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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

# Q: Should *N*-acetylcysteine be used routinely to prevent contrast-induced acute kidney injury?

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**A:** NO. USING *N*-ACETYLCYSTEINE (NAC) routinely to prevent contrast-induced acute kidney injury is not supported by the evidence at this time.[1,2] However, there is evidence to suggest using it for patients at high risk, ie, those with significant baseline renal dysfunction.[3,4]

**Routine use of *N*-acetylcysteine to prevent contrast-induced acute kidney injury is not supported by evidence**

## INCIDENCE AND IMPACT OF ACUTE KIDNEY INJURY

Intraarterial use of contrast is associated with a higher risk of acute kidney injury than intravenous use. Most studies of NAC for the prevention of contrast-induced acute kidney injury have focused on patients receiving contrast intraarterially. The reported rates of contrast-induced acute kidney injury also vary depending on how acute kidney injury was defined.

Although the incidence is low (1% to 2%) in patients with normal renal function, it can be as high as 25% in patients with renal impairment or a chronic condition such as diabetes or congestive heart failure, or in elderly patients.[5]

The development of acute kidney injury after percutaneous coronary intervention is associated with a longer hospital stay, a higher cost of care, and higher rates of morbidity and death.[6]

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## RATIONALE FOR USING *N*-ACETYLCYSTEINE

Contrast-induced acute kidney injury is thought to involve vasoconstriction and medullary ischemia mediated by reactive oxygen species.[5] As an antioxidant and a scavenger of free radicals, NAC showed early promise in reducing the risk of this complication, but subsequent trials raised doubts about its efficacy.[1,2] In clinical practice, the drug is often used to prevent acute kidney injury because it is easy to give, cheap, and has few side effects. Recently, however, there have been suggestions that giving it intravenously may be associated with adverse effects that include anaphylactoid reactions.[7]

## THE POSITIVE TRIALS

**Tepel et al**[3] performed one of the earliest trials that found that NAC prevented contrast-induced acute kidney injury. The trial included 83 patients with stable chronic kidney disease (mean serum creatinine 2.4 mg/dL) who underwent computed tomography with about 75 mL of a nonionic, low-osmolality contrast agent. Participants were randomized to receive either NAC (600 mg orally twice daily) and 0.45% saline intravenously or placebo and saline. Acute kidney injury was defined as an increase of at least 0.5 mg/dL in the serum creatinine level 48 hours after the contrast dye was given.

The rate of acute kidney injury was significantly lower in the treatment group (2% vs 21%, $P = .01$). None of the patients who developed acute kidney injury needed hemodialysis.

**Shyu et al**[4] studied 121 patients with chronic kidney disease (mean serum creatinine 2.8 mg/dL) who underwent a coronary procedure.

Patients were randomized to receive NAC 400 mg orally twice daily or placebo in addition to 0.45% saline in both groups. Two (3.3%) of the 60 patients in the treated group and 15 (24.6%) of the 61 patients in the control group had an increase in creatinine concentration greater than 0.5 mg/dL at 48 hours ($P < .001$).

Both of these single-center studies were limited by small sample sizes and very short follow-up. Further, the impact of the drug on important clinical outcomes such as death and progression of chronic kidney disease was not reported.

**Marenzi et al**[8] randomized 354 patients undergoing coronary angioplasty as the primary treatment for acute myocardial infarction to one of three treatment groups:

- NAC in a standard dosage (a 600-mg intravenous bolus before the procedure and then 600 mg orally twice daily for 48 hours afterward)
- NAC in a high dosage (a 1,200-mg intravenous bolus and then 1,200 mg orally twice daily for 48 hours)
- Placebo.

The two treatment groups had significantly lower rates of acute kidney injury than the placebo group. In addition, the hospital mortality rate and the rate of a composite end point of death, need for renal replacement therapy, or need for mechanical ventilation were significantly lower in the treated groups. However, the number of events was small, and a beneficial effect on the death rate has not been confirmed by other studies.[5]

## THE NEGATIVE TRIALS

Several studies found that NAC did not prevent contrast-induced acute kidney injury.[1,2,9]

**The Acetylcysteine for Contrast-induced Nephropathy Trial** (ACT), published in 2011,[1] was the largest of these trials. It included 2,308 patients undergoing an angiographic procedure who had at least one risk factor for contrast-induced acute kidney injury (age > 70, renal failure, diabetes mellitus, heart failure, or hypotension). Patients were randomly assigned to receive the drug (1,200 mg by mouth) or placebo.

The incidence of contrast-induced acute kidney injury was 12.7% in the treated group and 12.7% in the control group (relative risk 1.00; 95% confidence interval 0.81–1.25; $P = .97$). The rate of a combined end point of death or need for dialysis at 30 days was also similar in both groups (2.2% with treatment vs 2.3% with placebo).

Importantly, only about 15% of patients had a baseline serum creatinine greater than 1.5 mg/dL. Of these, most had an estimated glomerular filtration rate between 45 and 60 mL/min. Indeed, most patients in the ACT were at low risk of contrast-induced acute kidney injury. As a result, there were low event rates and, not surprisingly, no differences between the control and treatment groups.

Subgroup analysis did not suggest a benefit of treatment in those with a baseline serum creatinine greater than 1.5 mg/dL. However, as the authors pointed out, this subgroup was small, so definitive statistically powered conclusions cannot be drawn. There was no significant difference in the primary end point among several other predefined subgroups (age > 70, female sex, diabetes).[1]

The ACT differed from the "positive" study by Marenzi et al[8] in several ways. The ACT patients were at lower risk, the coronary catheterizations were being done mainly for diagnosis rather than intervention, a lower volume of contrast dye was used (100 mL in the ACT vs 250 mL in the Marenzi study), and patients with ST-elevation myocardial infarction were excluded. Other weaknesses of the ACT include use of a baseline serum creatinine within 3 months of study entry, variations in the hydration protocol, and the use of a high-osmolar contrast agent in some patients.

**Clarification of its efficacy in high-risk patients is needed, especially those with baseline renal dysfunction and diabetes**

**Webb et al**[2] found, in a large, randomized trial, that intravenous NAC did not prevent contrast-induced acute kidney injury. Patients with renal dysfunction (mean serum creatinine around 1.6 mg/dL) undergoing cardiac catheterization were randomly assigned to receive either NAC 500 mg or placebo immediately before the procedure. All patients first received isotonic saline 200 mL, then 1.5 mL/kg per hour for 6 hours, unless contraindicated. The study was terminated early because of a determination of futility.

**Gurm et al**[9] found that a database of 90,578 consecutive patients undergoing nonemergency coronary angiography from 2006 to 2009 did not show differences in the rate of contrast-induced acute kidney injury between patients who received NAC and those who did not (5.5% vs 5.5%, $P = .99$). There was also no dif-

ference in the rate of death or the need for dialysis. These negative findings were consistent across many prespecified subgroups.

## MIXED RESULTS IN META-ANALYSES

Results from meta-analyses have been mixed,[10,11] mainly because of study heterogeneity (eg, baseline risk, end points, dose of the drug) and publication bias. None of the previous meta-analyses included the recent negative results from the ACT.

## CURRENT GUIDELINES

After the publication of the ACT, the joint guidelines of the American College of Cardiology and the American Heart Association were updated, designating NAC as class III (no benefit) and level of evidence A.[12]

However, recently published guidelines from the Kidney Disease: Improving Global Outcomes Acute Kidney Injury Working Group recommend using the drug together with intravenous isotonic crystalloids in patients at high risk of contrast-induced acute kidney injury, although the level of evidence is 2D (2 = suggestion, D = quality of evidence very low).[5]

**The PRESERVE study may clarify the role of this drug in a high-risk cohort**

## WHAT WE RECOMMEND

The routine use of NAC to prevent contrast-induced acute kidney injury is not supported by the current evidence. However, clarification of its efficacy in high-risk patients is needed, especially those with baseline renal dysfunction and diabetes mellitus.

The Prevention of Serious Adverse Events Following Angiography (PRESERVE) study (ClinTrials.gov identifier NCT01467466) may clarify the role of this drug in a high-risk cohort using the important clinical outcomes of death, need for acute dialysis, or persistent decline in kidney function after angiography. This important study was set to begin in July 2012, with an anticipated enrollment of more than 8,000 patients who have glomerular filtration rates of 15 to 59 mL/min/1.73 $m^2$.

In the meantime, we recommend the following in patients at high risk of contrast-induced acute kidney injury:

- Clarify whether contrast is truly needed
- When possible, limit the volume of contrast, avoid repeated doses over a short time frame, and use an iso-osmolar or low-osmolar contrast agent
- Discontinue nephrotoxic agents
- Provide an evidence-based intravenous crystalloid regimen with isotonic sodium bicarbonate or saline
- Although it is not strictly evidence-based, use NAC in patients with significant baseline renal dysfunction (glomerular filtration rate < 45 mL/min/1.73 $m^2$), multiple concurrent risk factors such as hypotension, diabetes, preexisting kidney injury, or congestive heart failure that limits the use of intravenous fluids, or who need a high volume of contrast dye
- Avoid using intravenous NAC, given its lack of benefit and risk of anaphylactoid reactions.[7,13]

We do not yet have clear evidence on the optimal dosing regimen. But based on the limited data, we recommend 600 to 1,200 mg twice a day for 1 day before and 1 day after the dye is given. ■

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