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No Requirement for Targeted Theophylline Levels for Diuretic Effect of Aminophylline in Critically Ill Children

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Objectives: To determine the relationship between theophylline trough levels and urine output in critically ill children administered aminophylline as adjunctive diuretic therapy.

Design: Retrospective cohort study.

Setting: The PICU of a tertiary care children's hospital.

Patients: A mixed population of medical/surgical including postoperative cardiothoracic surgery patients less than 18 years old.

Interventions: Electronic medical records of all PICU patients admitted from July 2010 to June 2015 were reviewed, and patients who received aminophylline as diuretic therapy were identified.

Measurements and Main Results: Patient cohort data including demographics, daily aminophylline, furosemide and chlorothiazide dosing, theophylline trough levels, fluid intake, urine output and total fluid balance, blood urea nitrogen, and creatinine levels were abstracted. Multivariate analysis based on a generalized estimating equations approach demonstrated that aminophylline administration, when analyzed as a categorical variable, was associated with an increase in urine output and decreased fluid balance. However, aminophylline dosing, when analyzed as a continuous variable, was associated with neither an increase in urine output nor decreased fluid balance. Theophylline trough levels were not correlated with urine output at 24 hours ($p = 0.78$) and were negatively correlated with urine output at 48 hours ($r^2 = 0.078$; $p < 0.005$).

Conclusions: Aminophylline administration provided a measure of increased diuresis, regardless of dosage, and theophylline trough levels. Therefore, achieving a prescribed therapeutic trough level may not be necessary for full diuretic effect. Because, as opposed to the diuretic effect, the side effect profile of aminophylline is dose-dependent, low maintenance dosing may optimize the balance between providing adjunctive diuretic effect while minimizing the risk of toxicity. (*Pediatr Crit Care Med* 2018; 19:e425–e432)

Key Words: aminophylline; diuretic; fluid balance; pediatric intensive care unit; theophylline

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

Drs. Tamburro and Halstead disclosed off-label product use of aminophylline as a diuretic. Dr. Tamburro's institution received funding from the U.S. FDA Office of Orphan Product Development Grant Program, and he disclosed that Ony, LLC provided calfactant free of charge for the above listed U.S. FDA Office of Orphan Product Development Grant. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/PCC.0000000000001608

Early fluid resuscitation of critically ill pediatric patients has been become standard of care (1, 2). However, once a patient is stabilized, the focus must change to preventing or treating fluid overload as it is a risk factor for PICU mortality (3, 4) and has been associated with prolonged mechanical ventilation (5, 6). Typically, the first line of therapy for fluid overload in pediatric patients is intermittent furosemide, although some studies suggest that continuous furosemide administration is more beneficial than intermittent furosemide dosing due to more stable hemodynamics and improved urine output (UOP) (7). However, continuous infusions of furosemide are often prohibited in pediatric patients due to drug compatibility issues and the lack of a dedicated IV lumen. Furosemide is rarely used alone, and adjunctive diuretics such as chlorothiazide and spironolactone have been used for decades in pediatric patients (8).

The use of methylxanthine derivatives as diuretic adjuncts was first described in adults with congestive heart failure in the 1950s (aminophylline) (9), and as an adjunctive diuretic in 1978 (theophylline) (10), although their use in critically ill children was not reported until the late 1990s (11–13). Aminophylline

is a methylxanthine derivative, a soluble compound of theophylline and ethylenediamine, that has bronchodilator properties through inhibition of phosphodiesterase type IV at high concentrations (> 10 μg/mL). However, it exhibits diuretic effects at lower concentration (2–3 μg/mL) via adenosine receptor antagonism (12), probably by acting as an afferent arteriole vasodilator and improving glomerular blood flow. Aminophylline is useful as prophylaxis against tacrolimus-induced nephrotoxicity (14), although it does not prevent acute kidney injury (AKI) in children following cardiopulmonary bypass (15). The pharmacokinetics of theophylline/aminophylline have recently been investigated in children following congenital heart surgery with cardiopulmonary bypass and revealed that lower dosages were needed in this population to target serum concentrations of 5–10 mg/L (16).

Our institution recently published a prospective, open-label study of the administration of aminophylline to 35 critically ill pediatric patients and examined its effects on UOP and inflammatory profiles (17). In this study, patients were administered an initial bolus of IV aminophylline, and dosing was adjusted to maintain theophylline levels 4–8 μg/mL. In this previous study, a large proportion (20%) had side effects including agitation, increased nasogastric output, cardiac ectopy, and tachydysrhythmias. Whether the maintenance of a minimum theophylline level is necessary for effective diuresis has never been examined. We hypothesized that low dose aminophylline therapy would be an effective diuretic regardless of theophylline trough level. We undertook a retrospective, single-center study of theophylline trough concentrations and UOP before and after the initiation of aminophylline diuretic therapy in a tertiary care PICU to determine whether theophylline trough levels would correlate with the change in UOP after the initiation of aminophylline.

MATERIALS AND METHODS

Study Design and Participants

This study is a single-center, retrospective chart review of patients who received aminophylline as an adjunctive diuretic during PICU admission between July 2010 and June 2015. To answer our primary research question of whether aminophylline/theophylline trough levels were correlated with diuresis, we screened patients less than 18 years old admitted to the PICU who were prescribed intermittent IV aminophylline for inclusion using the Pharmnet system by Cerner (Kansas City, MO). Patients were excluded if they 1) received continuous aminophylline infusion for bronchodilator purposes, 2) received aminophylline less than 48 hours after admission (so that adequate baseline laboratory values and UOP could be assessed), 3) received aminophylline for less than 48 hours, 4) received dialysis during admission, and 5) expired within 48 hours of admission. The Institutional Review Board of the Pennsylvania State University College of Medicine approved the study (STUDY00003422) prior to any patient screening or data collection.

Standard Aminophylline Dosing and Monitoring

The administration and dosing of aminophylline for diuresis were protocolized in our PICU prior to this study (17), and this Penn State Health Medical Center aminophylline dosing and monitoring guideline were built into our provider order entry system as an order set (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A667). However, all decisions regarding the initiation, dosing, frequency of dosing, and termination of aminophylline were made at the discretion of the clinical team. Typically, per the guideline, a loading dose of 3 mg/kg of aminophylline was administered IV, and maintenance dosing was administered based on the patient's age. Because aminophylline is the 2:1 complex salt of theophylline and ethylenediamine, the laboratory measure of aminophylline levels is a serum theophylline concentration. Per the guideline, serum theophylline trough levels were drawn every morning, and dosing was adjusted to targeted trough concentrations of 4–8 μg/mL, although changes were made at the discretion of the attending physician and the clinical team.

Patient Screening and Data Collection

Patient data were collected from the Cerner Electronic Medical Record and transferred into a secure electronic database using REDCap software (Research Electronic Data Capture, Vanderbilt University). Data collected included admission date and time, sex, age, race, height (cm), weight (kg), diagnosis, details of aminophylline administration (including aminophylline loading dose and maintenance dosing, date and time), laboratory values including theophylline trough levels collected the morning after initiation, blood urea nitrogen (BUN) and serum creatinine (sCr) values, total fluid intake, and output from 48 hours before to 48 hours after the initiation of aminophylline therapy. For consistency, the 24 hours fluid intake, UOP, and fluid balance were recorded at 7 AM each day, and output included urinary drainage tube, indwelling foley catheter, or diaper weight. The use of inotropes and vasopressors, as well as other diuretics, was collected.

Statistical Analysis

Summary statistics including means and SDS were computed for continuous variables (i.e., UOP) and frequencies and percentages were determined for categorical variables (i.e., ethnicity, diagnosis). For this and future analyses, clinical time intervals were defined relative to the initiation of aminophylline administration, for example, the period 24–48 hours prior to initiation was defined as "day –2," the period 0–24 hours prior to initiation was defined as "day –1," etc. All fluids, including intake, output, and balance, were recorded hourly, and hourly UOP was averaged over each 24 hours period and divided by the patients' last recorded weight prior to the administration of aminophylline. The percent daily fluid balance was also calculated as fluid balance (L)/weight (kg) × 100 (18).

Correlation analysis between UOP and theophylline concentration was conducted based on Pearson's correlation coefficient. The normality assumption was checked based on the Shapiro tests; thus, paired *t* tests or Wilcoxon signed-rank tests were used to assess the changes in primary (UOP) and secondary outcomes (e.g., sCr, BUN, fluid balance) before and after aminophylline initiation, as appropriate. Generalized estimating equation (GEE) regression models, a form of multivariate

TABLE 1. Demographics of Patients Fulfilling Eligibility Criteria

Characteristics	*n* (%)
Age	
3 d to 6 wk	21 (5.22)
6 wk to 6 mo	49 (42.6)
6 mo to 1 yr	22 (19.1)
1–9 yr	21 (18.3)
9–12 yr	3 (2.61)
12–18 yr	14 (12.2)
Ethnicity	
Asian	2 (1.74)
Black	11 (9.57)
Mixed	3 (2.61)
Unknown	14 (12.2)
White	85 (73.9)
Diagnosis	
Apnea	3 (2.61)
Leukemia/lymphoma	4 (3.48)
Other	2 (1.74)
Respiratory failure	67 (58.3)
Sepsis	5 (4.35)
Surgical, congenital heart	25 (21.7)
Surgical, general	9 (7.83)

TABLE 2. Frequency of Various Aminophylline Dosing Regimens, Other Diuretics Vasoactive Medications, and Other Medication Administration

Class	Medication	*n* (%)
Aminophylline dosing		
	Loading dose	44 (38.3)
	Maintenance dosing, mg/kg/dose	
	1.5	55 (48)
	2.0	29 (25)
	3.3	13 (11)
Other diuretics		
	Furosemide	110 (95.7)
	Chlorothiazide	56 (48.7)
	Spironolactone	10 (8.70)
Inotropes/vasopressors		
	Epinephrine	4 (3.57)
	Dobutamine	57 (49.6)
	Dopamine	1 (0.92)
	Milrinone	35 (31.5)
	Norepinephrine	0 (0)

analysis used to estimate the variables of a generalized linear model with a possible unknown correlation between outcomes, were employed to investigate the marginal association between potential risk factors and UOP or fluid balance with daily repeated measures, where the variable estimates were obtained by Quasi-likelihood approach, and the *p* values for significance were based on Wald tests. The analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC), and the statistical significance threshold of *p* value of less than 0.05 was applied for all hypothesis testing.

RESULTS

Study Population and Characteristics

A total of 452 patients admitted to our PICU during the 5-year period received aminophylline. Since our primary research question was whether theophylline levels were correlated with diuretic effect, we only included patients for whom 48 hours of baseline characteristics could be recorded, and then who received at least 48 hours of maintenance dosing of aminophylline. Therefore, 337 patients were excluded based upon criteria, leaving 115 patients for analysis. The patient population was predominantly young with 67% of the patient being less than 1 year old (**Table 1**) and overwhelmingly Caucasian (*n* = 85; 73.9%). The most common diagnosis was respiratory failure (*n* = 67; 58.3%), which included bronchiolitis, viral and bacterial pneumonia, and status asthmaticus (Table 1). The second most common diagnosis was surgical, congenital heart (*n* = 25; 21.7%).

Forty-four of the 115 patients (38.3%) received an aminophylline loading dose, although more frequently only aminophylline maintenance dosing was given (**Table 2**). Maintenance aminophylline dosing varied by age per protocol and physician discretion: 55 patients (48%) received 1.5 mg/kg/dose, 29 patients (25%) received 2 mg/kg/dose, and 13 patients (11%) received 3.3 mg/kg/dose of aminophylline. Only 13 of the patients had dose adjustments within 48 hours, three patients had dosing decreased due to high theophylline levels, and 10 patients had dosing increased due to low theophylline levels. A large proportion of our patients received furosemide, whereas chlorothiazide was less frequently used, and spironolactone was only administered on occasion (Table 2). It is a common practice in our PICU to use low dose inotropes (dobutamine) to increase cardiac output and indirectly increase renal perfusion. This fact, and our inclusion of surgical, congenital heart patients, accounts for our relatively frequent use of dobutamine, milrinone, and epinephrine in patients being administered diuretics (Table 2).

Diuretic Dosing

The total daily dosing of aminophylline averaged 8.2 ± 2.9 mg/kg/d on day +1 and 7.0 ± 2.9 mg/kg/d on day +2, with the

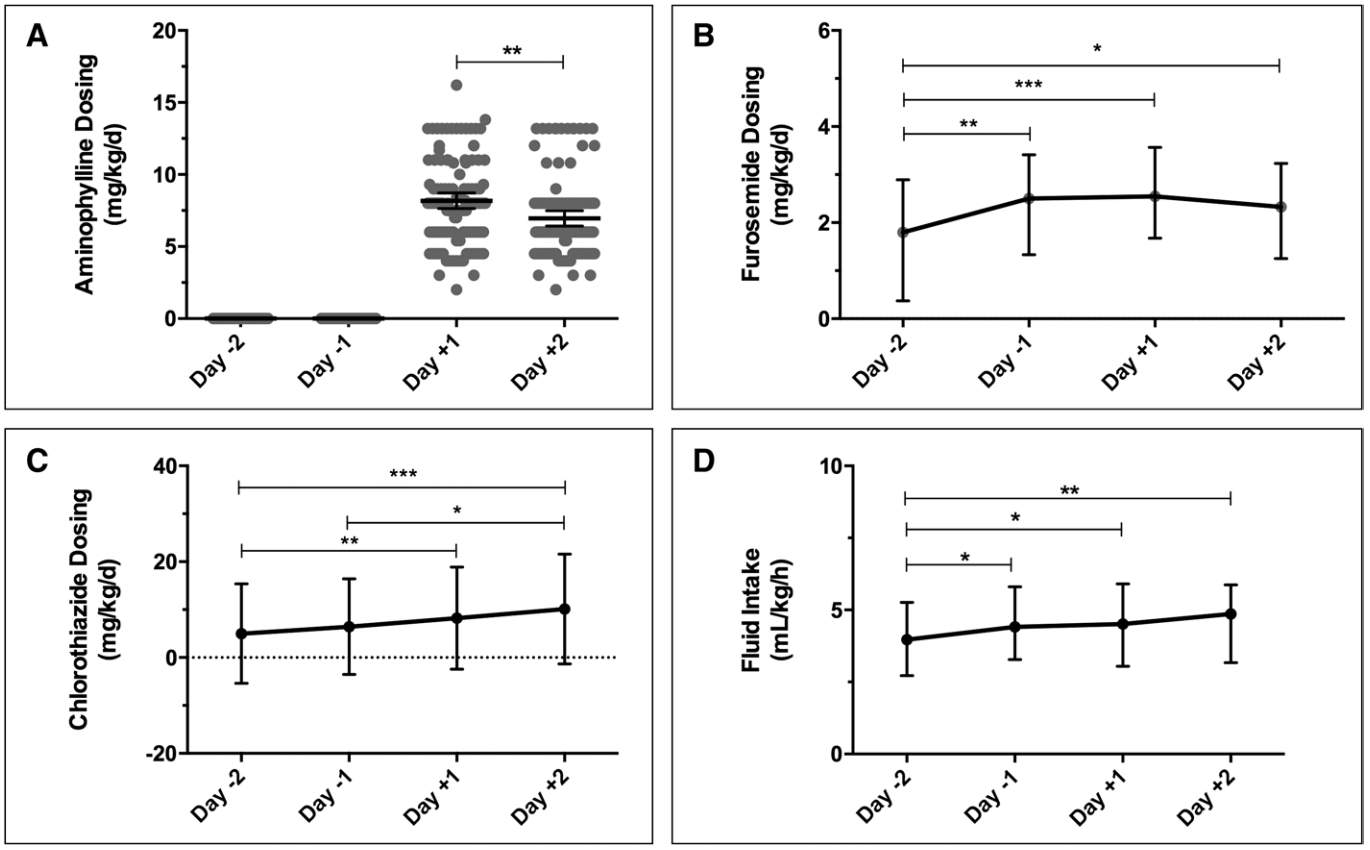

Figure 1. Diuretic dosing and fluid intake before/after aminophylline initiation. Scatter dot plot of daily aminophylline dosing of individual patients before (days −2, −1) and after (days +1, +2) aminophylline initiation (**A**). Furosemide dosing significantly increased during the study period (**B**), as did chlorothiazide dosing (**C**), and fluid intake (**D**). Statistical differences were calculated using nonparametric comparisons for each pair using the Wilcoxon method ($^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$).

difference between days likely being due to bolus dosing being included in average daily dosing on day +1 (**Fig. 1*A***). In our PICU, aminophylline is administered as an adjunctive diuretic; therefore, it is not surprising that furosemide (**Fig. 1*B***) and chlorothiazide (**Fig. 1*C***) dosing also increased significantly during the 4-day study period. Importantly, no patients received alternative diuretics such as mannitol or acetazolamide during the study period to enhance UOP. Interestingly, total fluid intake also increased significantly during the study period (**Fig. 1*D***).

Aminophylline and UOP

Average hourly UOP (mL/kg) increased significantly with the addition of aminophylline as compared with the day –2 and day –1 preaminophylline baseline (**Fig. 2*A***). Theophylline troughs at 24 hours did not correlate with day +1 average hourly UOP ($p = 0.78$) (**Fig. 2*B***), but the 48 hours theophylline levels did correlate with day +2 average hourly UOP ($r^2 = 0.080$; $p = 0.0022$), although interestingly this relationship had a negative slope (**Fig. 2*C***). Aminophylline therapy was assessed in two different ways in our statistical analyses: as a categorical variable (0, 1) where all patients were aminophylline "0" on days –2 and –1, then aminophylline "1" on days +1 and +2 and as a continuous variable using the total daily aminophylline dosage (mg/kg/d), where on days –2 and –1 this value was "0 mg/kg/d." Univariate analysis demonstrated that the administration of aminophylline (categorical variable) was associated with increased UOP ($p < 0.0001$), whereas the amount of aminophylline administered or dosing (mg/kg/d, continuous variable) did not correlate with UOP ($p = 0.59$).

We next investigated what factors, in addition to aminophylline administration, were associated with increased diuresis. Univariate analysis demonstrated that total daily furosemide dosing ($p < 0.0001$), chlorothiazide dosing ($p < 0.0001$), and fluid intake ($p < 0.0001$) were all significantly correlated with UOP over the 4-day time period, whereas inotrope and vasopressor use were not. A multivariate analysis using a GEE approach for repeated measures analysis was employed to investigate the association between UOP and the fluid intake and the administration of diuretics. Multivariate analysis demonstrated continued correlations with furosemide dosing ($p = 0.0001$), chlorothiazide dosing ($p = 0.0168$), fluid intake ($p < 0.0001$), and aminophylline administration when analyzed as a categorical variable ($p < 0.0001$) (**Table 3**).

Aminophylline and Fluid Balance

Given the ultimate importance of fluid balance in critically ill pediatric patients, the relationship between aminophylline administration and daily fluid balance (% volume/weight) was also examined (**Fig. 3*A***). Fluid balance decreased significantly after the initiation of

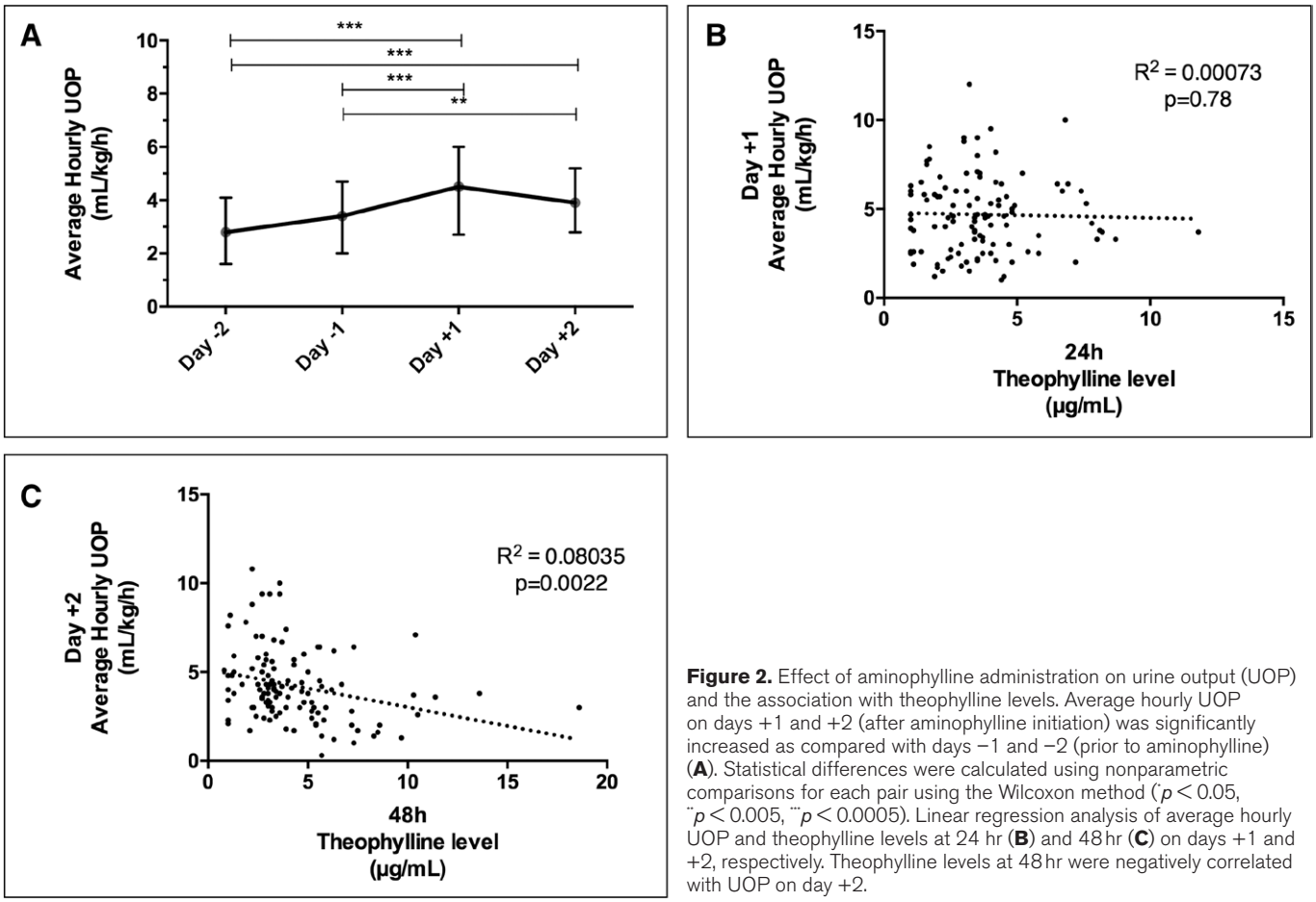

Figure 2. Effect of aminophylline administration on urine output (UOP) and the association with theophylline levels. Average hourly UOP on days +1 and +2 (after aminophylline initiation) was significantly increased as compared with days −1 and −2 (prior to aminophylline) (**A**). Statistical differences were calculated using nonparametric comparisons for each pair using the Wilcoxon method ($^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$). Linear regression analysis of average hourly UOP and theophylline levels at 24 hr (**B**) and 48 hr (**C**) on days +1 and +2, respectively. Theophylline levels at 48 hr were negatively correlated with UOP on day +2.

TABLE 3. Linear Regression Analysis of Factors Associated With Urine Output by Generalized Estimating Equation

Factor	Estimate	SE	*p*
Aminophylline (yes/no)	0.7583	0.1365	< 0.0001
Furosemide dosing (mg/kg/d)	0.2079	0.0541	0.0001
Chlorothiazide dosing (mg/kg/d)	0.0206	0.0086	0.0168
Fluid intake (mL/kg/hr)	0.5772	0.0421	< 0.0001

aminophylline on day +1 and day +2. The relationships between theophylline levels and fluid balance were also examined, and no correlations were found between theophylline levels at 24 hours or 48 hours and fluid balance on day +1 or +2 (**Fig. 3**, ***B*** and ***C***). Univariate analysis demonstrated that fluid balance correlated with fluid intake ($p < 0.0001$), aminophylline administration when analyzed as a categorical variable ($p < 0.0001$), and chlorothiazide dosing ($p = 0.025$), but not aminophylline dosing ($p = 0.59$) or furosemide dosing ($p = 0.5$). Multivariate analysis using GEE regression analysis of factors associated with fluid balance continued to demonstrate a correlation between fluid balance and fluid intake ($p < 0.0001$), chlorothiazide dosing ($p = 0.0002$), and aminophylline administration as a categorical variable ($p < 0.0001$)(**Table 4**).

Effect of Aminophylline on Laboratory Variables

The effect aminophylline administration had on renal function as measured by sCr and BUN levels was also assessed. Although the sCr levels seemed to trend upwards slightly during the 4-day time interval, there was no statistically significant increase in sCr (**Fig. S1**, Supplemental Digital Content 2, http://links.lww.com/PCC/A668). In comparison, BUN levels rose significantly after aminophylline administration on day +2 when compared with day –2 ($p < 0.001$) and day –1 ($p < 0.01$) (**Fig. S2**, Supplemental Digital Content 3, http://links.lww.com/PCC/A669), presumably due to an increased prerenal state, although this could not be tested as fractional excretions of sodium were not available given the retrospective design. Importantly, no patients were known to have gastrointestinal bleeding, and thus,

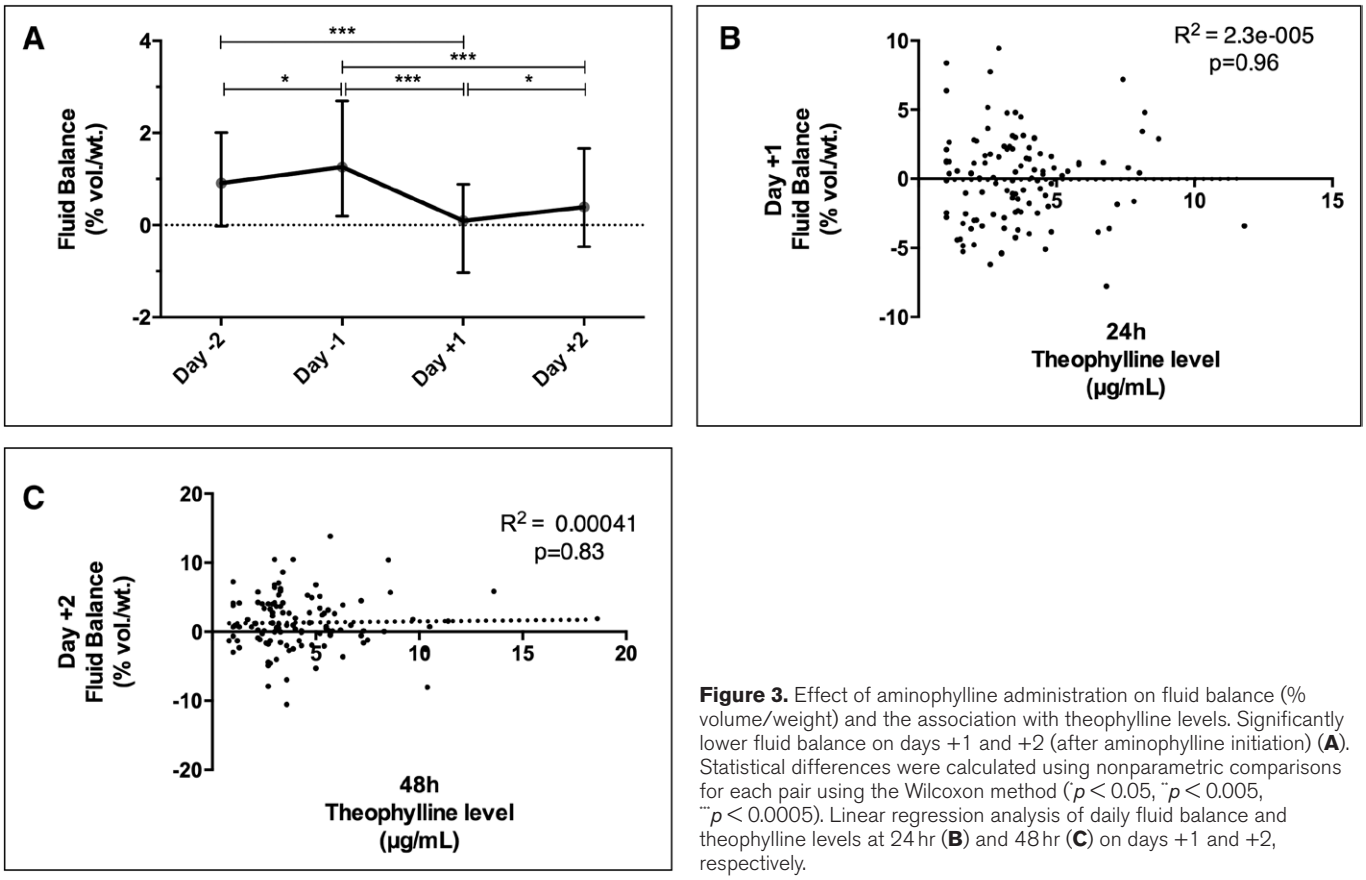

Figure 3. Effect of aminophylline administration on fluid balance (% volume/weight) and the association with theophylline levels. Significantly lower fluid balance on days +1 and +2 (after aminophylline initiation) (**A**). Statistical differences were calculated using nonparametric comparisons for each pair using the Wilcoxon method ($^{*}p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0005$). Linear regression analysis of daily fluid balance and theophylline levels at 24 hr (**B**) and 48 hr (**C**) on days +1 and +2, respectively.

TABLE 4. Linear Regression Analysis of Factors Associated With Fluid Balance by Generalized Estimating Equation

Factor	Estimate	SE	*p*
Aminophylline (yes/no)	−0.0241	0.0040	< 0.0001
Chlorothiazide dosing (mg/kg/d)	−0.0008	0.0002	0.0002
Fluid intake (mL/kg/hr)	0.0111	0.0012	< 0.0001

blood resorption was less likely to be the cause of elevated BUN over time.

DISCUSSION

Methylxanthines (caffeine) were first reported to increase urine production in patients with congestive heart failure and edema in 1864 (19). In more recent times, methylxanthines have been replaced by more powerful diuretics (20), although the use of aminophylline in the PICU as an adjunctive diuretic, albeit uncommon, has continued (13, 17). The peak serum concentration of aminophylline is reached within 30 minutes after IV dose, and its half-life varies with age: 20 hours for premature neonates, 3.5 hours for children, and 8.5 hours for adults. However, the clearance is quite variable, and it has been suggested that levels be closely monitored (21). Although there are no universal theophylline levels used among institutions for diuresis, our PICU standard guideline for aminophylline dosing targeted a goal theophylline trough of 4–8 µg/mL. However, it is possible that there is no need to target theophylline levels, and given the level-dependent negative side effect profile of aminophylline, we examined if theophylline trough levels correlated with UOP.

This study adds to the literature as it demonstrates that 24- and 48-hour theophylline trough levels are not predictive of UOP, and at 48 hours, in fact, are negatively correlated with UOP. Given that theophylline is partially renally cleared, these data suggest that theophylline levels are more dependent upon renal clearance, than renal clearance is dependent upon theophylline levels. Although intermittent measurement of theophylline levels may be warranted to guarantee the lack of toxicity, our data suggest that maintenance of theophylline trough levels above an arbitrary trough level is not necessary for the provision of the diuretic effect of aminophylline.

By evaluating aminophylline therapy in our statistical analyses as both as a categorical and continuous variable, we were able to ask two separate questions regarding the relationship between aminophylline and diuresis: 1) does adding aminophylline

increase UOP and improve fluid balance and 2) does a higher dose of aminophylline further increase UOP and improve fluid balance? Aminophylline administration, treated as a categorical variable, was correlated with increased UOP, but surprisingly, increased aminophylline dosing did not correlate with increased UOP. These data suggest that the addition of very low dose aminophylline is sufficient to generate improved diuresis and that further increases in aminophylline dosing may not enhance the diuretic effect. This result is in accordance with other studies that have found the diuretic benefit of aminophylline therapy (12, 13, 17, 22–25). Specifically, Tamburro et al (17) demonstrated an increase of UOP in 24 hours after aminophylline therapy from 35 patients, whereas BUN and creatinine concentration remained unchanged. Axelrod et al (24) demonstrated an improvement of renal function and UOP from aminophylline over a 7-day period among 31 cardiovascular ICU patients who had AKI. However, the same group performed a subsequent double-blinded, placebo-controlled, randomized control trial in 144 patients and did not demonstrate the same effect (15). In our retrospective study, aminophylline was used as an adjunctive diuretic, not to prevent or reverse AKI. To the best of our knowledge, this is the first article to investigate whether targeted theophylline levels are necessary for diuretic effect.

The diuretic benefit of low dose aminophylline can be explained by its mechanism of adenosine receptor blockade at low dosage (theophylline concentration of 2–3 μg/mL) versus type IV phosphodiesterase inhibition at high levels (theophylline concentration > 10 μg/mL). Also, although low dose aminophylline augments diuresis, it likely does not confer bronchodilatory or anti-inflammatory properties from phosphodiesterase inhibition: an important caveat given that the majority of our patients suffered from respiratory failure. Elevated theophylline concentrations are associated with increased adverse effects including tachycardia, agitation, an increased risk for premature ventricular contractions, and arrhythmias. Due to our study design, inclusion only of patients that continued to receive aminophylline for 48 hours, we were not able to investigate the physiologic side effects of aminophylline/theophylline. However, given that our data indicate that diuretic effect is not dose-dependent, lower dosing may be more appropriate to optimize the risk-benefit ratio, and it may be prudent to avoid aminophylline boluses.

Any conclusions drawn from this report regarding the correlation of aminophylline dosing and diuretic effect must be tempered by the obvious study limitations, most notably its retrospective design. Because our primary research question investigated the relationship between theophylline levels and UOP, we excluded many patients who received less than maintenance dosing aminophylline, or those that received aminophylline less than 48 hours after PICU admission. Hence, our study was not designed, nor should it be used, to investigate differential adverse effects of aminophylline dosing. Also, the demographics of our patient population are skewed toward a large Caucasian bias. However, no study has ever reported an ethnicity effect of aminophylline pharmacokinetics or pharmacodynamics. UOP was sometimes based on urine collection with diaper weights, which is inherently inaccurate although, we anticipate no systematic error from this practice. Our demographics were also skewed toward younger patients with more than 60% of our patient cohort between the ages of 6 weeks and 1 year old; however, this accurately reflects the general PICU/cardiac ICU patient population age demographics (26).

Surprisingly, although furosemide dosing correlated with UOP, it did not correlate with fluid balance. This may be a power issue or due to a decrease in furosemide dosing because of improving fluid balance (Fig. 1*B*). Along this same line of thought, the diuretic effect seen with the initiation of aminophylline could be due to temporally related natural improvement of disease processes. We tried to account for this by establishing a 48 hours UOP and fluid balance baseline for each patient prior to the initiation of aminophylline, but we could not control for time in our analysis. To definitively determine how varying theophylline concentrations affect UOP would require a randomized control trial of several cohorts of patients, with each cohort having a theophylline trough goal and a protocol for attaining the goal. In the absence of such a trial, this study demonstrates that targeted theophylline levels are likely not needed for the maximal diuretic effect of aminophylline.

CONCLUSIONS

In conclusion, aminophylline significantly improved UOP, and its diuretic effect was independent of both bolus dosing and the trough level. These results suggest that low dose aminophylline is a useful adjunctive diuretic and that no therapeutic trough level is required, although intermittent levels may be appropriate to assess for toxicity.

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