Aminophylline Improves Urine Flow Rates but Not Survival in Childhood Oliguric/Anuric Acute Kidney Injury

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Abstract

Introduction: Acute kidney injury (AKI) morbidity and mortality rates remain high. Variable AKI outcomes have been reported in association with aminophylline treatment. This study evaluated AKI outcome in a group of Nigerian children treated with aminophylline.

Methods: This is a retrospective study of AKI in children treated with (N=9) and without (N=8) aminophylline. Studied outcome indices comprised urine flow rate (UFR), duration of oliguria/anuria, progression through AKI stages, number of patients requiring dialysis and mortality.

Results: Mean ages for the control and aminophylline arms were 4.6±2.7 and 4.9±2.1 years (P=0.7), respectively. All patients progressed to stage-3 AKI. Baseline median UFRs in the aminophylline and control arms were similar (0.13 Vs 0.04 ml/kg/hour respectively, P=0.5). The median UFR was significantly higher on day-5 (0.8 Vs 0.1; P=0.03), day-6 (1.0 Vs 0.2; P=0.02), and day-7 (1.2 Vs 0.2; P=0.03) in the aminophylline than the control arm, respectively. Short duration of oliguria/anuria (≤ 6 days) was more frequently observed in aminophylline-treated patients compared to controls (77.8% Vs 25.0%; odds ratio 0.09; 95% CI: 0.01-0.89; P=0.04). Only the aminophylline group maintained steady serum creatinine levels. Four out of five patients in the control group were dialyzed compared to only one out of eight patients in the aminophylline group (odds ratio 0.16; 95% CI: 0.04-0.71; P=0.03). Mortality rates were similar in aminophylline-treated and control patients (33%Vs 25%; hazard ratio 0.8; 95% CI: 0.1-5.5; P=0.8).

Conclusion: Aminophylline therapy was beneficial for patients with AKI in terms of improved UFR and reduced need for dialysis, but failed to impact positively on survival.

Keywords: Aminophylline; Dialysis; Survival; Urine Flow

Introduction

Acute kidney injury (AKI) is a sudden perturbation of kidney function that is frequently associated with high morbidity and mortality rates [1-3]. A diagnostic time limit of 48 hours was recently introduced to ensure early diagnosis, management and prevention of progression to irreversible renal function loss [4]. Furthermore, early AKI biomarkers that can ensure prompt diagnosis have been identified. When these biomarkers become widely available to clinical practice, informed therapeutic interventions capable of aborting disease progression, morbidity and mortality multiplication can be applied[5,6].

In the injured kidney, adenosine is released endogenously from the macula densa causing vasoconstriction of the renal afferent arterioles via the adenosine A1 receptor as well as vasodilatation of the renal efferent arterioles via the adenosine A2 receptor; thereby reducing the renal blood flow and glomerular perfusion pressure leading to ischemic kidney injury [7]. One measure that has been tried with the objective of achieving better AKI outcome is the use of aminophylline (an ethylenediamine coupled theophylline) [7-11]. Aminophylline is converted to theophylline in the human body, which in turn vasodilates the renal afferent arterioles through competitive inhibition of adenosine on the adenosine A1 receptor. Thereby, aminophylline improves renal blood flow and glomerular perfusion pressure and filtration [7, 8]. Because studies involving children are few [9-11, 13, 14], little is known about the efficacy and outcome of aminophylline therapy in childhood AKI. Children with AKI managed in our unit between January 2004 and December 2009 received different drug treatments aimed at improving outcome; one of such drugs was aminophylline. In this study we compared the outcome of aminophylline treated children to those who did not receive aminophylline treatment.
Aminophylline therapy in acute kidney injury

The peak of kidney injury (highest recorded Scr before onset) was delivered in 10% dextrose water infusion. The clinical records revealed that the renal hemodynamics, such as dobutamine, dopamine and adrenaline. The positive impacts of aminophylline on the hemodynamic responses were significant.

Methods

This retrospective case control study was conducted by reviewing the clinical charts of all AKI patients treated with or without aminophylline during the period between January 2004 and December 2009. Investigated outcome indices comprised urinary output, duration of oliguria/anuria, progression through AKI stages, need for dialysis and mortality. Exclusion criteria comprised non-oliguric AKI, nephrotoxic oliguria, bilateral congenital kidney anomaly or other forms of chronic kidney disease as well as administration of diuretics and/or calcium channel blockers. None of our patients received other drugs that can modify renal hemodynamics, such as dobutamine, dopamine and adrenaline. The clinical records revealed that the aminophylline arm received 5 mg/kg/24h (or 0.21 mg/kg/h) of the medication for 72 hours, usually 6 to 9 hours after oliguria/anuria onset. Serum theophylline level was not determined. No adverse effect of aminophylline was recorded for any of the patients. Aminophylline was delivered in 10% dextrose water infusion. The AKI network (AKIN) committee diagnostic and staging criteria were used [4]. Where baseline Scr was unknown, it was determined using the modification of diet in renal disease formula: estimated glomerular filtration rate (eGFR) =186 x [Scr]^{-1.154} x Age^{-0.203} x 0.742 (if female) x 1.210 (if black) [12] by assuming a normal pre-morbid steady state Scr [11, 15] and reversal of nephrotoxic oliguria [10]. In this study, aminophylline improved urine flow rates. This effect probably explains the difference in the relatively steady Scr levels found in the aminophylline arm compared to controls (Figure-2). The median baseline and peak Scr for the aminophylline arm were 4.9 ±2.1 and 4.6 ± 2.7 (1.5-10.0) mg/dl, respectively (P=0.01). Times to peak Scr were 2.0 (1.5-5.3) and 8.2 (6.0-11.0) mg/dl, respectively (P=0.6). The aminophylline arm maintained a relatively constant Scr level compared to controls that showed progressive and statistically significant increases in Scr levels. The median baseline and peak Scr for the control group were 4.9 (1.5-11.6) and 7.4 (5.6-15.4) mg/dl, respectively (P=0.2). Patients in the aminophylline arm received more frequent dialysis while eight out of nine patients in the control arm required dialysis (P=0.08) at 6-12 days (median 8.0) and 4-12 days (median 8.0) respectively (P=0.6). The aminophylline arm maintained stable clinical and laboratory status as well as death in the aminophylline arm who required dialysis was improved urine flow rates. This effect probably explains the positive impacts of aminophylline on the hemodynamic responses.

Results

Sixteen AKI cases were treated with aminophylline overall. Seven of the 16 patients were excluded because they had received in addition to aminophylline either furosemide or a calcium channel blocker or both. Overall, 17 patients satisfied the inclusion criteria with nine and eight patients in the aminophylline and control arms, respectively. The mean ages for the control and aminophylline arms were 4.6 ± 2.7 (1.5-10.0) and 4.9 ±2.1 (2.2-8.5) years, respectively (P=0.7). The aminophylline arm contained seven males and two females while the control arm contained four males and four females (P=0.2). Patients in the aminophylline arm received 50-125 (81 ± 25) mg of aminophylline per day. Etiologies of AKI in both groups of patients are summarized in Table-1. All patients progressed to the most severe form of AKI (stage 3). Four patients were anuric and four

Table 1: Etiology of acute kidney injury in the aminophylline and control arms

<table>
<thead>
<tr>
<th>Acute kidney injury etiology</th>
<th>Aminophylline arm (N=9)</th>
<th>Control arm (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum malaria associated hemoglobinuria</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Glucose 6-phosphate dehydrogenase enzyme deficiency associated hemoglobinuria</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Septicemia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis associated severe dehydration</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
The baseline UFR was determined from at least a 6-hour period during which there was no oliguria/anuria. Times to peak of kidney injury (highest recorded Scr before oliguria/anuria onset) were compared. UFR in the aminophylline and control arms were oliguric in the control arm while there were four and five anuric and oliguric patients in the aminophylline arm, respectively (P=1.0). While the UFRs for days 5, 6, and 7 increased significantly from the baseline in the aminophylline arm, this was not the case in the control group (Figure-1). Similarly, the UFRs for days 5, 6, and 7 were significantly higher in the aminophylline arm compared to controls (Figure-2). Seven out of nine aminophylline-treated patients had short duration of oliguria/anuria compared to two out of eight control patients (77.8% Vs 25.0%; odds ratio 0.09; 95% CI: 0.0-0.89; P=0.04). The median baseline and peak Scr for the control group were 4.9 (1.5-11.6) and 7.4 (5.6-15.4) mg/dl respectively (P=0.01). Similar measurements for the aminophylline arm were 2.0 (1.5-5.3) and 8.2 (6.0-11.0) mg/dl, respectively (P=0.01). Times to peak Scr in both the control and aminophylline arms were 6-12 days (median 8.0) and 4-12 days (median 8.0) respectively (P=0.6). The aminophylline arm maintained a relatively constant Scr level compared to controls that showed progressive and statistically significant increases in Scr level (Figure-3). Five out of eight control patients required dialysis while eight out of nine patients in the aminophylline arm required dialysis (P=0.08) at baseline. Four out of five patients who required dialysis in the control arm were dialyzed owing to clinical and laboratory deterioration. Only one out of eight patients in the aminophylline arm who required dialysis was dialyzed. Stable clinical and laboratory status as well as early diuresis onset following aminophylline treatment precluded dialysis in the remaining seven patients (odds ratio 0.16; 95% CI: 0.04-0.71; P=0.03). Two out of eight patients among the controls died while three out of nine patients in the aminophylline arm died (hazard ratio 0.77; 95% CI: 0.11-5.45; P=0.8). All patients were follow-up for 7-42 days (median 19 days).

**Discussion**

Emerging data on aminophylline treatment of AKI showed that the agent could be useful in improving outcome as demonstrated by improved urine flow rates [9-11, 13-15], steady state Scr [11, 15] and reversal of nephrotoxic oliguria [10]. In this study, aminophylline was significantly associated with improved outcome with regards to UFR, oliguria/anuria duration, number of patients dialyzed, and Scr level. This occurred despite both groups having similar age, gender, etiology and severity of kidney injury. Both groups had similar baseline Scr, time to peak Scr and prevalence of oliguria/anuria and all patients progressed to stage 3 AKI. The increase in UFRs from baselines for days 5, 6, and 7, was significantly higher for the aminophylline arm compared to controls. This is similar to findings in two other controlled studies in children [10, 11]. This study also showed aminophylline to be protective against prolonged oliguria/anuria. The relatively steady Scr levels found in the aminophylline arm suggest increased creatinine excretion following improved urine flow rates. This effect probably explains why patients treated with aminophylline were less likely to be dialyzed compared to controls. However, these positive impacts of aminophylline on the hemodynamic...
events of the initiation and extension phases of AKI failed to translate to improved survival. Progression to stage 3 AKI which could not be prevented by aminophylline was probably a factor. Stage 3 AKI is especially associated with dismal prognosis [1, 16, 17]. As in other studies, small sample size was an important limitation of this study. A large prospective randomized controlled study is therefore warranted to further evaluate the effect of aminophylline treatment on childhood AKI survival. Notwithstanding this limitation, the study has revealed that with improved UFR and reduced number of dialyzed patients, aminophylline treatment could potentially reduce the treatment cost of AKI.

**Conclusion**

Although there was no improvement in patients’ survival, the improved urine flow rates in the aminophylline treated group obviated the need for dialysis treatment in the majority of patients. This could impact positively on the overall AKI treatment cost.

**Acknowledgement**

This study was presented in abstract form at the Nigerian Association of Nephrology meeting in Nigerian February 2011 and at the World Congress of Nephrology in Canada in April 2011.

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