

## EDITORIAL

# N-acetylcysteine for prevention of radiocontrast induced nephrotoxicity: the importance of dose and route of administration

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Dose and route of administration of N-acetylcysteine are key factors to consider when evaluating whether this agent is effective in preventing radiocontrast induced nephropathy

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N-acetylcysteine (NAC) is commonly used for the prevention of radiocontrast induced nephropathy (RCIN) despite inconsistent results from numerous clinical trials and meta-analyses. While most research has been carried out using a specific oral dosage regimen, the intravenous route allows more rapid administration and may be particularly advantageous for urgent procedures such as coronary angiography. However, pharmacokinetic studies and clinical trial evidence suggest that the dose and route of administration are key factors in determining the therapeutic effectiveness of NAC for this indication.

## PHARMACOLOGY OF NAC FOR RCIN

The exact mechanism by which NAC may prevent RCIN is unknown, although antioxidant and vasodilatory effects likely play a key role. NAC directly scavenges oxygen free radicals, and also serves as a precursor of glutathione, itself a natural antioxidant. In addition, NAC increases the concentrations of both nitric oxide, a potent but short acting vasodilator, and S-nitrosothiol, which has more prolonged vasodilatory effects.<sup>1</sup>

NAC is well absorbed intact from the small intestine, but undergoes extensive first pass metabolism in the gastric mucosa and liver. This results in low oral bioavailability with substantial intra-patient variability (3–20%), as well as inconsistency between available oral products.<sup>2</sup> Furthermore, the sulfhydryl group, potentially key to its mechanism of action, is highly reactive and may be affected by the other substances used in oral formulations or administered concomitantly. Therefore, although rarely mentioned in published studies, the specific product selected may be critical to the efficacy of NAC for RCIN.<sup>1</sup>

The route of administration may also be important to consider. During metabolism, NAC undergoes deacetylation to produce cysteine, a precursor of glutathione.<sup>1</sup> Since first pass metabolism is specific to oral administration, glutathione concentrations may be higher after oral administration of NAC than after an intravenous dose calculated to be equivalent based

on oral bioavailability. Unfortunately, serum concentrations of NAC and glutathione are rarely measured in clinical trials since assays are not commercially available. Consequently, their relative role in preventing RCIN remains unknown, and no study to date has compared glutathione values after oral and intravenous NAC dosing.

## CLINICAL TRIALS OF ORAL NAC

The use of NAC for the prevention of RCIN gained widespread interest after a study by Tepel and colleagues demonstrated that the incidence of RCIN after radiocontrast enhanced computed tomographic (CT) scanning was significantly reduced by oral NAC administration compared to placebo.<sup>3</sup> Many clinical trials followed, particularly in the setting of cardiac catheterisation. Results from these trials have been inconsistent, prompting several meta-analyses, which themselves have produced conflicting results.

The first three meta-analyses included eight or fewer studies and a relatively small combined number of study subjects. All three authors reported significant heterogeneity and acknowledged the possibility of publication bias, but concluded that there was a protective benefit of NAC for the prevention of RCIN (ranging from 56–63%).<sup>4–6</sup> More recently, Kshirsagar and colleagues performed a meta-analysis of 16 prospective controlled trials of oral NAC.<sup>7</sup> They also found substantial heterogeneity between studies, to the extent that it prevented determination of a meaningful summary effect estimate. Using slightly different inclusion criteria, Pannu and colleagues performed a meta-analysis of 15 studies, four of which were not included in the Kshirsagar paper.<sup>7,8</sup> They concluded that NAC significantly reduced the incidence of RCIN, although this finding was of borderline statistical significance (pooled random effect relative risk 0.65, 95% confidence interval (CI) 0.43 to 1.00;  $p = 0.049$ ). Furthermore, their results were not robust to the addition of hypothetical new trials and at least one study demonstrating no effect of oral NAC in preventing RCIN has since been published.<sup>9</sup> Only one clinical trial published to date has demonstrated a clinical benefit, that being reduced length of hospital stay which was assessed as a secondary end point.<sup>10</sup> Both Pannu and Kshirsagar suggest that a large, prospective, randomised trial is required before conclusions

**Abbreviations:** NAC, N-acetylcysteine; RCIN, radiocontrast induced nephropathy

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can be drawn regarding the routine use of NAC for preventing RCIN.<sup>7,8</sup>

The divergent results from oral NAC trials may be attributed to the widespread use of a dosage regimen that could be subtherapeutic for some patients. The rationale for the dose chosen by Tepel and colleagues in the initial NAC study, 600 mg twice daily for two days starting the day before the procedure, was not explained and results from at least one study suggest that twice this dose may be safe and more effective.<sup>3,11</sup> Furthermore, it has been noted that many negative studies were carried out in North America where the available preparations differ from those available in Europe or Asia.<sup>1</sup> Not only does NAC activity vary between oral products, the liquid preparations used in most US studies may make it more difficult to mask the noxious smell and taste of NAC, thus compromising blinding strategies.

### CLINICAL TRIALS OF INTRAVENOUS NAC

Oral NAC regimens initiated the day before exposure to radiocontrast are often impractical for same day and emergency procedures. Two studies have been published evaluating intravenous NAC for RCIN, one positive and the other negative, but with substantial methodological differences.

Baker and colleagues prospectively randomised 80 patients with stable renal dysfunction undergoing cardiac catheterisation to intravenous NAC (150 mg/kg over 30 minutes, followed by 50 mg/kg over four hours) with isotonic saline hydration versus isotonic saline hydration alone.<sup>12</sup> The NAC dose was based on a standard regimen used for paracetamol (acetaminophen) overdose. RCIN, defined as a 25% increase in serum creatinine, was significantly reduced in the NAC group compared to the control group (5% v 21%). The study was terminated following interim analysis after having achieved borderline significance ( $p = 0.045$ ), which is unusual given that most clinical trials require much greater levels of significance (for example,  $p < 0.005$ ) to support early termination. Furthermore, by design, patients in the NAC arm received a different hydration regimen than the control arm (1 litre over four hours versus 2 litres over 24 hours, 12 hours pre- and post-procedure). Recently, we published a prospective, randomised, placebo controlled trial ( $n = 487$ ) evaluating a single bolus dose of intravenous NAC (500 mg over 15 minutes) immediately before cardiac catheterisation.<sup>13</sup> The incidence of RCIN, defined as a decline in creatinine clearance of  $>5$  ml/min, was not significantly different between the study groups.

There are several important differences between these two trials that may explain the discrepant results. First, the dosages were notably dissimilar. We selected a 500 mg intravenous dose to provide NAC exposure at least as high as that achieved with the 2400 mg oral regimen used in most previous studies, assuming a maximum oral bioavailability of 20%. However, as previously mentioned, first pass metabolism of oral NAC may produce higher glutathione values than bioequivalent intravenous doses. The dose utilised by Baker and colleagues was nearly 30 times higher for a 70 kg patient, which likely explains the higher incidence of adverse effects relative to other NAC studies. It is possible that other protocol differences contributed to the divergent results including the type and volume of radiocontrast agent, the timing of serum creatinine assessment, and, in particular, the differing hydration regimens in the two arms of the Baker study.<sup>14</sup> It should be noted that both studies initiated NAC immediately before the procedure, though there is likely a delay between NAC administration and accumulation of glutathione serum concentration, which may be important if glutathione has an effect.<sup>1</sup> Possibly, the use of NAC for prevention of RCIN will mirror the development of regimens for paracetamol over-

dose, which resulted in prolonged, high dose infusion protocols.

As in several other positive studies, the beneficial effect in the Baker study appeared to result from a reduction in mean serum creatinine concentration relative to baseline in the NAC group, with no significant increase in mean creatinine in the control arm. Crucially, NAC administration itself has been shown to lower creatinine concentrations, thus the effect noted in this and other studies may be artefactual.<sup>15</sup>

### CONCLUSIONS

Results from clinical trials evaluating the effectiveness of NAC for preventing RCIN have been remarkably inconsistent. Variable results from studies utilising the oral NAC protocol introduced by Tepel and colleagues may be at least partially explained by the wide range of products studied, and some evidence supports the use of higher doses. A single 500 mg intravenous bolus is insufficient. One study supports the use of a much higher intravenous dose, equivalent to that used for paracetamol overdose, although questions regarding study design prevent these findings from being considered definitive. Importantly, all trials conducted to date, including our own, have relied on serum creatinine as a surrogate marker for glomerular filtration rate and NAC itself appears to directly lower creatinine concentrations. Furthermore, there is little evidence that any studied dosage regimen reduces RCIN associated morbidity or mortality. A large dose ranging study utilising creatinine independent estimates of glomerular filtration rate and clinical end points is warranted.

In the meantime, although it is likely that NAC will continue to be utilised for this indication since it appears to be safe and inexpensive at low doses, clinicians should be aware of the uncertainties concerning its effectiveness. Whether or not NAC is administered by any route, other strategies for preventing RCIN should be employed including adequate hydration with isotonic saline or bicarbonate solutions, avoidance of potentially nephrotoxic medication, and the use of minimal amounts of appropriate radiocontrast media.

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## IMAGES IN CARDIOLOGY

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### ST segment elevation mimicking acute myocardial infarction in hypercalcaemia

A 56 year old man was admitted to our clinic with the diagnosis of ST segment elevation myocardial infarction (MI). He had prolonged burning, crushing type of chest pain, and his ECG showed ST segment elevation in leads V1-V6, I, and II, and small Q waves in leads V2 and V3 (upper panel). Because more than 12 hours had passed since the onset of his chest pain thrombolytic treatment was not given. His troponin T and creatine kinase-MB (CK-MB) values were normal. No evolutive changes typical for MI or pericarditis were seen in his ECG, and echocardiographic examination revealed normal wall motion. Therefore the diagnosis of acute MI was ruled out. His biochemical analysis showed a pronounced increase in serum calcium concentration (4.05 mmol/l) and parathyroid hormone concentration (230.4 pmol/l). Ultrasonographic examination revealed a parathyroid adenoma. Serum calcium concentration returned to normal after saline infusion and administration of furosemide, calcitonin, and pamidronate; the patient then

underwent parathyroid adenomectomy. His ECG after the operation was normal (lower panel). His chest pain was attributed to a peptic ulcer resulting from hypercalcaemia, and alleviated with antacid treatment.

In hypercalcaemia ST segment elevation in leads V1-V3 can be seen, but such extensive ST segment elevation along with the transient Q waves as in our case has not been previously reported. Measurement of QTc interval along with lack of evolutive changes may help in the diagnosis. In our patient, in the hypercalcaemic ST elevated phase, the QTc interval was 362 ms and returned to 436 ms after hypercalcaemia was corrected.

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