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Aminophylline Does Not Protect Against Radiocontrast Nephropathy in Patients Undergoing Percutaneous Angiographic Procedures

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ABSTRACT: *Background.* Radiocontrast nephropathy (RCN) is one of the leading causes of hospital-acquired acute renal insufficiency. Adenosine, a renal vasoconstrictor, is thought to play a role in RCN. In this study, aminophylline, a non-selective adenosine-competitive inhibitor, was evaluated as a potential agent to protect against RCN.

Methods. Twenty-six patients treated with 200 mg intravenous aminophylline immediately prior to percutaneous coronary and peripheral procedures were individually matched to 26 controls for baseline creatinine (Cr), diabetes mellitus and amount of contrast used. The aminophylline-treated group was also similar to control with respect to baseline ejection fraction, amount of post-procedure hydration, age, blood pressure and the use of nephrotic drugs.

Results. There was no significant difference between the change from baseline Cr to peak measured Cr in either cases or controls. Also, when a change in Cr $\geq 25\%$ from baseline was considered significant, Fisher's exact test did not show a difference between the 2 groups.

Conclusion. Aminophylline does not appear to add a protective role in preventing against RCN in patients undergoing percutaneous angiographic procedures.

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Key words: aminophylline, contrast nephropathy, renal insufficiency

Radiocontrast nephropathy (RCN) is a well-recognized cause of hospital-acquired renal insufficiency.¹ Risk factors for RCN include baseline renal dysfunction, diabetes mellitus, high contrast volume, congestive heart failure, dehydration, advanced age, multiple myeloma and nephrotic drugs.²⁻⁴ Mortality is significantly increased in patients who develop RCN following percutaneous interventional procedures.^{5,6} The exact mechanism of RCN is unknown, but thought to be secondary to renal ischemic injury, probably at the level of the medullary thick ascending limb and proximal convoluted tubule.^{6,7} Renal hypoxia can also lead to the production of adenosine and subsequently renal afferent arteriolar vasoconstriction and a decline in glomerular filtration rate (GFR).^{8,9}

Theophylline, a non-selective adenosine competitive antagonist, was shown in animal models of acute ischemic

renal injury to attenuate the reduction in GFR^{10,11} and effective renal plasma flow (ERPF).⁸ However, human studies have yielded conflicting data. Kolonko et al.¹⁰ and Erley et al.⁸ have shown that contrast-induced reduction in GFR can be prevented by theophylline, but no change in ERPF was seen.⁸ In contrast, Abizaid et al.¹¹ have shown no effect of aminophylline on prevention of RCN in patients undergoing coronary intervention.

We performed a case-control matched study to evaluate whether intravenous aminophylline administered immediately prior to interventional angiographic procedures in patients with renal insufficiency (Cr ≥ 1.4) would prevent against RCN.

METHODS

It is the practice of one of the authors (NWS) to administer intravenous aminophylline (200 mg over 10 minutes) to patients with chronic renal insufficiency (Cr ≥ 1.4) immediately prior to coronary or peripheral angiographic procedures. All patients are generally well hydrated (1.0-1.5 liters) with normal or half-normal saline starting immediately after the procedure. A total of 1,665 patients

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at Genesis Medical Center were screened during a 23-month period (July 1998 to May 2000). One hundred and four patients had a Cr \geq 1.4. Thirty-six patients were pre-treated with intravenous aminophylline prior to the angiogram procedure. It was possible to individually match each of the 26 aminophylline-treated patients (cases) to a control from the pool of untreated patients with renal insufficiency. The cases were matched to the presence or absence of diabetes mellitus, baseline Cr (within 0.1 in 23 patients, 0.2 in 2 patients, and 0.3 in 1 patient), and amount of contrast used (24 patients within 50 cc, 2 patients within 75 cc). All patients received a low-osmolar dye. None of the patients had a history of multiple myeloma. A detailed chart review was conducted on all cases and controls. The following variables were collected: age, gender, diabetes mellitus, hypertension, ejection fraction, blood pressure, post-procedure hydration, amount of contrast utilized, baseline Cr and peak Cr if measured within 2 weeks following the procedure.

The change in Cr from baseline to recorded peak value was calculated. A change of Cr \geq 25% from baseline was considered significant. Differences in wait times between cases and controls for measurements of Cr changes were also calculated. The proportion of patients who had a Cr measured within 48 hours, 72 hours to 1 week, and 1 to 2 weeks was determined for both cases and controls.

Statistical analysis. Continuous variables were tested with 2-sample, 2-tailed t-tests of differences in means. Dichotomous variables were tested with Chi-square and Fisher exact tests.

RESULTS

Twenty-six patients with Cr \geq 1.4 who received intravenous aminophylline were individually matched to controls for the presence of diabetes mellitus, amount of contrast used and baseline Cr. Descriptive analyses of all collected variables are shown in Table 1. There were no significant differences among all the variables collected. Baseline Cr was 1.6 ± 0.2 and 1.6 ± 0.2 in cases and controls, respectively. Forty-four percent of patients were diabetics. Post-procedure hydration was also similar in the two groups (1.2 ± 0.5 liters versus 1.3 ± 0.4 liters for cases and controls, respectively).

There were no significant differences between the change of Cr from baseline to peak value in either cases or controls (0.1 versus 0.2, respectively; $p = ns$). When Cr change was compared as a dichotomous variable (a change of Cr \geq 25% was considered significant), there continued to be no significant differences between cases and controls ($p = 1.00$) (Table 2). The differences in wait times for measurements of Cr change after procedure were also similar between the 2 groups (Table 3).

Table 1. Descriptive statistics of aminophylline-treated cases and controls

Variable	Case	Control	p-value
Patients	26	26	—
Age (years)	72.4 ± 7.8	70.8 ± 9.5	0.85
Gender (% males)	54	70	0.39
Diabetes mellitus (%)	44	44	1.00
Hypertension (%)	76	60	0.24
Ejection fraction (%)	45.8 ± 18.3	45.8 ± 15.7	0.096
Systolic BP (mmHg)	147.1 ± 34.7	137.6 ± 22.6	0.74
Diastolic BP (mmHg)	74.2 ± 18.2	72.7 ± 13.1	0.95
Post-procedure hydration (liters)	1.2 ± 0.5	1.3 ± 0.4	0.72
Use of diuretics (%)	76	58	0.56
Use of CCB (%)	44	50	1.00
Use of ACE (%)	60	46	0.78
Baseline creatinine	1.6 ± 0.2	1.6 ± 0.2	0.85
Amount of dye utilized (cc)	200.4 ± 118.4	179.6 ± 112.9	0.75

BP = blood pressure; CCB = calcium channel blockers; ACE = angiotensin-converting inhibitor

Table 2. Number of patients with significant creatinine change*

Creatinine Change	Case	Control	Total
Not significant	23	23	46
Significant	3	3	6
Total	26	26	52

*significant change: creatinine \geq 25% baseline

Table 3. Differences in wait times for measurement of creatinine changes

Measurement Time Frame	Case	Control
Within 48 hours	58%	54%
72 hours to 1 week	28%	31%
1-2 weeks	14%	15%

DISCUSSION

Radiocontrast nephropathy is one of the leading causes of hospital-acquired renal insufficiency.¹ The exact mechanism is yet unknown. It is thought, however, that ischemia at the medullary level is the main reason for RCN.^{2,7} Adenosine is produced in response to ischemia and was shown to cause afferent arteriolar vasoconstriction and a drop in GFR.⁸⁻¹³ Theophylline, an adenosine-competitive inhibitor, was shown in some animal models of acute renal failure and in humans to attenuate the drop in GFR caused by radiocontrast agents.⁸⁻¹⁴ In our study, we could not demonstrate a benefit on RCN when 200 mg of aminophylline was used immediately prior to angiographic procedures. Our cases and controls were individually matched

for the three most important risk factors for RCN,² namely, diabetes mellitus, baseline Cr and amount of contrast used. Also, the 2 groups were well matched for post-procedure hydration, ejection fraction, the use of nephrotic drugs and age. Therefore, there were no significant differences between the 2 groups to account for the apparent lack of effectiveness of aminophylline in preventing RCN.

It is possible to speculate that the lack of effectiveness of aminophylline in our study could be due to the small dose of the drug administered. We have not measured aminophylline blood levels in our patients, and therefore it is unknown whether adequate renal levels of aminophylline were achieved. Also, given the small number of patients in this study and the failure to reject the null hypothesis of equal means between cases and controls, we cannot rule out the possibility of a type II sampling error. Our data, however, are in concordance with a small randomized study by Dr. Abizaid et al.¹⁵ that also showed no benefit of aminophylline in preventing RCN. Although theophylline might increase GFR, it might not alter the ongoing ischemia to the medulla, which is thought to be the main mechanism for RCN. Similarly, dopamine also increases cortical blood flow and increases GFR but does not augment perfusion to the medulla,¹⁶ hence its apparent failure in protecting against RCN.¹⁵ In contrast, drugs such as fenoldopam (which increases both cortical and medullary perfusion)¹⁷ and acetylcysteine (which protects against ischemia-producing oxygen-free radicals)¹⁸ might prove to be beneficial. Randomized studies are ongoing to test these hypotheses.

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