

CONTRAST NEPHROTOXICITY

Definition

Nephrotoxicity is attributed to radiologic iodinated contrast media when there has been a sudden deterioration in renal status after the administration of a contrast media and no other etiology appears likely from the clinical records. The risk of nephrotoxicity is related to the degree of pre-existing renal disease and hydration. Clinically significant nephrotoxicity after administration of iodinated contrast media is highly unusual in patients with normal renal function.

There is no standard definition for reporting contrast media induced nephrotoxicity (CIN); definitions used have included percent change in the baseline serum creatinine (e.g., a 20% to 50% rise in serum creatinine) and absolute elevation from baseline (increase of 0.5 to 2.0 mg/dl). Studies also vary in the length of time and number of data points over which serum creatinine was obtained following contrast media administration. Few studies have followed patients for more than 72 hours. Porter [1] defined CIN as a serum creatinine increase of: (a) greater than 25% if baseline serum creatinine is less than 1.5 mg/dl, or (b) greater than 1.0 mg/dl if baseline serum creatinine is greater than 1.5 mg/dl, when either occurs within 72 hours after the contrast administration. Solomon et al [2] defined CIN as an acute decrease in renal function manifested by an increase in baseline serum creatinine of at least 0.5 mg/dl (44 μ mol/l) within 48 hours of injection of contrast. The prevalence of CIN, therefore, varies depending on the definition used.

The clinical significance of these definitions remains open to debate. Even a 50% rise in serum creatinine in a patient with normal renal function may not be clinically significant, because it may not require intervention or affect prognosis if the change is transient, which is usually the case. Two

studies have recently been published which highlight the normal variation in serum creatinine in the absence of contrast administration. In more than 30,000 patients studied by Newhouse et al [3] who did not receive any contrast material, more than half showed a change in serum creatinine of at least 25% and more than a 40% change of at least 0.4 mg/dL. The author's comment that had some of these patients received iodinated contrast, the rise would have undoubtedly been attributed to it, rather than to physiologic variation. Bruce et al [4] showed that a rise in serum creatinine of 0.5 mg/dL or an increase of 25% was similar in a control group of patients who did not receive contrast material as to that found in patients who received either iodixanol or iohexol during contrast-enhanced CT examinations in patients with baseline serum creatinine levels below 1.8 mg/dL.

Serum creatinine has limitations as an accurate measure of renal function because it is influenced greatly by the patient's gender, muscle mass, nutritional status, and age. Normal serum creatinine levels are maintained until the glomerular filtration rate (GFR) — at least as reflected in creatinine clearance — is reduced by nearly 50%; that is, impaired renal function may exist even when serum creatinine levels are "normal." For this reason, it has been suggested that radiologists stratify patients at risk for CIN according to the classification system promulgated by the National Kidney Foundation which is based on the GFR (see Fig 1 at the end of this chapter). Although direct measurement of GFR with insulin or a similar clearance marker would be most accurate in defining renal function before and after contrast administration, this is generally impractical. One alternative is to use a formula to calculate creatinine clearance, (estimated GFR or eGFR) based on age, gender, body weight, and serum creatinine (e.g., Cockcroft-Gault [5] formula or Modification of Diet in Renal Disease [MDRD] formula;

calculators are available on various Web pages). Furthermore, the clinical benefit of using calculated creatinine clearance in assessing CIN risk is uncertain because much of our published knowledge comes from studies that used only serum creatinine measurements. The threshold values at which different clinical actions should be taken (e.g., active intravenous hydration, avoidance of contrast material administration) are neither proven nor generally agreed upon for either serum creatinine measurement or calculated creatinine clearance.

In addition, the accuracy of these formulae has only been validated in the patient population for whom they were developed. The MDRD formula is known to underestimate eGFR in patients with normal or near normal renal function [6]. A paper published by Herts et al [7] showed when patients were evaluated by eGFR, as calculated by the MDRD formula, a significantly higher percentage of patients had an eGFR of < 60 ml/min than had a serum creatinine of >1.4 mg/dl. These patients might have been denied contrast media administration had eGFR been used to determine suitability for injection (6.2 % vs 15.3%).

In a recent paper, Thomsen et al [8], however reviewed the relative risk of CIN from two randomized trials using eGFR calculated from serum creatinine by the MDRD formula in patients who received intravenous (IV) contrast media for MDCT examinations. The risk of CIN was found to be 0.6% in patients with an eGFR greater than 40 ml/min and 4.6% in patients with an eGFR less than 40 ml/min but greater than 30 ml/min. In patients with an eGFR < 30 ml/min, the CIN rate was 7.8%.

Another confounding variable in the literature is related to whether contrast media is injected intravenously or intra-arterially. Many of the studies of CIN are obtained from patients undergoing cardiac catheterization. Such patients are more likely to have diabetes and hypertension and are thus at higher risk. Also, many of these

studies investigate contrast media effects in patients who are sick enough to be inpatients long enough to obtain postcontrast creatinine measurements. Additionally, there may be nephrotoxic effects from the angiography procedure itself (e.g., atherosclerotic emboli). Therefore data from cardiac angiography studies may be applicable in that situation but may not predict how the general population of patients undergoing computed tomography (CT) studies will do when the contrast media are injected intravenously.

There is no uniform definition of renal dysfunction. When creatinine clearance is less than 60 ml/min (in a normal young adult equivalent to a serum creatinine of 133 mmol/l or 1.5 mg/dl) the term “renal insufficiency” has been used, and when creatinine clearance is less than 30 ml/min the term “renal failure” is often used.

There is no data on the risk of CIN in children.

Pathogenesis

The exact pathophysiology of CIN is not fully understood. Renal effects are seen with high-osmolality ionic contrast media (HOICM), low-osmolality contrast media (LOICM), and iso-osmolality contrast media (IOICM). Etiologic factors that have been suggested include: 1) renal hemodynamic changes (vasoconstriction), and 2) direct tubular toxicity of the contrast material. Both osmotic and chemotoxic mechanisms may be involved, and some investigations suggest agent-specific chemotoxicity. Regardless, it does appear that the nephrotoxicity of contrast media is related to the dose administered.

Risk Factors

Numerous studies have attempted to isolate risk factors for CIN. The classic review by Byrd and Sherman [9] listed predisposing factors for radiologic contrast media-induced acute renal failure as pre-existing renal insufficiency (serum creatinine level ≥ 1.5 mg/dl), diabetes mellitus, dehydration,

cardiovascular disease and the use of diuretics, advanced age (≥ 70 years), multiple myeloma, hypertension, and hyperuricemia. However, studies by Parfrey et al [10] and Schwab et al [11] documented that the patients at highest risk for developing contrast media induced acute renal failure are those with both diabetes *and* pre-existing renal insufficiency. These investigators did not find that, given equal states of hydration, either diabetes alone or renal insufficiency alone (although yielding a somewhat higher risk for renal failure than the normal population) resulted in a statistically greater incidence of renal dysfunction after contrast administration. The age threshold for a high risk of contrast-induced nephrotoxicity is not well established and seems to be changing, as people are becoming healthier at older ages.

One additional risk factor is thought to be the use of multiple contrast examinations within a short time interval. It is known that it takes close to 24 hours for the entire administered dose of contrast media to be excreted by the kidneys, so it has long been a recommendation that intervals of shorter than this be avoided except in urgent situations. There is little hard data to support this recommendation. But a recent paper [12], although criticized by some authorities [13] for methodological issues, seems to support this recommendation. However, despite the recommendation of obtaining a serum creatinine prior to a repeat dose made in this study, we do not believe that there is sufficient evidence to justify this recommendation.

Consequence

The clinical course of CIN depends on baseline renal function, coexisting risk factors, degree of hydration, and other factors. Serum creatinine usually begins to rise within the first 24 hours following IV contrast media administration, peaks within 96 hours (4 days), and usually returns to baseline within 7 to 10 days. It is unusual for patients to develop permanent renal failure, and this usually occurs in the setting of multiple risk factors. However, when

chronic renal failure develops it is associated with lifelong morbidity.

Patients who are taking the antihyperglycemic agent metformin are not at increased risk of CIN compared to other similar patients not on metformin. However, there is the risk of metformin-related complications (including lactic acidosis) if such patients were to develop CIN and their renal excretion of metformin was to diminish (see the Chapter on Metformin).

Prevention or Amelioration

Avoidance of Iodinated Contrast Media

The risk of developing CIN is not an absolute but a relative (and often weak relative) contraindication to the administration of IV iodinated contrast media. With the use of the maneuvers described below to reduce risk, and the usual short clinical course of CIN, the risk of clinically relevant renal dysfunction is very low in many situations. In other cases, the risk may be sufficiently great, and the information that may be obtained by using no contrast media (e.g. noncontrast CT) or by other modalities (e.g., ultrasound or magnetic resonance imaging [MRI]) may be sufficiently useful, that IV iodinated contrast may be avoided. (See the Chapter on Nephrogenic Systemic Fibrosis [NSF] for a discussion on the risk of development of NSF following administration of gadolinium chelates to patients with renal disease). In some clinical situations, the use of iodinated contrast media may be necessary regardless of CIN risk. The use of the minimum dose of radiographic iodinated contrast media that provides sufficient diagnostic information may reduce risk.

Choice of Iodinated Contrast Media

Barrett and Carlisle [14] reported a meta-analysis of the literature concerning the relative nephrotoxicity of HOCM and LOCM. They concluded that LOCM are, generally, less nephrotoxic than HOCM in patients with underlying renal insufficiency. However, LOCM were *not* shown to confer

a significant benefit in patients with normal renal function where the risk is low. Rudnick et al found similar results in a large prospective study.

Some studies have suggested a benefit for the iso-osmolality contrast agent, iodixanol. Aspelin et al [15] were the first to suggest that iodixanol was associated with a lower risk of CIN than the LOCM, iohexol. This and other studies were initially performed in high-risk diabetic patients undergoing cardiac catheterization. Subsequent reports [16-19] have failed to establish a clear advantage of iodixanol over the other low-osmolality contrast media with regard to CIN, whether administration is IV or intra-arterial. A recent meta-analysis using data pooled from 25 trials failed to demonstrate the superiority of iodixanol compared to LOCM after IV administration [20]. The study was unable to draw a conclusion as to the relative benefit of iodixanol for intra-arterial administration, however.

Hydration

Not all clinical studies have shown dehydration to be a major risk factor for CIN. However, in the dehydrated state, renal blood flow and glomerular filtration rate are decreased, the magnitude of the effects of contrast media on these parameters is accentuated, and there is the theoretical concern of prolonged tubular exposure to contrast media because of low tubular flow rates. Solomon et al [19] studied adult patients with chronic renal insufficiency that underwent cardiac angiography. The incidence of CIN was decreased by hydration with 0.45% saline or 0.9% saline administered at a rate of 100 ml/hr beginning 12 hours before and continuing 12 hours after angiography. In another study, IV 0.9% saline hydration was shown to reduce CIN risk more than 0.45% saline hydration. Hydration with sodium bicarbonate [21] was shown to be more effective than using 0.9% saline in one study, but these results have been challenged and cannot be considered definitive at this time [22-23].

Diuretics: Mannitol and Furosemide

In the study by Solomon et al [2], there were no beneficial effects from the osmotic diuretic mannitol when it was added to saline hydration in patients with or without diabetes. Also, there was an exacerbation of contrast media-induced renal dysfunction when the loop diuretic furosemide was used in addition to saline hydration.

Other Agents

The efficacy of N-acetylcysteine (Mucomyst), an antioxidant, to reduce the incidence of CIN is controversial. A number of individual studies, and a number of meta-analyses, have disagreed as to whether this agent reduces the risk of CIN [24-28]. There is evidence that it reduces serum creatinine in normal volunteers without changing cystatin C (said to be a better marker of GFR than serum creatinine). This raises the possibility that N-acetylcysteine might be simply lowering serum creatinine, so patients do not meet the laboratory criteria for CIN, but not preventing the renal damage. As considerably more investigation is needed, the use of N-acetylcysteine should not be considered as a substitute for close attention to renal function and adequate hydration.

The popular regimen of oral acetylcysteine, 600 mg twice daily on the day before and on the day of administration of iodinated contrast media, is simple, inexpensive, and has few contraindications (although allergic reactions have been rarely reported). However, higher doses may be more effective if the agent is effective at all, and there is controversy over whether solid (not currently available in the USA) or liquid preparations are equally effective. Alternatively, an IV regimen beginning 30 minutes prior to contrast media administration may be considered (150 mg/kg in 200 ml of D₅W over 30 minutes, followed by 50 mg/kg in 500 ml of D₅W over 4 hours). However, IV administration may have a higher rate of adverse effects than oral administration [26].

The evidence for other potentially renal-protective medications, such as theophylline, enothelin-1, and IV infusion of fenoldopam, is even less convincing without any provable benefit to date.

Recommendations for Prevention of Contrast Induced Nephrotoxicity

Fortunately, patients with normal renal function are at extremely low risk for CIN. In fact, it may actually not occur if renal function (as opposed to serum creatinine) is truly normal. Indeed, Rao and Newhouse [29] have argued that few properly controlled studies of IV use of iodinated contrast media have been published; in a literature review they found only two properly controlled studies and neither demonstrated renal damage from IV iodinated contrast media. The fear of renal failure should not, therefore, dictate avoidance of diagnostic studies using iodinated contrast media. However, radiologists should be attentive to the possibility of risk factors for renal injury, especially the combination of pre-existing renal insufficiency, diabetes, and dehydration.

There is no universally agreed upon threshold of serum creatinine elevation (or degree of renal dysfunction) beyond which iodinated contrast media should not be administered. In a survey of radiologists by Elicker et al [30] published in 2006, it was clear that policies regarding the cutoff value for serum creatinine varied widely among radiology practices. Thirty-five percent of respondents used 1.5 mg/dL, 27% used 1.7 mg/dL, and 31% used 2.0 mg/dL (mean, 1.78 mg/dL) as a cutoff value in patients with no risk factors other than elevated creatinine; threshold values were slightly lower in diabetics (mean 1.68 mg/dL). Patients in end-stage renal disease who have no remaining natural renal function are no longer at risk for CIN and may receive LOCM or IOCM (but see “Renal Dialysis Patients and the Use of Iodinated Contrast Media” below).

The major preventive action against CIN is to ensure adequate hydration. If the patient cannot be hydrated orally, one could consider IV infusion of 0.9% saline at 100 ml/hr in adults, beginning 6 to 12 hours before and continuing 4 to 12 hours after the administration of contrast media. In healthy outpatients, a state of euhydration should be considered optimal; in any situation where there has been intentional dehydration (i.e. NPO, etc.), an active hydration regimen should be considered prior to contrast media administration.

Addition of a medication that may mitigate the nephrotoxic effect of iodinated contrast media, e.g., N-acetylcysteine, could be considered for patients at risk (i.e., exhibiting renal insufficiency, particularly when associated with diabetes mellitus), but not in lieu of adequate hydration and close surveillance of renal function, especially given its questionable efficacy. A good understanding of the particular patient and communication between radiologist and referring clinician are critically important.

For all patients with suspected renal dysfunction or those considered at risk for contrast nephrotoxicity for other reasons, a baseline serum creatinine level should be obtained before the injection of contrast media. If renal dysfunction is identified, the referring clinician should be advised regarding alternative imaging approaches. Other precautionary recommendations are to increase the interval between contrast media examinations and reduce the contrast dose.

The issue of whether to require *routine* renal function testing prior to contrast administration has also been addressed. Choyke, et al [31] identified six patient survey questions which could exclude patients with abnormal serum creatinine with a high specificity, and suggested that if all of these questions were answered in the negative, 94% would have a normal creatinine and 99% would have a creatinine level under 1.7 mg/dL. These subjects could be reasonably excluded from creatinine screening prior to contrast injection resulting in a significant cost saving. This is

especially applicable to outpatient examinations [32].

In patients with acute renal failure, whatever the etiology, administration of iodinated contrast material should only be undertaken with extreme caution where the benefit to the patient clearly outweighs the risk of permanent renal damage.

Suggested Indications for Serum Creatinine Measurement before Intravascular Administration of Iodinated Contrast Media

- History of “kidney disease” as an adult, including tumor and transplant.
- Family history of kidney failure.
- Diabetes treated with insulin or other medications prescribed by a licensed physician.
- Paraproteinemia syndromes or diseases (e.g., multiple myeloma).
- Collagen vascular disease (e.g., scleroderma, systemic lupus erythematosus)
- Prior renal surgery.
- Certain medications:
 - Metformin or metformin-containing drug combinations.
 - Chronic or high dose use of non-steroidal anti-inflammatory drugs.
 - Regular use of nephrotoxic medications, such as aminoglycosides.
- All inpatients

Although there is little data to support a specific time interval between the date of measurement of the serum creatinine and the proposed contrast administration, in otherwise stable outpatients, many authorities will accept an interval of 30 days as being sufficiently recent to proceed with contrast administration. For inpatients, a much shorter interval seems prudent.

Routine blood urea nitrogen (BUN) testing may be useful as a reflection of hydration but should not be relied on solely in evaluating renal dysfunction.

Other patients who are scheduled for a routine intravascular study do *not* necessarily need a serum creatinine determination before the examination.

Renal Dialysis Patients and the Use of Iodinated Contrast Media

In patients suffering from end-stage renal disease, the question arises as to the emergent need for dialysis after a contrast media examination. Because contrast agents are not protein-bound and have relatively low molecular weights, they are readily cleared by dialysis. The primary concern about patients who are dialysis-dependent is the osmotic load of the contrast media, although direct chemotoxicity on the heart and blood-brain barrier is also of theoretical concern. Unless there is significant underlying cardiac dysfunction, or very large volumes of contrast media are used, there is no need for urgent dialysis [33]. It is important, however, to limit the dose of contrast media used in such patients and to use LOCM or IOCM (rather than HOCM) to reduce the risk of adverse effects related to hypertonicity.

Patients with renal insufficiency who require only intermittent or occasional dialysis are at substantial risk for contrast media-induced nephrotoxicity with further permanent worsening of their renal function. Alternative imaging studies that do not require contrast media should be considered.

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Suggested Reading (Articles that the Committee recommends for further reading on this topic are provided here.)

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Table 4. National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification, Prevalence, and Action Plan for Stages of Chronic Kidney Disease*

Stage†	Description	GFR, mL/min per 1.73 m ²	Prevalence, n (%)‡	Action§
—	At increased risk	≥60 (with chronic kidney disease risk factors)	—	Screening; chronic kidney disease risk reduction
1	Kidney damage with normal or increased GFR	≥90	5 900 000 (3.3)	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Kidney damage with mild decreased GFR	60–89	5 300 000 (3.0)	Estimating progression
3	Moderately decreased GFR	30–59	7 600 000 (4.3)	Evaluating and treating complications
4	Severely decreased GFR	15–29	400 000 (0.2)	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	300 000 (0.1)	Kidney replacement (if uremia present)

* CVD = cardiovascular disease; GFR = glomerular filtration rate. Modified and reprinted with permission from reference 7.

† Stages 1 to 5 indicate patients with chronic kidney disease; the row without a stage number indicates persons at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR less than 60 mL/min per 1.73 m² for 3 or more months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

‡ Prevalence for stage 5 is from the U.S. Renal Data System (1998); it includes approximately 230 000 patients treated with dialysis and assumes 70 000 additional patients not receiving dialysis. Prevalence for stages 1 to 4 is from the Third National Health and Nutrition Examination Survey (1988 to 1994). Population of 177 million adults age 20 or more years. Glomerular filtration rate is estimated from serum creatinine measurements by using the Modification of Diet in Renal Disease study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage is estimated by using untimed urine samples to determine the albumin-creatinine ratios; greater than 17 mg/g in men or greater than 25 mg/g in women on two measurements indicates kidney damage. The proportion of persons at increased risk for chronic kidney disease has not been estimated accurately.

§ Includes actions from preceding stages.

Figure 1 Annals of Internal Medicine, Levey et al [34]