

Oral N-acetylcysteine (NAC) to prevent contrast-induced nephrotoxicity:

Is NAC the answer?

By Lori D. Wazny, PharmD

Several recent trials demonstrate a benefit of N-acetylcysteine (NAC) in the prevention of contrast-induced nephrotoxicity (CIN). As a result, oral NAC has become a more common prescription in the retail pharmacy setting. An understanding of the development of contrast-induced nephrotoxicity and the role of NAC in its prevention is consequently important for the retail pharmacy practitioner.

Contrast-induced nephrotoxicity

Contrast-induced nephrotoxicity is an important cause of acute renal failure. The incidence of CIN has risen as the number of diagnostic and interventional procedures using contrast media increased in recent years. Only intravenous and intra-arterial administration of contrast media is associated with CIN. Oral contrast agents, such as Gastrografin, do not cause CIN.

CIN is now the third leading cause of new onset acute renal failure in hospitalized patients.¹ Sequelae of CIN may include prolonged hospital stay, need for temporary or permanent dialysis (about 5% of cases), or death.^{2,3} One group of investigators reported an increased odds ratio for mortality of 5.5 after controlling for other comorbidities.⁴ Risk factors for development of CIN include:

- Advanced age
- Pre-existing renal dysfunction
- Diabetes mellitus
- Conditions that cause intravascular volume depletion (congestive heart failure, cirrhosis, or dehydration)
- Concurrent administration of drugs that reduce renal blood flow (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, loop diuretics, nonsteroidal anti-inflammatory drugs).^{5,6}

As well, the administration of larger doses of contrast media increases risk while the use of iso-osmolar or low osmolar contrast may decrease risk in specific patients.^{7,8}

Of all these risk factors, pre-existing renal impairment is the most important, and patients with diabetes mellitus and renal impairment have a substantially higher risk of CIN than do patients with renal impairment alone.⁶ Some prospective studies note that patients without any significant risk factors have only a 3% risk of developing CIN.⁹ The risk of CIN rises significantly with the number of risk

factors; one study demonstrated that the frequency of renal failure increased from 1.2% to 100% as the number of risk factors increased from zero to four.¹⁰

NAC mechanism of action

The antioxidant NAC was trialled based on the assumption that radiocontrast administration may generate reactive oxygen species that cause renal injury. The theory was that NAC would scavenge circulating free radicals and inhibit their ability to damage renal tissues.¹¹ Other mechanisms may also be involved. It has been proposed that NAC may chemically bind with nitric oxide to form S-nitrosothiol, a potent vasodilator that would increase perfusion to the renal tissues, and that NAC increases the expression of nitric oxide synthase that may also contribute to enhanced renal perfusion.^{12,13}

Evidence

A MEDLINE search (January 1966-January 2004) was performed for prospective trials of English-language literature pertaining to acetylcysteine and contrast media. A total of 10 studies met the search criteria.¹⁴⁻²³ Two meta-analyses have also been published.^{24,25}

The first human study assessing the effects of NAC in preventing CIN was published in 2000 by Tepel et al.¹⁴ This prospective, randomized, placebo-controlled trial assigned 83 patients with chronic kidney disease (serum creatinine > 106 µmol/L or creatinine clearance < 50 mL/min) undergoing computed tomography to receive either oral NAC or placebo twice daily plus intravenous saline. NAC was given as 600 mg orally twice daily the day before and the day of contrast administration. Half normal (0.45%) saline was given to both groups intravenously at 1 mL/kg per hour for 12 hours before and 12 hours after administration of a low osmolar non-ionic contrast medium. A modest dose (75 mL) of contrast was administered to all patients. All patients were encouraged to drink

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if they were thirsty. Acute CIN was defined as an increase in the serum creatinine concentration of at least 44 $\mu\text{mol/L}$ within 48 hours after contrast administration.

Forty-eight hours after radiocontrast exposure, there was a significant decrease in both serum creatinine and blood urea nitrogen in the NAC group ($p < 0.001$). Ten patients (12%) developed CIN: one patient from the NAC group (2%) and nine patients from the control group (21%) (absolute risk reduction [ARR] 19%; number needed to treat [NNT] 5; $p = 0.01$; 95% CI 0.02–0.9). Five of ten patients who developed CIN had diabetes mellitus. In patients with a baseline serum creatinine of greater than 221 $\mu\text{mol/L}$, none (0 of 13 patients) in the NAC group and 42% (5 of 12 patients) in the control group developed CIN (ARR 42%; NNT 2.4; $p = 0.02$). The authors concluded that prophylactic administration of NAC twice daily the day before and on the day of contrast administration reduced the incidence of acute CIN.

Other studies have examined prevention of CIN in patients undergoing cardiac angiography alone,^{15,19} cardiac angiography with or without angioplasty,^{16-18,21-23} and cardiac and peripheral vascular procedures.²⁰ It is important to note that cardiac procedures tend to use larger doses of radiocontrast than CT scans. All studies used low osmolar radiocontrast, with the exception of the study of Tadros and colleagues, in which patients received both low and high osmolar contrast.²² The doses averaged 81 mL to 230 mL. The results of these studies have been mixed: four trials^{15,17,18,22} reported a benefit with NAC administration, while the remainder^{16,19-21,23} reported no significant difference in the rate of CIN between the NAC and control groups (Table 1).

In response to this conflicting evidence, two meta-analyses have recently been published.^{24,25} Both studies included the same seven randomized controlled trials¹⁴⁻²⁰ and concluded that the use of NAC significantly reduces the risk of CIN compared with pre-procedure hydration alone. Overall, the meta-analyses indicated an ARR in the range of 10% to 11% (95% CI 3%–19%) with a NNT in the range of 9–10 (95% CI 5–33), meaning that for every nine or 10 patients treated with oral NAC, one case of CIN will be prevented. Interestingly, meta-regression of these studies¹⁴⁻²⁰ indicated no significant relationship between the risk of CIN and baseline serum creatinine, contrast volume, age, and proportion of diabetics. However, the small numbers of patients in these subgroups (i.e., severe renal insufficiency, administered large volume contrast [> 140 mL], age less than 65 years, percent diabetic) severely limits the power of these analyses (Table 2).

Interpretation and application

Though the meta-analyses shed some light on the benefit of oral NAC for the prevention of CIN, many questions remain unanswered. In particular, the data provide little guidance as to:

- Which patients should receive NAC²⁶

KEY POINTS

Contrast-induced nephropathy (CIN)

- Common cause of acute renal failure
- Associated with increased morbidity, mortality, and health care costs
- Can lead to dialysis and chronic renal disease

Risk factors for CIN

- Pre-existing renal dysfunction
- Diabetes mellitus
- Age 65+
- Dehydration
- Concomitant use of nephrotoxic drugs

N-acetylcysteine (NAC)

- Inexpensive
- Few side effects
- In combination with hydration, may prevent CIN
- Usual dose: 600 mg orally every 12 hours — two doses before and two doses after the diagnostic procedure
- Available in vials — doses are removed from vials and mixed with orange juice or carbonated beverages before oral administration.

— *The Editors*

- How much drug should be given
- When it should be given to provide optimal protection.

Clinical relevance of populations studied

In the meta-analyses, trials were included that enrolled patients with serum creatinine as low as 106 $\mu\text{mol/L}$ or creatinine clearance less than 70 mL/min (Table 1). In fact, only one study specifically enrolled subjects with moderate to severe renal insufficiency (sCr > 177 $\mu\text{mol/L}$ or CrCL < 40 mL/min).¹⁷ Therefore, it is likely that some patients had normal or near normal renal function. Critics have stated that it would be more clinically relevant to include only subjects with baseline creatinine clearances less than 30 mL/min.²⁷

In several trials, including those in the meta-analyses, only about one-third (21% to 39%) of subjects had both concomitant diabetes mellitus and renal dysfunction^{14-16,18,22,23} (Table 2). Therefore, the majority of the study populations have been at relatively low risk of developing CIN, and some reviewers have questioned whether the beneficial effect of NAC may be restricted to lower-risk clinical scenarios.²⁸

In addition, the trials did not provide information on the patients' specific cause of chronic kidney disease.

TABLE 1 — Studies of acetylcysteine in cardiac and peripheral vascular imaging procedures

Study	APART trial ¹⁵	Briguori ¹⁶	Shyu ¹⁷	Kay ¹⁸	Durham ¹⁹	Allaqaband ²⁰	Boccalandro ²¹	Tadros ²²	Oldemeyer ²³
Patient population	54 patients sCr ≥ 124 µmol/L or CrCL < 50 mL/min	183 patients sCr > 106 µmol/L or CrCL < 70 mL/min; ECA +/- angioplasty	121 patients sCr > 177 µmol/L or CrCL < 40 mL/min; CA +/- angioplasty	200 patients sCr > 106 µmol/L or CrCL < 60 mL/min; ECA +/- angioplasty	79 patients sCr > 150 µmol/L; ECA	123 patients sCr > 142 µmol/L or CrCL < 60 mL/min; cardiac and peripheral vascular procedures	179 patients sCr > 106 µmol/L or CrCL < 50 mL/min; CA +/- angioplasty	110 patients sCr > 106 µmol/L; CA +/- angioplasty.	96 patients sCr > 106 µmol/L or CrCL < 50 mL/min; ECA +/- angioplasty
Intervention ^a	NAC 600 mg bid x 4 doses (1 dose before cath, 3 doses after cath) + 0.45% saline 2-12h prior to cath and 12h post cath	NAC 600 mg po bid x 4 doses (day before and day of procedure) + 0.45% saline 12h prior and 12h post cath	NAC 400 mg po bid x 4 doses (day before and day of procedure) + 0.45% saline 12h prior and 12h post cath	NAC 600 mg po bid x 4 doses (3 doses before cath and 1 dose after cath) + 0.9% saline x 12h prior and 6h post	NAC 1200 mg 1h prior and 1200 mg 3h after cath + 0.45% saline up to 12h pre and up to 12h post contrast	NAC 600 mg po bid x 4 doses (day before and day of procedure) + 0.45% saline x 12h prior and 12h post	NAC 600 mg po bid x 4 doses (day before and day of procedure) + 0.45% saline x 12h prior and 12h post	NAC 600 mg po bid x 4 doses (day before and day of procedure) + 0.45% or 0.9% saline x 6-12h prior and 6h post	NAC 1500 mg po q12h x 4 doses (started evening prior to procedure) + 0.45% saline x 12h prior and 12h post
Comparator	Placebo + 0.45% saline hydration as described above	0.45% saline hydration as described above	Placebo + 0.45% saline hydration as described above	Placebo + 0.9% saline hydration as described above	Placebo + saline hydration as described above	0.45% saline hydration as described above or fenoldopam 0.1 µg/kg/min 4h pre and 4h post + 0.45% saline hydration	0.45% saline hydration as described above	0.45% or 0.9% saline hydration as described above	0.45% saline hydration as described above
Outcome CIN	2/25 (8%) NAC vs 13/29 (45%) placebo (ARR 37%; NNT 2.7; <i>p</i> = 0.0005; 95% CI 0.06-0.8)	6/92(6.5%) NAC vs 10/91 (11%) placebo (<i>p</i> = NS)	2/60 (3.3%) NAC vs 15/61 (24.6%) placebo (ARR 21.3%; NNT 4.7; <i>p</i> < 0.001)	4/102 NAC (3.9%) vs 12/98 (12%) placebo (ARR 8.1%; NNT 12; <i>p</i> = 0.03; 95% CI 0.10-0.96)	10/38 (26%) NAC vs 9/41 (22%) placebo (<i>p</i> = NS)	17.7% NAC vs 15.7% fenoldopam vs 15.3% placebo (<i>p</i> = NS)	10/75 (13%) NAC vs 13/106 (12%) placebo (<i>p</i> = NS)	3/55 (5%) NAC vs 9/55 (16%) placebo (ARR 11%; NNT 9; <i>p</i> = 0.02)	4/49 (8.2%) NAC vs 3/47 (6.4%) placebo (<i>p</i> = NS)
Subgroup analysis	Subgroup with baseline sCr > 177 µmol/L: 3/4 (75%) placebo vs 0/6 NAC developed CIN (ARR 75%; NNT 1.3; <i>p</i> = 0.01)	Subgroup with < 140 mL contrast dose, 5/60 (8.5%) placebo vs 0/60 in NAC (ARR 8.5%; NNT 12; <i>p</i> = 0.02; 95% CI 0.35-0.54)	Subgroup with baseline sCr > 266 µmol/L: 9/22 (41%) placebo vs 2/18 (11%) NAC (ARR 30%; NNT 3.3, <i>p</i> < 0.05)				Subgroup analyses with baseline sCr > 221 µmol/L or patients undergoing percutaneous intervention found no treatment effect	Subgroup analysis of patients with baseline sCr > 177 µmol/L found a larger mean change in creatinine after 48 hours in favour of the NAC group (-35±35 µmol/L vs +44±27 µmol/L, <i>p</i> < 0.001)	Subgroup analysis of diabetic patients found no difference in development of CIN

^a Saline infusion rate for all studies was 1 mL/kg/hr, except Boccalandro at 75 mL/hr and Tadros at 0.5-1 mL/kg/hr.

^b Variable hydration regimens used at the discretion of the attending cardiologist. ECA: elective cardiac angiography; CA: cardiac angiography.

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Therefore, patients with chronic kidney disease caused by conditions other than hypertension or diabetes mellitus may not have been well represented and it is uncertain whether these patients would also benefit from NAC prophylaxis.

Not all contrast procedures studied

To date, only CT scan, coronary angiography with or without angioplasty, and peripheral vascular imaging have been studied. Only the Tepel trial has evaluated NAC for patients undergoing CT scans, while the Allaqaband trial evaluated peripheral vascular imaging.^{14,20} Both these trials were of relatively small sample size. No studies of other locations of contrast administration, such as into the renal artery, have been published.

Lack of long-term assessment

All the trials defined CIN as either an increase in baseline serum creatinine of 44 µmol/L or a 25% increase from baseline at 48 hours after catheterization. This is a potential confounder, as it may take as long as 72 hours for CIN to develop, and so it is not known whether NAC administration merely delays, rather than prevents, the development of CIN.^{12,29} In addition, using surrogate endpoints for CIN, such as a 25% increase in serum creatinine, may not accurately reflect clinically important long-term outcomes such as residual renal impairment, need for dialysis, length of hospitalization, or mortality.²⁷

Optimal dose and administration regimen of NAC and saline not established

Most of the published studies have used NAC doses of 600 mg given twice daily for four doses (Table 1).^{15,16,18,20-22} It has been speculated that in patients undergoing coronary procedures, where a large amount of contrast may be

Patients at high and moderate risk of developing CIN^{30,34}

High-risk patients

- Patients with CrCL < 25 mL/min
- Patients with CrCL 25-50 mL/min + risk factor(s)*

Moderate-risk patients

- Patients with CrCL 25-50 mL/min and no risk factors.
- Patients with CrCL 50-75 mL/min + risk factor(s)*

* Risk factors include: diabetes mellitus, congestive heart failure, cirrhosis, multiple myeloma, sepsis, anticipated large dose of contrast (> 140 mL), recent (< 7 days prior) administration of contrast.

administered, a higher dose of NAC may be more effective than the 600 mg dose.³⁰ The Briguori group, who were unable to demonstrate a benefit to NAC in their first study using 600 mg doses,¹⁶ recently reported the results of a head-to-head trial comparing doses of 600 mg versus 1200 mg given twice daily for four doses plus 0.45% saline hydration prior to coronary angiography and/or angioplasty.³¹ In this study, CIN occurred in 11% (12/109) of patients in the 600 mg group versus 3.5% (4/114) of patients in the 1200 mg group ($p = 0.038$; ARR 7.5%, NNT 13; 95% CI 0.09–0.94). However, a more recent study has demonstrated no benefit of four 1500 mg doses of NAC in preventing CIN in patients undergoing cardiac angiography and/or angioplasty.²³ Certainly, more data are needed before we will know the optimal dose of NAC.

The optimal timing of NAC administration has also not been established. The majority of studies administered two

TABLE 2 — Risk factors for CIN in published studies

Risk factor	Tepel ¹⁴	APART ¹⁵	Briguori ¹⁶	Shyu ¹⁷	Kay ¹⁸	Durham ¹⁹	Allaqaband ²⁰	Boccalandro ²¹	Tadros ²²	Oldemeyer ²³
Average age (yrs)	65.5	73	64	70	69	70.5	71	65.5	70	76
Average contrast dose	75 mL	184 mL	197 mL	117 mL	125 mL	81 mL	1.55 mL/kg	192 mL	139 mL	130 mL
Diabetic patients	33%	39%	38%	64%	38%	48%	50%	62%	21%	21%
Elevated baseline sCr	> 221 µmol/L 30%	≥ 177 µmol/L 18.5%	> 159 µmol/L 35%	> 177 µmol/L 100% >266 µmol/L 33%	> 221 µmol/L 3.5%	> 221 µmol/L 24%	> 221 µmol/L 21%*	> 221 µmol/L 16.5%	> 177 µmol/L 24%	Not reported

*Personal communication, S. Allaqaband.

doses the day before procedure and two doses the day of procedure.^{14,16,17,20-22} However, other trials have administered one dose prior to and three doses after catheterization,¹⁵ or three doses prior to and one dose after catheterization (Table 1).¹⁸

Hydration regimens have also differed between studies. The duration of the saline infusion varied from two to 12 hours prior to contrast and from six to 12 hours after contrast administration (Table 1). The studies also differed as to the concentration of saline used. All of the published studies used 0.45% saline, except two trials that used 0.9% saline.^{18,22} However, a recently published article has reported that isotonic (0.9%) saline significantly reduces the incidence of CIN versus 0.45% saline hydration.³²

For outpatient procedures, a protocol using oral hydration by the patient at home prior to the procedure (1000 mL of water over 10 hours prior to procedure) and intravenous 0.45% saline at 300 mL per hour started "on call" to the cardiac catheterization laboratory (30-60 minutes prior to contrast exposure) and continued for a total of six hours has been shown to be as effective as intravenous hydration in preventing CIN.³³ However, this outpatient approach to hydration has not yet been published in com-

bination with NAC. This is an important and practical issue, as it may not always be possible to administer intravenous saline 12 hours before an outpatient procedure. In addition, patients with poor left ventricular function or more severe renal failure may not be able to tolerate intravenous fluid administration for 24 hours.

Application of evidence

Based on the current evidence, recommendations for the prevention of CIN include adequate pre-procedure hydration, use of a low osmolality contrast agent, and limiting the dose of contrast used.³⁰ With regard to NAC, two separate meta-analyses have supported its benefit in reducing the risk of CIN with low numbers needed to treat.^{24,25} Given that NAC is a relatively low-cost agent with general availability, ease of administration, and limited adverse effects, it is reasonable to consider NAC, in combination with adequate hydration, for patients at moderate and high risk of developing CIN.

Conclusion

As contrast administration is often an elective procedure, patients at risk can be identified before the investigation and/or intervention. All clinicians should ensure that their patients receive adequate hydration prior to contrast administration. As the potential benefits of oral NAC administration outweigh the risks, oral NAC should be considered in high- and moderate-risk patients who are to receive radiocontrast for radiologic and/or interventional procedures. ■

MONITORING PLAN

1. Instructions for NAC preparation and administration

NAC 20% (200 mg/mL) 10 mL vials

Acetylcysteine does not react with glass, plastic, aluminum, or stainless steel, therefore, doses may be drawn up in polyvinylchloride (PVC) syringes or other appropriate storage container. Avoid storage in containers that use rubber or other metals not listed.

Acetylcysteine is stable for 96 hours in the fridge.³⁵ Instruct patient to dilute dose in 1/2 cup (125 mL) of carbonated beverage (e.g., ginger ale, cola) or orange juice. The diluted solution should be used within one hour.³⁵ Warn patient about the rotten egg smell and counsel patient on possible nausea or diarrhea. (Note: These effects are much less common with the relatively small doses used for prevention of CIN.) Patient should also monitor for skin rash.

2. Monitoring checklist for CIN

The following are signs and symptoms of CIN. Monitor patient immediately after contrast administration and for the following 72 hours.

- Reduced urine output
- Weight gain
- Edema
- ↑blood pressure
- Acute rise (25% or 44 μmol/L) in baseline serum creatinine at 48 hr and 72 hr after contrast administration
- ↑urea
- ↑serum potassium

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