

# The Value of *N*-Acetylcysteine in the Prevention of Radiocontrast Agent-Induced Nephropathy Seems Questionable

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**Abstract.** Prevention of contrast agent-induced nephropathy is of crucial importance for a number of diagnostic studies. *N*-Acetylcysteine (NAC) was recently reported to decrease serum creatinine levels in this setting, and its administration before radiocontrast medium administration has been widely recommended. The objective of this prospective study was to investigate whether there are effects of NAC on serum creatinine levels that are independent of alterations in GFR. Volunteers with normal renal function who did not receive radiocontrast medium were studied. Fifty healthy volunteers completed the study protocol. NAC was administered orally at a dose of 600 mg every 12 h, for a total of four doses. Surrogate markers of renal function, such as serum creatinine, urea, albumin, and cystatin C levels, were measured and estimated

GFR (eGFR) was assessed immediately before the administration of NAC and 4 and 48 h after the last dose. There was a significant decrease in the mean serum creatinine concentration ( $P < 0.05$ ) and a significant increase in the eGFR ( $P < 0.02$ ) 4 h after the last dose of NAC. The cystatin C concentrations did not change significantly. In several studies, a protective effect of NAC on renal function after radiocontrast medium administration has been postulated. This is the first study to demonstrate an effect of NAC on creatinine levels and eGFR, surrogate markers of renal injury, without any effect on cystatin C levels. Before renoprotective effects of NAC against contrast agent-induced nephropathy are considered, the direct effects of NAC on creatinine levels, urea levels, and eGFR should be assessed.

Nephropathy and subsequent renal failure constitute a major concern when radiocontrast agents are administered to patients. With the use of radiocontrast agents in more than 10 million procedures annually in the United States, an incidence of radiocontrast agent-induced nephropathy of 0.5%, and mortality rates reported to be as high as 34% among those patients (1,2), the occurrence and prevention of adverse events have substantial medical and economic effects. Hydration of the patient and administration of *N*-acetylcysteine (NAC) are currently recommended to prevent renal injury (3). In studies to establish the protective effects of any given regimen, serum creatinine levels serve as a surrogate marker of GFR and changes are thought to reflect renal injury. However, any changes in serum creatinine levels that are not based on corresponding alterations of GFR should raise significant concerns regarding application of the model.

A recent study suggested additive protective properties of NAC used in conjunction with hydration. Interestingly, that

advantage was based on a decrease in serum creatinine concentrations among patients exposed to contrast agent plus NAC, whereas unchanged serum creatinine concentrations were observed after radiocontrast agent exposure among patients without NAC (3). This decrease in serum creatinine concentrations might reflect either an increase in creatinine excretion or a decrease in creatinine production attributable to NAC or interference by NAC with the method of creatinine determination. Because a direct renoprotective effect of NAC remains questionable, we sought to clarify the potential mechanism for the observed phenomenon. In our study, we assessed the effects of NAC, among volunteers with normal renal function who did not receive radiocontrast agents, on two surrogate measures of the GFR, *i.e.*, the estimated GFR (eGFR), calculated as described by Levey *et al.* (4), and serum cystatin C levels. Serum creatinine levels were measured enzymatically and with the Jaffé method.

## Materials and Methods

### Patients

A total of 55 healthy volunteers were prospectively enrolled in the study between July and December 2002; 50 subjects completed the study according to the protocol. Demographic information was recorded at baseline, including age ( $32.8 \pm 5.6$  yr), gender (24 male and 26 female subjects), weight ( $68.7 \pm 12.5$  kg), and height ( $173 \pm 10$  cm). None of the volunteers was receiving any medication, except for 12 women who were using contraceptives.

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### Study Protocol

Beginning in the evening at 8 p.m., NAC was administered orally at a dose of 600 mg every 12 h for a total of four doses, ending in the morning at 8 a.m. Serum creatinine, urea, albumin, total protein, and cystatin C levels were measured before the administration of NAC (baseline) and 4 and 48 h after the last dose. Serum creatinine levels were measured enzymatically and with the Jaffé method. eGFR was estimated on the basis of serum creatinine, urea, and albumin concentrations and weight, age, and gender, as described by Levey *et al.* (4). The study protocol was approved by the local ethics committee, and all volunteers gave written informed consent.

### Statistical Analyses

Data are expressed as the mean  $\pm$  SD. Differences in serum creatinine concentrations before (baseline) and 4 and 48 h after the administration of NAC were analyzed with the paired *t* test. All statistical tests were two-sided. *P* values of  $<0.05$  were considered statistically significant.

### Results

There was no significant difference between the serum creatinine concentrations measured enzymatically and those measured with the Jaffé method. The results of the enzymatic measurements alone are reported here. The mean serum creatinine concentrations significantly decreased from  $0.85 \pm 0.14$  mg/dl to  $0.82 \pm 0.13$  mg/dl ( $P < 0.05$ ) (Figure 1A) and the urea concentrations decreased from  $29.8 \pm 7.5$  mg/dl to  $27.5 \pm 5.9$  mg/dl ( $P < 0.005$ ) 4 h after the last dose of NAC. These changes resulted in a significant increase in eGFR (from  $102 \pm 19$  ml/min to  $106 \pm 20$  ml/min,  $P < 0.02$ ) (Figure 1A). The changes in serum creatinine levels, urea levels, and eGFR

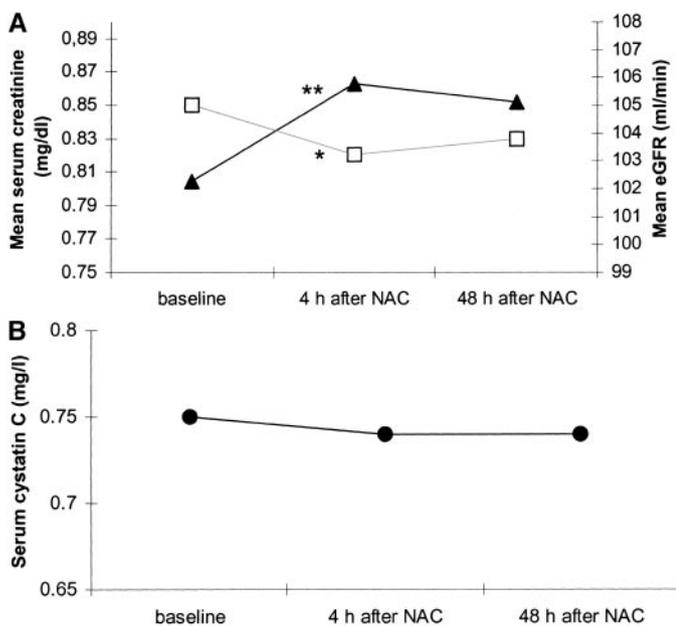


Figure 1. Surrogate markers of renal function. Renal function was assessed with serum creatinine levels ( $\square$ ) and estimated GFR (eGFR) ( $\blacktriangle$ ) (A) and cystatin C levels (B), determined before (baseline) and 4 and 48 h after the last administration of *N*-acetylcysteine (NAC). \* $P < 0.05$ , \*\* $P < 0.02$ , compared with baseline concentrations.

between baseline and 48 h after the last dose of NAC and between 4 h and 48 h after the last dose were not significant. The cystatin C concentrations did not change significantly (baseline,  $0.75 \pm 0.10$  mg/L; 4 h after NAC,  $0.74 \pm 0.09$  mg/L; 48 h after NAC,  $0.75 \pm 0.10$  mg/L) (Figure 1B).

### Discussion

The estimated mortality rate among patients who develop radiocontrast agent-induced nephropathy has been reported to be as high as 34% (2). The medical and socioeconomic consequences of radiocontrast agent-induced nephropathy are thus substantial, and numerous attempts have been made to minimize the risk of radiocontrast agent administration that cannot be avoided. Effective regimens are lacking, however, because the pathogenesis of contrast agent-induced renal dysfunction is only partially understood. The precise physiologic insult underlying radiocontrast agent-induced nephropathy is likely to involve the interplay of several factors, including vasoconstrictive forces resulting in medullary ischemia (5,6), direct effects on renal tubular cells (7), and damage caused by oxygen radicals (8,9).

On the basis of this pathophysiologic model, a number of interventions have been evaluated in animal models and human studies, including dopamine, calcium channel antagonists, endothelin receptor blockers, theophylline, adenosine receptor antagonists, antioxidants, and others (10–25). Although animal studies seemed encouraging, adequately powered human trials failed to demonstrate any relevant benefit. With a number of undisputed beneficial effects on these detrimental mechanisms, NAC seemed of potential interest for a human trial. When human radiocontrast agent-induced nephropathy is studied, special attention must be paid to the endpoint used to determine the presence or absence of renal injury. Prolonged hospitalization, a need for dialysis therapy or even maintenance dialysis therapy, and death undoubtedly indicate serious morbidity. However, because of the rare occurrence of such severe adverse events, surrogate markers of reduced GFR (such as creatinine or urea levels) are frequently used and renal injury is extrapolated from changes in serum chemical findings. This approach constitutes a major limitation of such studies.

These data from positive human trials represent a special dilemma. NAC actually improves serum creatinine levels, the surrogate marker used for assessment of GFR after radiocontrast agent exposure (3,26–28). However, serum creatinine concentrations are determined not only by glomerular filtration. Alterations in renal handling, *e.g.*, tubular secretion and metabolism of creatinine, and methodologic interference with measurements may affect the serum creatinine concentrations. Because of dietary creatinine intake, tubular secretion of creatinine, and variations in patients' muscle mass, the use of serum creatinine levels may inaccurately estimate GFR (29–31). Therefore, it seems prudent to assess the renal effects of NAC on at least one other surrogate marker of renal function.

Cystatin C is a nonglycosylated basic protein that is produced at a constant rate by all investigated nucleated cells; it consists of 120 amino acids, with a molecular mass of 13.36 kD. It is freely filtered by renal glomeruli and is completely

reabsorbed and catabolized by proximal tubular cells. It is not secreted or reabsorbed as an intact molecule. Because serum cystatin C concentrations are independent of age, gender, and muscle mass, they are thought to be a better indicator of GFR than are serum creatinine levels (32–36).

In our study, we were able to reproduce the effects of NAC that are considered to reflect nephroprotection. Furthermore, we demonstrated, for the first time, direct effects of NAC administration on serum creatinine levels, one surrogate marker of GFR. Four hours after the last dose of NAC, the mean serum creatinine and urea concentrations were significantly decreased among subjects with normal renal function. There was a significant increase in eGFR. However, levels of another surrogate marker, cystatin C, remained unchanged after NAC administration. The latter observation is novel but not unexpected, because direct effects of NAC on human renal function have not been reported. When these findings are taken together, two explanations are possible. The first explanation is that NAC truly improves GFR but cystatin C fails to detect such an improvement. This seems unlikely, because previous studies of GFR that compared cystatin C and creatinine levels by using the  $^{51}\text{Cr}$ -EDTA clearance method, which is the standard method for measurement of GFR, documented that cystatin C determination was superior to creatinine measurement (37–39).

The second explanation is that NAC does not alter GFR but causes a decrease in serum creatinine levels through another mechanism. A number of findings favor this assumption. Creatinine is predominantly but not exclusively eliminated through glomerular filtration. Especially among patients with impaired renal function, tubular secretion may contribute significantly to total creatinine excretion. Furthermore, creatinine metabolism is affected by NAC, either through direct activation of creatinine kinase or through reversal of inhibition by free radicals (40). Although these data were obtained with healthy adults, it is likely that the underlying physiologic mechanisms are unchanged among individuals with renal disease. The effects of NAC on renal tubular creatinine secretion or muscle metabolism may be even more prominent among such patients. However, additional studies among patients with impaired renal function, using a similar protocol without administration of contrast agent, must be performed. Another limitation of our study is the lack of a placebo-treated control group. This is of particular importance because the differences in serum creatinine levels between baseline and 4 or 24 h are very small.

Nevertheless, the data obtained in this study clearly cast some doubt on the present practice of administering NAC for protection against radiocontrast agent-induced nephropathy. Furthermore, it must be kept in mind that human studies performed to date have demonstrated conflicting results even for the surrogate endpoint of creatinine levels and no effect on morbidity or mortality rates has ever been reported (3,24,26–28,41–43). In light of these problems, we strongly suggest that future studies in this area should address the issue of morbidity and mortality rates. If surrogate parameters are used, then the use of creatinine measurements alone seems questionable; studies should include direct measurement of the GFR or at

least measurement of another marker (e.g., cystatin C). With the frequency of radiocontrast agent administration throughout the world, even the small cost of NAC is multiplied to substantial health care expenditures. With these considerations, the value of NAC for the prevention of radiocontrast agent-induced nephropathy seems questionable at best and should be seriously reconsidered.

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