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Overestimating the Risk of Intravenous Contrast Medium-Induced Nephropathy: A Pitfall in Imaging the Genitourinary System

Lyndon Luk, MD, and Jeffrey H. Newhouse, MD

History

Iodinated contrast media (CM) were first discovered and used in diagnostic radiology nearly a century ago,[1] leading to the first clinical pyelogram performed by Osborne et al,[2] and the first femoral arteriogram by Berberich and Hirsch[3] in 1924. Not long after, Wallingford,[4] a chemist, created the first iodine-containing benzoic acid ring. The contributions of Wallingford, Swick,[5] and Hoppe et al[6] in the 1950s led to markedly improved contrast opacification as well as patient tolerance.

By the 1970s, annual consumption of CM surpassed 2000 metric tons, fueled by the discovery of computer tomography (CT).[7] At first, there was little thought given to the idea that iodinated CM were potentially nephrotoxic. Multiple publications documenting this phenomenon were published starting in the 1960s; Manitz and Matthes,[8] and Ansell[9] documented transient anuria in patients with renal failure after intravenous (IV) pyelography. The concept of acute renal dysfunction caused by IV CM has become fundamental and axiomatic in both practice and literature of modern medicine,[10] with articles numbering in the thousands.

Definition of Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is typically defined as an absolute or percentage increase in serum creatinine (SCr) level greater than baseline; 0.5 mg/dL is the most common threshold for an absolute rise; 25%, 50%, and 100% have all been used in published series dealing with CIN. With these thresholds, the risk of CIN in a cohort of patients receiving contrast ostensibly determined by clinical series has ranged from 0% to nearly 50%, and the decades-long flow of publications purporting to document CIN has led to a widespread conviction that the risk is considerable, both among practitioners who refer patients for various contrast-requiring examinations and among radiologists and interventional cardiologists. The most widely-cited quotes from articles dealing with CIN risk[11] state that contrast is the third most common cause of acute kidney injury (AKI) in hospitalized patients.

Although the most common course of CIN consists of a transient rise in SCr,[12] it has been claimed that in some cases renal function does not return to baseline, and may require chronic dialysis.[13] It has also been found that patients who experience CIN are at risk for longer hospital stays than patients without it, and even run a higher risk of death.[14] Given these concerns, radiology departments and practices usually have established policies, which preclude administering IV contrast in patients deemed to be at risk. As the risk is felt to rise in proportion to degrees of chronic renal failure,[15] thresholds of SCr or estimated glomerular filtration rate (eGFR) are usually used to identify patients for whom contrast administration is precluded. Patients may also have contrast withheld if SCr is below the threshold but is rising, despite lack of rigorous evidence that contrast is deleterious in this circumstance. Radiology practices and departments may establish policies requiring a recent creatinine or eGFR to be measured even for patients whose risk of renal disease is very small. Many also require that informed consent be formally obtained and documented.[16,17] All these practices (not to mention fear of litigation) have led to great reluctance to administer contrast to patients whose management requires information only available from its use.

Discussion

Our thesis is that the perception of risk of nephropathy from IV CM throughout the medical community is much higher than the real risk warrants. The 2 major sources of this misconception are the overestimation of risk in nearly all publications

Department of Radiology, Columbia University Medical Center, New York, NY.

Address reprint requests to Lyndon Luk, MD, Department of Radiology, Columbia University Medical Center, 622 W 168th St, PB-1-301, New York, NY 10032. E-mail: lyl9009@nyp.org

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caused by the serious error of omitting controls and the conflation of the risk of procedures requiring IV contrast administration with the administration of contrast during cardiac angiography. We would deal with each of these in order.

From the initial recognition that contrast may cause renal dysfunction, there has been an increasing rate of publications regarding the risk of CIN. Hundreds of clinical series on the topics have appeared. The experiments detailed within these publications were performed with varying degrees of scientific rigor, but nearly all assumed that any renal dysfunction that was found after administration of contrast was caused by the contrast. Control series of patients to estimate the incidence of renal dysfunction without contrast were, for decades, never provided. Studies performed by Cramer et al[18] and Heller et al[19] did include such controls. Each found rates of postcontrast nephropathy within the ranges reported in previous publications, however, each also found that these rates did not exceed those assessed in their control groups, and concluded that, at least in the circumstances they reported, contrast-induced changes might not, in fact, occur.

Despite their potential importance, these 2 publications were rarely cited in subsequent reported experiments. In 2006, they were stressed in a critical review of the literature.[20] This review was shortly followed in 2009 by an experiment in which the incidence of short-term creatinine increases were assessed in a very large group of patients who had no contrast.[21] These figures were strikingly similar to the rates of postcontrast nephropathy found in all the previous literature involving IV contrast administration, further calling into question the validity of these experiments.

In the few years following this series, several additional clinical series appeared, which did include control groups.[22-26] All but 1 found no excess cases of nephropathy after contrast beyond those, which appeared in control patients. The 1 which did reported results from 2 contrast agents, with no difference from control groups found for 1 agent and a slight increase in nephropathy rates for the other.[27]

Subsequently, these controlled studies were criticized, since control patients were those receiving noncontrast CT scans, and the data from the 2 groups were compared retrospectively. Since many of the control patients were steered to noncontrast scans because their referring physicians felt their renal function to be particularly at risk, a selection bias could well have arisen and a real tendency for contrast to cause renal dysfunction might have been masked by the control patients' excess tendency to experience renal dysfunction for noncontrast-related reasons.

Multiple articles addressed possible selection bias by performing 1:1 propensity matching and propensity score analysis,[15,28,29] a statistical technique intended to reduce the effects of differences between experimental and control groups in retrospective studies by evaluating variables that may predict either increased or decreased likelihood of receiving a particular treatment. A study by Davenport et al identified low-contrast material as a risk for CIN in patients with GFR less than 30 mL/min/1.73 m^2[15] after propensity score adjustment. Other studies found no significant difference in AKI risk between patients undergoing noncontrast or contrast studies in any risk subgroup after propensity score adjustment[28,29] and identified AKI risk as independent of CM exposure, even in patients with eGFR less than 30 mL/min/1.73 m^2.[30]

Angiocardiography has long been recognized as a procedure that can lead to AKI.[31,32] In the past 2 decades, most of the literature regarding CIN reports studies involves angiocardiography, and much of the current consensus regarding increased morbidity and mortality of CIN has arisen from these publications. As an example, a study by Gruberg et al[33] of patients undergoing percutaneous coronary intervention with baseline creatinine $\geq$1.8 mg/dL found a 37.7% rate of CIN, a 7.1% rate of CIN requiring hemodialysis, and a 22.6% mortality rate in patients requiring dialysis. In the discussion sections of these articles, and those dealing with IV contrast, CIN risk tends to be considered as a single entity, with little attention given to the differences in risk between the 2 types of procedures. Conflation of these study results has led to a serious overestimate of risk of IV contrast, as detailed by Katzberg and Newhouse[34] in a detailed literature review published in 2010.

The incidence of CIN with IV CM has been overstated because of extrapolation of angiocardiography experience despite the literature detailing the significantly safer profile of IV CM in comparison to contrast-enhanced cardiac studies that dates back to as early as 1979.[35] Moore et al[36] found a greater than 2-fold increase in the rate of nephrotoxicity in patients undergoing angiocardiography vs those undergoing contrast-enhanced (CE) CT. Review of more contemporary prospective studies investigating the use of low-osmolar contrast material and iso-osmolar CM show an overall CIN rate of approximately 5.4%,[15,37-43] including a post-IV CM CIN rate of 5.2% in patients with renal insufficiency and diabetes mellitus.[41] In comparison, overall CIN rate in patients with chronic kidney disease and diabetes as depicted by the cardiology literature are upwards of 33%, noted by Rudnick et al[44] in the Iohexol Cooperative Study.

The overall difference in the rate of morbidity and mortality ostensibly caused by CIN in patients receiving IV CM and those receiving intraarterial CM during cardiac angiography and intervention is even more pronounced. The same CIN literature review in 2006 evaluating CE CT in patients with renal insufficiency[20] found no documented cases of CIN requiring dialysis or death out of 1175 subjects. A study by McDonald et al[45] evaluating rates of AKI, emergent dialysis and mortality in a large, propensity matched cohort with stage III-V chronic kidney disease revealed no significant differences in morbidity or mortality between the noncontrast and contrast groups. A recent systematic review and meta-analysis of greater than 25,000 patients demonstrated similar rates of AKI, dialysis, and death between CE and control groups.[46]

There is no doubt that nephropathy can be a serious condition. After all, it constitutes failure of an important organ system that may in turn have effects on other systems. Further, nephropathy may not only be a primary event, it may be the result of, and act as a marker for, failure of other organs. These events would be expected to lengthen hospital stays, occasionally require dialysis and even increase mortality rates, but if they occur for reasons other than IV contrast, their temporal