

PREVENTION OF RADIOGRAPHIC-CONTRAST-AGENT-INDUCED REDUCTIONS IN RENAL FUNCTION BY ACETYLCYSTEINE

MARTIN TEPEL, M.D., MARCUS VAN DER GIET, M.D., CAROLA SCHWARZFELD, ULF LAUFER, M.D.,
DIETER LIERMANN, M.D., AND WALTER ZIDEK, M.D.

ABSTRACT

Background Radiographic contrast agents can cause a reduction in renal function that may be due to reactive oxygen species. Whether the reduction can be prevented by the administration of antioxidants is unknown.

Methods We prospectively studied 83 patients with chronic renal insufficiency (mean [\pm SD] serum creatinine concentration, 2.4 ± 1.3 mg per deciliter [216 ± 116 μ mol per liter]) who were undergoing computed tomography with iopromide, a nonionic, low-osmolality contrast agent. Patients were randomly assigned either to receive the antioxidant acetylcysteine (600 mg orally twice daily) and 0.45 percent saline intravenously, before and after administration of the contrast agent, or to receive placebo and saline.

Results Ten of the 83 patients (12 percent) had an increase of at least 0.5 mg per deciliter (44 μ mol per liter) in the serum creatinine concentration 48 hours after administration of the contrast agent: 1 of the 41 patients in the acetylcysteine group (2 percent) and 9 of the 42 patients in the control group (21 percent; $P=0.01$; relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.9). In the acetylcysteine group, the mean serum creatinine concentration decreased significantly ($P<0.001$), from 2.5 ± 1.3 to 2.1 ± 1.3 mg per deciliter (220 ± 118 to 186 ± 112 μ mol per liter) 48 hours after the administration of the contrast medium, whereas in the control group, the mean serum creatinine concentration increased nonsignificantly ($P=0.18$), from 2.4 ± 1.3 to 2.6 ± 1.5 mg per deciliter (212 ± 114 to 226 ± 133 μ mol per liter) ($P<0.001$ for the comparison between groups).

Conclusions Prophylactic oral administration of the antioxidant acetylcysteine, along with hydration, prevents the reduction in renal function induced by iopromide, a nonionic, low-osmolality contrast agent, in patients with chronic renal insufficiency. (N Engl J Med 2000;343:180-4.)

©2000, Massachusetts Medical Society.

ADMINISTRATION of radiographic contrast agents often results in an acute reduction in renal function.¹⁻⁵ The reduction can cause substantial morbidity and mortality during hospitalization and can lead to chronic end-stage renal disease.^{1,5} Important risk factors for contrast-agent-induced reductions in renal function are preexisting renal dysfunction, particularly that caused by diabetic nephropathy; reduced effective arterial volume; concomitant administration of drugs that interfere with the regulation of re-

nal perfusion, such as angiotensin-converting-enzyme inhibitors; and a higher volume of contrast agent administered.^{1,2,6}

In patients with chronic renal insufficiency, hydration has been reported to ameliorate contrast-agent-induced reductions in renal function, but the administration of drugs such as calcium antagonists, theophylline, dopamine, and atrial natriuretic peptide does not prevent the reduction.⁵⁻¹² Contrast agents reduce renal function by altering renal hemodynamics and by exerting direct toxic effects on tubular epithelial cells. There is accumulating evidence that reactive oxygen species have a role in the renal damage caused by contrast agents.¹³⁻¹⁵ In rats, contrast agents increased lipid peroxidation,¹⁶ and superoxide dismutase, a scavenger of reactive oxygen species, preserved renal function.¹⁴

On the assumption that reactive oxygen species might be involved in the pathogenesis of acute contrast-agent-induced reductions in renal function, we studied the effects of the prophylactic oral administration of the antioxidant acetylcysteine in a prospective, placebo-controlled, randomized trial involving patients with chronic renal insufficiency who were at high risk for contrast-agent-induced renal damage.

METHODS

Patients

We prospectively studied 83 patients with a serum creatinine concentration above 1.2 mg per deciliter (106 μ mol per liter) or creatinine clearance of less than 50 ml per minute (0.8 ml per second). Creatinine clearance was estimated on the basis of the serum creatinine concentration, weight, age, and sex.¹⁷ Only patients known to have a history of chronic renal failure and with stable serum creatinine concentrations were included. Repeated measurements during the week before the administration of the contrast agent revealed only minor changes in serum creatinine concentrations (mean [\pm SD] variation, 0.1 ± 0.3 mg per deciliter [9 ± 26 μ mol per liter]; $P=0.12$). No patient with acute renal failure was included. The cause of renal insufficiency was diabetic nephropathy in 27 patients, nephrosclerosis in 20 patients, glomerulonephritis in 12 patients, tubulointerstitial nephritis in 4 patients, and unknown in 20 patients. All the patients underwent elective computed tomography (CT) with a nonionic low-osmolality radiographic contrast agent. The indications for CT were determined by each patient's physician. Most patients underwent CT for the evaluation of an abdominal or thoracic illness.

From the Medizinische Klinik I (M.T., M.G., W.Z.) and the Radiologische Klinik (C.S., U.L., D.L.), Universitätsklinik Marienhospital, Ruhr-Universität Bochum, Herne, Germany. Address reprint requests to Dr. Tepel at the Medizinische Klinik I, Universitätsklinik Marienhospital, Ruhr-Universität Bochum, Hölkeskampring 40, D-44625 Herne, Germany, or at martin.tepel@ruhr-uni-bochum.de.

The study 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 600 mg twice daily, on the day before and on the day of administration of the contrast agent, for a total of two days. Saline (0.45 percent) was given intravenously at a rate of 1 ml per kilogram of body weight per hour for 12 hours before and 12 hours after administration of the contrast agent. All patients were encouraged to drink if they were thirsty. The dose of nonionic, low-osmolality contrast agent (iopromide; Ultravist-300, Schering, Berlin, Germany) was 75 ml for all patients. The infusion contained 0.623 g of iopromide per milliliter, and the iodine content was 300 mg per milliliter. None of the patients received theophylline, dopamine, mannitol, or furosemide during the study. Serum creatinine and urea nitrogen were measured repeatedly during the week before administration of the contrast agent, as noted above, and immediately before, 48 hours after, and 6 days after administration of the contrast agent. An acute contrast-agent-induced reduction in renal function was defined as an increase in the serum creatinine concentration of at least 0.5 mg per deciliter (44 μ mol per liter) 48 hours after administration of the contrast agent.

Acetylcysteine (final concentration, 2.5 mmol per liter) was added in vitro to serum samples from the patients, and serum creatinine was measured. In the presence of acetylcysteine, the mean serum creatinine concentration was 100 \pm 1 percent of the serum creatinine concentration in the absence of acetylcysteine.

Statistical Analysis

The final analysis was conducted on an intention-to-treat basis. Categorical variables (e.g., the incidence of acute contrast-agent-induced reductions in renal function) were analyzed by Fisher's exact test. Differences between the groups in serum creatinine concentrations were analyzed by the nonparametric Wilcoxon-Mann-Whitney test. A multiple logistic-regression analysis was used to examine the effect of acetylcysteine, with adjustment for base-line blood pressure. The logistic-regression analysis was performed with the acute contrast-agent-induced reduction in renal function as the dependent variable. Analyses were performed with GraphPad Prism software (version 3.0, GraphPad Software, San Diego, Calif.), or SPSS software (release 8.0.0, SPSS, Chicago). All statistical tests were two-sided.

RESULTS

The clinical and biochemical characteristics of the patients are shown in Table 1. The mean weights of the patients were similar at the start of the study (control group, 76 \pm 13 kg; acetylcysteine group, 77 \pm 12 kg) and at the end (control group, 77 \pm 13 kg; acetylcysteine group, 78 \pm 12 kg), suggesting a similar fluid balance.

The mean serum creatinine concentration for all patients was 2.4 \pm 1.3 mg per deciliter (216 \pm 116 μ mol per liter). In the control group, the mean serum creatinine concentration increased from 2.4 \pm 1.3 to 2.6 \pm 1.5 mg per deciliter (212 \pm 114 to 226 \pm 133 μ mol per liter) 48 hours after administration of the contrast agent (P=0.18) (Fig. 1). In the acetylcysteine group, the mean serum creatinine concentration decreased from 2.5 \pm 1.3 to 2.1 \pm 1.3 mg per deciliter (220 \pm 118 to 186 \pm 112 μ mol per liter) 48 hours af-

TABLE 1. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	ACETYLCYSTEINE GROUP (N=41)	CONTROL GROUP (N=42)
Age — yr	66 \pm 11	65 \pm 15
Sex — M/F	24/17	23/19
Body-mass index	27.1 \pm 4.3	26.4 \pm 4.7
Blood pressure — mm Hg	139/79 \pm 18/10	141/77 \pm 24/12
Serum creatinine — mg/dl	2.5 \pm 1.3	2.4 \pm 1.3
Diabetes mellitus — no. (%)	13 (32)	14 (33)
Diuretic therapy — no. (%)	28 (68)	24 (57)
Calcium-channel blocker — no. (%)	8 (20)	5 (12)
Angiotensin-converting-enzyme inhibitor — no. (%)	8 (20)	6 (14)

*Plus-minus values are means \pm SD. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. There were no significant differences between the groups (P>0.05 for all comparisons).

ter administration of the contrast agent (P<0.001). The absolute change in serum creatinine concentration was significantly greater in the control group than in the acetylcysteine group (P<0.001) (Table 2).

In the control group, the mean serum urea nitrogen concentration was 44 \pm 26 mg per deciliter (15 \pm 9 mmol per liter) before and 47 \pm 29 mg per deciliter (17 \pm 10 mmol per liter) 48 hours after administration of the contrast agent (P=0.38). In the acetylcysteine group, the mean serum urea nitrogen concentration significantly decreased from 51 \pm 28 mg per deciliter (18 \pm 10 mmol per liter) before to 44 \pm 29 mg per deciliter (16 \pm 10 mmol per liter) 48 hours after administration of the contrast agent (P<0.001).

An acute contrast-agent-induced reduction in renal function was defined as an increase in the serum creatinine concentration of at least 0.5 mg per deciliter (44 μ mol per liter) 48 hours after administration of the contrast agent. Such an increase occurred in 10 of the 83 patients (12 percent): 1 of the 41 patients in the acetylcysteine group (2 percent) and 9 of the 42 patients in the control group (21 percent; P=0.01; relative risk, 0.1; 95 percent confidence interval, 0.02 to 0.9). Base-line systolic and diastolic blood pressure did not influence the findings. Five of the 10 patients with an acute contrast-agent-induced reduction in renal function had diabetes mellitus.

In the acetylcysteine group, 13 patients (32 percent) had base-line serum creatinine concentrations above 2.5 mg per deciliter (221 μ mol per liter), as did 12 patients (29 percent) in the control group. Among these patients with elevated base-line creatinine concentrations, none of the 13 patients in the acetylcysteine group and 5 of the 12 patients in the

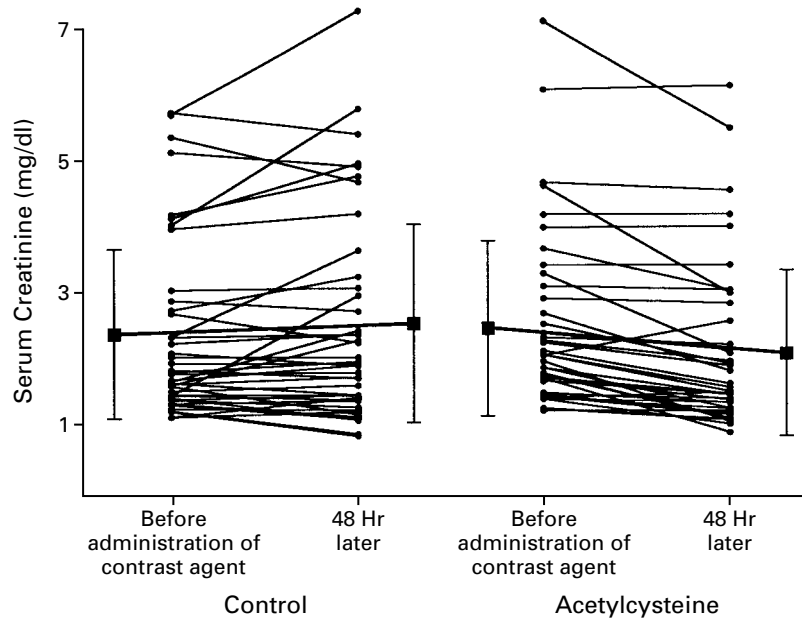


Figure 1. Serum Creatinine Concentrations before and 48 Hours after the Administration of Contrast Agent to Patients with Chronic Renal Insufficiency.

Mean (\pm SD) concentrations for the acetylcysteine group (41 patients) and for the control group (42 patients) are indicated by squares and vertical lines. To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

TABLE 2. BASE-LINE SERUM CREATININE CONCENTRATIONS, ABSOLUTE CHANGES IN SERUM CREATININE CONCENTRATIONS AFTER ADMINISTRATION OF THE CONTRAST AGENT, AND INCIDENCE OF ACUTE REDUCTIONS IN RENAL FUNCTION IN THE ACETYLCYSTEINE AND CONTROL GROUPS.*

VARIABLE	ACETYLCYSTEINE GROUP (N=41)	CONTROL GROUP (N=42)	P VALUE
Serum creatinine concentration — mg/dl			
Base line	2.5 \pm 1.3	2.4 \pm 1.3	0.55
Change 48 hr after administration of contrast agent	-0.4 \pm 0.4	+0.2 \pm 0.6	<0.001†
Incidence of acute reductions in renal function — no. (%)	1 (2)	9 (21)	0.01‡

*Plus-minus values are means \pm SD. To convert values for serum creatinine to micromoles per liter, multiply by 88.4. Mean serum creatinine concentrations decreased significantly ($P<0.001$) in the acetylcysteine group and increased nonsignificantly ($P=0.18$) in the control group.

†The Wilcoxon–Mann–Whitney test was used for the comparison between the groups.

‡Fisher’s exact test was used for the comparison between the groups.

control group (42 percent) had an acute contrast-agent–induced reduction in renal function ($P=0.02$).

Among the patients with an acute contrast-agent–induced reduction in renal function, the mean serum creatinine concentration was still elevated on day 6 after the administration of the contrast agent (by 0.5 ± 0.6 mg per deciliter [43 ± 50 μ mol per liter] over base line). None of the patients required dialysis. Three of the 41 patients in the acetylcysteine group (7 percent) and 5 of the 42 patients in the control group (12 percent) reported temporary gastrointestinal discomfort during the study; 4 patients in the acetylcysteine group (10 percent) and 3 patients in the control group (7 percent) reported dizziness. There were no other adverse effects.

DISCUSSION

The important finding of this study is that prophylactic oral administration of the antioxidant acetylcysteine reduced the incidence of acute contrast-agent–induced reductions in renal function. In addition, the absolute change in the serum creatinine concentration after administration of the contrast agent was less in the acetylcysteine group than in the control group. The results were similar in the subgroup of patients with initial serum creatinine concentrations above 2.5 mg per deciliter. To exclude the possibility that the effects of acetylcysteine were due only to a

direct effect on the tubular secretion of creatinine, with renal function left unaffected, we also measured serum urea nitrogen. The changes in serum urea nitrogen concentrations were similar to those in serum creatinine concentrations, suggesting that changes in glomerular filtration may underlie the observed changes in serum creatinine concentrations.

The incidence of acute contrast-agent-induced reductions in renal function varies from 0 to 90 percent, depending on the presence of risk factors, including chronic renal insufficiency, diabetes mellitus, and a higher volume of contrast agent administered.¹⁻⁸ The incidence of acute contrast-agent-induced reductions in renal function among patients with diabetes has been reported to be 9 to 40 percent in patients with mild-to-moderate chronic renal insufficiency and 50 to 90 percent in patients with severe chronic renal insufficiency.^{1,2} The present study included diabetic as well as nondiabetic patients with chronic renal insufficiency, since diabetic patients are thought to be at high risk for contrast-agent-induced reductions in renal function.

As recommended in earlier studies, we defined an acute contrast-agent-induced reduction in renal function as an increase in the serum creatinine concentration of at least 0.5 mg per deciliter 48 hours after administration of the contrast agent.¹⁻⁸ Such an increase may be important, because it can increase the duration of hospitalization.⁵ To avoid any bias due to the use of different types of contrast agent or the administration of different volumes, 75 ml of the same nonionic, low-osmolality contrast agent was given to all the patients. The use of such agents is associated with a lower incidence of acute reductions in renal function than the use of ionic, high-osmolality agents.^{6,18} Earlier studies support the use of hydration in patients with chronic renal insufficiency to prevent acute contrast-agent-induced reductions in renal function.⁴⁻⁸

How can the beneficial effect of acetylcysteine be explained? Contrast-agent-induced reductions in renal function are due to alterations in renal hemodynamics and direct toxic effects on tubular epithelial cells. The toxic renal damage may contribute to the formation of reactive oxygen species or to reduced antioxidant activity.¹³⁻¹⁵ Recent studies suggest that acetylcysteine has vasodilatory properties.^{19,20} In animals, acetylcysteine can ameliorate ischemic renal failure,^{21,22} and it has been reported to block the expression of vascular-cell adhesion molecule 1 and the activation of nuclear factor- κ B in glomerular mesangial cells.²³ Early administration of acetylcysteine prevents a reduction in renal function in patients with acetaminophen poisoning who have liver failure.^{24,25} A recent nonrandomized study suggested that acetylcysteine may improve renal function in patients with the hepatorenal syndrome.²⁶ Therefore, it may be capable of preventing a contrast-agent-induced

reduction in renal function both by improving renal hemodynamics and by preventing direct oxidative tissue damage.

In conclusion, prophylactic oral administration of the antioxidant acetylcysteine at a dose of 600 mg twice daily on the day before and on the day of administration of the contrast agent, together with hydration with saline, is an effective means of preventing renal damage induced by a nonionic, low-osmolality contrast agent in patients with chronic renal insufficiency.

REFERENCES

1. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both: a prospective controlled study. *N Engl J Med* 1989;320:143-9.
2. Rich MW, Creelius CA. Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older: a prospective study. *Arch Intern Med* 1990;150:1237-42.
3. Schwab SJ, Hlatky MA, Pieper KS, et al. Contrast nephrotoxicity: a randomized controlled trial of a nonionic and an ionic radiographic contrast agent. *N Engl J Med* 1989;320:149-53.
4. Stevens MA, McCullough PA, Tobin KJ, et al. A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the P.R.I.N.C.E. Study: Prevention of Radiocontrast Induced Nephropathy Clinical Evaluation. *J Am Coll Cardiol* 1999;33:403-11.
5. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;331:1416-20.
6. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial: the Iohexol Cooperative Study. *Kidney Int* 1995;47:254-61.
7. Eisenberg RL, Bank WO, Hedgcock MW. Renal failure after major angiography can be avoided with hydration. *AJR Am J Roentgenol* 1981;136:859-61.
8. Weisberg LS, Kurnik PB, Kurnik BRC. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 1994;45:259-65.
9. Erley CM, Duda SH, Schlepckow S, et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. *Kidney Int* 1994;45:1425-31.
10. Kapoor A, Sinha N, Sharma RK, et al. Use of dopamine in prevention of contrast induced acute renal failure — a randomised study. *Int J Cardiol* 1996;53:233-6.
11. Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998;31:674-80.
12. Hans SS, Hans BA, Dhillon R, Dmuchowski C, Glover J. Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. *Am Surg* 1998;64:432-6.
13. Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. *Am J Kidney Dis* 1997;29:465-77.
14. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC Jr. Radiocontrast medium-induced declines in renal function: a role for oxygen free radicals. *Am J Physiol* 1990;258:F115-F120.
15. Yoshioka T, Fogo A, Beckman JK. Reduced activity of antioxidant enzymes underlies contrast media-induced renal injury in volume depletion. *Kidney Int* 1992;41:1008-15.
16. Parvez Z, Rahman MA, Moncada R. Contrast media-induced lipid peroxidation in the rat kidney. *Invest Radiol* 1989;24:697-702.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
18. Katholi RE, Taylor GJ, Woods WT, et al. Nephrotoxicity of nonionic low-osmolality versus ionic high-osmolality contrast media: a prospective double-blind randomized comparison in human beings. *Radiology* 1993;186:183-7.
19. Jones AL, Haynes W, MacGilchrist AJ, Webb DJ, Hayes PC. N-acetylcysteine (NAC) is a potent peripheral vasodilator. *Gut* 1994;35:Suppl 5: S10. abstract.
20. Zhang H, Spaten H, Nguyen DN, Rogiers P, Bakker J, Vincent JL. Effects of N-acetyl-L-cysteine on regional blood flow during endotoxic shock. *Eur Surg Res* 1995;27:292-300.
21. DiMari J, Megyesi J, Udvarhelyi N, Price P, Davis R, Safirstein R. N-acetyl cysteine ameliorates ischemic renal failure. *Am J Physiol* 1997;272:F292-F298.

- 22.** Salom MG, Ramirez P, Carbonell LE, et al. Protective effect of N-acetyl-L-cysteine on the renal failure induced by inferior vena cava occlusion. *Transplantation* 1998;65:1315-21.
- 23.** Khachigian LM, Collins T, Fries JW. N-acetyl cysteine blocks mesangial VCAM-1 and NF-kappa B expression in vivo. *Am J Pathol* 1997;151:1225-9.
- 24.** Brady HR, Singer GG. Acute renal failure. *Lancet* 1995;346:1533-40.
- 25.** Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995;346:547-52.
- 26.** Holt S, Goodier D, Marley R, et al. Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* 1999;353:294-5.