2 (9.1)	7 (31.8)	
• 7 to 12 mcg/mL	19 (86.4)	15 (68.2)	
• >12 mcg/mL	1 (4.5)	0 (0.0)	

mcg/mL = microgram per millilitre

* Mann-Whitney U test

Data presented as median (min, max)

ranging from 13 to 29 hours, relatively large volume of distribution, and prolonged elimination[1,11,15]. To achieve the therapeutic levels, a loading dose followed by maintenance doses is needed. The serum levels of theophylline within therapeutic range in newborn infants (7 to 12 mcg/mL) are lower than in adults, and slightly lower than those associated with early signs of toxicity[1,5]. In addition, there is substantial inter-individual variability in pharmacokinetic properties of theophylline[15-17]. Therefore, it is necessary to monitor serum theophylline levels and adjust the dose accordingly. The proper time to monitor serum theophylline levels should be at 1 to 4 hours after an intravenous loading dose, and after 1 to 2 half-lives to ensure that they have reached the therapeutic levels[1,6,15]. Further blood samples should be measured whenever no clinical response or toxicity is suspected[6].

The result of the present study corresponded to a previous study that compared the effect of aminophylline between using a high (8 mg/kg) and a low (6 mg/kg) loading doses[9]. Both studies showed that the first serum theophylline levels and the rate of achieving the desired target range were significantly higher in the group receiving a higher loading dose. These differences between the groups were not observed at the time before receiving the fifth or sixth maintenance doses. One infant of group 1 had serum theophylline level of 12.8 mcg/mL before the sixth maintenance dose. We did not adjust dosage of aminophylline in this infant since he did not experience any side effect and repeated serum theophylline was within therapeutic range.

Regarding clinical response, we were not able to demonstrate the improvement of apnea episodes after the treatment since some infants received aminophylline for prophylaxis before endotracheal extubation. One infant of group 1 required endotracheal intubation at 60 hours after the treatment due to frequent apnea episodes; though, the serum theophylline levels was 9 mcg/mL. We postulated that infection was the most

Table 3. Comparison of apnea episodes between the two groups

Data	Group 1 (n = 22)	Group 2 (n = 22)	*p*-value*
Frequency of apnea episodes			
Before treatment	1 (0, 7)	1 (0, 2)	0.248
After treatment (hour)			
• 0 to 24	1 (0, 10)	1 (0, 6)	0.300
• 24 to 48	1 (0, 8)	0 (0, 10)	0.537
• 48 to 72	0 (0, 5)	0 (0, 4)	0.269
Differences in frequency of apnea episodes			
After (hour) vs. before treatment			
• 0 to 24	0 (-5, 9)	0 (-2, 5)	0.894
• 24 to 48	0 (-6, 7)	0 (-2, 8)	0.294
• 48 to 72	0 (-7, 4)	0 (-2, 4)	0.885

* Mann-Whitney U test

Data presented as median (min, max)

Table 4. Heart rate, urine volume, and blood glucose levels compared within each group and compared between two groups

Data	Group 1 (n = 22)	*p*-value*	Group 2 (n = 22)	*p*-value*	*p*-value**
Heart rate (beats/minute)					
Before treatment	149.93 (126.75, 167.50)		139.50 (121.67, 162.00)		0.149
After treatment (hour)					
• 0 to 4	147.88 (116.38, 173.00)	0.935	142.88 (120.00, 187.00)	0.007	0.842
• 4 to 8	149.50 (119.00, 175.00)	0.808	150.75 (117.25, 189.38)	0.008	0.453
• 8 to 24	154.66 (130.00, 177.75)	0.073	153.55 (133.00, 179.94)	0.001	0.907
• 24 to 48	157.42 (140.67, 179.35)	0.005	157.17 (136.83, 181.40)	<0.001	0.656
• 48 to 72	165.20 (146.00, 176.67)	<0.001	163.97 (148.83, 180.00)	<0.001	0.639
Urine (mL/kg/hour)					
Before treatment	2.57 (0.00, 6.00)		0.69 (0.00, 5.88)		0.078
After treatment (hour)					
• 0 to 4	4.77 (0.00, 11.67)	0.001	4.48 (0.49, 11.60)	<0.001	0.842
• 4 to 8	5.00 (1.97, 10.21)	<0.001	5.54 (1.33, 8.33)	<0.001	0.925
Blood glucose (mg/dL)					
Before treatment	81.00 (34.00, 135.00)		74.50 (30.00, 141.00)		0.581
After treatment (hour)					
• 2 to 4	84.00 (50.00, 135.00)	0.603	76.50 (57.00, 137.00)	0.407	0.534

mL = millilitre; kg = kilogram; mg = milligram; dL = decilitre

* Comparison within each group between before and after initiation of aminophylline treatment by using Wilcoxon signed ranks test

** Comparison between two groups by using Mann-Whitney U test

Data presented as median (min, max)

likely cause of apnea in this infant.

Tachycardia is one of the most common side effects of aminophylline treatment. Therefore, we monitored heart rate for the first eight hours after initiation of treatment to determine the immediate effect of the loading dose. We demonstrated a significant increase in heart rate within eight hours in the group receiving an 8 mg/kg loading dose. Moreover, three infants of this group had heart rate above 180 beats/minute. Although this issue was not raised in previous studies[9-12], these findings bring up a concern. Thus, closely heart rate monitoring is essential when using the high loading dose of aminophylline therapy in preterm infants.

After 24 hours of aminophylline treatment, we continued to monitor heart rate to determine the accumulative effect of maintenance doses. We observed that heart rates continued to increase, and more infants developed tachycardia in both groups. Tachycardia in preterm infants could be related to many conditions that were not evaluated in the present study such as infection, hypoxia, dehydration, or hyperthermia. Moreover, no correlation between heart rate and serum theophylline levels before the sixth maintenance doses was found. It is difficult to conclude whether the ongoing increased heart rate was directly due to the effect of aminophylline. We suggested that not only after a bolus dose, heart rate should be continuously monitored throughout the course of aminophylline treatment. Whenever an infant developed tachycardia, the next scheduled dose of aminophylline should be withheld. Measurement of serum theophylline level and adjustment of the aminophylline dosage accordingly should be considered.

Aminophylline has diuretic effect due to increased renal blood flow and the inhibition of solute reabsorption in various segments of nephron[18,19]. A previous study reported that marked diuresis occurred immediately after a loading dose but did not last after 24 hours despite continuation of therapy[19]. Likewise, we demonstrated a significant diuretic effect within eight hours after the loading dose in both groups. Since the present study did not assess fluid balance and signs of dehydration, it was not possible to determine whether the diuretic effect of aminophylline aggravated the effect of increasing heart rate in preterm infants.

Conclusion

The high loading-low maintenance regimen of aminophylline had advantage in achieving the therapeutic level more rapidly, whereas the low loading-high maintenance regimen had lower risk of tachycardia. Physicians should weigh between benefit and risk before choosing a regimen of aminophylline for preterm infants. Close observation on the side effects is strongly suggested during the treatment. Whenever side effect or no clinical response is observed, adjustment of the dosage, or interval of aminophylline administration should be considered.

What is already known on this topic?

Aminophylline is useful for treatment or for prophylaxis of apnea of prematurity in preterm infants[20]. The side effects include tachycardia and diuresis.

What this study adds?

The present study showed the advantage in achieving the therapeutic level more rapidly in the high loading-low maintenance regimen of aminophylline, whereas there was higher risk of tachycardia. On the other hand, therapeutic level was also achieved when using low loading-high maintenance regimen of aminophylline, though, at slower rate with lower risk of tachycardia.

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Potential conflicts of interest

The authors declare no conflict of interest.

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