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A Rapid Protocol for the Prevention of Contrast-Induced Renal Dysfunction: The RAPPID Study

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OBJECTIVES This study was designed to test a rapid protocol of intravenous acetylcysteine for prevention of radiocontrast-induced nephropathy (RCIN).

BACKGROUND Oral acetylcysteine (NAC) may provide better prophylaxis against RCIN than intravenous (IV) hydration alone. Current protocols preclude prophylaxis of same-day or emergency patients owing to the need for prolonged pretreatment.

METHODS We prospectively randomized 80 patients with stable renal dysfunction undergoing cardiac catheterization/intervention to a rapid protocol of IV NAC (150 mg/kg in 500 ml N/saline over 30 min immediately before contrast followed by 50 mg/kg in 500 ml N/saline over 4 h, n = 41, 67 ± 10 years, 90% men) or IV hydration (1 ml/kg/h N/saline for 12 h pre- and post-contrast, n = 39, 71 ± 8.8 years, 85% men).

RESULTS Radiocontrast-induced nephropathy occurred in 2 of the 41 patients in the NAC group (5%) and in 8 of the 39 patients in the hydration group (21%; p = 0.045; relative risk: 0.28; 95% confidence interval 0.08 to 0.98). In the NAC group, mean serum creatinine *fell* from 1.85 ± 0.59 to 1.77 ± 0.73 and 1.79 ± 0.73 mg/dl 48 h and four days post-contrast (p = 0.02 and 0.023 vs. baseline, respectively). In the hydration group, serum creatinine increased from 1.75 ± 0.41 to 1.81 ± 0.6 48 h and 1.80 ± 0.50 mg/dl four days post-contrast (p = 0.99 and 0.23, respectively). NAC infusion was ceased after the bolus in three patients (7%) due to flushing, itching, or a transient rash.

CONCLUSIONS Administration of IV NAC should be considered in all patients at risk of RCIN before contrast exposure when time constraints preclude adequate oral prophylaxis, provided the patient is able to tolerate this degree of volume loading. (J Am Coll Cardiol 2003;41: 2114–8) © 2003 by the American College of Cardiology Foundation

Radiocontrast-induced nephropathy (RCIN) is reported to occur in as many as 14.5% of unselected patients undergoing coronary angiography/intervention (1), and is the third most common cause of in-hospital acute renal failure after hypotension and surgery (2). Important risk factors for RCIN include pre-existing renal dysfunction, especially that due to diabetic nephropathy; reduced circulating volume; the volume and type of contrast agent employed; and concomitant administration of potentially nephrotoxic drugs (3,4). Several agents have been proposed to provide prophylaxis against RCIN (3). However, until recently, only saline hydration (1 ml/kg 0.45% saline for 12 h pre- and post-contrast exposure) has been confirmed to be effective (5).

The precise mechanisms leading to RCIN remain a matter of debate, although the root of the problem appears to be an injury to the renal medulla resulting from a combination of reduced blood flow, an osmotic effect, and direct tubular toxicity. The last of these may be a direct result of toxic free radical release, which occurs after contrast administration (6). Recent studies have highlighted the potential protective effect of oral acetylcysteine (NAC), an antioxidant, in addition to saline hydration in preventing RCIN (7–10), although this has not been a universal finding (11–13). The successful protocols tested to date require the initiation of therapy on the day before contrast exposure, precluding the treatment of same-day and emergency patients.

We therefore conducted a prospective, randomized, multicenter controlled trial to test the hypothesis that a rapid protocol of intravenous (IV) acetylcysteine would be more effective at inhibiting RCIN in high-risk patients undergoing coronary angiography/intervention than prolonged saline hydration alone.

METHODS

Patients. We studied prospectively patients undergoing coronary angiography or intervention at three London hospitals (London Chest Hospital, St. Bartholomew's Hospital, and the Hammersmith Hospital) between October 2001 and August 2002. All patients had a serum creatinine (SCr) concentration >1.36 mg/dl (120 μmol/l) or a creatinine clearance <50 ml/min calculated on the basis of SCr, age, weight, and gender {creatinine clearance = [(140 − age in years) × weight in kg]/(creatinine in mg/dl × 72)} (14). No patients with acute renal failure or end-stage renal failure on dialysis were included. Patients who had received a nonsteroidal anti-inflammatory agent (except aspirin 75 to 150 mg) within 24 h of the study and those with a systolic blood pressure <90 mm Hg or hemodynamically significant valvular heart disease were excluded. Patients with signs of

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Abbreviations and Acronyms

BUN = blood urea nitrogen
IV = intravenous
NAC = N-acetylcysteine
RCIN = radiocontrast-induced nephropathy
SCr = serum creatinine

cardiac failure at the time of randomization or during the current admission were excluded. Serum creatinine was measured in μmol/l and was converted to milligrams per deciliter by dividing by 88.4. Serum urea was measured in mmol/l and has been converted to blood urea nitrogen (BUN) in mg/dl by dividing by 0.357.

Power calculations indicated a study design requiring 80 patients per group to demonstrate a 0.6 mg/dl difference in the mean change in creatinine (similar to that seen in previous studies [7]) with a power of 80% and a two-tailed significance level of $p < 0.05$. It was pre determined that the data should be analyzed at the midpoint of the study, after the first 80 patients had been randomized, as such numbers had previously proved sufficient (7).

The study protocol was approved by the local ethics committee and all patients gave written informed consent.

Study protocol. Patients were randomly assigned to receive either acetylcysteine and IV saline or intravenous saline alone, before and after contrast administration. Acetylcysteine was given IV at a dose of 150 mg/kg in 500 ml saline (0.9%) over 30 min immediately before contrast exposure and followed by 50 mg/kg in 500 ml saline (0.9%) over the subsequent 4 h. In the control group, saline was given at a rate of 1 ml/kg/h for 12 h pre- and post-procedure. Free oral fluids were commenced immediately post-procedure in all patients. The isotonic, nonionic contrast medium iodixanol (Visipaque, Amersham Health, United Kingdom) was used in all cases. Unless clinically contraindicated, diuretics and angiotensin-converting enzyme inhibitors were stopped 24 h before contrast exposure and restarted only when renal function had been shown to be stable post-procedure. No patient received nitrates (oral or IV), theophylline, dopamine, furosemide, or mannitol during the procedure. Serum creatinine was measured immediately before angiography/intervention and at 48 and 96 h thereafter. An acute contrast-induced reduction in renal function was defined as an increase in SCr concentration by 25% at either two or four days after contrast administration (15,16).

Statistical analysis. Analysis was conducted on an intention-to-treat basis. Categorical variables such as the incidence of RCIN were analyzed by Fisher's exact test. Differences between groups were analyzed by the nonparametric Wilcoxon-Mann-Whitney test. Analyses were performed with GraphPad Prism software (version 3.0, GraphPad Software, San Diego, California). All statistical tests were two-sided and a p value of <0.05 was taken as significant.

Table 1. Baseline Characteristics of the Two Treatment Groups

Characteristic	Acetylcysteine Group (n = 41)	Control Group (n = 39)
Age (yrs)	67.4 ± 10.3	70.9 ± 8.8
Gender (M/F)	37/4	33/6
Weight (kg)	79.2 ± 15.5	81.2 ± 16.0
Serum creatinine (mg/dl)	1.85 ± 0.59	1.75 ± 0.41
Calculated creatinine clearance	45 ± 13	44 ± 18
Diabetes mellitus, no. (%)	17 (41)	17 (44)
Calcium channel blockers, no. (%)	17 (41)	14 (36)
Diuretic therapy, no. (%)	19 (46)	26 (67)
Angiotensin-converting enzyme inhibitor, no. (%)	25 (61)	23 (59)
Angiogram/angioplasty	20/20	21/18
Volume of radiocontrast (ml)	238 ± 155	222 ± 162

Plus-minus values are means ± SD. There were no significant differences between the groups ($p > 0.05$ for all comparisons).

RESULTS

The trial was halted early following the interim analysis and after randomization of the first 80 patients. A single patient did not proceed to contrast administration owing to the development of acute pulmonary edema following the initial 30-min infusion of acetylcysteine. At 48 and 96 h after angiography/intervention, 76 out of 80 and 74 out of 80 patients had SCr measurements available for analysis. A single patient from each group had no post-contrast SCr value for analysis at either time point.

The clinical and baseline characteristics of the patients are shown in Table 1. Mean SCr for all patients was 1.80 ± 0.51 mg/dl (multiply by 88.4 to convert to μmol/l) (159.5 ± 44.9 μmol/l). In the control group, mean SCr increased from 1.75 ± 0.41 (155.0 ± 36.6 μmol/l) to 1.81 ± 0.6 (160.1 ± 53.0 μmol/l) and 1.80 ± 0.5 mg/dl (159.4 ± 44.5 μmol/l), 48 and 96 h after administration of the radiocontrast agent ($p = 0.99$ and 0.23 respectively). In the acetylcysteine group, mean SCr decreased from 1.85 ± 0.59 to 1.77 ± 0.73 (163.7 ± 51.8 and 156.1 ± 64.5 μmol/l) and 1.79 ± 0.73 mg/dl (157.9 ± 64.4 μmol/l), 48 and 96 h after administration of the contrast agent ($p < 0.02$ and <0.023, respectively) (Fig. 1).

In the control group, mean BUN concentration decreased from 29.4 ± 12.3 mg/dl (10.5 ± 4.4 mmol/l) (multiply by 0.357 to convert to mmol/l) to 26.1 ± 10.6 (9.3 ± 3.8 mmol/l) at 48 h and rose to 29.7 ± 13.4 mg/dl (10.6 ± 4.8 mmol/l) 96 h after administration of the radiocontrast agent ($p = 0.0012$ and 0.71 respectively). In the acetylcysteine group, mean BUN decreased from 30.8 ± 14.0 mg/dl (11.0 ± 5.0 mmol/l) to 28.0 ± 13.4 and 28.9 ± 15.1 mg/dl (10.0 ± 4.8 and 10.3 ± 5.4 mmol/l), 48 and 96 h after administration of the contrast agent ($p < 0.08$ and <0.02, respectively).

Acute RCIN occurred in 10 of the 80 patients (12.5%), 2 of the 41 (5%) acetylcysteine-treated patients, and 8 of the 39 fluid-treated patients (21%; $p = 0.045$; relative risk: 0.28; 95% confidence intervals: 0.08 to 0.98) (Fig. 2, Table 2). No

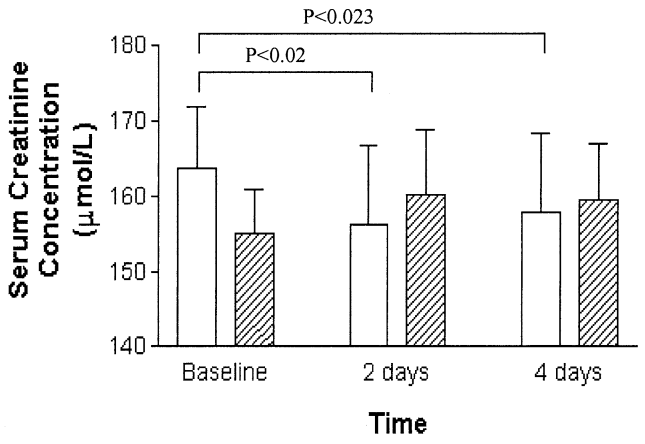

Figure 1. Changes in serum creatinine before and after radiocontrast exposure **White bars** = acetylcysteine; **striped bars** = control.

patient required renal replacement therapy. Five of the 10 patients with an acute contrast agent-induced reduction in renal function had diabetes mellitus. The mean contrast dose in patients developing an acute contrast agent-induced reduction in renal function was 253 ml (range 120 to 700 ml).

Adverse events occurred in 10 of the 80 patients (12.5%). Pulmonary edema occurred in two patients from each group (4 out of 80 patients, 5%). In one patient left ventricular failure occurred before angiography; the acetylcysteine infusion was stopped after the bolus and the procedure postponed. In three patients, this complication occurred after angiography alone (mean contrast dose 128 ± 21 ml) and infusions were halted early. Itching, flushing, or transitory rash was reported in six patients following the 30-min infusion of acetylcysteine (14.6%). In all six patients, symptoms resolved spontaneously with cessation of the infusion. Three patients declined the 4-h infusion owing to this complication. In the other three, the 4-h acetylcysteine infusion was commenced when the suspected side effect had resolved without further incident. A single patient received hydrocortisone and continued the acetylcysteine infusion. No patients received antihistamines.

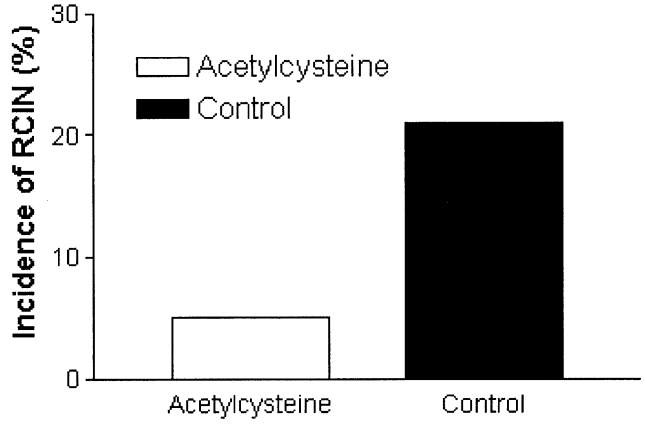

Figure 2. Incidence of post-cardiac catheterization/intervention radiocontrast-induced nephropathy (RCIN). p = 0.045; relative risk 0.28.

Table 2. Baseline Serum Creatinine, Change in Creatinine at 48 and 96 h and Incidence of Acute Reduction in Renal Function in the Acetylcysteine and Control Groups

Variable	Acetylcysteine Group (n = 41)	Control Group (n = 39)	p Value
Serum creatinine (mg/dl)			
Baseline	1.85 ± 0.59	1.75 ± 0.41	0.59
Change at 48 h	−0.08 ± 0.34	+0.05 ± 0.31	0.044*
Change at 96 h	−0.08 ± 0.32	+0.09 ± 0.29	0.008*
Incidence of acute reductions in renal function, no. (%)	2 (4.9)	8 (20.5)	0.045†

Plus-minus values are means ± SD. Mean serum creatinine concentration fell significantly in the acetylcysteine treated group and rose nonsignificantly in the fluid treated group. *The Wilcoxon-Mann-Whitney *U* test was used for the comparison between groups. †Fisher exact test was used for the comparison between groups.

DISCUSSION

The major finding of this study is that treatment of patients with a rapid protocol of IV acetylcysteine and 0.9% saline started immediately before coronary angiography/intervention reduced the incidence of radiocontrast-induced deterioration in renal function compared with a standard 12-h protocol of saline hydration alone. In addition, the absolute change in SCr concentration was less in the acetylcysteine-treated patients than in the hydration-alone group. This was due in part to a significant fall in SCr concentration in the acetylcysteine group.

Previous studies have demonstrated the efficacy of oral acetylcysteine in preventing RCIN in the setting of contrast-assisted computerized tomography (low volumes of IV contrast) (7,10) and following coronary angiography (8) or intervention (9). In all three studies, acetylcysteine was given for 12 to 24 h before contrast exposure. Our findings show that a similar degree of protection is afforded to patients undergoing either angiography or percutaneous coronary intervention by a rapid protocol of IV acetylcysteine administered immediately before the procedure.

The reduction in the incidence of RCIN we have observed is similar to those of previous studies that have reported an incidence of RCIN of between 2% and 8% (7–10) in patients treated with oral acetylcysteine. A similar incidence of RCIN was also seen between the control groups pretreated for 12 h with IV saline (21% to 25%) (7,9) though the rate was higher when saline hydration was less prolonged (8).

The fall in SCr concentration in response to acetylcysteine seen in this study is also consistent with previous reports (7–10). The mechanism of this decline remains unknown but is likely to be a result of changes in glomerular filtration rate. The rise in SCr concentration in the control group reflects, in all probability, a reduction in glomerular filtration rate. The apparently discrepant fall in serum urea likely results from reduced renal tubular urea reabsorption consequent upon hydration, together with the volume expanding effect of hydration itself.

The results of studies of acetylcysteine have varied in their

findings with no benefit reported from three randomized trials of oral acetylcysteine (11–13). Briguori et al. (11) failed to reproduce the original findings of Tepel et al. (7) in patients undergoing coronary angiography/intervention pretreated with drug. This discrepancy is not easy to account for. However, the incidence of RCIN in the control group (11%) was less than that of other studies, perhaps owing to the relatively well-preserved renal function of patients in this study group as a whole. Serum creatinine was measured only at 48 h, and a number of patients with late-developing RCIN may have been missed. Serum creatinine was measured up to 96 h in the current study, as RCIN can develop late. Previous evidence suggests that in approximately 90% of patients with RCIN the SCr will have risen by 72 h (3). This criticism may also apply to the studies of Durham et al. (12) and Allaqaband et al. (13). In the former study the protocol also differed in the timing of drug administration. Acetylcysteine was initiated only 1 h pre-contrast exposure although, as the authors point out, oral dosing produces peak drug levels at 1 h, and the results of our study would indicate that prolonged pre-exposure to acetylcysteine is not necessary.

The dose of IV acetylcysteine chosen for the current study was derived from the standard regimen for the treatment of paracetamol overdose and at this dose 14.5% of patients suffered flushing, itching or rash. These "anaphylactoid" or "hypersensitivity-like" side effects are, however, well recognized and easily managed. The data sheet recommendations of halting the infusion of acetylcysteine and reintroducing the drug at a reduced infusion rate were followed in this study without further complication. No incidence of acetylcysteine-associated death has been reported to date (company information). The incidence of treatment-induced pulmonary edema, though equal in both groups, was higher than might be expected. This may reflect the patient population studied, many of whom likely had impaired left ventricular function, judging by the extensive use of diuretics and angiotensin-converting enzyme inhibitors. In practice, excluding patients with significant echocardiographic impairment of left ventricular function could reduce the risk of pulmonary edema. This could be performed immediately before the contrast exposure and in place of left ventriculography with its attendant contrast load.

The reduced nephrotoxicity of low-osmolality contrast media has been demonstrated both in large studies and by meta-analysis (17,18). A nonionic iso-osmolar medium, iodixanol, was used in this study, as it had been suggested to be even less nephrotoxic on the basis of a reduction in renal tubular enzyme excretion following contrast exposure. Iodixanol had also been reported to reduce RCIN (as defined as a 10% rise in SCr) compared with iohexol in a high-risk group undergoing angiography (19). Evidence available since completion of the study has proven to be consistent with this view (20).

Study limitations. Limitations of our multicenter study include the small sample size. Additionally, the statistical difference between the groups, as in other similar studies, does not necessarily indicate that acetylcysteine will prevent clinically important RCIN, or reduce the incidence of RCIN requiring renal replacement therapy or the mortality from this complication.

An inevitable consequence of aiming to compare a same-day protocol with one requiring pre-admission of the patient was that the rate of saline infusion differed between the two groups. Our protocol dictated that patients in the acetylcysteine group receive 1 liter over 4 h, those in the control group receiving the more standard liter over 12 h. We think it more likely that the acetylcysteine was responsible for our findings than was the rate of fluid administration.

The influence of different renal pathologies on the effectiveness of acetylcysteine in preventing RCIN was not explored in this study, nor was the effect of acetylcysteine on the long-term outcomes of patients with abnormal renal function exposed to radiocontrast. The dose of acetylcysteine chosen was, it may be argued, larger than necessary to prevent RCIN. It may be that a substantially lower intravenous dose would be equally effective and might result in a reduced risk of side effects. This question merits further study.

Conclusions. The IV infusion of acetylcysteine (150 mg/kg in 500 ml 0.9% saline) immediately before coronary angiography/intervention and followed by a 4-h infusion of acetylcysteine (50 mg/kg in 500 ml 0.9% saline) is an effective means of preventing transient renal dysfunction due to the non-ionic, iso-osmolar radiocontrast medium iodixanol. Administration of intravenous NAC should be considered in all patients at risk of RCIN before contrast exposure when time constraints preclude adequate oral prophylaxis. Care must be taken in the treatment of patients with impaired left ventricular function.

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REFERENCES

1. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103:368–75.
2. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med 1983;74:243–8.
3. Solomon R. Contrast-medium-induced acute renal failure. Kidney Int 1998;53:230–42.
4. Baker CS, Baker LR. Prevention of contrast nephropathy after cardiac catheterisation. Heart 2001;85:361–2.

5. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994;331:1416–20.
6. 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:F115–20.
7. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000;343:180–4.
8. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). Am J Cardiol 2002;89:356–8.
9. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J Am Coll Cardiol 2002;40:1383.
10. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA 2003;289:553–8.
11. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. J Am Coll Cardiol 2002;40:298–303.
12. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int 2002;62:2202–7.
13. Allaqaband S, Tumuluri R, Malik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. Catheter Cardiovasc Interv 2002;57:279–83.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
15. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. Kidney Int 1994;45:259–65.
16. Steinberg EP, Moore RD, Powe NR, et al. Safety and cost effectiveness of high-osmolality as compared with low-osmolality contrast material in patients undergoing cardiac angiography. N Engl J Med 1992;326:425–30.
17. 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.
18. Barrett BJ, Carlisle EJ. Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 1993;188:171–8.
19. Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. Br J Radiol 1999;72:701–3.
20. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ. Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 2003;348:491–9.

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