J Anesth (2012) 26:118–123
DOI 10.1007/s00540-011-1250-0

CLINICAL REPORT

Additive diuretic response of concurrent aminophylline and furosemide in children: a case series and a brief literature review

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Received: 11 January 2011 / Accepted: 20 September 2011 / Published online: 18 October 2011

Abstract Aminophylline exerts a renovascular effect, acting by adenosine receptor blockade or type IV phosphodiesterase inhibition. Clinically, these drugs have been used with furosemide to induce diuresis in adults and neonates. However, reports on use of aminophylline in diuretic-dependent children are limited to a few studies. We report a case series of four critically ill children unresponsive to furosemide continuous infusion who were subsequently given aminophylline as an adjunct diuretic in the treatment of fluid overload. No side effects were evident. Administration of aminophylline at low doses (3 mg/kg) successfully promoted increased urine output over the 6-h study period in all four children.

Keywords Aminophylline · Children · Diuretics · Fluid overload · Theophylline

Introduction

Fluid administration in critically ill patients is essential and lifesaving when used appropriately [1, 2]. These patients are at increased risk for fluid overload, often as a result of widespread systemic inflammation, reduced plasma oncotic pressure, and an increased propensity for capillary leak. This patient group is more likely to develop edema, such as peripheral-dependent interstitial edema, ascites, and pleural effusions [3]. Such fluid accumulation may contribute to additional cardiopulmonary complications including congestive heart failure, pulmonary edema, increased pulmonary restrictive defects, and reduced pulmonary compliance [4]. Moreover, several studies have suggested an association between excessive fluid retention and worse outcome in the ICU. Adult surgical ICU patients who develop fluid retention have higher morbidity, greater requirement for blood products, prolonged dependency on pressors, and a twofold increase in mortality [1, 4, 5]. On the other hand, decreased fluid overload can be associated with improved outcomes in neonates on extracorporeal membrane oxygenation (ECMO) [6], adults with acute respiratory distress syndrome (ARDS) [7–9], and children requiring continuous hemofiltration [10, 11].

Although native kidney response is preferred, urine output is often suboptimal as a result of associated renal ischemia or the effects of medications used in the treatment of critical illness [11–13]. The administration of loop diuretics to hypervolemic or oliguric patients in the ICU is a relatively common clinical practice. However, in some critically ill patients, conventional doses of loop diuretics do not always result in optimal diuresis. In such cases, patients are considered "diuretic resistant" [14].

Aminophylline and theophylline are methylxanthine derivatives that act as adenosine receptor antagonists. Studies in adult and pediatric patients have demonstrated a diuretic effect of aminophylline resulting from increased renal blood flow and the inhibition of solute reabsorption in various segments of the nephron [15]. Clinically, these drugs have been used with furosemide or other loop diuretics to induce diuresis in adults [16, 17] and children [15, 18–29]. Nevertheless, most of the studies describe neonates [15, 18–20, 23–29]. The published data on use of

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aminophylline/theophylline in diuretic-dependent critically ill children are limited to two studies [25, 28].

We report a prospective case series of four critically ill children unresponsive to furosemide continuous infusion who were given aminophylline as an adjunct diuretic in the treatment of fluid overload.

Methods

This trial was an open, controlled study of consecutive patients fulfilling the admission criteria. The study was reviewed and approved by the Institutional Research Ethics Board, and informed consent was obtained from parents or legal guardians. Patients eligible for the study included all those admitted to the pediatric intensive care unit (PICU) deemed resistant to diuretic therapy that were started on aminophylline to increase urine output. We carried on the data collection from June 2009 to May 2010. Four consecutive patients were enrolled in this study. Patients were hemodynamically stable, defined as in sinus rhythm, and had values for heart rate and systolic blood pressure within the 5th and 95th percentile for age. All patients had an indwelling arterial, central venous, and urinary catheter in place. Clinical criteria for fluid overload included at least two of the following: weight increase from time of admission, peripheral or periorbital edema, or evidence of pulmonary edema on chest radiograph [28]. Need for improved diuresis was defined as at least two of the following: positive fluid balance, weight gain, worsening pulmonary edema, or anasarca despite diuretic therapy. All patients were receiving a continuous infusion of furosemide (6 mg/kg/day) and vasoactive drugs. Patients were considered "diuretic resistant" if diuresis was not optimal despite this furosemide dose.

All patients received theophylline in its intravenous form (aminophylline) as a single bolus (3 mg/kg) diluted with D_5W to a concentration of 25 mg/ml and infused over 30 min. The study periods consisted of the 24 h before and the 6 h immediately after starting theophylline. Data collection consisted of urine volume measured hourly, urine sodium, urine potassium, and urine creatinine measured at baseline and at 2 and 6 h after aminophylline infusion, and serum electrolytes measured both at baseline and at study endtime. Aminophylline levels were measured as peak levels and were determined 30 min after administration of the bolus dose. Calculation of urine flow rate, sodium and potassium excretion rates, and creatinine clearance was performed at baseline, and at 2 and 6 h after administration of the aminophylline bolus. Mean airway pressure (MAP) and PaO_2/FiO_2 ratio were registered before and 6 h after the aminophylline infusion. Other data included fluid intake, vasoactive agents and their doses, heart rate, and blood pressure.

Statistical analyses were performed using SPSS for Windows (version 12.0). Baseline statistics were reported as mean (SD) for continuous variables, and number (%) for categorical variables.

Results

The four children were aged from 7 to 28 months, and the diagnosis included septic shock (Table 1). All patients remained on the same inotropic agents at the same dosages throughout the study period. At the time of the study intervention all patients had increased weight compared to admission, with an average increase of 15%. The mean increase in urine output was 275% in the first 2 h after bolus administration and remained 195% above baseline at 6 h after infusion. The mean peak level of aminophylline was 7.4 μg/ml. Aminophylline level was within the therapeutic range in only one of the four children.

Compared to baseline levels, a mean increase in sodium excretion, potassium excretion, and creatinine clearance was detected at 2 h after infusion (Table 2). Despite a drop in mean levels of sodium excretion, potassium excretion, and creatinine clearance at 6 h after infusion, the values of these means represented nearly a doubling of the respective variables from baseline.

The average of serum sodium at baseline and 2 h after aminophilline was 142 and 139 mmol/l, respectively; the average for urinary sodium at these time points was 49.7 and 107.3 mmol/l, respectively.

Levels of serum potassium, chloride, blood urea nitrogen, and creatinine showed no change during the course of the study.

Patients presented a slight reduction in mean P_{aw} (from 16.8 ± 1.3 to 15.4 ± 1.1 cmH_2O) and an increase in mean PaO_2/FiO_2 ratio (from 111.2 ± 14.3 to 159.8 ± 17) (Table 2).

Mean heart rate increased less than 10% in the first 2 h, and by the sixth hour it had decreased by 3% in relation to the baseline. The mean arterial pressure increased around 20% by the end of the second hour, and at the end of the study it had decreased 9% in relationship to the second hour, but was still 9% above the baseline datum (Table 2).

Table 3 shows the studies on aminophylline/theophylline as an adjunct diuretic for neonates and children.

Discussion

We found in our case series that concurrent use of aminophylline in critically ill children receiving a continuous infusion of furosemide may be associated with improved urine output. Our data agree with the findings of two

Table 1 Characteristics of children with furosemide-resistant fluid overload receiving adjunct aminophylline

	Case 1	Case 2	Case 3	Case 4
Gender	Male	Female	Female	Male
PRISM score	12	21	16	11
PELOD score	11	11	11	11
Diagnosis	Pneumonia/septic shock	Pneumonia/septic shock	Fournier's syndrome/ septic shock	Appendicitis/septic shock
Fluid intake (ml/kg/day)	60	60	50	70
Inotropes (μg/kg/min)	Dobutamine (5)	Dobutamine (7.5)	Dobutamine (20)/noradrenaline (0.4)	Dopamine (10)
Percent (%) increase in admission weight	19	12	23	17
Peak aminophylline level	11.0	8.4	3.4	5.6
Mean P_{aw} (cmH_2O)				
Baseline	15.7	16.5	20.7	14.4
6 h	15.3	14.4	18.6	13.5
PaO_2/FiO_2 ratio				
Baseline	111.4	106.2	78.8	148.3
6 h	138.3	196.0	122.8	182.0

PELOD Pediatric Logistic Organ Dysfunction, *PRISM* Pediatric Risk of Mortality score, P_{aw} airway pressure, PaO_2 partial pressure of arterial oxygen, FiO_2 fractional inspired oxygen concentration

Table 2 Cardiovascular and renal variables at baseline and post-aminophylline infusion periods

	Baseline	2 h	6 h
Urine output (ml/kg/h)	2.4 (±0.42)	6.6 (±2.55)	4.7 (±1.16)
Sodium excretion (mmol/kg/h)	1.44 (±0.37)	6.25 (±2.23)	2.95 (±1.06)
Potassium excretion (mmol/kg/h)	0.26 (±0.03)	2.1 (±0.40)	0.5 (±0.15)
Creatinine clearance (ml/min/1.73 m^2)	19.53 (±4.06)	60.9 (±20.7)	39.6 (±14.0)
Heart rate (beats/min)	131.75 (±3.97)	141.0 (±3.89)	128.0 (±8.83)
Mean arterial pressure (mmHg)	6.97 (±0.31)	8.35 (±0.88)	7.62 (±0.27)

Data are presented as mean for time period (±SD)

previous studies in PICU patients [25, 28]. Bell et al. [25] demonstrated that a single dose of theophylline (3 mg/kg) increased urine output by 240% in 10 diuretic-dependent children, 3 of whom were transplant recipients. In a study involving 8 children, Pretzlaff et al. [28] reported a mean increase in urine output of 88% in the first 2 h of administration of a single bolus of aminophylline (6 mg/kg), but found that this level returned to near-baseline values at 4–6 h after infusion. In our study, administration of aminophylline at low doses (3 mg/kg) promoted a 275% increase in urine output.

All patients in the present study had received continuous infusion of furosemide in an attempt to increase urine flow before the administration of aminophylline. Because the response to these agents was judged to be inadequate for the clinical situation, aminophylline was administered. Urine output increased after aminophylline administration, suggesting an additive effect.

The diuretic effect of aminophylline is mediated by inhibition of the adenosine receptor at the afferent arteriole [28]. Adenosine is a potent renal vasoconstrictor. Thus, nonspecific blockade of adenosine receptors by aminophylline may result in diuresis via hemodynamic and renal tubular mechanisms [15].

Nonspecific adenosine receptor antagonists (aminophylline and 8-phenyltheophylline) promote renovascular action by two mechanisms: adenosine receptor blockade at low dosage (theophylline level <2–3 μg/ml) and type IV phosphodiesterase (PDE4) inhibition at high dosage (theophylline level >10 μg/ml) [25]. It is important to consider that the diuretic property of adenosine A1 receptor antagonists is much weaker compared with loop diuretics. Thus, these drugs will most likely be added to loop diuretics, particularly in patients with acute heart failure, although an additive effect of aminophylline in combination with furosemide compared with furosemide alone is not observed in healthy subjects [30].

Several points arising from this case series are worth highlighting. First, we used a different dosage of aminophylline than that used in the two previous pediatric

Table 3 Published studies on aminophylline/theophylline as diuretic adjunct in pediatric population

Reference	Study design	Population	Patients (*n*)	Doses	Comments
Harkavy et al. [18]	Case series	NICU patients	10	2–5 mg/kg	Theophylline induced diuresis in newborns with idiopathic neonatal apnea. Hyponatremia is a potential consequence of theophylline therapy for apnea
Huet et al. [27]	Retrospective case series	NICU patients	6	1 mg/kg	Urinary water excretion and creatinine clearances increased significantly with aminophylline
Mazkereth et al. [23]	Prospective case series	NICU patients	19	6 mg/kg followed by maintenance therapy at a dose of 2 mg/kg every 12 h	In premature infants, the aminophylline loading dose, but not maintenance therapy, affected renal functions
Lochan et al. [24]	RCT	NICU patients	24	2 mg/kg (single doses)	Low doses of theophylline given before furosemide administration significantly enhanced diuretic response in infants with fluid retention during ECMO
Bell et al. [25]	Prospective case series	PICU patients	10	3 mg/kg followed by infusion rate of 0.5 mg/kg/h	Theophylline increased urine output in diuretic-dependent critically ill children
Pretzlaff et al. [28]	Prospective case series	PICU patients	8	6 mg/kg (single dose)	Aminophylline proved an effective adjunct to furosemide in increasing diuresis in critically ill children with fluid overload
Jenik et al. [19]	RCT	NICU patients	24	8 mg/kg (single dose)	Prophylactic theophylline, given early after birth, had beneficial effects on reducing renal dysfunction in asphyxiated full-term infants
McLaughlin et al. [21]	Retrospective case series	Multivisceral transplant recipients	10	6 mg/kg (10 episodes) followed by 5 mg/kg (4 episodes), 4 mg/kg (1 episode), and 3 mg/kg (2 episodes)	Aminophylline increased urine output during episodes of acute tacrolimus toxicity in patients on concomitant diuretic and/or dopamine therapy after renal insufficiency
McLaughlin and Abitbol [22]	RCT	Renal transplant recipients	10	5 mg/kg (single doses)	Theophylline induced solute diuresis during furosemide-resistant oliguric tacrolimus toxicity
Ng et al. [15]	Retrospective case series	NICU patients	5	4 mg/kg followed by a continuous infusion of 0.2–0.6 mg/kg/h	Aminophylline was successfully used as an adjunct diuretic with increased urine output
Bakr [20]	RCT	NICU patients	20	5 mg/kg (single doses)	Prophylactic theophylline treatment, given early after birth, has beneficial effects in reducing the renal involvement in asphyxiated full-term infants
Bhat et al. [26]	RCT	NICU patients	40	8 mg/kg (single doses)	Single dose of theophylline within the first hour of birth in term neonates with perinatal asphyxia resulted in significant decrease in serum creatinine level and urinary excretion of beta 2 microglobulin, with an increase in creatinine clearance
Cattarelli et al. [29]	RCT	NICU patients	50	1 mg/kg (single doses)	Early theophylline administration improved renal function during the first 2 days of life in very preterm infants with respiratory distress syndrome

RCT randomized clinical trial, *NICU* neonatal intensive care unit, *PICU* pediatric intensive care unit, *ECMO* extracorporeal membrane oxygenation

studies [25, 28]. Bell et al. [25] used aminophylline at a dosage of 3 mg/kg followed by infusion rate of 0.5 mg/kg/h over 24 h whereas Pretzlaff et al. [28] used a higher single dose of aminophylline (6 mg/kg). Second, we found that increases in urine output, sodium excretion, potassium excretion, and creatinine clearance remained at 6 h after administration of the bolus. Our findings contrasted with those of Pretzlaff et al. [28], who showed that all variables had returned to baseline levels by 4–6 h, although agreeing with the findings of Bell et al. [25], who demonstrated an increase in urinary output during the day after the patients received theophylline. Aminophylline has a half-life of

8–9 h in adults and would therefore have a residual action during the post-administration period [21]. Thus, the rise in all these variables with progressive return toward baseline levels after withdrawal of drug therapy suggests a true pharmacological effect. Also, despite a decrease in creatinine clearance at baseline, our patients had an increased diuretic response. However, we were unable to determine a correlation between renal function and diuretic response after aminophylline because our sample size was small. Third, patients in this case series presented increased diuresis despite of low serum aminophylline levels (mean, 7.4 μg/m). Theophylline improves urine output in critically ill children with furosemide-resistant oliguria, at relatively low dosages (theophylline concentration, 2–4 mg/l). This level of theophylline is less than the target level required to treat critically ill children with status asthmaticus. Concentrations attained with this use are higher at 12–17 mg/l [21, 28]. Therefore it is possible that theophylline improves urine output in critically ill children with furosemide-resistant oliguria, at relatively low dosages (theophylline concentration, 2–4 mg/l) and without incurring significant toxicity, as classically. Toxicities associated with theophylline concentrations occur at >20 mg/l and include headache, nausea, vomiting, and seizures [28].

In fact, in our small case series, no adverse events were observed during aminophylline administration. The changes that occurred in the observed cardiovascular variables can be considered expected in light of the clinical effect obtained with aminophylline administration (increased diuresis). Other clinical effects of aminophylline include relaxation of the smooth muscles, stimulation of the central nervous system, increased respiratory drive, decreased peripheral vascular resistance, and positive inotropic and chronotropic effects [28].

In this series of four critically ill children with furosemide-resistant fluid overload, aminophylline was successfully used as an adjunct diuretic with no significant adverse effects. We believe that use of aminophylline at low doses could represent an attractive option in view of the drug's potential adverse effects and that further work with a larger population exploring this possibility is warranted.

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