

## Can the Nephroprotective Effect of N-Acetylcysteine Be Optimized?

### To the Editor:

Carbonell et al<sup>1</sup> recently published an interesting study on the potential benefits of using N-acetylcysteine to prevent contrast-induced nephropathy after coronary angiography in patients with kidney disease. To this end the authors conducted a prospective, randomized, double-blind trial in patients with chronic renal failure (serum creatinine  $\geq 1.4$  mg/dL) undergoing coronary angiography. Patients were randomized to receive intravenous N-acetylcysteine (600 mg/12 h) or placebo. A total of 81 patients were included. The overall incidence of contrast nephropathy was significantly lower in patients treated with N-acetylcysteine (5.1% compared to 23.8%,  $P=.027$ ). Multivariate analysis also showed N-acetylcysteine to be an independent protective

factor for a composite variable of contrast-induced nephropathy, need for dialysis, and mortality during the stay in the coronary unit.

Although the results seem clear, not all studies have been favorable to the use of N-acetylcysteine in preventing contrast nephropathy, with sometimes conflicting results.<sup>2-5</sup> For example, in a clinical trial in China<sup>4</sup> which included 200 patients with stable moderate kidney failure (creatinine clearance  $<60$  mL/min) scheduled for coronary angiography, a protective effect of N-acetylcysteine was observed. For example, in a clinical trial in China which included 200 patients with stable moderate kidney failure (creatinine clearance  $<60$  mL/min) scheduled for coronary angiography, a protective effect of N-acetylcysteine was observed: 12% of patients randomized to placebo showed an increase of over 25% in serum creatinine values within 48 h after administration of contrast, compared with 4% treated with N-acetylcysteine ( $P=.03$ ). However, a systematic review of 10 clinical trials, including 1,163 patients, by Adabag et al<sup>5</sup> indicated that the use of perioperative prophylactic N-acetylcysteine did not reduce cardiac surgery, acute renal damage, the need for hemodialysis, or death, although in patients with chronic underlying renal disease treated with N-acetylcysteine there was a trend towards a reduction in acute renal damage.

These differences likely stem from several factors, including differences in study design, differences in patient baseline characteristics (mainly whether there was pre-existing renal damage or not), differences in procedures, or the use of different doses or routes of administration of N-acetylcysteine. A further potentially very important factor is concomitant medication.

Although the main mechanism by which N-acetylcysteine is able to prevent contrast nephropathy is its antioxidant capacity, it could be potentiated by concomitant use of other treatments,<sup>6</sup> such as inhibitors of angiotensin converting enzyme (ACE). Thus, while the presence of an inhibitor of nitric oxide synthesis reduces the antihypertensive effect of ACE inhibitors, the addition of an SH group donor such as N-acetylcysteine could enhance the antihypertensive activity of ACE inhibitors through a mechanism dependent on nitric oxide.<sup>7</sup> This enhancement in the effect of both medications when used concomitantly might have beneficial effects on blood pressure control and the prevention of contrast nephropathy.

In Carbonell et al, prescription of ACE inhibitors was similar in both groups, as would be expected if randomization is adequate. However, in light of this evidence, it would be very interesting if the authors could analyze whether there are differences in the prevention of contrast nephropathy by

N-acetylcysteine according to whether it is administered with ACE inhibitors or not.

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