N-Acetylcysteine in the Prevention of Contrast-Induced Nephropathy

Steven Fishbane
Winthrop-University Hospital, Mineola, New York, and State University of New York School of Medicine, Stony Brook, New York

Background and objectives: Contrast-induced nephropathy (CIN) is a common clinical problem that is growing in importance as an increasing number of tests and procedures that utilize contrast media are performed.

Design, setting, participants, and measurements: The biological and pharmacological properties of n-acetylcysteine (NAC) are reviewed, as well as the current literature relevant to the ability of NAC to prevent CIN.

Results: After publication of a seminal study by Tepel et al. in 2000, there has been a surge in interest regarding the ability of NAC to reduce the risk for CIN. Since then a large number of studies, mostly with relatively small sample sizes, have been published.

Conclusions: The results have been remarkably varied with some studies finding great efficacy with NAC but most finding no significant benefit.

Contrast-induced nephropathy (CIN) is most precisely defined as an acute deterioration in renal function after exposure to, and as a result of, contrast media (CM). In actuality, however, acute renal failure (ARF) occurring after procedures associated with contrast administration may be caused by several different factors including volume depletion, atheroembolic disease, congestive heart failure, and a functional increase in serum creatinine (SCr) after preprocedure hydration. Because it is not always possible to clinically differentiate the cause of the renal dysfunction, it may be more appropriate to term this condition contrast-associated nephropathy.

It is certain that different causes of contrast-associated renal dysfunction require different preventive strategies. Prevention of renal failure that is truly caused by contrast requires interventions based on our knowledge of the pathophysiology of this disorder. Consequences of exposure to CM may include renal vasoconstriction and redistributed blood flow (1–6), tubular epithelial cell toxicity (disruption of cell integrity, oxygen radical generation, and apoptosis (7–13), intratubular obstruction, and hemoglobin oxygen saturation curve shifts. A variety of therapeutic agents aimed at ameliorating these changes have been studied. This article discusses one specific agent, n-acetylcysteine (NAC).

N-Acetylcysteine
NAC’s primary use in clinical medicine has been as a mucolytic agent, where inhalation leads to splitting of disulfide linkages between the glycopeptides in mucus and loosening of obstructive plugs (14,15). In addition, NAC plays an important role in the treatment of acetaminophen overdose, where administration of large doses results in improved outcomes (16–18). Hepatic metabolism of acetaminophen results in production of N-acetyl benzoquinoneimine, which depletes cellular glutathione stores, leaving the liver vulnerable to oxidative injury (19,20). Administration of NAC provides cysteine as a substrate to replenish glutathione stores and reduce hepatic damage (21,22).

Pharmacology
N-acetylcysteine is an acetylated derivative of the amino acid cysteine. The chemical formula is C₅H₉NO₃S, and the molecular mass is 163.2 g/mol (Figure 1). The drug can be administered via oral, intravenous, or respiratory routes. Early studies of NAC pharmacology were hindered by the complexity of the analysis. The problem is caused by the drug’s highly reactive sulfhydryl group, which rapidly binds to and reacts with plasma and tissue proteins, forming disulfide linkages, with oxidation of the drug (23). The drug may circulate free in plasma or may become associated with other proteins in a wide variety of forms (24). Analytic systems testing the concentration of NAC in plasma must be able to differentiate between reduced and oxidized NAC as well as free and bound NAC found in proteinaceous complexes in the sample.

Older studies reported NAC to have a plasma half-life of several hours, but with modern techniques the bioavailability...
has been found to be poor and the actual half-life closer to 6 to 40 min. After oral administration, Moldeus and Cotgreave were able to detect only very small quantities of oxidized drug in circulation, with no free drug detectable (23). Bioavailability was <5%, probably because of extensive first-pass hepatic metabolism. Numerous other investigators have confirmed the low bioavailability of oral NAC including slow-release preparations (25–28). After intravenous injection, Harada et al. found that NAC was highly bound to plasma and tissue proteins, forming various disulfide compounds. Only small amounts of NAC were found in circulation despite the intravenous route of administration (29). It is clear from these reports that, after oral administration, NAC is almost completely metabolized before entering the systemic circulation. When considering the mechanism by which NAC can have a potential benefit in preventing CIN, its poor bioavailability must somehow be reconciled.

The poor bioavailability of NAC after oral dosing is the result of extensive first-pass metabolism. With intestinal transit and absorption, NAC is effectively deacetylated by the enzyme acylase I in the intestines and liver (30–35). The resulting free amino acid cysteine has a highly reactive sulfhydryl group that readily reacts with plasma and tissue proteins yielding a variety of sulfur-containing molecules and compounds. In rats, the major metabolites entering the circulation include cysteine, cystine, inorganic sulfites, homodisulfides of NAC, and labile disulfide protein complexes (34,36). In the circulation of the portal vein, the deacetylation of NAC is so efficient that the concentration of metabolites is 300% to 500% higher than that of NAC (34). The liberated cysteine molecules can be used by cells as precursors for glutathione production.

**Biological Actions of NAC**

The pharmacology of NAC, particularly its deacetylation and poor bioavailability, make clear that the drug’s *in vitro* effects must be considered separately from its *in vivo* actions. The beneficial therapeutic effects of NAC may well be a result of indirect effects such as induction of glutathione synthesis. NAC has a variety of biological actions. The following discussion will highlight those most relevant to the pathogenesis of CIN.

The antioxidant properties of NAC have been studied extensively. Bursts of oxidative stress occur naturally, and the body’s cells and tissues possess antioxidant systems to protect against oxidative damage (37). After exposure to CM there is a surge in oxidative stress that may overwhelm these systems and result in tissue injury (38). The most plausible mechanism of NAC’s putative protective effect against CIN is supplementation of the body’s antioxidant capacity.

NAC is very effective in neutralizing certain free radicals *in vitro*. The drug reacts with and deactivates hydroxyl radicals (39,40); the reaction is rapid, with a rate constant of $1.36 \times 10^{10}$ M$^{-1}$sec$^{-1}$, yielding NAC thiol radical intermediates and ultimately NAC disulfide (39). Regarding other reactive oxygen species, such as superoxide anion and hydrogen peroxide, NAC is a somewhat less effective antioxidant (40).

Because NAC is extensively degraded *in vivo* (as discussed above), it is likely that any antioxidant effects it exerts in humans would be indirect. For example, NAC might work by inducing glutathione synthesis. Glutathione plays a central role in the body’s defense against cellular oxidative damage (41,42). It generally cannot enter cells; instead it must be synthesized intracellularly from glycine, glutamate, and cysteine. Cysteine is the moiety that supplies glutathione’s active sulfhydryl group and plays a critical role as the rate-limiting factor in glutathione synthesis. After deacetylation in the intestines and liver, NAC yields cysteine as one of its metabolites. This circulating cysteine may enter renal cells and serve as a precursor for glutathione production. In fact, several studies have found that NAC prevents glutathione depletion (43,44). The relevance for the kidney is suggested by the demonstration of glutathione depletion in ischemia reperfusion injury (46,47). In rats, administration of NAC has been found to increase renal glutathione levels (48).

In addition to its antioxidant properties, NAC has other biological actions that might be helpful for preventing CIN. Vasoconstriction has often been considered as a factor contributing to the pathogenesis of CIN. By stabilizing nitric oxide, NAC may have a vasodilatory effect in certain situations (49–51). In addition, NAC’s sulfhydryl group may inhibit angiotensin-converting enzyme, reducing production of the vasoconstrictor angiotensin II (52). The vasoconstriction in CIN may be somewhat selective, particularly affecting the kidney’s medullary circulation (53). In a study of ARF induced by inferior vena cava obstruction, a model with reduced medullary blood flow, Conesa et al. found that NAC reduced medullary vasoconstriction and improved blood flow (54). Heyman and colleagues (55) found that NAC administration in rats resulted in reduced total, cortical, and medullary vascular resistance by 7% to 10%. Another recently demonstrated action of NAC is in reducing urinary albumin excretion (56).

**Clinical Studies of NAC in the Prevention of CIN**

The salutary properties of NAC described in the previous section form the rationale for why NAC might be helpful in the prevention of CIN. Tepel et al. published the first clinical study on this subject in 2000 (57). Since that time there have been many published studies with great heterogeneity in results,
some finding substantial benefit for NAC, others reporting no effect. Most of the studies included patient populations at relatively increased risk for CIN, generally defined by an increased baseline SCr. ARF developing after contrast exposure has generally been defined as an increase in SCr of \( \geq 0.5 \text{mg/dl} \) or \( \geq 25\% \) above the baseline value. Studies generally did not attempt to differentiate ARF induced by CM from other possible causes.

In Tepel's seminal report, 83 patients undergoing contrast-enhanced CT scanning were studied. Only subjects with SCr \( >1.2 \text{mg/dl} \) or creatinine clearance \( <50 \text{ml/min} \) were studied. Randomization was followed by double-blind treatment with either oral NAC 600 mg twice daily on the day before and the day of the CT scan or with placebo. ARF, defined as an increase in SCr of \( \geq 0.5 \text{mg/dl} \), occurred in 21% of placebo subjects compared with 2% in the NAC group (\( P = 0.01 \)). This dramatic reduction in risk with NAC drew great attention and led to an almost immediate change in clinical practice (57).

Shortly after Tepel's publication, our group attempted to reproduce the finding in patients undergoing cardiac angiography. Subjects with SCr \( >1.7 \text{mg/dl} \) were randomized to double-blind administration of placebo or NAC 1200 mg orally with doses 1 h before the procedure and 3 h afterwards. ARF was defined as an increase in SCr of 0.5 mg/dl. We found no significant difference in the rate of CIN between the NAC and placebo groups (26.3% versus 22.0%). The remarkable disparity between our results and those of Tepel et al. presaged the literature that has paralleled this pattern of great heterogeneity of results (58).

**Other Studies**

There are \( >20 \) published studies investigating NAC for the prevention of CIN, with 30 to 487 subjects enrolled in each study. Studies with negative results outnumber those with positive results by a 2-to-1 margin. However, the magnitude of benefit in some of the positive studies was substantial. Studies by Tepel et al., Shyu et al., Kay et al., and Diaz-Sandoval et al. reported that NAC reduced the risk of CIN by 90.5%, 86.6%, 67.7%, and 82.2%, respectively (57.59–61). There are few areas in clinical medicine where a treatment has demonstrated such a dramatic magnitude of benefit. There are even fewer examples in which such a small number of studies found a substantial benefit, whereas most other studies found no benefit at all. For this reason the literature on NAC has been so difficult to interpret and synthesize into clinical treatment recommendations.

Most published studies have been underpowered to adequately test efficacy end points. In the largest published study, by Webb et al., 487 patients with renal dysfunction were randomized to receive either placebo or NAC 500 mg intravenously before undergoing cardiac catheterization. The study was terminated prematurely by the Data Safety Monitoring Committee because of futility and the lack of any trend toward benefit with NAC treatment (62). Because of the larger sample size of this study compared with other NAC studies, the negative findings carry particular weight.

In contrast to Webb's findings is the recent publication of Marenzi et al., which reports on 354 patients with myocardial infarction undergoing coronary angiography with primary angioplasty (63). Patients were randomized to treatment with placebo, a standard dose of NAC (600 mg by intravenous bolus before primary angioplasty and 600 mg orally twice daily for 48 h after angioplasty), or a double dose of NAC (1200 mg by intravenous bolus and 1200 mg orally twice daily for 48 h after intervention). ARF was defined as a 25% increase in SCr level. The risk for CIN was reduced by 54.5% in the standard-dose NAC group and by 75.8% in the high-dose NAC group. This gradient of effect was particularly impressive and not found in prior studies. More remarkable, the risk for death was also reduced by the use of NAC at both dosage strengths (63). The most likely explanation for this find is that NAC may have had a cardioprotective effect, as has been recently suggested (64). However, this result would be strengthened by confirmation by other investigators. It should be noted that intravenous NAC is associated with a small risk for anaphylactoid reactions. The findings of Marenzi et al. stand in stark contrast to the other large study, that of Webb et al., and further add to the murkiness of the literature on NAC for prevention of CIN. Another recent publication found benefit for the combination of NAC with intravenous bicarbonate. Briguori and colleagues studied patients with CKD undergoing coronary or peripheral vascular procedures (65). Subjects were randomly assigned to administration of 0.9% saline infusion plus NAC (n = 111), sodium bicarbonate infusion plus NAC (n = 108), or 0.9% saline plus ascorbic acid plus NAC (n = 107). An increase of 25% in serum creatinine occurred in 9.9% in the saline plus NAC group, compared with 1.9% in the bicarbonate plus NAC group (P = 0.019) and 10.3% in the saline plus ascorbic acid plus NAC group. The authors concluded that NAC was more effective paired with bicarbonate compared with saline hydration (65).

Because most of the studies published on NAC for the prevention of CIN are quite small in size (even the studies of Webb et al. and Marenzi et al. were not adequately powered to fully evaluate the spectra of efficacy and safety), meta-analyses have been performed to increase the probability of explaining the full spectrum of utility for NAC. To date, 11 meta-analyses have been published on this subject (66–76), seven of these reports found a net benefit for NAC in the prevention of CIN. However, a recent review by Bagshaw et al. noted the marked heterogeneity in study results; indeed 10 of the 11 meta-analyses found statistically significant heterogeneity to be present. Bagshaw et al. cautioned that “pooling of data to arrive at a summary estimate for treatment efficacy should generally be avoided in situations where the trials exhibit significant statistical and/or clinical heterogeneity” (77). Because clinical heterogeneity has been an important feature of these studies, it is not clear whether meta-analyses are a useful tool to clarify the role of NAC.

Publication bias is an important issue to consider with respect to NAC. Vaitkus and Brar reported that this appears to be a substantial problem, noting that, among abstracts presented at scientific meetings, far fewer negative studies on NAC resulted in publications (78). Therefore, the results of meta-analyses should be interpreted with caution.


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yses probably reflect an overly optimistic view of NAC’s treatment efficacy.

**NAC and Measurement of SCr**

Because almost all studies of NAC in the prevention of CIN defined ARF as a small increase in SCr, any interference by NAC on measurement of SCr could be problematic. In 2001, Izzedine et al. reported on in vitro testing of NAC with respect to its effect on SCr determinations by adding NAC to samples of human plasma to achieve different concentrations (79). Izzedine and coworkers estimated that plasma NAC levels achieved in the study of Tepel et al. would probably have been approximately 465 mg/L, and they tried to approximate this concentration in vitro. They measured SCr using the modified Jaffe method and found no analytic interference for SCr for NAC concentrations of 102 to 600 mg/L. Only at very high concentrations of NAC (50,000 mg/L), well above what would occur after typical dosing, were SCr levels significantly affected, decreasing by >50% (79). Somewhat at odds with these results, was the work of Hoffmann et al., who studied the effect of NAC in vivo (80). Fifty volunteers with normal renal function were given NAC 600 mg twice daily for 2 d. Cystatin C, used as the assay for GFR, was unchanged, indicating that NAC had no substantive effect on actual renal function. In contrast, SCr level was significantly decreased. The magnitude of the change, however, was quite small; a mean decrease in SCr at 4 h after dosing from 0.85 ± 0.14 mg/dl to 0.82 ± 0.13 mg/dl (P < 0.05). Even at 2 SD below the mean (2.5% of patients), the reduction in SCr would have been only 0.29 mg/dl (80). These results indicate that although NAC may have a small effect on measurement of SCr, it is probably not large enough to diminish the value of SCr as a study end point.

**Research Directions**

The published literature on NAC in the prevention of CIN is composed of many studies, although almost all are inadequately powered. The primary end point used in these studies has always been a relatively small increase in SCr. It is unclear the extent to which this is a reasonable surrogate for higher-level outcomes such as need for dialysis, extended hospital stays, or death. Moreover, the small magnitude of change in SCr used to define CIN increases the vulnerability of this outcome measure, requiring larger sample sizes. This factor is probably responsible for much of the heterogeneity in study results.

At this point in time, no additional underpowered studies should be performed as they will have no impact on clinical practice, meta-analyses, or practice guidelines. A large, well-powered, preferably multicenter study is needed to clarify the current murky literature and determine the true utility of NAC. Clinically relevant high-level outcomes should be used.

Additional areas for research include explorations of NAC’s mechanism of action in CIN and further studies on the pathobiology of CIN. Without a more complete understanding of the pathogenesis of CIN, selection of new candidate drugs will remain somewhat arbitrary. Although NAC shows promise, its mechanism of action has not been fully elucidated. A better understanding would help in the design of future agents as well as help better guide dose timing, route of administration, and other aspects of treatment. In particular, there remains controversy about whether the oral or intravenous route of administration of NAC is preferred. Because the efficacy of NAC has not been completely established, research on newer agents must continue to be encouraged.

**Treatment Recommendations**

The only well established treatment for the prevention of CIN is intravenous hydration. With the remarkable heterogeneity in study results, it is difficult to determine whether NAC is truly effective in preventing CIN. Until a well-powered definitive study is performed, use of NAC in higher-risk patients undergoing CM-enhanced procedures is probably reasonable. The drug is inexpensive, safe, and well tolerated by patients. The oral route of administration is probably acceptable as it is less expensive and avoids the minor risk for anaphylaxis. However, the decision to perform CM-enhanced tests and procedures on high-risk patients requires a careful balancing of risk and benefit. The availability of NAC should not sway these decisions since its efficacy is not clearly established. Contrast-enhanced tests and procedures should be avoided, if possible, in high-risk patients when alternative tests are available.

When NAC is to be used, the original Tepel dose should be used (600 mg twice daily on the day before and the day of exposure to contrast). Alternatively, a higher dose may be given only on the day of the procedure. The intravenous route of administration is reasonable when oral treatment is not possible. In addition to NAC, intravenous hydration should be used where clinically appropriate.

**Disclosures**

None.

**References**

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