LETTERS TO THE EDITOR

Did Contrast Nephropathy in RAPPID Really Occur?

Ever since Tepel et al. (1) first reported that \(n\)-acetylcysteine (NAC) was effective in preventing radiocontrast-induced nephropathy (RCIN) in patients undergoing computed tomography, there has been considerable debate regarding the ideal strategy to prevent RCIN. Several studies have suggested that NAC may also prevent RCIN in patients undergoing coronary angiography (2–4). In contrast, others have suggested that neither NAC nor fenoldopam offers additional protection against RCIN compared with hydration therapy (5).

In the June 18, 2003, issue of the Journal, Baker et al. (6) reported the results of the RAPPID study comparing intravenous (IV) NAC to standard hydration therapy in patients undergoing coronary angiography. Patients were randomized to either hydration therapy with saline or hydration plus IV NAC (150 mg/kg immediately before contrast exposure followed by 50 mg/kg over the following 4 h). The study was terminated following the interim analysis after the first 80 patients had been randomized (planned enrollment was 160 patients). The incidence of RCIN was reduced by 72% in patients given IV NAC compared to those receiving hydration alone (5% vs. 21%, \(p = 0.045\); relative risk [RR] 0.28; 95% confidence interval [CI] 0.08 to 0.98). The investigators concluded that IV NAC should be considered in all patients at risk for RCIN when time constraints prevent oral prophylaxis.

If one looks closely at the definition of RCIN (25% increase in serum creatinine [SCr]) provided by Baker et al. (6) and the absolute changes reported in SCr values at both 48 and 96 h, the findings appear inconsistent. Although IV NAC dramatically reduced the risk of RCIN, the mean changes in SCr values at both 48 and 96 h, considerably less than the 0.6-mg/dl difference reported in SCr values at both 48 and 96 h, considerably less than the 0.6-mg/dl difference required to meet a priori power calculations. Because the study was terminated due to changes in secondary outcomes yet failed to show a difference in the primary outcome, the significance of these findings is in question. Despite the dramatic reduction in RCIN seen during the interim analysis, perhaps completing enrollment of all 160 patients would have allowed the study to reach power, giving it more merit.

The larger question here is how one defines nephropathy in this setting, a controversial topic surrounding each of these studies. Which end point is more reflective of deteriorating renal function: changes in SCr, changes in creatinine clearance, or should a clinical correlate be added to this definition such as a corresponding decrease in urine output or need for hemodialysis? It may be helpful if the RAPPID investigators provided more information regarding patients who developed RCIN. A comparison of the characteristics (SCr, radiocontrast volumes administered, clinical consequences of RCIN, and length of stay) of patients developing RCIN to those who did not may be helpful for readers when interpreting the clinical significance of the data given the questionable statistical merit of the investigators’ findings.

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REFERENCES


REPLY

DiDomenico and Eyrich question the definition of radiocontrast-induced nephropathy (RCIN) and whether contrast nephropathy occurred in the RAPPID study. The definition of RCIN employed (a rise in serum creatinine \(\geq 25\%\)) is a widely accepted one and has been used extensively (1–4). Furthermore, the clinical importance of this definition has been demonstrated by the attendant increase in in-hospital mortality when coronary intervention is associated with this degree of renal impairment (1). The other commonly used definition is a 0.5-mg/dl increase in serum creatinine post-contrast exposure (5–9). Using this definition, the incidence of RCIN in both control and \(n\)-acetylcysteine (NAC)-treated groups of our study remains unchanged (Fig. 1).

Other suggested end points are unlikely to provide a more appropriate reflection of deteriorating renal function. The incidence of RCIN requiring renal replacement therapy, although of considerable importance, is low following intra-arterial contrast (7.7 cases per 1,000) and thus would require the study of many thousands of patients (1). Change in urine output would be a difficult end point to analyze, being dependent on standardization of fluid intake. In addition, RCIN is frequently nonoliguric (10).