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Acetylcysteine Protects Against Acute Renal Damage in Patients With Abnormal Renal Function Undergoing a Coronary Procedure

Kou-Gi Shyu, MD, PHD, FACC, Jun-Jack Cheng, MD, PHD, Peiliang Kuan, MD, FACC

Taipei, Taiwan

OBJECTIVES We sought to evaluate the efficacy of the antioxidant acetylcysteine in limiting the nephrotoxicity after coronary procedures.

BACKGROUND The increasingly frequent use of contrast-enhanced imaging for diagnosis or intervention in patients with coronary artery disease has generated concern about the avoidance of contrast-induced nephrotoxicity (CIN). Reactive oxygen species have been shown to cause CIN.

METHODS We prospectively studied 121 patients with chronic renal insufficiency (mean [±SD] serum creatinine concentration 2.8 ± 0.8 mg/dl) who underwent a coronary procedure. Patients were randomly assigned to receive either acetylcysteine (400 mg orally twice daily) and 0.45% saline intravenously, before and after injection of the contrast agent, or placebo and 0.45% saline. Serum creatinine and blood urea nitrogen were measured before, 48 h and 7 days after the coronary procedure.

RESULTS Seventeen (14%) of the 121 patients had an increase in their serum creatinine concentration of at least 0.5 mg/dl at 48 h after administration of the contrast agent: 2 (3.3%) of the 60 patients in the acetylcysteine group and 15 (24.6%) of the 61 patients in the control group ($p < 0.001$). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly from 2.8 ± 0.8 to 2.5 ± 1.0 mg/dl ($p < 0.01$) at 48 h after injection of the contrast medium, whereas in the control group, the mean serum creatinine concentration increased significantly from 2.8 ± 0.8 to 3.1 ± 1.0 mg/dl ($p < 0.01$).

CONCLUSIONS Prophylactic oral administration of the antioxidant acetylcysteine, along with hydration, reduces the acute renal damage induced by a contrast agent in patients with chronic renal insufficiency undergoing a coronary procedure. (J Am Coll Cardiol 2002;40:1383–8)
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Contrast nephropathy is a known risk of coronary intervention (1,2). Significant improvements in interventional techniques and procedures have markedly reduced the risks of periprocedural complications (3,4). Ongoing advances in catheter-based technologies for the treatment of coronary artery disease (CAD) have resulted in a steady increase in the volume of percutaneous coronary interventional procedures. Patients with renal disease frequently also have severe CAD and are referred for percutaneous coronary intervention (PCI). Therefore, the renal complications of PCI have an increasingly important role as a cause of periprocedural morbidity and mortality (5). The likelihood of contrast nephropathy occurring is closely related to pre-existing renal dysfunction and the dose of contrast agent used (6,7). The best approach to contrast nephropathy is prevention. However, prevention or mitigation of renal failure after the administration of contrast agent has been difficult to obtain. Hydration has been reported to ameliorate contrast nephropathy in patients with chronic renal dysfunction (8). Administration of drugs such as calcium antagonists, theophylline, dopamine, and atrial natriuretic peptide does not prevent contrast-induced nephropathy (CIN) (9–13).

Contrast agents reduce renal function by altering renal hemodynamics and exerting direct toxic effects on tubular epithelial cells (14). Renal free-radical production increases after the administration of a contrast agent (15). Although the pathogenesis of CIN is not fully understood, reactive oxygen species have a role in CIN (15–17). In animal studies, superoxide dismutase, a scavenger of reactive oxygen species, prevents renal damage by contrast agents (15). Recently, Tepel et al. (16) reported that acetylcysteine, an antioxidant, prevents contrast-induced renal damage in patients with renal insufficiency undergoing elective computed tomography, and Diaz-Sandoval et al. (17) reported the beneficial effect of acetylcysteine in patients undergoing cardiac catheterization. The contrast volume used during coronary interventional procedures is greater than that used during computed tomography or diagnostic catheterization. The procedure time for coronary interventional procedures is also longer than that for computed tomography and diagnostic catheterization. It is not known whether acetylcysteine has the same protective effect in patients with renal dysfunction undergoing PCI. Therefore, we conducted a prospective, placebo-controlled, randomized trial to study the protective effects of the antioxidant acetylcysteine on contrast-induced renal damage in patients with severe chronic renal insufficiency who underwent elective diagnostic catheterization and PCI.

From the Division of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan. Financial support was provided by the Research Committee of Shin Kong Wu Ho-Su Memorial Hospital.

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Abbreviations and Acronyms
BUN = blood urea nitrogen
CAD = coronary artery disease
CIN = contrast-induced nephropathy
CrCl = creatinine clearance
PCI = percutaneous coronary intervention

METHODS

Patients. Patients scheduled for cardiac angiography who had serum creatinine concentrations >2.0 mg/dl and <6.0 mg/dl or rates of creatinine clearance (CrCl) <40 ml/min and >8 ml/min, calculated on the basis of their serum creatinine concentration, weight, age, and gender (18), were eligible for the study. Only patients known to have a history of chronic renal failure and with stable serum creatinine concentrations were studied. Stable serum creatinine concentration was defined as a difference of ≤0.1 mg/dl between baseline serum creatinine at 12 to 24 h before coronary angiography and serum creatinine measured one to two weeks before angiography. The indications for coronary angiography were determined by each patient's cardiologist. Most patients were studied because of symptomatic coronary ischemia. Exclusion criteria included acute myocardial infarction requiring primary or rescue coronary intervention, use of vasopressors before the procedure, cardiogenic shock, current peritoneal dialysis or hemodialysis, planned post-contrast dialysis, or allergies to the study medications. Patients were not allowed to take medications that may elevate serum creatinine, independent of changes in the glomerular filtration rate. Both the cardiologist and patient were not aware of the treatment status. The protocol was approved by the local Ethics Committee, and all patients gave written, informed consent.

Study protocol. The patients were randomly assigned to receive either the antioxidant acetylcysteine and intravenous saline before and after administration of the contrast agent (acetylcysteine group) or placebo and saline (control group). Acetylcysteine was given orally at a dose of 400 mg twice a day, on the day before and on the day of coronary angiography, for a total of two days. Saline (0.45%) was given intravenously at a rate of 1 ml/kg body weight per hour for 12 h before and 12 h after angiography. All patients were encouraged to drink if they were thirsty. Serum creatinine and blood urea nitrogen (BUN) were measured 12 to 24 h before angiography, 48 h after, and 7 days after coronary angiography. None of the patients received theophylline, dopamine, or mannitol during the study. An acute contrast-induced reduction in renal function was defined as an increase in the serum creatinine concentration of at least 0.5 mg/dl at 48 h after injection of the radiocontrast medium.

Coronary procedures. Biplane coronary angiography with or without angioplasty was performed according to standard clinical practice, using the femoral approach. A 6F catheter was used for diagnostic coronary angiography, and a 7F catheter was used for angioplasty. All patients received iopamidol (Iopamiro, Bracco, Milan, Italy) as their contrast agent. The iopamidol content was 0.755 mg/ml, and the iodine content was 370 mg/ml. The dose of contrast agent was decided by each patient's cardiologist. Patients who underwent coronary angioplasty received a bolus of 10,000 U heparin during the procedure, followed by an additional bolus, if deemed necessary.

Statistical analysis. For a study with a power $(1 - \beta)$ of 90%, a two-sided type I error (α) of 0.05, and an expected absolute difference of 0.6 mg/dl in serum creatinine at 48 h, with a standard deviation of 1.0 mg/dl between the acetylcysteine and control groups, we calculated that we had to enroll 58 patients in each group.

Data are expressed as the mean value ± SD. Categorical variables were analyzed by the Fischer exact test. Differences in serum creatinine concentrations between the groups were analyzed by the Student *t* test. Differences in serum creatinine and BUN before and 48 h after coronary angiography in the same group were analyzed by the paired *t* test. Multiple logistic regression analysis was used to examine the effect of acetylcysteine, with adjustment for baseline blood pressure, the presence or absence of diabetes, and baseline serum creatinine. Analyses were performed with SPSS software (release 8.0, Chicago, Illinois). All statistical tests were two-sided. P values <0.05 were considered as statistically significant.

RESULTS

Patient population. A total of 121 patients were enrolled. Their clinical and biochemical characteristics are shown in Table 1. The number of patients with diabetes mellitus, hypertension, or hyperlipidemia was similar in each group, as was the number receiving diuretics, calcium-channel antagonists, or angiotensin-converting enzyme inhibitors before coronary angiography. There were eight diabetic patients in the acetylcysteine group and six diabetic patients in the control group who required treatment with insulin. The volume of contrast agent in both groups was similar. The number of coronary angiograms or angioplasty procedures in both groups was also similar. The mean weight of the patients was similar at the start of the study (acetylcysteine group: 68 ± 10 kg; control group: 68 ± 9 kg) and at 48 h after coronary angiography (acetylcysteine group: 69 ± 10 kg; control group: 69 ± 9 kg), suggesting a similar fluid status.

Changes in renal function. The mean serum creatinine concentration for all patients was 2.8 ± 0.8 mg/dl. The mean serum creatinine and BUN concentrations and estimated CrCl were similar in each group before contrast agents were injected. In the control group, the mean serum creatinine concentration significantly increased from 2.8 ± 0.8 to 3.1 ± 1.0 mg/dl at 48 h after injection of the contrast agent ($p < 0.01$). The mean BUN concentration also significantly increased from 42 ± 16 to 49 ± 23 mg/dl at

Table 1. Clinical and Biochemical Characteristics of the Study Patients

Characteristics	Acetylcysteine Group (n = 60)	Control Group (n = 61)
Age (yrs)	70 ± 7	70 ± 7
Gender (M/F, n)	42/18	40/21
Body mass index (kg/m^2)	25.9 ± 4.5	25.9 ± 3.8
Systolic blood pressure (mm Hg)	140 ± 24	138 ± 22
Diastolic blood pressure (mm Hg)	81 ± 14	79 ± 16
Serum creatinine (mg/dl)*	2.8 ± 0.8	2.8 ± 0.8
Blood urea nitrogen (mg/dl)†	41 ± 11	42 ± 16
Estimated CrCl (ml/min)‡	23.6 ± 10.2	23.1 ± 8.9
Hypertension	42 (70%)	41 (67%)
Diabetes mellitus	38 (63%)	39 (64%)
Hyperlipidemia	28 (47%)	24 (39%)
Diuretic therapy	34 (57%)	34 (56%)
Calcium channel blocker therapy	24 (40%)	27 (44%)
Angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist	24 (40%)	26 (43%)
Dose of contrast agent (ml)	119 ± 3	115 ± 48
Angiolpasty/angiography (n)	43/17	40/21

*To convert from mg/dl to μmol/l, multiply by 88.4. †To convert from mg/dl to mmol/liter, multiply by 0.357. ‡Estimated creatinine clearance: CrCl = (140 − age in years × weight in kg/creatinine in mg/dl × 72). $CrCl_{male}$ = 1 × CrCl; $CrCl_{female}$ = 0.85 × CrCl. There were no significant differences between the groups ($p > 0.05$ for all comparisons). Data are presented as the mean value ± SD or number (%) of patients or control subjects.

48 h after injection of the contrast agent ($p < 0.01$). In the acetylcysteine group, the mean serum creatinine and BUN concentrations significantly decreased from 2.8 ± 0.8 and 41 ± 11 mg/dl to 2.5 ± 1.0 and 35 ± 14 mg/dl, respectively, at 48 h after injection of contrast agents ($p < 0.01$ and $p < 0.01$, respectively). The mean serum creatinine concentration in the acetylcysteine group was significantly lower than that in the control group at 48 h and 7 days after the administration of contrast agents (Fig. 1). The absolute change in serum creatinine concentration was significantly greater in the control group than in the acetylcysteine group ($p < 0.001$) (Table 2).

Table 2. Absolute Changes in Serum Creatinine Concentrations After Coronary Procedures and the Incidence of Acute Reductions in Renal Function in the Acetylcysteine and Control Groups

Variable	Acetylcysteine Group (n = 60)	Control Group (n = 61)	p Value
Change in serum creatinine 48 h after coronary intervention (mg/dl)*	−0.29 ± 0.41	0.24 ± 0.56	<0.001
Incidence of acute reduction in renal function	2 (3.3%)	15 (24.6%)	<0.001

*To convert from mg/dl to μmol/l, multiply by 88.4. Data are presented as the mean value ± SD or number (%) of patients or control subjects.

Effect of acetylcysteine. An acute contrast-induced reduction in renal function occurred in 17 (13.2%) of the 121 patients: 2 (3.3%) of the 60 patients in the acetylcysteine group and 15 (24.6%) of the 61 patients in the control group ($p < 0.001$; relative risk 0.13; 95% confidence interval 0.08 to 0.20) (Table 2). Baseline systolic and diastolic blood pressure did not influence the findings. Ten of the 16 patients with an acute contrast-induced reduction in renal function had diabetes mellitus: 2 in the acetylcysteine group and 8 in the control group. The presence or absence of diabetes mellitus did not affect the therapeutic efficacy of acetylcysteine.

In the acetylcysteine group, 18 patients (30%) had a baseline serum creatinine concentration >3.0 mg/dl, as did 22 patients (36%) in the control group. Among these patients with an elevated baseline creatinine concentration, 2 (11%) of the 18 patients in the acetylcysteine group and 9 (41%) of the 22 patients in the control group had an acute contrast-induced reduction in renal function ($p < 0.05$) (Fig. 2). None of the patients with a serum creatinine concentration <3 mg/dl in the acetylcysteine group had an acute reduction in renal function. In the control group, increases in the serum creatinine concentration after admin-

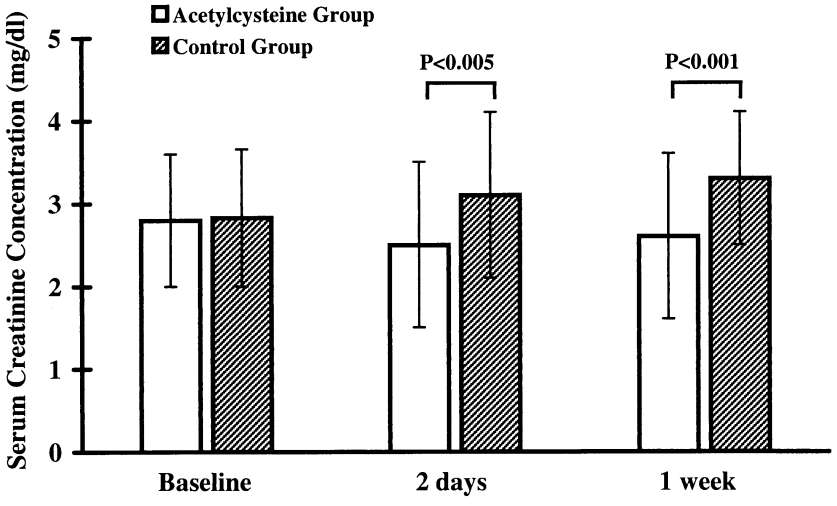

Figure 1. Changes in serum creatinine concentration before and after injection of contrast agent in the acetylcysteine and control groups.

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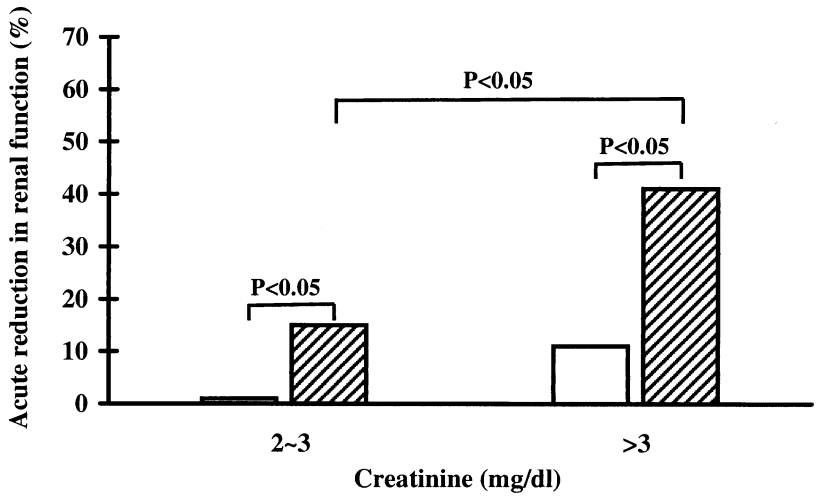

Figure 2. Comparison of the incidence of an acute reduction in renal function in serum creatinine concentration between 2 and 3 mg/dl and >3 mg/dl in the acetylcysteine **(open bars)** and control groups **(cross-hatched bars)**.

istration of contrast agent were related to the severity of the serum creatinine concentration before hydration: 9 (41%) of the 22 patients with a serum creatinine concentration >3 mg/dl and 6 (15%) of the 39 patients with a serum creatinine concentration between 2 and 3 mg/dl had an acute contrast-induced reduction in renal function ($p < 0.05$). One of the 15 patients with an acute reduction in renal function in the control group finally received continuous ambulatory peritoneal dialysis because of progressive deterioration of renal function. None of the patients in the acetylcysteine group received dialysis during the follow-up period of three months. Although control subjects with a higher baseline serum creatinine concentration tended to have CIN, the baseline serum creatinine concentration did not influence the effect of acetylcysteine in the treatment group.

DISCUSSION

In this study, we found that prophylactic oral administration of the antioxidant acetylcysteine reduced the incidence of an acute reduction in renal function by contrast agent in patients with abnormal renal function who underwent coronary angiography with or without intervention. The development of contrast-induced renal failure after coronary angiography or intervention, though infrequent, is a serious complication with significant intermediate and long-term implications for patient outcome and health-care costs (2,18). The incidence of acute CIN among patients with diabetes mellitus has been reported to be 50% to 90% in patients with severe chronic renal insufficiency (19,20). Although many methods were used to prevent acute renal damage by contrast agents, most of the results were disappointing (9–13). How to prevent acute renal damage by contrast agent injection becomes an important issue, because the application of PCI to the treatment of CAD has grown dramatically since the first balloon angioplasty was performed in 1979. Even small increments in serum creatinine can translate into significant increases in morbidity and mortality (21,22).

An acute contrast-induced reduction in renal function was defined as an increase in the serum creatinine concentration of at least 0.5 mg/dl at 48 h after injection of contrast medium (16,19). Such an increase occurred in 13.2% of patients in our study and in 12% of patients reported by Tepel et al. (16). The severity of renal insufficiency before contrast injection was more severe in our study than in that reported by Telpel et al. (2.8 ± 0.8 vs. 2.4 ± 1.3 mg/dl; $p < 0.01$ by *t* test). The volume of contrast agent was also larger in our study (118 ± 50 vs. 75 ml; $p < 0.01$). None of the patients with a serum creatinine concentration <3.0 mg/dl in the acetylcysteine group developed an acute reduction in renal function after a coronary procedure. The incidence of an acute reduction in renal function in patients with a serum creatinine concentration >3.0 mg/dl was also significantly lower in the acetylcysteine group than in the control group (11% vs. 41%, $p < 0.05$). This finding implies that acetylcysteine protects against acute renal damage induced by contrast agent not only in patients with moderate renal insufficiency but also in patients with severe renal insufficiency. The beneficial effects of acetylcysteine also appear to extend to elderly patients in our study (mean age 70 ± 7 years). Although previous studies have used antioxidants to reduce acute renal damage in a small number of patients with abnormal renal function undergoing cardiac catheterization (17,23,24), the baseline serum creatinine concentration in those studies was >1.5 mg/dl. In this study, we enrolled a larger number of patients, assessed patients with a higher baseline serum creatinine concentration (>2.0 mg/dl), and included cardiac catheterization and patients undergoing PCI.

The contrast volume during cardiac procedures has important implications for postprocedural renal function. An average contrast volume of 200 to 350 ml has been reported in previous studies of coronary interventions (1,25). Coro-

nary intervention was performed at the time of diagnostic catheterization in our study, and left ventriculography was omitted in most of the patients. This strategy resulted in a smaller contrast volume (~120 ml) used in our study. Although we have proved the protective effect of acetylcysteine during cardiac intervention for patients with severe renal insufficiency, this same effect may not be extrapolated to patients who were in need of larger doses of contrast agents.

Administration of contrast agent increases the hypoxia of the renal medulla and increases renal free-radical production (15,26). Acetylcysteine has several potential physiologic effects on the protection of renal damage: 1) it may reduce the ability of generated oxygen free radicals to damage cells by scavenging; 2) it increases the expression of nitric oxide synthase and improves blood flow; and 3) it inhibits cell apoptosis (27,28). Acetylcysteine has been used as a therapeutic agent in a variety of clinical settings. For example, acetylcysteine serves as a mucolytic agent in chronic bronchitis (29), an antidote in acetaminophen-induced hepatotoxicity (30), and as an inhibitor of hemorrhagic cystitis caused by cyclophosphamide and ifosfamide (31).

Study limitations. Limitations of our study include the small sample size and the fact that it was a single-center study, which may reduce the power of the study. The study design, however, did allow us to make acetylcysteine-specific inferences. Whether different pathologies of renal disease influence the acetylcysteine effect is not explored, because the underling etiology of chronic renal insufficiency in our study was not investigated. Finally, our data are limited to one week after coronary procedures; the effect of acetylcysteine on long-term outcomes in patients with abnormal renal function remains unknown.

Clinical implications. The data presented in this study suggest that the use of acetylcysteine could be beneficial for ameliorating the acute renal failure observed during coronary angiography with or without intervention. Our prospective, randomized study showed that the beneficial effects of acetylcysteine appear to extend to elderly patients with even more severe chronic renal insufficiency. As suggested by Safirstein et al. (32), because of the low cost of acetylcysteine and its general availability, ease of administration, and limited side effects, the use of acetylcysteine to reduce acute renal failure induced by contrast agents should be encouraged. Enhanced physician awareness of the renal implications of PCI, in conjunction with careful patient selection, risk assessment, and the use of acetylcysteine, will help to minimize the incidence of renal failure and the associated increases in morbidity, mortality, and health-care costs.

Conclusions. We conclude that prophylactic oral administration of the antioxidant acetylcysteine, along with hydration, reduces acute renal damage induced by contrast agents in patients with chronic renal insufficiency undergoing a coronary procedure. Because acetylcysteine can decrease the incidence of nephrotoxicity after coronary procedures, the general use of acetylcysteine to prevent acute renal damage in patients with abnormal renal function treated with a coronary procedure may be warranted.

Reprint requests and correspondence: Dr. Kou-Gi Shyu, Division of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital, 95 Wen-Chang Road, Taipei 111, Taiwan. E-mail: shyukg@ms12.hinet.net.

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