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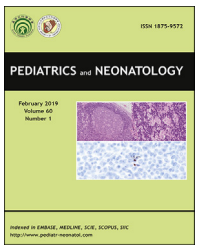

Original Article

Factors affecting the efficacy and safety of aminophylline in treatment of apnea of prematurity in neonatal intensive care unit

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Key Words
aminophylline;
apnea of prematurity;
concentration;
efficacy;
factor

Background: The factors affecting the safety and efficacy of aminophylline use in the treatment of apnea of prematurity (AOP) in the neonatal intensive care unit (NICU) are not clear. In this study, we aimed to evaluate the potential factors affecting the efficacy and safety of aminophylline in AOP treatment at standard doses and to determine appropriate patients for this therapy.

Methods: Over a 3-year period (January 2012 to December 2014), the medical records of 206 preterm infants with apnea who were admitted to the NICU of our hospital to receive aminophylline infusions were retrospectively reviewed. These infants were subjected to routine theophylline monitoring by reversed-phase high performance liquid chromatography. The primary outcome measures were the efficacy of aminophylline treatment and adverse reactions observed upon administration.

Results: One-hundred and twenty-seven (61.65%) infants were considered to have undergone effective therapy and classified accordingly. Gestational age, body weight at the initiation of aminophylline, and serum theophylline concentration were identified as protective factors of therapeutic efficacy. Receiver operating characteristic (ROC) analysis indicated cutoff values of 30.36 weeks for gestational age and 1.69 kg for body weight at initiation of aminophylline administration for ensuring high efficacy of aminophylline for AOP. Fifty-three (25.73%) infants had adverse reactions. Birth weight and serum concentration of theophylline were associated with an increased risk of adverse reactions, with odds ratios of 0.167 and 1.346, respectively. The ROC curves indicated a birth weight cutoff value of 1.48 kg.

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Conclusion: Infants with apnea and gestational age >30.36 weeks, body weight at initiation of aminophylline treatment above 1.69 kg, and birth weight >1.48 kg are suitable for treatment with aminophylline. Monitoring of serum theophylline concentration should be implemented in the absence of clinical response or in case of suspected adverse reactions.

1. Introduction

Apnea of prematurity (AOP) is the most common clinical condition of premature newborns, potentially leading to multiple organ dysfunction and affecting the mental development of neonates.[1,2] Although respiratory malfunction and suboptimal neurodevelopment of preterm newborns are considered to be the basis for developing apnea,[3,4] the exact pathogenesis of primary AOP is not clear.[5] Current guidelines derived from expert consensus include choices of medication as well as respiratory supportive therapy.[3,6]

The methylxanthine aminophylline, an IV form of theophylline, is often used to treat AOP.[6,7] The pharmacological mechanism underlying its action is multifactorial, and it also has immunomodulatory effects.[8] Due to its narrow therapeutic window,[6] several adverse effects have been associated with aminophylline use at doses recommended for the treatment of AOP, such as tachycardia, irritability, vomiting, high blood sugar, and gastrointestinal bleeding.[9,10] Therefore, there are still some controversies surrounding optimal dosage regimens and desired serum theophylline concentrations during the therapeutic administration of aminophylline for AOP.[6,11] The judicious use of aminophylline with close monitoring of its concentration is essential to reach efficacy and maintain safety in its therapeutic window. Recently, aminophylline has been superseded by caffeine citrate in many developed countries.[10–13] However, caffeine citrate is expensive, and drug shortages may be frequent in some parts of the world, especially in developing countries. In addition, more studies examining the effects of caffeine in preterm infants at higher risk of apnea are needed, including important clinical outcomes such as neonatal morbidity, length of hospital stay, and long term development.[11] On the contrary, aminophylline is inexpensive compared with caffeine, and the clinical use value in treating AOP is confirmed despite certain disadvantages.[9,14] Aminophylline may still be the preferred therapy for some apnea patients.

Skouroliakou reported that serum concentration of theophylline, when it was within the recommended therapeutic range, was not significantly associated with apnea events,[15] indicating other factors may affect the efficacy of aminophylline in the treatment of AOP. Evaluation of the factors influencing the efficacy and safety of aminophylline may help determine appropriate patients for the treatment of aminophylline. Currently, only a few reports have examined the factors associated with either the efficacy and safety of theophylline for AOP treatment.[6,9] In addition, gestational age, post-conceptional age, and birth weight are the risk factors for AOP.[16,17] Whether these risk factors are associated with either therapeutic efficacy or adverse reactions related to aminophylline administration for the treatment of AOP is still unclear. Current available data suggest the following factors influence the population pharmacokinetics of theophylline in premature infants with apnea: gestational age, post-conceptional age, body weight, parenteral nutrition, oxygen support, and the volume of distribution.[18–20] Unfortunately, the correlations between these factors and treatment outcomes have not been clearly explored.

We conducted a retrospective analysis of routine monitoring data on premature infants in our hospital, with the goal to identify factors that influence the effectiveness and safety of aminophylline in the treatment of AOP, when administered at a regular dosage. It reinforces the need for therapeutic drug monitoring in the NICU. Through the above results, we hope to clarify the clinical application of aminophylline for AOP in suitable patients.

2. Methods

2.1. Subjects

We performed a retrospective review of preterm infants admitted to the NICU at our hospital from January 2012 to December 2014 with the diagnosis of apnea and receiving intravenous aminophylline (theophylline ethylenediamine) as treatment. The study protocol was approved by the hospital ethics committee. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Analysis was conducted using anonymized data. Apnea is defined as cessation of breathing lasting more than 20 s except in the presence of bradycardia (heart rate < 100 bpm), hypoxia (oxygen saturations < 85%), cyanosis, or pallor, in which case the duration may be shorter.[21] We identified preterm infants who received aminophylline infusion for apnea through an established electronic medical record (EMR) after excluding exhibiting major congenital anomalies, metabolic diseases, neuromuscular disorders, seizures, serious infections, intracranial hemorrhage-grade II, anemia, sepsis, severe gastroesophageal reflux, patent ductus arteriosus, or neonatal necrotizing enterocolitis which could cause episodes of secondary apneas during the study period. Treatment was performed if an infant had ≥3 apneic attacks requiring vigorous intervention within 24 h.

All patients were started on intravenous aminophylline at a standard loading dose of 6 mg/kg over 30 min followed by maintenance dose of 2—6 mg/kg/day, divided into two or three doses a day.[15,19] The basic recruitment flow chart for the study is shown in Fig. 1.

2.2. Data collection

The following basic parameters for each apnea patient treated with aminophylline were collected: sex, gestational age, birth weight, post-conceptional age at initiation of aminophylline administration, body weight at initiation of aminophylline administration, presence/absence of oxygen support, feeding situation, enteral nutrition, creatinine clearance rate, liver enzyme blood levels, and aminophylline dosage regimens. Data reflecting therapeutic efficacy were collected as well as adverse reactions such as number of apnea events, tachycardia, irritation, abdominal distension, anorexia, high blood glucose, and electrolyte disorder. During the treatment period, the levels of blood glucose and electrolytes were monitored every two days.

Serum trough level of theophylline was measured via reversed-phase high performance liquid chromatography (RP-HPLC) analysis one week after treatment was started. The blood samples (1 mL) were collected 15 min prior to the administration of maintenance doses, and only one blood sample per patient was analyzed in our study. The serum sample (200 μL) was mixed with 20 μL of caffeine solution (internal standard) and 3 mL of organic phase (chloroform and ethyl acetate mixture in 1:1 v/v ratio) in a 10 mL polytetrafluoroethylene (PTFE) tube. The samples were ultrasonicated for 2 min, followed by centrifugation at 20 °C for 5 min at 2500 g. Supernatant (2 mL) was decanted and dried in a N2 atmosphere at 60 °C in a water bath. Subsequently, the residue was dissolved in 1 μL of methanol solution. RP-HPLC was performed using Agilent 1200 RP-HPLC (Agilent Technologies, Palo Alto, CA) equipped with a manual injector and a XDB-C18 column (Agilent Technologies, Palo Alto, CA) containing an octadecyl silica (ODS) column (Agilent Technologies, Palo Alto, CA). The mobile phase comprised two buffers: buffer A (distilled H2O) and buffer B (methanol). Ten microliters of the above sample was injected into the RP column. The column was eluted by an isocratic gradient of 22/78 (v/v) methanol-water at 30 °C for 12 min at a total solvent flow rate of 1.0 mL/min. Absorbance was measured at 275 nm. The detection limit was 0.05 mg/L.

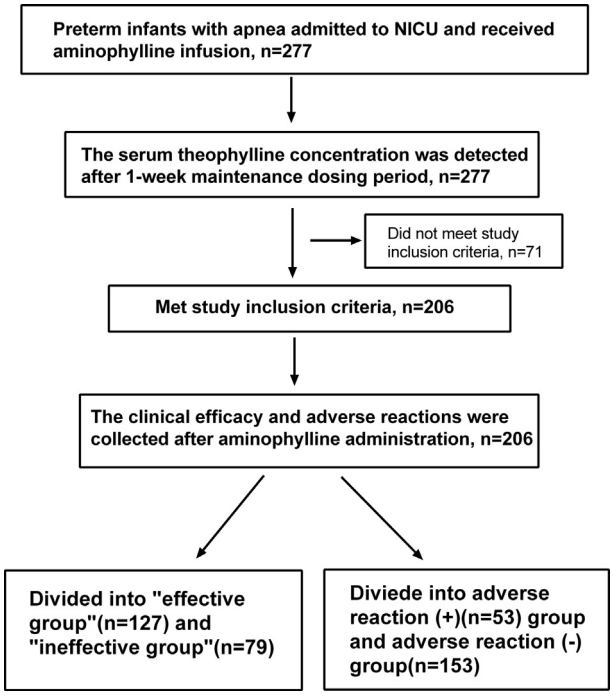

Figure 1 Study design and recruitment flow chart.

2.3. Outcomes measurement

Apneic episodes were monitored by ECG monitor and pulse oximetry before and after aminophylline administration. Apnea events were counted when nurses noted the cessation of breathing lasting more than 20 s or shorter but accompanied by hypoxia (oxygen saturations <85%) or bradycardia (heart rate <100 bpm) in premature infants. Patients were divided into the effective and ineffective groups based on the efficacy of treatment. We mainly studied the therapeutic effect of aminophylline rather than prevention of apneic episodes. Effective was defined in this study as apnea frequency (number of apnea events per day) less than 1 for a period of 8—12 days after aminophylline administration.[15] All infants whose condition did not meet this criterion were categorized as ineffective. The adverse reactions of aminophylline were assessed when physicians noted tachycardia, irritation, abdominal distension, anorexia, high blood glucose, and electrolyte disorder, in which other etiologies were ruled out after aminophylline administration (time interval 8—12 days). Each group was further classified into two subgroups based on observed adverse reactions following aminophylline treatment as noted by pediatricians during treatment: adverse reaction (+) group and adverse reaction (−) group.

2.4. Statistical analysis

Enumeration data and categorical data were expressed as means ± standard deviation (SD) and numbers, respectively, and were subjected to statistical analysis using analysis of variance, chi-square test, and multivariate regression. Moreover, univariate crude odds ratios (OR) with 95% confidence intervals (CIs) for significant factors associated with the therapeutic efficacy and adverse reactions in premature infants were calculated using multiple logistic regression analyses. A receiver operating characteristic (ROC) curve for the efficacy or safety of aminophylline administration was created, with area under the curve (AUC) recorded, to determine cutoff values. All data were analyzed using statistical software NASDAQ: SPSS Statistics 17.0 from SPSS Inc. A p-value less than 0.05 was considered statistically significant.

3. Results

Overall, 206 infants (122 males, 84 females) met inclusion criteria, and all 206 patients received respiratory support

while receiving IV aminophylline. The demographic characteristics of the patients are summarized in Table S1.

3.1. Effectiveness

Based on the criteria stated above, 127 (61.65%) infants were in the effective group and 79 (38.35%) infants in the ineffective group. Notably, 42 infants in the ineffective group had more than two episodes of apnea per day after aminophylline administration over a period of 8–12 days. The dose of aminophylline in 48 infants in the ineffective group was increased modestly, and the enhanced treatment was effective in 22 (45.83%) of these infants.

Table 1 shows the clinical characteristics of the effective and ineffective groups. Statistically significant differences were observed in gestational age ($p < 0.001$), birth weight ($p < 0.001$), body weight at the initiation of aminophylline administration ($p < 0.001$), and serum concentrations of theophylline ($p = 0.005$). As shown in Fig. S1, these characteristics were significantly higher in the effective group than in the ineffective group.

From multiple logistic regression analysis, gestational age, body weight at initiation of aminophylline administration, and serum concentration of theophylline were shown to act as predictive factors for the efficacy of aminophylline treatment of AOP, with ORs of 1.351 (95% CI: 1.070–1.705; $p = 0.011$), 3.272 (95% CI: 1.004–10.662; $p = 0.049$), and 1.164 (95% CI: 1.005–1.348; $p = 0.042$), respectively. Fig. 2 shows the ROC curve of these three factors. Gestational age was shown to be the most significant predictor of efficacy, with an AUC of 0.705 (95% CI: 0.633–0.778; $p < 0.001$) (Fig. 2). The gestational age cutoff value of 30.36 weeks had a specificity of 65.9% and a sensitivity of 68.4% in predicting the efficacy of aminophylline treatment. The ROC curves obtained for body weight at the initiation of aminophylline therapy also showed significance in predicting efficacy of aminophylline treatment, with an AUC of 0.691 (95% CI: 0.618–0.764; $p < 0.001$) (Fig. 2). The cutoff value of 1.69 kg for this factor had a specificity of 59.7% and a sensitivity of 74.7% in predicting the efficacy of aminophylline treatment. In contrast, the ROC curves for serum concentration of theophylline had an AUC of 0.581 (95% CI: 0.501–0.661; $p = 0.044$), indicating low predictive value of this parameter (Fig. 2).

3.2. Safety

Among the 206 infants, 53 (25.73%) were in the adverse reaction (+) group, and the remaining 153 (74.27%) were classified as adverse reaction (−). We properly reduced the aminophylline dose in 25 infants in the adverse reaction (+) group, and the symptoms of 21 (84.00%) infants improved.

The adverse reactions observed included gastrointestinal reactions, electrolyte disturbance, hyperglycemia, and tachycardia. Within the adverse reaction (+) group, 23 infants had more than one adverse reaction. Table 2 shows details of infants in the adverse reaction (+) and the adverse reaction (−) groups. Male to female ratio, gestational age, birth weight, body weight at initiation of aminophylline therapy, serum concentration of theophylline, and serum alanine aminotransferase levels were significantly different between the two groups according to Table 2. As shown in Fig. S2, the levels of serum concentration of theophylline and serum alanine aminotransferase were significantly higher, while birth weight and body weight at initiation of aminophylline administration were significantly lower in the adverse reaction (+) group than in the adverse reaction (−) group.

Multiple logistic regression analysis of the factors affecting the safety of aminophylline therapy showed that birth weight and serum concentration of theophylline were

Table 1 Characteristics of infants who were classified into the effective group based on the efficacy of aminophylline in treating AOP.

Characteristic	Effective, mean ± SD (range)	Ineffective, mean ± SD (range)	p-Value
Sex (M/F) — no.[a]	127 (73/54)	79 (49/30)	0.519
Gestational age (days)	30.93 ± 1.78	29.76 ± 1.64	<0.001
Birth weight (kg)	1.53 ± 0.33	1.35 ± 0.24	<0.001
Postnatal age (days)[b]	10.10 ± 9.63	9.37 ± 7.27	0.561
Body weight (kg)[b]	1.76 ± 0.38	1.54 ± 0.34	<0.001
Aminophylline use duration (days)	17.28 ± 6.21	25.73 ± 10.23	<0.001
Serum concentration of theophylline (mg/L)	5.44 ± 3.11	4.47 ± 1.77	0.005
Serum creatinine (μmol/L)	60.20 ± 16.50	63.56 ± 17.17	0.165
ALT (U/L)	7.15 ± 3.72	6.18 ± 2.93	0.050
AST (U/L)	38.69 ± 34.15	37.20 ± 31.34	0.755
Respiratory support			
Supplemental oxygen-air mixture— no.[a]	88	53	0.741
Nasal CPAP — no.[a]	39	26	
Enteral feeding (Y/N) — no.[a]	113/14	65/14	0.227
Mean apnea frequency	0.45 ± 0.27	2.28 ± 1.00	<0.001

CPAP, continuous positive airway pressure.
[a] Number.
[b] at initiation of aminophylline.

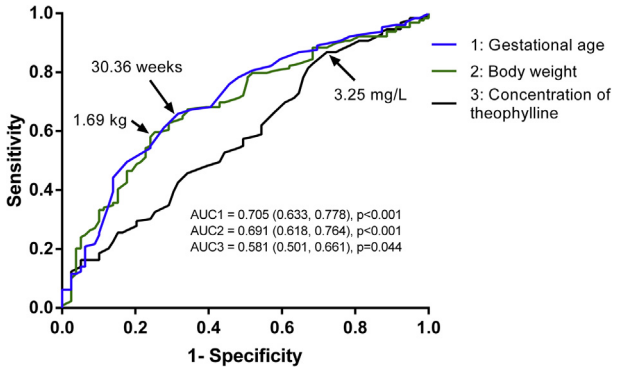

Figure 2 Receiver operating characteristic curve for predicting efficacy of aminophylline in treating AOP based on gestational age, body weight at the beginning of aminophylline administration, and serum concentration of theophylline (N = 206). 1: Blue, gestational age. 2: Dark green, body weight. 3: Black, serum concentration of theophylline. Data are expressed as medians (95% CI).

associated with an increased risk of adverse reactions, with ORs of 0.167 (95% CI: 0.029—0.953; p = 0.044) and 1.346 (95% CI: 1.157—1.568; p < 0.001), respectively. The ROC curves for serum concentration of theophylline, with an AUC of 0.718 (95% CI: 0.641—0.794; p < 0.001), indicate that this parameter is a significant predictor of safety (Fig. 3). At a cutoff of 5.15 mg/L, it had a specificity of 62.3% and a sensitivity of 72.9% in predicting adverse reactions resulting from aminophylline treatment. However, there were no statistically significant differences in the serum concentrations of theophylline among infants exhibiting different types of adverse reactions. The predictive value of birth weight for adverse reactions was lower, with an AUC of 0.612 (95% CI: 0.526—0.698; p = 0.015) (Fig. 3).

4. Discussion

The current study demonstrated that aminophylline is efficacious in treating infants with AOP in the NICU setting. Efficacy was observed in 61.65% of cases, while the incidence of adverse reactions was 25.73%. We further evaluated the clinical presentations of study subjects and identified the risk factors influencing the effectiveness and safety of aminophylline at regular doses for the treatment of AOP in premature infants.

Gestational age, birth weight, and body weight at the initiation of aminophylline therapy were significantly higher in the effective group than in the ineffective group. These factors are considered to affect the occurrence and development of apnea.[16] Eichenwald EC et al. showed that the underlying mechanism of AOP is immaturity of respiratory control, and that the incidence of AOP is inversely related to gestational age.[2,22] Taken together, these results indicate that the efficacy of aminophylline is associated with the degree of prematurity in infants. Multiple logistic regression analysis shows that gestational age and body weight at initiation of aminophylline treatment predict clinical efficacy. ROC curves reveal the cutoff for gestational age at 30.36 weeks and body weight at initiation of aminophylline administration at 1.69 kg (Fig. 2). Therefore, excluding other secondary causes of apnea, aminophylline therapy could be appropriate for AOP in infants with gestational ages >30.36 weeks and body weights >1.69 kg at the start of aminophylline treatment.

The serum trough level of theophylline was detected via RP-HPLC analysis. Data indicate that the serum concentration of theophylline was significantly higher in the effective group than in the ineffective group. Boutroy and colleagues confirmed that serum concentration of theophylline as low as 1.3 mg/L was related to effectiveness of aminophylline administration in treating AOP,[23] consistent with our results. Furthermore, multiple logistic regression

Table 2 Characteristics of infants who were classified into the adverse reaction (+) group based on the appearance of adverse reactions.

Characteristic	Adverse reaction (+), mean ± SD (range)	Adverse reaction (−), mean ± SD (range)	p-Value
Sex (M/F) — no.[a]	53 (24/29)	153 (98/55)	0.017
Gestational age (days)	30.26 ± 1.81	30.56 ± 1.82	0.244
Birth weight (kg)	1.36 ± 0.26	1.49 ± 0.32	0.008
Postnatal age (days)[b]	9.26 ± 7.13	10.01 ± 9.31	0.594
Body weight (kg)[b]	1.56 ± 0.39	1.72 ± 0.37	0.010
Serum concentration of theophylline (mg/L)	6.52 ± 3.43	4.56 ± 2.22	<0.001
Serum creatinine (μmol/L)	61.19 ± 16.13	61.59 ± 17.15	0.879
ALT (U/L)	7.62 ± 4.26	6.48 ± 3.10	0.078
AST (U/L)	48.57 ± 46.15	34.50 ± 26.30	0.039
Respiratory support			
Supplemental oxygen-air mixture— no.[a]	33	108	0.261
Nasal CPAP — no.[a]	20	45	
Enteral feeding (Y/N) — no.[a]	45/8	133/20	0.711
Mean heart rate (bmp)	150.58 ± 19.94	141.56 ± 5.35	<0.001

CPAP, continuous positive airway pressure.
[a] Number.
[b] at initiation of aminophylline.

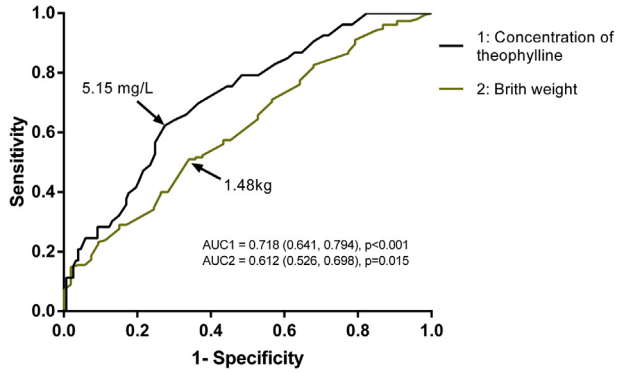

Figure 3 Receiver operating characteristic curve for predicting safety of aminophylline use in treatment of AOP based on serum concentration of theophylline and birth weight (N = 206). 1: Black, serum concentration of theophylline. 2: Dark green, birth weight. Data are expressed as medians (95% CI).

analysis showed that the efficacy of aminophylline treatment, at regular doses, is positively correlated with serum concentration of theophylline. On the contrary, Skouroliakou et al. found that no correlation could be established between serum concentration of theophylline after being administered at standard doses and apnea events in 37 infants.[15] This discrepancy might be due to the small number of participants and different ethnic background of the patients. In addition, theophylline is extensively metabolized in premature infants into its major metabolic product caffeine which is comparably effective in treating AOP.[10,23] This might also have affected the efficacy outcome in our study, i.e. low predictive value of serum concentration of theophylline with respect to treatment efficacy (Fig. 2). The ROC curve for serum concentration of theophylline, with an AUC of 0.581 (95% CI: 0.501—0.661; p = 0.044), indicated a cutoff value of 3.25 mg/L with a specificity of 86.8% and a sensitivity of 27.8% in predicting the efficacy of aminophylline in treating AOP (Fig. 2). Moreover, we increased the dose of aminophylline in 48 infants in the ineffective group and found that the enhanced treatment was effective in 22 (45.83%) of these infants. These findings suggest that the effectiveness of aminophylline in treating AOP is partially dependent on serum theophylline concentration and a level above 3.25 mg/L may benefit some patients who failed the treatment using regular dose.

Results of multiple logistic regression analysis showed that serum concentration of theophylline and birth weight were closely associated with the incidence of adverse events resulting from aminophylline treatment. The ROC curves indicate a serum concentration of theophylline cutoff value of 5.15 mg/L and a birth weight cutoff value of 1.48 kg (Fig. 3). When the aminophylline dose was downgraded in 25 infants in the adverse reaction (+) group, the symptoms of 21 (84.00%) infants improved. These results show that a higher serum concentration of theophylline is more likely to result in adverse reactions. The safety of aminophylline for AOP treatment could be guaranteed in premature infants with serum theophylline concentration lower than 5.15 mg/L and birth weight greater than 1.48 kg when using aminophylline as a treatment for AOP.

As a retrospective review of medical records, this study has limitations. First, apnea was not detected by polysomnography. In this study, apnea episodes were monitored by an ECG monitor and pulse oximetry and the events were counted by nurses. This may underestimate the frequency of apnea. Second, aminophylline use was selected by clinician's preference rather than randomization. The definition of "effectiveness" is thus not sufficiently objective. There may be unmeasured confounders associated with our observation, such as individual difference in attending physicians, nursing care, and medical devices. In addition, even though aminophylline did not eliminate all episodes of apnea, it may prevent additional episodes of apnea. Third, there might be a bias in reporting adverse reactions since physicians were not blinded. Fourth, due to the limited conditions, we did not study neurodevelopmental outcomes of patients in our work. Therefore, a prospective study with a larger sample population needs to be performed to investigate the factors concerned with the efficacy and safety of aminophylline use in AOP treatment. Recently, caffeine has been investigated for its possible advantages over aminophylline in treating very premature infants.[10,12,13] It is desirable to perform subsequent studies by using caffeine in very premature infants who fail aminophylline treatment.

In conclusion, we investigated the clinical features of infants who received aminophylline as a treatment for AOP over a period of 8—12 days and identified factors associated with the efficacy and safety of aminophylline treatment. Our data suggest that aminophylline treatment is probably appropriate for apneic infants with gestational age >30.36 weeks, body weight above 1.69 kg at initiation of aminophylline, and birth weight >1.48 kg. Possible adjustment of aminophylline dose based on serum concgs4entrations and lack of clinical response in conjunction with monitoring of adverse reaction should be implemented in clinical practice.

Conflicts of interest

All authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pedneo.2018.03.008.