# Serum Theophylline Concentrations in very Preterm Neonates Receiving Intravenous Aminophylline for Apnea

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## ABSTRACT

**Objective:** To determine the percentage of neonates who achieved therapeutic theophylline level (TTL) after receiving standard IV loading/maintenance aminophylline doses. To assess factors associated with achieving therapeutic theophylline concentrations and to describe adverse effects of aminophylline.

**Materials and Methods:** This was a pilot, cross-sectional study. Preterm neonates ≤34 weeks' gestation for which aminophylline was indicated for treatment of apnea were enrolled. Standard IV aminophylline dosage is 8 mg/kg loading dose, followed by 1.5 mg/kg maintenance dose every 8 hours. Serum theophylline concentrations were measured prior to the 8th maintenance dose. Descriptive statistics, univariate and multivariate analyses were performed.

**Results:** Twenty-five neonates (52% female) were enrolled: mean (standard deviation) gestational age and birth weight were 30.4 (2) weeks and 1,277 (415) grams, respectively. Aminophylline was initiated at a median (25%tile, 75%tile) postnatal age of 4 (1, 8) days. Baseline heart rate prior to the loading dose was 153 (13) beats-per-minute. Sixty percent of neonates achieved a therapeutic theophylline level. In the univariate analysis, being male and postnatal age ≤5 days were associated with successfully achieving a TTL. After adjusting for gender, postnatal age ≤5 days was the only factor associated with achieving a TTL (adjusted odds ratio 17.7, 95% confidence interval: 1.9, 164.4). Tachycardia and feeding intolerance were observed in 44% and 24% of neonates, respectively.

**Conclusion:** Current IV aminophylline dosing conditions in Thailand achieved TTL in approximately two-thirds of neonates, suggesting therapeutic drug monitoring is beneficial for guiding dosing. A higher maintenance dose could be considered for neonates older than 5 days.

**Keywords:** Aminophylline; apnea of prematurity; therapeutic drug monitoring; serum theophylline concentration; therapeutic drug level (Siriraj Med J 2021; 73: 526-531)

## INTRODUCTION

Apnea of prematurity (AOP) is one of the most common problems in very preterm neonates. The incidence of AOP is inversely correlated with gestational age.[1] Intermittent hypoxia secondary to AOP may activate pro-inflammatory cytokines and cascades, disturb bone metabolism, retinal development and cause cardiovascular instability.[2] Prolonged apnea and delayed resolution

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beyond 36 weeks of postmenstrual age is associated with an increased risk of neurodevelopmental disturbances.[3] Treatment for AOP, including respiratory support and medications, should be considered when apneic episodes become frequent and/or prolonged.[4] Methylxanthine therapy is considered the first-line treatment for AOP while doxapram is the second-line treatment used for refractory cases.[4] Caffeine citrate is the preferred choice for methylxanthine due to its once-a-day dose, broad therapeutic index and good safety profile.[1] Unfortunately, widespread access to Caffeine citrate is not yet available in Thailand and aminophylline remains the main methylxanthine available for treatment of AOP. Aminophylline is made up of theophylline and ethylenediamine (approximately 80% theophylline).

Theophylline-induced seizures have also been reported in neonates.[5] Due to its narrow therapeutic index, serum theophylline concentration (STC) measurement is commonly performed to ensure that a therapeutic drug level (TDL) between 7-12 mcg/mL is administered and to avoid any toxic reaction.[6,7] As routine STC is not available in many local hospitals in Thailand, we performed this pilot study to evaluate the necessity of measuring STC when following standard aminophylline IV dosing recommendations of 8 mg/kg per loading dose, then 1.5-3 mg/kg/dose every 8-12 hours.[8]

The objectives of this study were as follows: (1) determine STC in neonates receiving standard aminophylline IV dosing in Thailand; (2) assess factors associated with achieving TDL of theophylline; and (3) to describe adverse effects of aminophylline in neonates.

## MATERIALS AND METHODS

### *Design*

A single center, observational, cross-sectional study.

### *Setting*

The study was conducted at the Division of Neonatology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University between August 2015 and July 2016. Siriraj Hospital is a tertiary referral center with approximately 8,000 deliveries per year. Neonates were recruited for the study while in the neonatal intensive care unit (NICU) or the intermediate care unit.

### *Participants and intervention*

We enrolled preterm neonates less than or equal to a 34 week gestation period who were prescribed IV aminophylline for treatment of AOP. Neonates were excluded if they were receiving concomitant medications that could affect the pharmacokinetics of aminophylline such as phenobarbital, phenytoin, erythromycin and propranolol; had received aminophylline within 7 days prior to enrollment; had acute renal insufficiency or abnormal liver function test result; had congenital anomalies with CNS involvement; were referred back to local hospital; were dead; had no inform consent obtained from their parents.

Aminophylline dosing used to treat AOP at Siriraj Hospital was an 8 mg/kg loading dose, followed by an initial maintenance dose of 1.5 mg/kg every 8 hours. The aminophylline dose was prescribed by the attending physician as per standard of care. Prior to the 8$^{th}$ maintenance dose, one milliliter of blood was drawn for quantification of STC. Drug concentrations were determined using the ARCHITECT ci4100 Integrated Immunoassay and Clinical Chemistry System (Abbott 2009 USA).

### *Outcome measurement*

The primary outcome was the percentage of neonates who achieved TDL. Meanwhile, secondary outcomes were factors associated with success in achieving TDL and the adverse effects of aminophylline, including tachycardia, feeding intolerance and abnormal neurological symptoms.

Demographic data and clinical characteristics of neonates were collected from medical records. All neonates were monitored for adverse effects and toxicity of aminophylline by bedside nurses at NICU.

### *Operational definitions*

Acute renal insufficiency was defined as oliguria <1 ml/kg/h within 12 hours before enrollment or serum creatinine ≥1.6 mg/dL, 1.1 mg/dL and 1 mg/dL in preterm neonates ≤27 weeks, 28-29 weeks and 30-32 weeks gestation, respectively.[9] An abnormal liver function test was defined as total bilirubin >2 mg/dL, Aspartate aminotransferase (AST) >140 IU/L, or Alanine transaminase (ALT) >50 IU/L.[10]

Adverse effects of aminophylline recorded were tachycardia, which is defined as a heart rate of >180 beats-per-minute within 24 hours after loading dose; feeding intolerance, defined as residual gastric content >50% of feeding volume at least once within 24 hours after loading dose, and abnormal neurological symptoms, i.e., seizure and lethargy.

### *Statistical analysis*

This was a pilot study of 25 neonates. The data was analyzed using PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics, including frequency and percentage, mean and standard deviation (SD), or median and 25%tile and 75%tile were used as appropriate for type

and distribution of data. A comparison of continuous data was carried out using unpaired t-test or Mann-Whitney U test depending on data distribution. Chi-square test or Fisher's exact test was used for categorical variables and those with a *p*-value <0.2 from univariate analysis were chosen for multivariate analysis using binary logistic regression analysis. A *p*-value of <0.05 was accepted as statistically significant.

### *Ethics*

The study protocol was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 317/2015). A written informed consent was obtained from all parents.

## RESULTS

Between August 2015 and July 2016, 99 neonates born at less than or equal to 34 weeks' gestation were assessed for eligibility. A total of 25 neonates were enrolled (Fig 1) and the baseline characteristics of neonates are summarized in Table 1.

Median (25%tile, 75%tile) loading dose of aminophylline was 8 (8, 8.5) mg/kg and median (25%tile, 75%tile) maintenance dose was 1.5 (1.5, 1.5) mg/kg/dose every 8 hours. Mean STC was 6.9 ± 1.6 mcg/mL and the percentage of neonates who achieved TDL was 60%. None of the neonates had a STC >12 mcg/mL. Among the neonates who achieved TDL, there was a higher percentage of males and had a lower postnatal age compared to those neonates who did not achieve therapeutic STC (Table 2). After adjusting for gender, a postnatal age of ≤5 days was significantly associated with achieving TDL (adjusted odds ratio 17.7; 95% confidence interval 1.9, 164.4).

Tachycardia was reported in 11 (44%) neonates and spontaneously resolved over time without any treatment. Feeding intolerance occurred in 6 (24%) neonates: and 4 neonates were placed on NPO until the results of work up for cause of apnea came back normal, after which feeding was resumed; one neonate was treated for suspected sepsis, and the remaining neonate had continuation of feeding but with less milk. None of the enrolled neonates had any abnormal neurological symptoms.

## DISCUSSION

Following the current standard IV aminophylline dosing conditions for AOP in Thailand, 60% of neonates achieved TDL of theophylline. Factors associated with achieving TDL were being male and a postnatal age of ≤5 days. After adjusting for gender, postnatal age was the only factor associated with achieving TDL. Adverse effects associated with intravenous aminophylline were tachycardia and feeding intolerance in 44% and 24% of neonates, respectively.

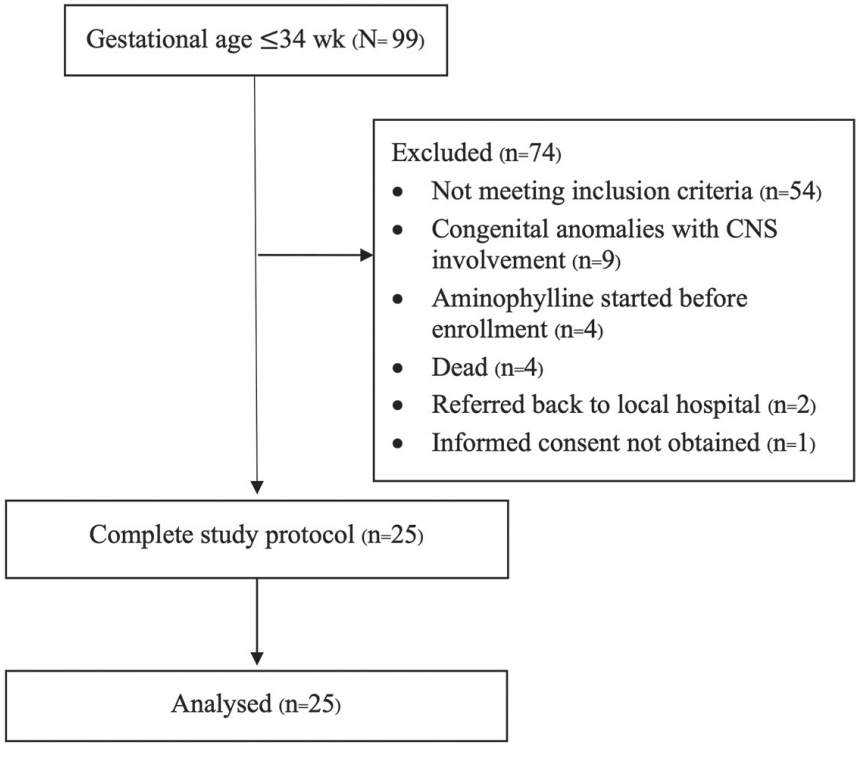


**Fig 1.** Diagram demonstrating the flow of participants.

**TABLE 1.** Demographic and clinical characteristics of infants (N=25).

| Characteristics | N = 25 |
|---|---|
| Female, n (%) | 13 (52) |
| Gestational age, week* | 30.4 ± 2 |
| Birth weight, gram* | 1278 ± 415 |
| Weight for gestational age, n (%) | |
| Small for gestational age | 6 (24) |
| Appropriate for gestational age | 18 (72) |
| Large for gestational age | 1 (4) |
| Apgar score† | |
| 1 minute | 8 (4.25, 8.75) |
| 5 minute | 9 (7.25, 9) |
| Postnatal age, day† | 4 (1, 8) |
| Heart rate before aminophylline loading, bpm* | 152.8 ± 13.1 |

†median (25%tile, 75%tile)
*mean ± standard deviation
**Abbreviation:** bpm, beat-per-minute

**TABLE 2.** Factors associated with achieving therapeutic drug level of theophylline and adverse effects of aminophylline.

| | Achieving therapeutic drug level | | *p*-value |
|---|---|---|---|
| | Yes (n=15) | No (n=10) | |
| Gestational age, week | 30.8 ± 1.9 | 29.9 ± 2.2 | 0.30 |
| Birth weight, gram | 1354 ± 371.9 | 1161 ± 468.8 | 0.26 |
| Gender, n (%) | | | 0.04* |
| Female | 5 (33.3) | 8 (80) | |
| Male | 10 (66.7) | 2 (20) | |
| Small for gestational age, n (%) | | | 0.65 |
| Yes | 3 (20) | 3 (30) | |
| No | 12 (80) | 7 (70) | |
| Postnatal age, day† | 2 (1, 4) | 7.5 (5.5, 15) | 0.005* |
| Postnatal age ≤ 5 days, n (%) | 13 (86.7) | 2 (20) | 0.002* |
| Serum theophylline concentration† | 7.5 (7.4, 8.1) | 5.5 (5.0, 6.3) | <0.001* |
| Adverse effects | | | |
| Tachycardia, n (%) | 7 (46.7) | 4 (40) | 1.0 |
| Feeding intolerance, n (%) | 6 (40) | 0 | 0.05 |

† median (25%tile, 75%tile)
*p-value <0.05 indicates statistical significance

Due to the narrow therapeutic range of theophylline, it is common practice to measure STC. Adjustments of aminophylline dosage and repeated blood draws for STC is often necessary to obtain drug levels in the therapeutic range. This iatrogenic blood loss can lead to excessive blood transfusion in some cases. Several studies have assessed different aminophylline dosing regimens to ensure TDL of theophylline and to reduce the need for dosage adjustments and repeating STC. A study of infants with birth weight ≤1,500 g with postnatal age range of 1-52 days comparing the loading dose of 8 mg/kg versus 6 mg/kg of aminophylline, followed by the maintenance dose of 2 mg/kg every 8 hours, had a 79% and 74% success rate in achieving TDL respectively.[6] These success rates were higher than the success rate observed in our study, possibly due to a higher maintenance dose. Another study, performed in infants with gestational age less than 35 weeks, birth weight less than 2,000 g with postnatal age range of 0.4-81.2 hours, compared low loading dose (5 mg/kg) and high maintenance dose (6 mg/kg/day, divided into 3 times) vs high loading dose (8 mg/kg) and low maintenance dose (4 mg/kg/day, divided twice) and noted a TDL success rates of 86% and 68% respectively.[11] This indicates that our starting maintenance dose of 1.5 mg/kg every 8 hours may be suboptimal. None of the participants in our study had a STC higher than 12 mcg/mL, so we still have room within the therapeutic window to increase the maintenance dose of aminophylline. Interestingly, this previous study limited the postnatal age of participants to less than 7 days[11] which related to our finding that a lower postnatal age (≤5 days) was associated with achieving TDL. Developmental changes in organs of premature neonates can have a major impact on drug distribution, metabolism and elimination. These developmental changes in pharmacokinetics have been shown to be highly dependent on postnatal age, gestational age and postmenstrual age of the neonate.[7] The relationship between postnatal age and achieving TDL in our study supports postnatal age as a major factor. However, we did not find any association between gestational age and achieving TDL. Bhatt, *et al*[12] used different equations to predict maintenance theophylline dosages for neonates younger than and older than 30 weeks' gestation and the overall success rate of achieving TDL was 74% with requirements for dosage adjustments reduced by 50%.[12] We found that males had a higher chance of achieving TDL of theophylline than females. However, after adjusting for postnatal age ≤5 days, gender was not significantly associated with achieving TDL. The only factor associated with achieving TDL was a postnatal age ≤5 days. However, the adjusted odds ratio of postnatal age had a wide confidence interval, likely due to the relatively small sample size.

Pharmacodynamics in preterm neonates is also affected by developmental changes of the organs, resulting in differences in the expected efficacy or toxicity of theophylline. We observed tachycardia in 44% of participants, however, there was no association between TDL of theophylline and the occurrence of tachycardia. Feeding intolerance may be associated with STC since we observed this adverse event only in neonates who achieved TDL of theophylline. However, feeding intolerance is common in premature infants, especially during the first week of age. None of the participants had any abnormal neurological symptoms. Though these adverse effects were not severe and resolved spontaneously, we recommended that adverse effects should always be monitored and therapeutic drug monitoring is necessary to avoid aminophylline toxicity.

### *Limitation of this study*

Due to concerns of excessive blood loss in these preterm neonates, we only collected one time-point for the measurement of STC. Also, as this was a pilot study with a small sample size, the ability to make firm conclusions is limited.

## CONCLUSION

The current standard intravenous aminophylline dosing achieved TDL in 60% of neonates. A maintenance dose higher than 1.5 mg/kg every 8 hours could be considered, especially for neonates older than 5 days' postnatal age. Therapeutic drug monitoring should be performed where possible to ensure therapeutic levels and reduce the risk of theophylline toxicity.

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