Moving Points in Nephrology

Contrast-Induced Nephropathy: Is the Picture any Clearer?

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Although the clinical features of contrast-induced nephropathy (CIN) have been well described for some time (1,2), during the past 15 yr, interest among physicians on the subject of CIN has dramatically increased. A PubMed search of the phrase "contrast-induced nephropathy" between 1990 and 2007 produced 347 citations. During the past 5 yr alone, there were 290 citations, 159 of which appeared since 2006 (3).

Intravascular administration of contrast is widely known to be a common cause of hospital-acquired acute kidney injury (AKI). In 1983, Hou *et al.* (4) prospectively evaluated 2216 patients with hospital-acquired AKI and found decreased renal perfusion and major surgery to be the leading causes of AKI. Contrast medium (CM) was the next most common cause, accounting for 12% of cases of AKI, and was associated with an in-hospital mortality of 6%. In 1987, Shusterman *et al.* (5) demonstrated that CM was one of four major factors contributing to hospital acquired AKI (the others being volume depletion, congestive heart failure, and aminoglycosides).

The exact risk for CIN is difficult to determine. It is widely known that in patients with normal renal function, even in the presence of diabetes, the risk for CIN is ≤1 to 2% (1). In patients with chronic kidney disease (CKD), it is also well accepted that the risk for CIN is significantly increased and rises in proportion to the severity of underlying renal impairment (1,6,7). Another established observation is that the coupling of CKD and diabetes dramatically increases the risk for CIN compared with that observed for CKD alone (6). Recent studies on CIN in "high-risk" patients have demonstrated a wide range of incidences from 1 to 45% (8,9). Reasons for this wide variation in CIN risk include study differences in the number and severity of underlying risk factors, definition of CIN used, prospective or retrospective collection of data, exclusion or nonexclusion of patients with other AKI etiologies, timing of the baseline serum creatinine (SCr) relative to hydration administration, type and amount of CM used, type and amount of hydration, and presence or absence of other prophylactic measures. Unfortunately, the consequence of these multiple factors makes it difficult to state with reasonable accuracy the clinical risk for CIN in a "high-risk" patient. Additional problems caused by the apparently observed wide range of CIN incidences are methodologically inadequate comparisons of studies for the value of procedural or prophylactic strategies to minimize CIN risk and prospective, randomized, controlled trials that are underpowered to answer the question for which they were designed.

Despite the uncertainty of the incidence of CIN in "high-risk" patients, there are a number of reasons to believe that CIN will be an increasing cause of hospital- and outpatient-acquired AKI. Use of intravascular contrast is widespread and continues to expand. In 2003, 80 million doses of CM were administered worldwide (10,11). As of 2004, 3.3 million coronary angiograms, 25.7 million contrast-enhanced computed tomography (CT) scans, and 2.0 million conventional angiograms were performed in the United States alone (12). Although the number of coronary and conventional angiograms has been relatively stable, the number of contrast-enhanced CT scans is increasing by approximately 2 million per year. Another reason for the growing incidence of CIN is that these radiologic procedures are being performed in an increasingly elderly population of Americans, many of whom have underlying CKD, the principle risk factor for CIN. In 1998, the Third National Health and Nutrition Examination Survey (NHANES III) survey (conducted from 1988 to 1994) estimated that 6.2 million people in the United States had decreased renal function (defined as a SCr of ≥1.5 mg%) (13). Using the NHANES III data, a GFR <60 ml/min is estimated to be present in 26% of patients who are ≥70 yr of age (14). Finally, diabetes currently affects 194 million people worldwide, and the number of affected individuals in future years is expected to be significantly greater (10,15). It is estimated that diabetic nephropathy affects 25 to 40% of patients with this disease (16). This combination of increased CM use in patients with a greater likelihood of having CKD and diabetes creates the "perfect storm" for an expanding incidence of CIN.

In light of this predictable increase in CIN incidence, several key questions remain for physicians who are interested in CIN. These key questions are in the areas of pathogenesis, clinical consequences, and effective procedural and periprocedural prophylactic adjunctive therapies. It was in this regard that a symposium was convened in New York City on September 15 and 16, 2006, to critically analyze the current literature on specific unresolved topics in CIN. The symposium was made possible by an unrestricted educational grant from GE Healthcare, and *CJASN* has agreed to publish the proceedings of this symposium in its Moving Points in

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Nephrology series. The articles introduced next all have been updated since the symposium to contain the latest data and have undergone external peer review.

Does the development of CIN increase the risk for death? Although it is widely known that severe forms of AKI that require renal replacement therapy are heralds of a high in-hospital mortality, the impact of a transient rise of SCr by 25% or ≥0.5 mg/dl remains uncertain. Drs. Rudnick and Feldman use careful epidemiologic tools to assess the possibility that there is a causal effect of CIN on increased mortality.

Clinicians are aware that saline infusions are useful in preventing CIN, but there are few careful analyses of the data on which this assumption is based. Drs. Weisbord and Palevsky provide a critical assessment of the published data on the effects of various forms of fluid and solute administration as a preventive strategy for CIN, including bicarbonate, and provide recommendations to the clinician for fluid prophylaxis.

In 2000, Tepel *et al.* (17) reported that oral N-acetylcysteine (NAC) in patients undergoing contrast-enhanced CT scanning resulted in a 2% incidence of CIN compared with a 21% incidence in placebo-treated patients. As a result of this publication, NAC quickly became "standard of care" in the prevention of CIN in "high-risk" patients because of its low cost, ease of administration, and absence of serious adverse effects. Since this publication, studies of NAC's efficacy have been conflicting. Dr. Fishbane critically reviews these conflicting reports and provides current treatment recommendations for NAC use.

An exact understanding of the pathogenesis of CIN is critical for producing future CM that are devoid of nephrotoxicity and developing effective prophylactic strategies to be used with current contrast agents. Failure to elucidate completely the pathogenetic mechanisms in CIN is a major reason for our failure to reach a consensus on prevention. Toxic renal tubular damage and hypoxic injury caused by CM are the leading proposed causes of CIN pathogenesis (18). Drs. Heyman, Rosen, and Rosenberger review the scientific studies supporting CM-induced medullary hypoxemia, provide new data demonstrating an accumulation of hypoxia-inducible factors in the medulla after contrast administration, and discuss the implications of these findings.

We hope that you will find these articles that are based on the current evidentiary medical literature to be comprehensive, informative, and useful to you as a guide for treatment of the "high-risk" patient who is exposed to intravascular CM.

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