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Original article

Efficacy of N-acetylcysteine and aminophylline in preventing contrast-induced nephropathy

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KEYWORDS
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Summary
Background: Contrast-induced nephropathy (CIN) is one of the important complications of coronary angiography (CAG) and percutaneous coronary intervention (PCI), especially in patients with chronic kidney disease (CKD). Prophylactic administration of N-acetylcysteine (NAC) and aminophylline has been reported to be effective in some trials, but the results still remain controversial. We investigated the efficacy of NAC or aminophylline in preventing CIN.
Methods and results: Forty-five consecutive patients undergoing CAG and/or PCI were randomly assigned to receive hydration and NAC (704 mg orally twice daily; NAC group, $n = 15$), hydration and aminophylline (250 mg intraveneously 30 min before CAG and/or PCI; aminophylline group, $n = 15$), or hydration alone (control group, $n = 15$). We compared serum creatinine (SCr), creatinine clearance (Ccr), blood beta-2 microglobulin, and urinary beta-2 microglobulin levels at baseline and 48 h after CAG and/or PCI. In the NAC group, SCr decreased from 1.00 ± 0.36 to 0.67 ± 0.16 mg/dl ($p < 0.01$), and Ccr significantly increased from 62.4 ± 15.6 to 80.4 ± 8.39 ml/min ($p < 0.01$). In the aminophylline group, SCr and Ccr were unchanged. In the control group, SCr significantly increased from 0.94 ± 0.21 to 1.28 ± 0.21 mg/dl ($p < 0.01$), and Ccr significantly decreased from 63.7 ± 16.1 to 46.1 ± 10.6 ml/min ($p < 0.01$) after CAG and/or PCI. In the NAC group, mean blood beta-2 microglobulin significantly decreased from 2.38 ± 0.58 to 1.71 ± 0.38 mg/dl ($p < 0.01$), and in the aminophylline group, mean urinary beta-2 microglobulin concentration significantly decreased from 337 ± 31.0 to 239 ± 34 μg/ml ($p < 0.01$).

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Conclusions: These results suggest that both prophylactic NAC and aminophylline administration are effective in preventing CIN, but not with hydration alone. It appears that the two compounds work in different ways against CIN.

Introduction

Contrast-induced nephropathy (CIN) is a significant complication after coronary angiography (CAG) and percutaneous coronary intervention (PCI) that has been associated with prolonged hospitalization and adverse clinical outcomes [1—3]. Ongoing advances in catheter-based technologies for the treatment of coronary artery disease (CAD) have been accompanied by a steady increase in the use of PCI. Patients with renal disease also frequently have critical CAD and require PCI. Therefore, renal complications after PCI become increasingly important as a cause of periprocedural morbidity and mortality [4]. The best approach to CIN is prevention, and efficacious and safe prophylactic prevention of CIN should decrease morbidity and mortality during hospitalization, including the need for dialysis, and thus reduce medical costs.

Renal free-radical production increases after the administration of a contrast medium [5], and reactive oxygen species have a role in CIN [5—8]. In animal studies, superoxide dismutase, a scavenger of reactive oxygen species, prevents renal damage with contrast agents [5]. Recently Tepel et al. [7] reported that N-Acetylcysteine (NAC), an antioxidant, prevented CIN, and Diaz-Sandoval et al. [8] also reported the beneficial effect of NAC on preventing CIN in patients undergoing CAG.

Adenosine, another key mediator of CIN, has been suggested as a possible candidate for mediating renal vasoconstriction after contrast-media administration in animal studies [9]. This postulate is derived from the observation that adenosine can induce afferent arteriolar vasoconstriction and a fall in glomerular filtration rate after intrarenal injection and infusion in rats and dogs [10—14]. Several clinical studies have investigated the competitive adenosine antagonist aminophylline as a prophylaxis [15—20].

The pathogenesis of CIN is not fully understood. However, prophylactic administration of NAC and aminophylline has previously been reported to be effective, although the results still remain controversial [7,8,15—29]. There are few reports investigating the efficacy of NAC and aminophylline in Japanese patients with normal renal function. We investigated the efficacy of NAC and aminophylline in preventing CIN in patients undergoing CAG and/or PCI in patients undergoing CAG and/or PCI.

Subjects and methods

Patients

Between April 1, 2006, and March 31, 2007, all consecutive patients who were admitted to our hospital, Kanmon Medical Center in Japan, with stable coronary artery disease who underwent CAG and/or PCI, and with stable serum creatinine concentrations were included in the study. Stable serum creatinine concentration was defined as a difference of $\leqq$0.1 mg/dl between baseline serum creatinine at 12—24 h before CAG and/or PCI. Serum creatinine was measured at 1—2 weeks before CAG and/or PCI. Exclusion criteria of this study included acute myocardial infarction requiring primary or rescue PCI, use of vasopressors before PCI, cardiogenic shock, current peritoneal dialysis or hemodialysis, planned post-contrast dialysis, or allergies to the medications being studied. We did not enroll patients with overt congestive heart failure, severe valvular disease, or advanced severe left ventricular dysfunction, defined as a left ventricular ejection fraction of less than 30%. Further exclusion criteria were pregnancy, multiple myeloma and amyloidosis. The use of diuretics or nephrotoxic medications was not restricted. All patients were encouraged to drink, if they were thirsty. Informed consent was obtained from all patients and this study protocol was approved by the hospital's Ethics Committee.

Study protocol

The patients were randomly assigned to receive either NAC and intravenous saline (NAC group), and intravenous aminophylline and saline (aminophylline group) or intravenous saline alone (control group). NAC (Mucofilin, Eisai, Tokyo, Japan) was given orally at a dose of 704 mg twice a day, the day before and on the day of CAG and/or PCI, for a total of 2 days. Aminophylline (Neophylline, Eisai, Tokyo, Japan) was given intravenously at a dose of 250 mg as a short infusion (100 ml saline, 0.9%) 30 min before CAG and/or PCI. Saline (0.9%) was given intravenously at a rate of 1 ml/kg body weight per hour for 30 min before and 10 h after angiography. Serum creatinine (SCr), blood urea nitrogen (BUN), and blood beta-2 microglobulin were measured 12—24 h before angiography, and 48 h after angiography. Urinary beta-2 microglobulin was measured 24 h before angiography, and 48 h after angiography. Creatinine clearance (Ccr) was confirmed by collection of urinary creatinine over 24 h. Ccr was also measured 24 h before angiography, and 48 h after angiography.

CAG and/or PCI

Single-plane coronary angiography with or without angioplasty was performed according to standard clinical practice, using the transbrachial or transradial approach. A 5F catheter was used for diagnostic CAG, and a 6F catheter was used for PCI. All patients received iopamidol (Oypalomin, Konica Minolta, Tokyo, Japan) as their contrast agent. The iopamidol content was 0.755 g/ml, and the iodine content was 370 mg/ml. The dose of contrast agent was decided by each cardiologist. Patients who underwent PCI received a bolus of 5000 U heparin during the procedure, followed by an additional bolus, if deemed necessary.

Table 1 Baseline patient characteristics.

Characteristics	Control group ($n=15$)	Aminophyline group ($n=15$)	NAC group ($n=15$)	p-Value
Age (years)	70 ± 8	71 ± 3	70 ± 10	0.734
Gender (M/F, n)	9/6	10/5	9/6	0.900
Body mass index (kg/m^2)	22.1 ± 2.1	22.8 ± 2.2	224 ± 2.3	0.739
Systolic blood pressure (mmHg)	140 ± 14	144 ± 13	144 ± 16	0.478
Diastolic blood pressure (mmHg)	70 ± 8	72 ± 8	72 ± 8	0.675
Left ventricular ejection fraction (%)	63 ± 7	62 ± 9	63 ± 12	0.863
Hypertension	12 (80%)	13(87%)	13(87%)	0.844
Diabetes mellitus	6 (40%)	6(40%)	7 (47%)	0.910
Dyslipidemia	7 (47%)	7 (47%)	8(53%)	0.909
Diuretic therapy	4 (26%)	4(26%)	5(33%)	0.893
Calcium-channel blocker therapy	10 (67%)	11(73%)	11 (73%)	0.895
Angiotensin II receptor antagonist	6 (40%)	8(53%)	7 (47%)	0.765
Dose of contrast agent (ml)	141 ± 14	142 ± 15	147 ± 23	0.134
PCI/CAG (n)	6/9	7/8	7/8	0.687
BUH (mg/dl)	12.0 ± 2.5	13.1 ± 3.6	13.8 ± 34	0.195
SCr (mg/dl)	0.94 ± 0.21	0.97 ± 0.29	1.00 ± 0.36	0.919
Ccr (ml/min)	63.7 ± 16.1	63.4 ± 18.9	62.4 ± 15.6	0.884
Blood beta-2 microglobulin (mg/dl)	2.34 ± 048	23.37 ± 0.28	238 ± 0.58	0.828
Urinary beta-2 microglobulin (μg/ml)	333 ± 99.7	337 ± 31.0	333 ± 91	0.657

PCI, perculaneous coronary intervention; CAG, coronary angiography; BUN, blood urea nitrogen; SCr, serum creatinine; Ccr, creatinine clearance.

Statistical analysis

All results are expressed as the mean ± standard deviation (SD). The Differences between the 3 groups were determined using the Kruskal—Wallis test. The differences between baseline and follow-up of all parameters in each group were also determined using the Kruskal—Wallis test. When differences were found, the Wilcoxon—Mann—Whitney test was used to test the significance of the difference. Categorical variables (incidence of hypertension, diabetes, dyslipidemia, and CIN, use of medications, gender, and procedure of CAG and/or PCI) were compared using the Chi-square test. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using StatView J-5.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

A total of 45 patients were enrolled. Baseline patient characteristics are shown in Table 1. There were no CKD patients. The number of patients with diabetes mellitus, hypertension, or dyslipidemia was similar in each group, as was the number receiving diuretics, calcium-channel blocker, or angiotensin II receptor antagonist before CAG and/or PCI. The volume of contrast agent used in the groups was similar. The number of CAG and/or PCI in the groups was also similar. No patients in this study developed acute nephrotoxicity requiring dialysis as a result of the administration of contrast media. There were no major adverse cardiac events throughout the study. Major adverse cardiac events were defined as cardiac death, non-fatal myocardial infarction (defined as >3 times upper limit of creatine kinase-MB levels), or revascularization of the target lesion.

Incidence of CIN

We defined CIN as an increase in SCr of more than 0.5 mg/dl from baseline to 48 h after angiography. CIN occurred in 4 (8.9%) of the 45 patients: 4 (26.7%) of the 15 patients in the control group. There were no CIN patients in either the NAC group or the aminophylline group ($p = 0.0109$; 95% confidence interval 0.102—5.991).

Changes in renal function

Baseline BUN concentration was similar among the 3 groups. In the control group, the mean BUN concentration significantly increased from 12.0 ± 2.5 to 15.3 ± 2.5 mg/dl at 48 h after CAG and/or PCI ($p < 0.01$). In the NAC group, the mean BUN concentration significantly decreased from 13.8 ± 3.4 to 10.5 ± 1.5 mg/dl ($p < 0.01$). In the aminophylline group, the mean BUN concentration was unchanged (Fig. 1).

Baseline SCr concentration was similar among the 3 groups. In the control group, the mean SCr concentration significantly increased from 0.94 ± 0.21 to 1.28 ± 0.21 mg/dl ($p < 0.01$), while in the NAC group, the mean SCr concentration significantly decreased from 1.00 ± 0.36 to 0.67 ± 0.16 mg/dl ($p < 0.01$). In the aminophylline group, the mean SCr concentration was unchanged (Fig. 2).

In the control group, the mean Ccr significantly decreased from 63.7 ± 16.1 to 46.1 ± 10.6 ml/min ($p < 0.01$), while in the NAC group, the mean Ccr concentration significantly increased from 62.4 ± 15.6 to 80.4 ± 8.39 ml/min ($p < 0.01$). In the aminophylline group, the mean Ccr concentration was unchanged (Fig. 3).

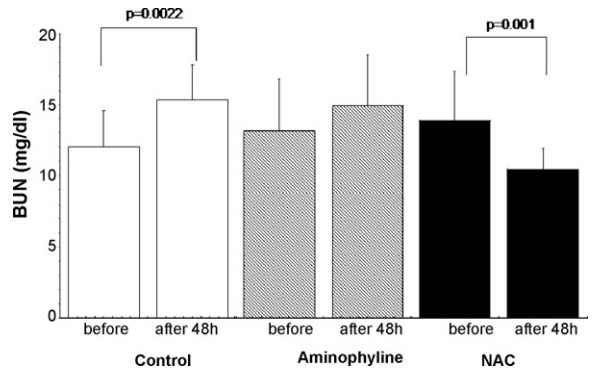

Figure 1 Changes in blood urea nitrogen (BUN) concentration at baseline and at 48 h after CAG and/or PCI. Brackets represent the standard deviation.

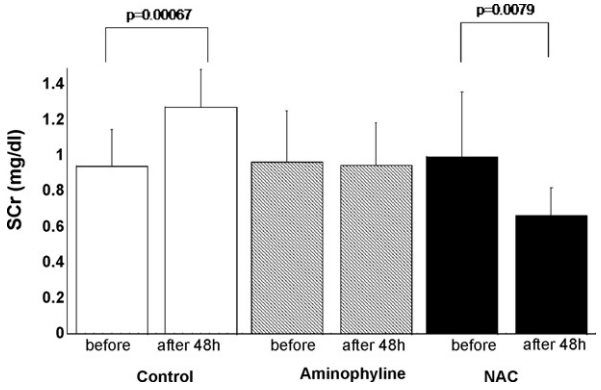

Figure 2 Changes in serum creatinine (SCr) concentration at baseline and at 48 h after CAG and/or PCI. Brackets represent the standard deviation.

In the control group, the mean blood beta-2 microglobulin significantly increased from 2.34 ± 0.48 to 2.97 ± 0.49 mg/dl ($p < 0.01$), while in the NAC group, the mean blood beta-2 concentration significantly decreased from 2.38 ± 0.58 to 1.71 ± 0.38 mg/dl ($p < 0.01$). In the aminophylline group, the mean blood beta-2 concentration was unchanged (Fig. 4).

In the control group, the mean urinary beta-2 microglobulin concentration significantly increased from 333 ± 69.7 to 513 ± 127 μg/ml ($p < 0.01$), while in the aminophylline group, the mean urinary beta-2 microglobulin concentration significantly decreased from 337 ± 31.0 to 239 ± 34 μg/ml ($p < 0.01$). In the NAC group, the mean urinary beta-2 microglobulin concentration was unchanged (Fig. 5).

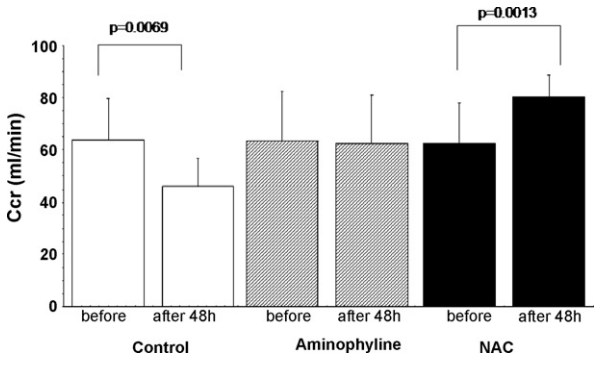

Figure 3 Changes in creatinine clearance (Ccr) at baseline and at 48 h after CAG and/or PCI. Brackets represent the standard deviation.

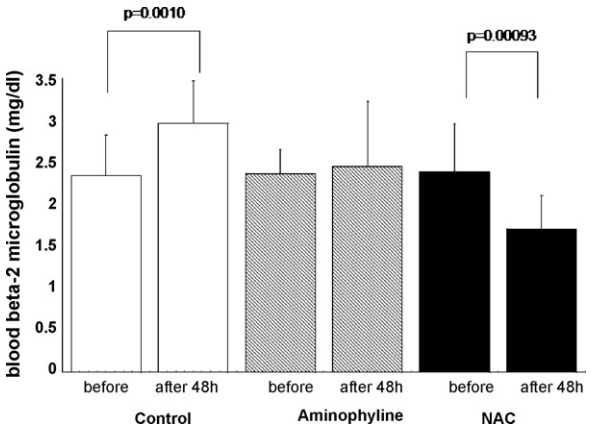

Figure 4 Changes in blood beta-2 microglobulin at baseline and at 48 h after CAG and/or PCI. Brackets represent the standard deviation.

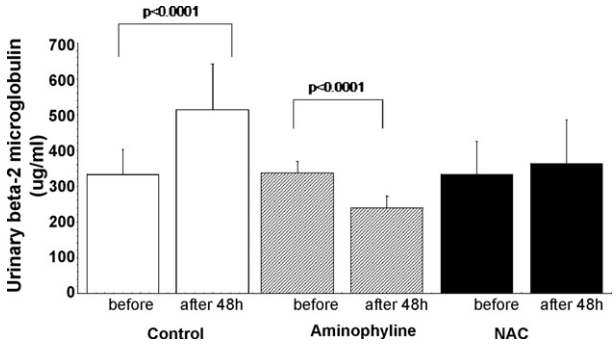

Figure 5 Changes in urinary beta-2 microglobulin at baseline and at 48 h after CAG and/or PCI. Brackets represent the standard deviation.

Discussion

The main conclusion of this study is that both prophylactic NAC and aminophylline administration are more effective in preventing CIN than hydration alone in patients undergoing CAG and/or PCI. The use of these agents is inexpensive, safe, immediate, and thus useful in emergency situations. To our knowledge, there have been no previous studies investigating the efficacy of aminophylline in Japanese patients with normal renal function.

CIN may be caused by the direct toxic effects of the contrast medium on both tubular cells and glomeruli. Therefore it seemed reasonable to investigate which segments of the nephron are mostly damaged by the contrast medium. The function of glomeruli and tubules was checked by measuring blood beta-2 microglobulin (a marker of glomerular function) and urinary beta-2 microglobulin (a marker of tubular function). There have been no previous studies investigating

the efficacy of NAC by evaluating blood and urinary beta-2 microglobulin.

Iopamidol is a non-ionic low osmolar contrast media. It is now well recognized that low osmolar contrast media are less nephrotoxic than high osmolar contrast media [30]. In this study, patients in the control group showed a significant increase in blood beta-2 microglobulin and urinary beta-2 microglobulin concentration. These results suggest that both glomerular and tubular injury may occur, even when a non-ionic low osmolar contrast media is used.

Early administration of NAC prevents a reduction in renal function in patients with acetaminophen poisoning who have liver failure [31]. A non-randomized study suggested that NAC may improve renal function in patients with hepatorenal syndrome [32]. In the present study NAC significantly improved the renal function. These results suggest that NAC may have a nephro-protective effect beyond the prevention of CIN in patients with normal renal function.

NAC improves endothelium dependent vasomotion in the coronary and peripheral circulation and is a potent antioxidant that may scavenge a wide variety of oxygen-derived free radicals [26]. The ability of NAC to increase intracellular and extracellular glutathione may be a crucial factor in contrast-induced damage. Therefore, NAC may be capable of preventing CIN by both improving renal hemodynamic and preventing direct oxidative tissue damage [26]. Patients receiving NAC showed a significant decrease in blood beta-2 microglobulin concentration, and an increase, although insignificant, in urinary beta-2 microglobulin secretion. These results suggest that the nephro-protective effect of NAC may be due mainly to its glomerular protection.

The nephro-protective effect of aminophylline is due to its non-selective adenosine antagonism. Contrast media osmotically irritate tubulus cells. This results in adenosine triphosphate turnover and the subsequent release of adenosine. In contrast to the other tissues in which adenosine results in hyperemia, in the kidney, adenosine induces marked vasoconstriction of the afferent arterioles via the adenosine-1-receptor [33]. In addition to the predominantly glomerular protective effect of aminophylline, the urinary beta-2 microglobulin data show that tubular protection also is taking place, correlating with the findings of a recent study. The urinary beta-2 microglobulin release is highly correlated with the initial tubular damage induced by the contrast medium. This tubuloprotective effect is more easily understood in the light of the observations of the previous report by Humes et al. [33] that the tubulotoxic effects of contrast media can be augmented with hypoxia. Aminophylline increases renal blood flow by antagonizing adenosine receptors, and the higher renal blood flow thus protects the tubulus cells.

These results suggest that NAC and aminophyline may act in different ways to prevent CIN. The combination of NAC and aminophylline seems to be superior to either NAC or aminophylline alone. However, we did not examine the combination. There are still many uncertainties regarding the efficacy of NAC and aminophylline for CIN. Further studies are needed to understand the pathophysiology of CIN in detail.

Study limitations

There are several limitations to this study, namely, the small sample size and the fact that it was a single-center study, which may reduce the credibility of this study. The results of the present study cannot be extended to patients at high or very high risk of CIN. Finally, our data are limited to the short term; the effect of NAC on long-term outcomes remains unknown.

Conclusions

This study suggests that both NAC and aminophylline administration for preventing CIN are more effective than hydration alone in patients undergoing CAG and/or PCI. NAC appears mainly to produce a glomerular protective effect, and aminophylline to act through tubular protection.

Conflict of interest

None of the authors had any conflict of interest to disclose.

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