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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 in the IV NAC group were −0.08 mg/dl and −0.06 mg/dl at 48 and 96 h, respectively, compared with 0.06 mg/dl and 0.05 mg/dl for the hydration-alone group at the same time periods. This corresponds to between-group differences in SCr of 0.14 mg/dl and 0.11 mg/dl at 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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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 ≥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).

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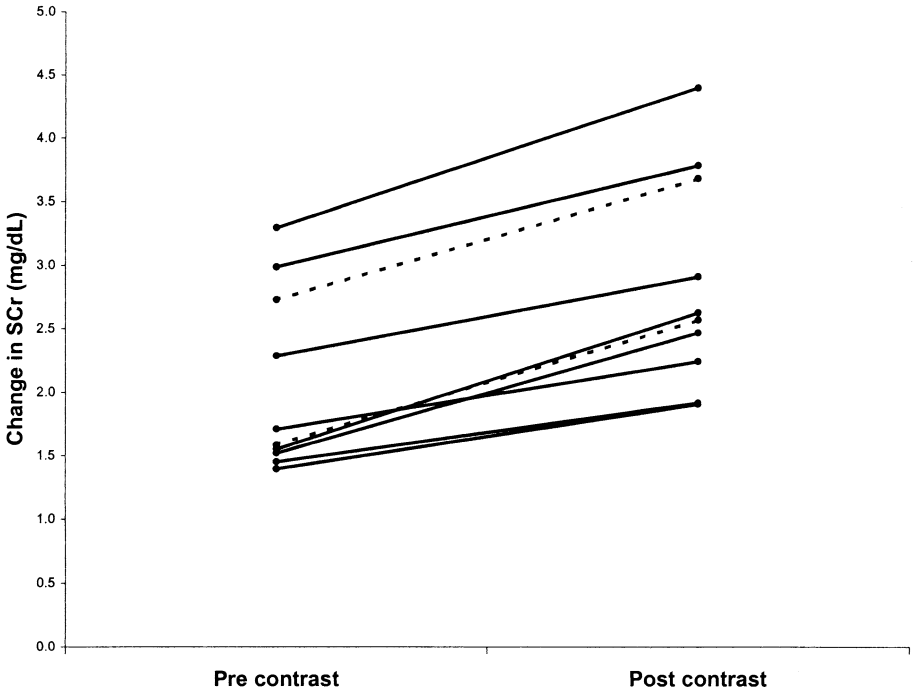

Figure 1. Change in serum creatinine (SCr) from baseline to peak in patients developing radiocontrast-induced nephropathy. **Solid line** = control patients; **dotted line** = *n*-acetylcysteine–treated patients.

Change in creatinine clearance is perhaps the most accurate measure of change in renal function and has been used in a limited number of studies (4). However, measurements of creatinine clearance are unlikely to be made in the day-to-day clinical management of RCIN.

The decision to terminate the study following the prespecified, midpoint analysis was prompted by two factors. The first was the significant reduction in the incidence of RCIN in the treatment group and the significant difference in changes in serum creatinine between the groups. We accept that this did not reach the estimated level used for the power calculation and that some of the difference is accounted for by the drop in creatinine in the NAC-treated group rather than a pure reduction in the incidence of RCIN. The second reason for our decision to halt the study was that at the time of the analysis (August 2003) two further studies had been published demonstrating a reduction in RCIN in patients treated with oral NAC and exposed to large (2) and small (3) doses of radiocontrast. We felt it unnecessary and perhaps unjustifiable to continue with the non–NAC-treated control group in the light of the data we had accumulated.

Of those patients who developed RCIN (8 in the control group and 2 in the NAC-treated group) the mean change in creatinine was 0.8 mg/dl (Fig. 1), reflecting a mean change from baseline of 40% (range 27% to 69%), thus demonstrating, in these patients, a substantial deterioration in renal function. No difference was seen in the volume of contrast used or baseline creatinine in those who developed RCIN compared to those who did not (253 ± 178 vs. 226 ± 156 ml, p = 0.65, and 2.0 ± 0.7 vs. 1.8 ± 0.5 mg/dl, p = 0.51, respectively). As we reported, no patient required renal replacement therapy.

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Should Intravenous *n*-Acetylcysteine Be Considered Standard of Care for Prevention of Radio-Contrast–Induced Nephropathy?

Baker et al. (1) in a recent issue of the *Journal* reported results from the RAPPID trial, which tested the hypothesis that intravenous (IV) administration of *n*-acetylcysteine (NAC) with saline was superior to saline hydration alone for emergent procedures. The investigators concluded that IV NAC should be considered for all patients at risk for radiocontrast-induced nephropathy (RCIN) when time precludes oral prophylaxis. Although this trial encourages further research into the use of IV NAC for prevention of RCIN, several questions must be answered before IV NAC should be considered standard of care, particularly in the U.S.

Comparing a high-dose IV NAC regimen with hydration alone, the researchers found that the risks of RCIN were decreased in patients receiving IV NAC. These findings are similar to others utilizing oral NAC prophylaxis, although in most cases the regimen was initiated several hours prior to a planned procedure (2–4). Data evaluating the use of oral NAC immediately prior to a procedure are limited (4,5). Diaz-Sandoval et al. (4) compared oral NAC with placebo in the APART trial, reporting significant results favoring the oral NAC regimen. Durham et al. (5) did not report benefits from oral NAC 1200 mg given 1 h prior to and 3 h after a procedure when compared with placebo and hydration alone. It is unclear whether the unique oral NAC regimen or the volume of saline hydration used contributed to negative results. Inclusion of an oral NAC regimen as a comparative arm in the RAPPID trial would have been helpful in clarifying whether an IV NAC regimen offers advantages over oral administration.

Intravenous NAC is not commercially available in the U.S., and although some support the IV use of the inhalation solution for acetaminophen overdose, such regimens are infrequently used in the U.S. (6). If used, the inhalational solution should be filtered using a 0.22-μm filter to assure product sterility (7); however, U.S. products are not currently tested for pyrogens or bacterial endotoxins, which would not be removed using this process (personal communication, Bristol-Myers Squibb Company, and American Regent Laboratories, July 2003).

Dribben et al. (7) recently reported the stability of inhalational NAC when compounded in 5% dextrose (D5W). Stability data using inhalational NAC in solutions other than D5W are limited, although RAPPID investigators used saline. The rate and volume of normal saline used as the diluent in this study may have contributed to their positive findings. Clinicians using IV NAC must proactively determine whether the most widely accepted diluent in the U.S. should be used, and whether adjunctive saline hydration has the potential to increase the incidence of adverse outcomes observed in the RAPPID trial if D5W is chosen as a diluent.

Until data establishing the appropriate dose and safety of inhalational NAC administered IV are available, we recommend administration of saline hydration in conjunction with immediate initiation of oral NAC 600 mg twice daily for four doses in patients undergoing emergent procedures. This regimen appears to be safe, inexpensive, and effective for minimizing the risk of RCIN.

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REPLY

We understand that intravenous (IV) *n*-acetylcysteine (NAC) as used in our study (Celltech Pharmaceuticals, Berkshire, SL1 3WE, United Kingdom) is not available in the U.S. We agree with Huxtable and colleagues' concerns over the use of inhalational NAC for the prevention of radiocontrast-induced nephropathy (RCIN), particularly as this preparation requires the use of 5% dextrose as the diluent. Although a saline-induced diuresis appears to be effective in reducing the incidence of RCIN (1) there is no evidence for the efficacy or otherwise of 5% dextrose.