I.3

Contrast-Induced Nephropathy: Managing At-Risk Patients

Richard Solomon

Introduction

The administration of iodinated contrast media (CM) is a standard component of many computed tomography (CT) examinations. The large number of procedures performed each year and the infrequency of adverse events attests to the safety of CM. However, a small number of patients experience adverse events that are directly related to the CM or the procedure being performed. In this chapter, we examine the issue of renal toxicity. Objectives of this review include recognizing the patients at risk for renal complications following CM administration and understanding strategies to minimize the risk in those who will receive CM.

Who is At-Risk?

Risk factors for the development of contrast-induced nephropathy (CIN) are well characterized. These risk factors include: (1) a baseline decrease in glomerular filtration rate (GFR <60 ml/min), (2) increasing age, (3) female gender, (4) intravascular volume depletion, such as might occur with chronic use of diuretics, (5) diabetes, congestive heart failure, or cirrhosis, and (6) the concomitant administration of drugs that diminish renal function, such as NSAIDs, cyclosporin, and cisplatin [1].

Appropriate screening before contrast administration is necessary to identify these high-risk patients. The most important risk factor, a low GFR, is most easily identified using a serum creatinine measurement and applying a formula to convert creatinine to GFR [2]. The most widely used formula, called the Modification of Diet in Renal disease (MDRD) or Levey formula (Fig. 1), can be found online at a number of sites (Table 1) or put on a personal digital assistant (PDA) for easy use in a screening protocol. A protocol to identify and manage high-risk patients is presented in Figure 2 [3]. Modification of this protocol to reflect the realities of the practice environment is appropriate, but the basic intent should not be lost. High-risk patients should be identified *before* contrast administration, and steps to minimize CIN need to be taken.

Estimated GFR/1.73 m^2 = 186 x Serum [creatinine]-1.154 x Age -0.203

x 0.74 if female x 1.21 if African American

Formula was empirically determined in a cohort of individuals (1628) (mostly white) with chronic kidney disease (determined by iothalamate clearance <55 mL/min/1.73 m^2).

Evidence from other studies suggests that it underestimates GFR by 25-30% in subjects with "normal" renal function.

Fig. 1. MDRD or Levey Formula

Table 1. Websites for Glomerular Filtration Calculators

Website	Calculation formula used
http://www.nkdep.nih.gov/ go to Health Professionals /Tools	MDRD
http://www.kidney.org/ go to professionals/Clinical tools/gfr calculator	MDRD
http://www.nephron.com/	MDRD
http://www.hdcn.com/calc.gfr.htm	MDRD

MDRD Modification of Diet in Renal Disease

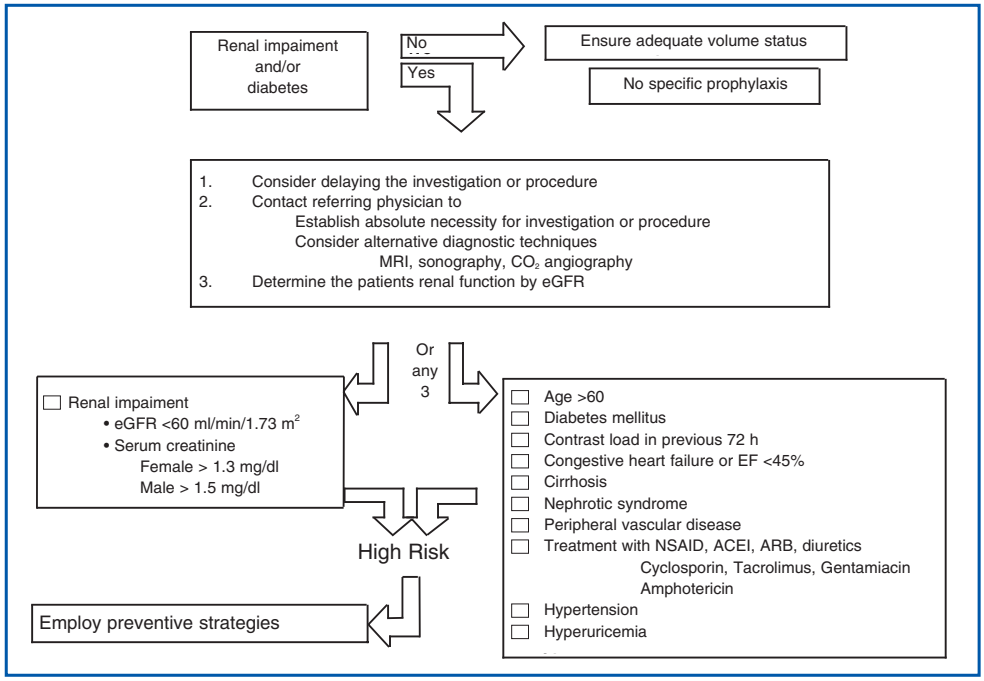

Fig. 2. Protocol (modified from [3])

Characteristics of the Contrast-Enhanced Examination That Enhance the Risk of CIN

In addition to these patient-specific risk factors, there are independent risk factors related to the procedure, including: (1) the volume of CM administered, (2) the route of administration, e.g., intraarterial versus intravenous, (3) a second CM study within 72 h, and (4) the specific CM used.

Since these are potentially modifiable factors, it is important to consider each factor when a high-risk patient has been identified. The risk of CIN is proportional to the volume of contrast administered, with no clear threshold dose [4]. There is an interaction with the patient's level of renal function. A smaller volume of contrast can cause CIN as the level of renal function (GFR) falls. This has led to the development of a recommended maximum volume of contrast based upon serum creatinine although this has not been extensively validated [5]. Multidetector CT (MDCT) technology offers the opportunity to decrease the volume of contrast needed for a number of applications. Contrast volume can be decreased by a higher initial injection rate with subsequent variable flow rates, saline flushing, and appropriate timing of the acquisition of images after contrast administration. Use of the contrast agent with the highest amount of iodine per unit volume will also reduce overall contrast volume. Strategies for protocol

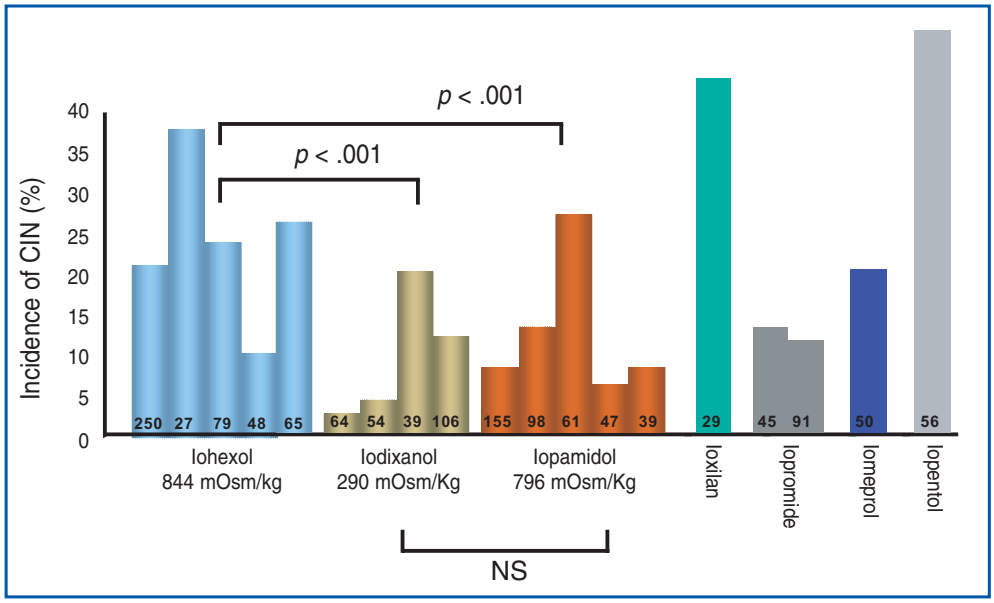

Fig. 3. Review of 17 prospective randomized trials of a single contrast agent in high-risk patients undergoing angiographic studies or interventions [9]. The studies included head-to-head comparisons and placebo arms of trials investigating prophylactic therapies such as theophylline, fenoldopam, and N-acetylcysteine. Number of patients studied is indicated on each bar. CIN = contrast-induced nephropathy, NS = not significant

building are beyond the scope of this chapter but are covered in other chapters in this volume.

At this time, CM use in CT is exclusively intravenous. Although the risk of CIN may be less with intravenous injection than with intra-arterial injection, this is not a reason to reduce one's efforts to prevent nephropathy. A second contrast exposure within 72 h increases the risk of nephropathy significantly. Often, the first indication that a patient was recently given contrast and is at risk for nephropathy is to see delayed retention of contrast in the cortex of the kidneys when performing the initial noncontrast scout images [6]. A second exposure to contrast should be delayed whenever possible in such a circumstance, and contrast should not be administered twice within 72 h unless it is urgently needed for patient management.

The type of contrast used also impacts on the development of nephropathy. Osmolality of the CM is one potential mediator of this toxic effect. Support for the role of osmolality comes from experimental animal data as well as clinical trial data. A meta-analysis of prospective randomized trials comparing high osmolality (>1,500 mOsm/kg) to low osmolality CM (700–800 mOsm/kg) found a reduction in the incidence of CIN with the use of low-osmolality CM. However, the risk reduction was statistically significant only in patients with a GFR <55 ml/min [relative risk (RR 0.50)] [7]. The recent availability of iso-osmolality CM (290 mOsm/kg) has raised the question of whether these agents would be less nephrotoxic than low-osmolality agents. One comparative trial of iso-osmolality (iodixanol) versus low-osmolality (iohexol) CM in patients with both diabetes and renal insufficiency showed a lower incidence of CIN with the use of the iso-osmolality CM [8]. However, a systematic review of available data in high-risk patients from prospective trials involving low- and iso-osmolality CM does not support a benefit of iso-osmolality CM over all other low-osmolality CM [9]. In particular, the data show comparable rates of CIN with the use of iodixanol and iopamidol, another nonionic monomer contrast agent. Indeed, it appears that the benefit observed in the study comparing iodixanol and iohexol may be related to the choice of that particular low-osmolality CM rather than a benefit attributable to the use of the iso-osmolality CM (Fig. 3). Randomized trials comparing the renal effects of iopamidol and iodixanol in high-risk patients may help answer this question more definitively.

Other Strategies to Minimize Contrast-Induced Nephropathy

A number of other strategies have been studied to minimize risk, particularly in high-risk patients. These include use of saline volume expansion and pharmacologic agents to produce renal vasodilation or interfere with generation of free oxygen radicals.

Contrast-induced toxicity to the kidneys is re-

duced by enhancing renal blood flow and urine flow. In practical terms, this means that patients should drink liberally the night before a contrast study or receive intravenous fluids starting the night before if they are high risk. The ideal combination of water and electrolytes is not known and may be patient specific. Correcting known extracellular volume depletion with saline, holding diuretics for 12 h, and encouraging oral water intake will suffice for most patients [1]. In situations that do not permit corrective measures beginning the evening before contrast exposure, a single-center trial found that an isotonic sodium bicarbonate solution (three ampules of $NaHCO_3$ in 1,000 ml D5W) significantly reduced the incidence of CIN in high-risk patients receiving intra-arterial CM. The isotonic sodium bicarbonate solution was given at 3 mL/kg/hr for 1 h before CM exposure and at 1 mL/kg/hr for 6 h postexposure [10].

Attempts to enhance renal blood flow with systemic vasodilator therapy have not been particularly successful. These agents – dopamine, fenoldopam, theophylline, atrial natriuretic peptide, endothelin antagonists, and calcium-channel blockers – have systemic effects that limit the degree of renal vasodilation. Strategies to find more specific renal vasodilators or to deliver these agents directly into the kidney are being evaluated.

Inhibition of the generation of reactive oxygen species may be protective in some patients. The initial trial of N-acetylcysteine (NAC) was performed in patients with renal insufficiency receiving contrast as part of abdominal CT procedures. A significant reduction in the incidence of CIN was found when NAC was administered orally at 600 mg twice daily on the day before and day of contrast exposure [11]. Subsequent prospective randomized trials conducted primarily in high-risk patients undergoing cardiac catheterization and percutaneous coronary intervention (PCI) found equivocal results [12]. Different patient populations and dosing schedules may account for some of these contradictory results. However, when taking into account the failure of many negative trials to get published (presented in abstracts at meeting), it seems our current enthusiasm for using NAC routinely in all high-risk patients needs to be tempered. Administration of NAC, however, is inexpensive and associated with little or no side effects. While this favors use of NAC, it does not obviate the necessity of the other protective strategies described above. Additional trials with other NAC dosing strategies – acute intravenous administration [13], double-dose oral administration [14] – have suggested an enhanced effect, but these strategies need further validation.

Conclusion

As the number of contrast-enhanced CT procedures increase and the target patient population has an increasing prevalence of comorbidities, the number of adverse renal effects will likely increase. However, appropriate screening for those patients at high risk and the employment of preventative strategies should minimize the percentage of patients who suffer from this adverse event.

For the CT service, a screening protocol (Fig. 2) can be employed to identify high-risk patients by using simple demographic, historical, and laboratory data. MDCT protocols to minimize the volume of CM used and the choice of an appropriate nonionic contrast agent may also reduce risk (Fig. 3). Collaboration with local nephrologists to develop practical pharmacologic interventions and volume expansion strategies is highly recommended.

References

1. Solomon R (1998) Contrast-medium-induced acute renal failure. Kidney Int 53:230–242
2. Levey A, Bosch JP, Lewis JB et al (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 130:461–470
3. Gleeson T, Bulugahapitiya S (2004) Contrast-induced nephropathy. AJR Am J Roentgenol 183:1673–1689
4. McCullough P, Sandberg KA (2003) Epidemiology of contrast-induced nephropathy. Rev Cardiovasc Med 4 [Suppl 5]:S3–S9
5. Cigarroa R, Lange RA, Williams RH, Hillis LD (1989) Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. Am J Med 86:649–652
6. Love L, Lind JA Jr, Olson MC (1989) Persistent CT nephrogram: significance in the diagnosis of contrast nephropathy. Radiology 172:125–129
7. Barrett B, Carlisle EJ (1993) Meta-analysis of the relative nephrotoxicity of high- and low-osmolality iodinated contrast media. Radiology 188:171–178
8. Aspelin P, Aubry P, Fransson S et al (2003) Nephrotoxic effects in high-risk patients undergoing angiography. N Engl J Med 348:491–499
9. Solomon R (2005) The role of osmolality in the incidence of contrast induced nephropathy: a systematic review of angiographic contrast media in high risk patients. Kidney Int 68(5):2256–2263
10. Merten G, Burgess WP, Gray LV et al (2004) Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. JAMA 291:2328–2334
11. Tepel M, Van Der Giet M, Schwarzfeld C et al (2000) Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 343:180–184
12. Kshirsagar A, Poole C, Mottl A et al (2004) N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective con-

trolled trials. J Am Soc Nephrol 15:761–769
13. Baker C, Wragg A, Kumar S et al (2003) A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J Am Coll Cardiol 41:2114–2118
14. Briguori C, Columbo A, Violante A et al (2004) Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. Eur Heart J 25:206–211