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EDITORIAL COMMENT

Contrast Loaded With N-Acetylcysteine for Coronary Imaging During Percutaneous Coronary Intervention

A New Concept for Renal and Myocardial Protection During Percutaneous Coronary Intervention*

Tim A. Fischell, MD, FACC

Kalamazoo, Michigan

In this issue of *JACC: Cardiovascular Interventions*, Meyer et al. (1) have presented an intriguing concept. They examined the potential use of N-acetylcysteine (NAC) mixed with contrast media to simultaneously provide both cardiac and renal protective effects in a porcine infarct/reperfusion model.

The study is carefully done. The results are provocative and suggest a potential benefit, particularly with regard to renal protection. Although there was evidence of myocardial "protection," from the NAC injected with the contrast media, this benefit carried a potential "cost," related to patchy myocardial necrosis, that was associated with serious ventricular arrhythmias after myocardial reperfusion. This will be addressed in more detail.

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NAC has fallen in and out of favor as an agent to reduce the risk of contrast-induced acute renal failure during cardiac angiography and/or percutaneous coronary intervention (PCI) (2). Many studies have demonstrated that NAC (either orally or intravenously) has a beneficial, renal protective effect when administered with appropriate hydration during angiography, particularly in patients who are at high risk of acute renal failure (2–6). A number of published meta-analyses have further strengthened the argument for routine use of NAC in patients with pre-existing renal insufficiency and/or other major risk factors for acute renal failure (e.g., diabetes mellitus) (7–13).

Despite this body of evidence suggesting utility of this agent in reducing the risk of contrast-induced nephropathy, this treatment is not used routinely at all medical centers. As such, it may be important to devise ways to simplify and encourage the use of NAC without requiring pre-treatment before contrast loading.

The concept of co-administration of NAC admixed with the contrast agent itself is appealing for the following reasons. 1) It does not require pre-treatment with the agent. 2) It provides a significant improvement in ease of use, particularly when compared with intravenous administration. 3) Dosing of NAC will be de facto; it will be given proportional to the contrast load. This may help to ensure optimal NAC dosing in each case. This may be important because underdosing of NAC may lead to the failure of this agent to prevent contrast-induced nephropathy (5).

Although there is an appeal of such an "NAC-enhanced" contrast agent for the prevention of contrast nephropathy, the current study also raises the prospect that this NAC/contrast mixture may provide cardioprotective effects during coronary reperfusion. These potential beneficial cardiac effects may be relevant in PCI of ST-segment elevation myocardial infarction and possibly in other high-risk acute coronary syndrome cases.

However, as Meyer et al. (1) point out, the patchy necrosis pattern seen in the NAC-protected animals, presumably due to this cardioprotective effect of NAC, led to a worrisome and substantial increase in serious (presumably re-entrant) ventricular arrhythmias in the treatment group. This could be a disabling adverse side effect if this were to be seen in this application in human trials.

Interestingly, the cardioprotective effects of NAC had the opposite effect in a canine model (14). In the Sochman et al. study (14), there was a significant reduction in life-threatening ventricular arrhythmias after reperfusion, using NAC, in dogs. Further investigation of the potential deleterious effect of cardioprotection should therefore be conducted before this approach is accepted for use in the setting of ST-segment elevation myocardial infarction in patients.

The practical aspect of NAC co-administration with contrast still needs to be worked out. There could some issues related to the "off-label" addition of NAC to the contrast bottle. This alteration of a Food and Drug Administration–approved drug by adding a second agent in the cardiac catheterization laboratory could be problematic from logistical and medical legal standpoints. Ideally, one of the pharmaceutical companies that manufactures contrast agents may appreciate the potential marketing differentiation of a combined product and could be willing to invest the resources required to bring such a product to the market, "on-label." However, there may be drug-to-drug interactions as well as NAC shelf-life issues that could complicate the development of such a product. This would also, most likely, require a new investigational new drug application or

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From the Borgess Heart Institute, Kalamazoo, Michigan.

supplement with the Food and Drug Administration, necessitating a large randomized clinical trial to bring this "dual" agent to the U.S. market.

In summary, the current study by Meyer et al. (1) provides a new concept with regard to effective dosing of NAC admixed with contrast to prevent contrast-induced nephropathy and potentially provides an added cardioprotective effect during high-risk PCI. Carefully designed feasibility trials should be considered. If these initial clinical trials are positive, a large randomized clinical trial will then be required before this novel NAC dosing approach could be considered as a mainstream therapy.

Reprint requests and correspondence: Dr. Tim A. Fischell, Director, Heart Institute at Borgess Medical Center, Professor of Medicine, Michigan State University, 1521 Gull Road, Kalamazoo, Michigan 49048. E-mail: tafisc@gmail.com.

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Key Words: contrast ■ N-acetylcysteine ■ acute renal failure ■ myocardial infarction ■ percutaneous coronary intervention (PCI).