EDITORIAL

N-acetylcysteine in Preventing Contrast-Induced Nephropathy. To Give, or Not To Give: That is the Question

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Iodinated contrast agents are widely used for diagnostic and therapeutic cardiovascular procedures. In the last 2 decades, there has been a 5-fold increase in the number of percutaneous coronary interventions (PCIs) in the United States, accounting for more than 1.3 million procedures in 2008.[1] Likewise, between 1992 and 2004, a 3-fold increase in coronary angiography and a 5-fold increase in PCI were reported in Europe.[2] This has resulted in an increasing incidence of patients with iatrogenic acute kidney injury (AKI) caused by exposure to contrast agents. Despite continuing efforts to improve the properties of iodinated contrast media (ie, iodine content, osmolarity, and viscosity), they continue to cause serious toxic effects on the kidney, resulting in contrast-induced AKI (CI-AKI). CI-AKI is the acute deterioration of renal function after parenteral administration of radiocontrast media in the absence of other causes. The common definitions of CI-AKI use an absolute (≥0.5 mg/dL) or relative (≥25%) increase in serum creatinine (sCR) after exposure to a contrast agent compared to the baseline value. The recent Contrast-Induced Nephropathy Consensus Panel recommended using a relative increase in sCR to define CI-AKI, given that this definition is independent of baseline renal function.[3] The acute renal failure observed after administration of contrast media is usually transient and typically develops within 24 to 72 hours post-exposure, but in some cases it can be severe enough to lead to permanent renal damage and life-long dialysis. CI-AKI is one of the most common causes of new renal failure in hospitalized patients[4] and is associated with a remarkable increase in morbidity, mortality, extended hospital stay, and costs.[5] Of note, among all procedures utilizing contrast media for diagnostic or therapeutic purposes, coronary angiography and PCI are associated with the highest rates of CI-AKI.[4]

The overall incidence of CI-AKI ranges from 2% in low-risk populations to 50% in high-risk populations, which include those with chronic renal insufficiency, diabetes mellitus, advanced age, congestive heart failure, and concurrent administration of nephrotoxic drugs.[6] The medical and socioeconomic consequences of CI-AKI are thus substantial, making its prevention of crucial importance. Numerous strategies have been evaluated to reduce the risk of CI-AKI. Other than periprocedural saline hydration and use of low-osmolar or iso-osmolar contrast agents, measures that were believed to prevent CI-AKI—such as diuretics, antioxidants, sodium bicarbonate, and various vasodilators—have either been reported to be neutral, to have deleterious effects, or to result in heterogeneous and conflicting results.[7]

N-acetylcysteine (NAC), a potent antioxidant that scavenges a wide variety of oxygen-derived –free radicals, may be capable of preventing CI-AKI, both by improving renal hemodynamics and by diminishing direct oxidative tissue damage. Numerous studies on the prophylactic effect of NAC have been published, with conflicting results. Several small, prospective, randomized trials showed that the administration of NAC, along with hydration, significantly reduced CI-AKI in high-risk patients, whereas other trials did not show any added beneficial effects.[8-10] The largest randomized study thus far assessing the efficacy of NAC to prevent CI-AKI (487 patients) was conducted by Webb et al.[8] Intravenous NAC 500 mg given immediately before the procedure did not provide renal protection in patients with impaired renal function compared with placebo. Discrepancy among these studies may be explained by the use of different procedures, different types and volumes of contrast media, different timing and dosage of NAC administration, and different routes (oral or intravenous) of administration. In some studies, the rates of renal dysfunction reported were much higher than predicted, producing statistically

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significant results in relatively small groups of patients.[9]

Data from several meta-analyses also are contradictory[9-11] and are limited by the heterogeneity of the included studies. In a recent meta-analysis of 26 studies involving a total of 5530 patients,[10] the pooled random effect RR was 0.62 (95% CI, 0.44-0.88), indicating that NAC significantly reduced the incidence of CI-AKI. This meta-analysis also showed, however, that treatment effect estimates within the NAC group showed moderate heterogeneity across the studies.

In this issue of the *Revista Española de Cardiología*, Carbonell et al[12] report elegantly that preprocedural treatment with NAC effectively reduced the risk for CI-AKI in high-risk patients. Eighty-one patients with chronic renal impairment (sCr ≥1.4 mg/dL) were randomly assigned to receive either 600 mg of intravenous NAC twice daily or a placebo. The primary endpoint was the development of CI-AKI (defined as an increase in sCr concentration of >0.5 mg/dL, or 25% above baseline within 48 hours of contrast administration). Overall, incidence of CI-AKI was 14.8%, amounting to 5.1% in the NAC group and 23.8% in the placebo group (OR=0.17; 95% CI, 0.03-0.84; *P*=.027). Furthermore, CI-AKI was identified as a protective factor for the composite endpoint of CI-AKI, death during the Coronary Unit stay, or need for hemodialysis. There were no significant differences in in-hospital and 1-year mortality rates between the 2 groups.

There are 2 strengths of the study reported by Carbonell et al.[12] First, it is a randomized placebo-controlled trial in patients at high risk for developing CI-AKI. Despite the small number of patients in this study, the homogeneous and restricted inclusion criteria of patients with baseline renal insufficiency allowed the investigators to appropriately assess the impact of NAC and placebo on a continuous variable such as sCr elevation after angiography. Second, high-dose[11] intravenous administration[13] of NAC (rather than low-dose oral administration as used in several other studies) might be the optimal regimen to be applied, given its rapid onset of effect, complete bioavailability, and higher peak serum NAC levels. Assuming that oral bioavailability of NAC is up to 20%, an intravenous dose of 600 mg twice a day, as reported by Carbonell et al,[12] ensures that NAC levels reaching the systemic circulation equal or exceed previously reported studies in which 2400 mg of oral NAC (600 mg twice daily for 4 doses) was used. In contrast to Carbonell et al,[12] Webb et al[8] did not find any protective effect of NAC in high-risk patients using the same route of administration in a larger population. A single, lower dose of NAC as well as a shorter, less aggressive hydration protocol may explain their negative results. Accordingly, NAC may prevent CI-AKI with a dose-dependent effect and may improve hospital outcome.[13,14]

Nevertheless, the study by Carbonell et al[12] has a few shortcomings. In this report, as in several others that aimed to establish the protective effects of a given regimen, sCr levels served as a surrogate endpoint for glomerular filtration rate (GFR); changes in sCr are thought to reflect renal injury. This approach constitutes one of the major limitations of such studies. Glomerular filtration of creatinine is only one of the variables that determine its concentration in serum. Alterations in renal handling, generation, intake and metabolism of creatinine may have a profound impact on sCR levels. Serum creatinine does not provide an adequate estimate of GFR. Other surrogate markers of renal injury, such as serum cystatin C, have been shown to be more sensitive than sCr levels. Furthermore, a decrease in sCr concentrations might reflect either an increase in renal tubular creatinine excretion or a decrease in creatinine production attributable to NAC. NAC has been shown to decrease sCr without improving GFR,[15] possibly by activating creatinine kinase activity and possibly by increasing tubular secretion. Hence, the value of NAC in the prevention of CI-AKI must be interpreted with caution. Most importantly, whether this risk reduction translates into a benefit in terms of clinical outcomes remains to be proven. Surrogate endpoints without direct, validated associations with clinical endpoints should not be taken as evidence of benefit. Moreover, the small sample size in this study is underpowered to demonstrate any clinical benefit in rare clinical endpoints such as death, dialysis dependency or in-hospital morbidity and mortality. The authors have shown a lower rate of the composite endpoint of CI-AKI, dialysis or death during Coronary Unit stay in the NAC group compared with the placebo group. However, the authors' decision to include endpoints of such imbalanced clinical impact (eg, biochemical tests such as sCr and death), makes it difficult to determine the actual relevance of this finding.

So, the question remains, "To give or not to give?" In general, the reported association of CI-AKI with increased morbidity, mortality, and hospital stay might justify the use of NAC as a routine intervention for prophylaxis of CI-AKI, given that NAC is readily available and inexpensive and has a favorable side effect profile. Although these study findings by Carbonell et al[12] provide even more support for the use of NAC in selected at-risk patients as a routine intervention to prevent CI-AKI, large, placebo-controlled randomized trials are still warranted. Special attention must be paid to the endpoint used to determine the presence or absence of renal injury. Clinical endpoints including

prolonged hospitalization, dialysis dependency or in-hospital morbidity and mortality must be examined as primary endpoints. Nothing but robust clinical evidence will enable us to unquestionably determine the role of NAC in preventing CI-AKI. Finally and most importantly, there should not be any feeling of safety on the part of the operator when NAC is given for protection against CI-AKI. The operator must remain cognizant of the volume of contrast and the need for good hydration regimen in every case.

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