Safe Use of Contrast Media: What the Radiologist Needs to Know[1]

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Abbreviations: CIN = contrast agent–induced nephropathy, GBCA = gadolinium-based contrast agent, NSF = nephrogenic systemic fibrosis

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Iodinated and gadolinium-based contrast media are used on a daily basis in most radiology practices. These agents often are essential to providing accurate diagnoses, and are nearly always safe and effective when administered correctly. However, reactions to contrast media do occur and can be life threatening. Therefore, it is critical for faculty and staff to know how reactions to contrast agents manifest and how to treat them promptly. The decline in renal function seen occasionally after intravenous administration of iodinated contrast agents is poorly understood and likely multifactorial, and its association with the contrast medium may be overemphasized. However, it is important that radiologists be aware of current understanding and strategies to decrease the incidence of renal dysfunction. Nephrogenic systemic fibrosis, a skin disease, is an adverse reaction related to use of some gadolinium-based contrast agents in patients with chronic renal failure. The types of gadolinium most often associated with this condition and the indications for withholding gadolinium are important and are discussed in this article. The use of enteric contrast agents and contrast agents during pregnancy and nursing are reviewed briefly. Current knowledge for safe use of contrast media and key concepts that all radiologists should know are summarized in this review.

Introduction

The rapid increase in the use of medical imaging during the last few decades has resulted in a substantial increase in the use of radiologic contrast media. Half of the approximately 76 million computed tomographic (CT) and 34 million magnetic resonance (MR) imaging examinations performed each year include the use of intravenous contrast agents (1,2). Many advanced clinical imaging applications were developed and refined with the use of intravenous contrast agents (3). Ideally, contrast agents should be injected and eliminated from the body without additional effects on the patient.

Although the currently available contrast agents generally are considered to be safe, their use is not completely without risk. Adverse effects vary from minor physiologic and mild allergic-like reactions

TEACHING POINTS

- Patient history of a previous severe reaction to a contrast agent increases the overall risk for a subsequent reaction approximately five- to six-fold.
- Distinguishing allergic from physiologic reactions is important because patients with physiologic reactions do not require premedication in the future, whereas those with allergic reactions may need premedication with steroids.
- Authors of several large studies have concluded that CIN and contrast agent–independent acute kidney injury are not significantly different and may be clinically indistinguishable when adjusting for patient risk factors.
- Aspiration of high-osmolar water-soluble contrast agents can lead to severe pulmonary edema; therefore, iso-osmolar or low osmolarity agents should be used for patients at increased risk for aspiration.
- Only a small percentage of iodinated contrast material or GBCA is excreted in breast milk and absorbed by the infant, and there have been no reported cases of direct toxicity, allergic sensitivity, or reaction to these agents. Although it is therefore not necessary to stop breast-feeding, depending on personal preference mothers may still choose to express and discard breast milk for 12–24 hours after they are given contrast agents.

to rare but severe and life-threatening events. Although the prevalence of these reactions is low for both CT (4) and MR imaging (5), reactions to contrast media do occur, and rapid evaluation and treatment of them requires designated and well-trained personnel and appropriate, readily available equipment and medications. Ideally, identification of patients likely to experience adverse effects with contrast agents should occur before approval and completion of these examinations. When an adverse event arises, knowledge of the types of reactions that manifest and prompt treatment are critical, and therefore, appropriate training must be provided to all individuals involved in administration of contrast material.

This review article should aid those who oversee administration of contrast agents in screening, recognizing, and managing the risks intrinsic to their use. Areas of focus include screening and patient selection strategies, premedication, and treatment of adverse events, including those related to renal function. The information on screening, premedication, and reactions can be applied either to iodinated contrast agents or gadolinium-based contrast agents (GBCAs). The sections on contrast agent–induced nephropathy (CIN) and nephrogenic systemic fibrosis (NSF) are specific to iodinated contrast agents and GBCAs, respectively. Finally, use of enteric contrast agents and contrast agents in pregnant or lactating patients and children is briefly discussed. In this review, we highlight several topics that the American College of Radiology has developed comprehensively, and we discuss recent scientific advances where appropriate. The latest edition of the Manual on Contrast Media (6) provides more detailed information and references.

Classification of Contrast Agents and Frequency of Acute Adverse Events

Iodine-based contrast agents can be divided according to osmolarity (high, low, or iso-), ionicity (ionic or nonionic), and the number of benzene rings (monomer or dimer) (7). Nonionic contrast agents cause less discomfort and fewer adverse reactions compared with ionic agents (7). In current practice, nonionic low or iso-osmolar preparations are used almost exclusively for intravascular injections; therefore, high-osmolar ionic agents are not discussed in this article. We use the term "low osmolality" for both low-osmolality and iso-osmolality radiographic contrast agents in this article for simplicity. Low-osmolar contrast agents are associated with significantly lower rates of acute reactions compared with high-osmolar agents. The rate of acute adverse events for low-osmolar contrast agents is approximately 0.2%–0.7% (8–10) and for severe acute reactions, 0.04% (4). Fatal reactions to contrast media are rare, with an incidence of one in 170,000 injections (4). In general, authors of clinical studies have not shown a significant difference in pharmacokinetics, pharmacodynamics, general safety, induction of thrombosis, and diagnostic effect among the nonionic agents (11).

Gadolinium chelates, approved for intravascular use for MR imaging since the late 1980s, are extremely well tolerated. GBCAs are classified according to their ionicity (ionic or nonionic), the chelating ligand (macrocyclic or linear), their pharmacokinetics (extracellular or organ specific) and their risk of causing NSF (7). In comparison with iodine-based contrast agents, both ionic and nonionic GBCAs can be used for intravascular injection with relatively little or no difference in acute reactions and discomfort (7). The incidence of adverse reactions to GBCAs is low, occurring in approximately one in 10,000–40,000 injections (12–14). Most reactions are mild and transient, with skin reactions most frequently seen. Severe, life-threatening anaphylactoid reactions to GBCAs are rare (15).

Patient Selection and Preparation

For any diagnostic procedure, the referring physician and radiologist should consider the risk-to-benefit profile of the proposed contrast material–enhanced examination and potential imaging alternatives that would provide the same or better diagnostic information and confirm a valid clinical indication. Unless state or local

Table 1: Risk Factors for Acute Adverse Reactions to Contrast Agents

Previous reactions to iodinated contrast agents
All severe allergies and reactions (to medications and food)
History of asthma, bronchospasm, or atopy
History of cardiac or renal disease
Especially those aged >60 y or <5 y

Source.—Reference 17.

regulations require it, obtaining consent for the injection of iodinated contrast material is not customary, because it generally is considered to be safe (16). However, most imaging centers provide information to and ask questions of patients before the examination to identify factors that may contraindicate the use of contrast agents or may increase the likelihood of a reaction. This process informs the patient of potential adverse outcomes and helps in assessment of risks, such as diabetes, renal function, prior reactions to contrast agents, and allergies (17). Radiologists should consider screening for the predisposing factors that increase the risk for reaction, both allergic-like and nonallergic reactions, which are listed in Table 1 and can be expanded to meet each institution's needs (18). Some practitioners consider hematologic conditions such as multiple myeloma to be risk factors, but this is not supported by available evidence (19).

Routine testing of creatinine before administration of iodinated contrast material is not necessary in all patients (20). Suggested indications for creatinine testing before administration of iodinated contrast material are listed in Table 2, with one of the most important risk factors being a personal or family history of renal disease (6). However, this list does not allow identification of all patients with elevated creatinine, and it is prudent to measure creatinine in patients with an illness or disability, even in the absence of specific risk factors. Referring physicians may request to omit testing in an emergency. There is no standard interval between measurement of baseline serum creatinine levels and administration of a contrast agent, but 6 weeks or less is the most common (6). The estimated glomerular filtration rate may be a more reliable indicator of renal function because it accounts for age, race, and sex (21,22).

Risk Factors

Although certain patients are at increased risk for an adverse reaction after intravascular contrast media exposure, contrast material reactions

Table 2: Suggested Indications for Obtaining Creatinine Levels before Administration of Contrast Agents

Iodinated contrast agents
Age older than 60 y
History of kidney disease as an adult, including tumor and transplant
Family history of kidney failure
Diabetes treated with insulin or other prescribed medications
Hypertension
Paraproteinemia syndromes or diseases (eg, myeloma)
Current use of nephrotoxic medications (eg, chemotherapy agents, chronic use of nonsteroidal anti-inflammatory medications)
GBCAs
Age older than 60 y
History of kidney disease as an adult, including tumor and transplant
Single kidney or kidney surgery
Diabetes treated with insulin or other prescribed medications
Hypertension requiring medical therapy

Sources.—References 6, 11, 20.

remain sporadic and unpredictable (6). Patient history of a previous severe reaction to a contrast agent increases the overall risk of a subsequent reaction approximately five- to six-fold (23). Patients with a history of allergies and those with features of atopy, such as asthma, dermatitis, and urticaria, have an approximately three- to six-fold increased risk of severe reaction to contrast media (24). Although minor allergies are common and do not appear to increase overall risk, a history of severe atopy, such as multiple allergies or a prior major anaphylactic response, should heighten concern before administration of contrast material. Patients with well-controlled asthma may not be at increased risk (25). Use of nonionic contrast agents may reduce the prevalence of recurrent adverse reactions to 5% (26). Reducing the volume and osmolality of the contrast agent also is suggested in patients with substantial cardiac disease.

CT Contrast Agents and Shellfish Allergies

It is now well established that there is no specific link between shellfish allergy and allergy to contrast agents; there is an increased risk of adverse reactions to contrast agents in patients with any history of allergy (27). The major allergens in shellfish are tropomyosins, which are unrelated to iodine. Iodine is an essential element with no potential to cause

Table 3: Classification of Acute Reactions to Contrast Agents

Degree of Severity	General	Cardiovascular	Gastrointestinal	Central Nervous System
Physiologic type				
Mild	Flushing, warmth, or chills; sneezing, rhinorrhea, or nasal congestion	Mild hypertension	Mild nausea or vomiting	Anxiety, self-limited syncope, or vasovagal reaction; dizziness or headache
Moderate	. . .	Chest pain without other symptoms or electrocardiographic changes, hypertensive urgency	Moderate nausea or vomiting	Vasovagal reaction requiring treatment
Severe	Seizures	Hypertensive crisis, arrhythmia, or electrocardiographic changes	. . .	Unresponsiveness or unconsciousness
Allergic type				
Mild	Limited urticaria, pruritus, or skin edema; mild nasopharyngeal symptoms such as sneezing, rhinorrhea, or nasal congestion	Mild hypertension	Nausea, mild vomiting	. . .
Moderate	Generalized erythema, urticaria, pruritus, or edema	Hoarseness or throat tightness with or without mild hypoxia; wheezing with mild hypoxia	. . .	. . .
Severe	Severe edema, including facial and laryngeal edema	Hypotension or hypoxia	. . .	. . .

Source.—Reference 6.

an allergic response. If a patient reports a history of iodine "allergy," it is important to clarify if the prior reaction was directly related to an iodinated contrast agent. Patients with an allergy to shellfish should be counseled that this does not increase the risk for an adverse reaction to contrast agents any more than do other allergies.

Acute Adverse Reactions

Classification

General adverse reactions to contrast agents remain incompletely understood and are likely multifactorial. Anaphylactoid (idiosyncratic) reactions are unpredictable but constitute most clinically important reactions and involve the release of histamine and other biologic mediators (18). Chemotoxic-type (physiologic) reactions are associated with the dose and molecular toxicity of each agent in addition to its physiologic characteristics.

Acute, nonrenal, adverse reactions to intravenous contrast agents are typically divided into three categories of severity: mild, moderate, and severe (Table 3) (6). Distinguishing allergic-like from physiologic reactions is important because patients with physiologic reactions do not require premedication in the future, whereas those with allergic reactions may need premedication with steroids. Mild reactions are typically self-limited and do not progress, and they require symptomatic or no treatment. However, these mild reactions sometimes become more severe, and therefore, patients should be observed briefly to ensure recovery (28). Moderate reactions such as bronchospasm with no or only mild hypoxia are usually not life threatening. However, they may progress to life-threatening reactions, so patients should be treated and monitored until symptoms have resolved completely. Severe adverse reactions are rare, unpredictable, and potentially fatal; therefore, they must be recognized promptly and treated to prevent permanent morbidity or death. Cardiopulmonary arrest can be caused by idiosyncratic or severe physiologic reactions.

Allergic-like Reactions

The classic allergic reaction requires a sensitizing exposure; however, many patients have allergic-like reactions at initial exposure (29). Serious reactions to contrast media are mediated by type 1 hypersensitivity reaction (anaphylaxis) mechanisms in which the reaction begins within minutes of exposure and involves multiple chemotactic, vasoactive, and spasmogenic compounds (23,29). Nonimmunologic (anaphylactoid), mast cell, and basophil degranulation in these reactions result from direct stimulation rather than from activation mediated by IgE (27,30,31). Therefore, there is no previous exposure required; however, these patients often do not experience a more serious reaction with repeat administration of contrast material (32). A small minority of severe reactions appear to be true allergic reactions, which are mediated by IgE and show positive results at skin testing (33,34).

Adverse Reactions Related to Pharmacologic Toxicity

Chemotoxic or physiologic reaction effects are believed to result from disruption of homeostasis and may be related to dose, molecular toxicity, and physical and chemical characteristics such as osmolality and viscosity, among others (29,35). For example, high osmolality can cause extracellular fluid shifts, leading to cell dehydration and increased intracellular fluid viscosity, which precipitates cellular dysfunction (36). The cardiovascular, respiratory, urinary, gastrointestinal, and nervous systems are most commonly affected by the physiologic changes of contrast agents such as symptoms of warmth, metallic taste, nausea, vomiting, bradycardia, hypotension, vasovagal reactions, and neuropathy (37).

Timing of Reaction Occurrence

Although most reactions occur in the first hour after administration, and many occur within the first 5 minutes (4), there are rare instances of late adverse reactions that occur between 1 hour and 1 week after injection of iodinated contrast agents (38). Delayed reactions are more common in young adults, women, and patients with a history of allergy (18). The incidence of delayed adverse reactions is 10.9% for iso-osmolar dimeric and 5%–6% for low-osmolar monomeric contrast agents (36). These reactions tend to be skin related, are typically mild to moderate and self-limiting (38), and include maculopapular rash, urticaria, and erythema. Similar to any drug-induced skin reaction, they often require only symptomatic or no treatment. Although the pathogenesis of late reactions is not understood completely, many of these reactions may be T-cell–mediated (33). In general, premedication for future administration of contrast agents is not warranted unless the patient experienced a previous severe late adverse reaction (18).

Treatment of Acute Nonrenal Adverse Reactions to Contrast Agents

Treating an acute reaction to a contrast agent can provoke anxiety for all involved. Authors of several recent studies (39–41) have found that many radiologists do not feel well prepared or confident in handing these incidents, particularly the rare severe reactions. Therefore, training to maintain familiarity with methods for evaluation and treatment of reactions and indications for and doses of medications used is crucial. Commonly used training methods are didactic teaching, virtual modules, simulation courses, and practicums. Tubbs et al (42) found that radiology residents who took part in medical simulation subsequently showed significant improvement in knowledge and confidence in treatment of adverse reactions. Niell et al (43) used a didactic module to improve knowledge and comfort levels for physicians, nurses, and technologists; however, a considerable percentage of personnel still reported feeling uncomfortable treating an adverse reaction to a contrast agent, and the authors concluded that didactic instruction alone may be inadequate. A combination of teaching methods is likely most effective, with training repeated yearly or more often. Current certification in basic life support also is encouraged for all physicians who oversee injection of contrast material.

All facilities in which injection of contrast material occurs should be equipped with the emergency supplies needed to treat any form of reaction. For all reactions, practitioners should maintain intravenous access; obtain vital signs; and assess patient appearance, voice quality, and symptoms. Mild reactions may require nothing more than observation or a dose of antihistamine medication. In moderate to severe adverse reactions, application of supplemental oxygen with a face mask and assessment of pulse oximetry values are recommended. Treatment methods and medications for moderate and severe reactions are included in Table 4. During acute events, it is crucial to remember that the correct dose of epinephrine depends on the route of administration, with the concentration at 1:1000 for intramuscular and at 1:10,000 for intravenous administration. When severe reactions occur, the level of patient care should be escalated either by calling paramedics for patient transportation to the closest emergency department in an outpatient setting or by calling a code in the inpatient setting. Occasionally, practitioners should escalate patient care for moderate reactions on the basis of clinical judgment.

Table 4: Recommended Treatment for Moderate to Severe Reactions to Contrast Agents in Adults

Reaction	Treatment	Dosage
Bronchospasm		
Mild	β-agonist inhaler (albuterol)	Two puffs (180 μg, 90 μg/puff), repeat up to three times
Moderate	β-agonist inhaler (same dose as that for mild bronchospasm), epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 dilution), repeat to total dose of 1 mg; or IV: 0.3 mg (1–3 mL of 1:10,000 dilution) slow infusion, repeat to total dose of 1 mg
Severe	Epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 dilution), repeat to total dose of 1 mg; or IV: 0.3 mg (1–3 mL of 1:10,000 dilution) slow infusion with saline, repeat to total dose of 1 mg
Laryngeal edema	Epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 dilution), repeat to total dose of 1 mg; or IV: 0.3 mg (1–3 mL of 1:10,000 dilution) slow infusion with saline, repeat to total dose of 1 mg
Hypotension (normal pulse, systolic blood pressure <90 mm Hg)	Elevate legs (>60°)	Consider 1000-mL bolus of 0.9% normal saline or lactated Ringer solution
Vasovagal reaction		
Mild	None	. . .
Moderate to severe (patient unresponsive)	Atropine	IV: 0.6–1.0-mg slow infusion followed by saline flush, repeat to total dose of 3 mg
Anaphylactoid reaction (systolic blood pressure <90 mm Hg, pulse >100 beats per minute)	Epinephrine	IM: 0.3 mg (0.3 mL of 1:1000 dilution), repeat to total dose of 1 mg; or IV: 0.3 mg (1–3 mL of 1:10,000 dilution) slow infusion with saline, repeat to total dose of 1 mg
Hypertensive crisis	Labetalol If labetalol is unavailable, nitroglycerin and furosemide (Lasix)	IV labetalol: 20-mg slow infusion over 2 min, double the dose every 10 min (eg, 40 mg 10 min later, then 80 mg 10 min after that) Sublingual nitroglycerin tablet, 0.4 mg; repeat every 5–10 min; IV furosemide, 20–40 mg, slow infusion over 2 min

Source.—Reference 6.
Note.—In all scenarios, consider transporting patient to the emergency department or calling emergency response team (911 in the outpatient setting) if the patient does not improve after therapy. In patients with profound hypotension, intravenous epinephrine should be administered because decreased circulation may limit adequate absorption after intramuscular administration. IM = intramuscular, IV = intravenous.

Premedication for Administration of Contrast Material

Premedication may be considered in patients at risk, but it has not been proven to prevent acute allergic-like reactions (44). Glucocorticoids bind and block proinflammatory genes, such as interleukin-1, to produce anti-inflammatory effects (28). These agents also impair migration of neutrophils, macrophage function, and both cytokine production and degranulation by mast cells, resulting in decreased effectiveness of the innate immune system, which typically activates immediately and independently of preformed antibodies (45). Therefore, premedication with corticosteroids may reduce mild or moderate reactions, such as that in a patient with a history of diffuse hives after inravenous administration of iodinated contrast material (46,47). Severe reactions occur much less frequently and have not shown a similar benefit in response to premedication with corticosteroids (23,33,48).

Active infection or impaired immunity is a relative contraindication to premedication with steroids (46). Oral administration is preferable, and medication should be given at least 6 hours before injection of the contrast agent, whenever possible. Two frequently recommended premedication oral regimens for elective examinations and three protocols for patients at high risk in emergency settings are listed in Table 5. An intravenous dose of 200 mg of hydrocortisone may be given to patients unable to take oral medication (6).

Table 5: Elective and Emergent Premedication Protocols

Protocol	Option 1	Option 2	Option 3
Elective			
Steroid	Prednisone, 50 mg by mouth at 13, 7, and 1 h before injection of contrast agent	Methylprednisolone, 32 mg by mouth 12 h and 2 h before injection of contrast agent	. . .
Antihistamine	Diphenhydramine, 50 mg IV, IM, or by mouth 1 h before injection of contrast material	Diphenhydramine, 50 mg IV, IM, or by mouth 1 h before injection of contrast material	. . .
Emergent			
Indication	Most desirable in emergency	Less desirable than option 1; may be used in patients with allergies to methylprednisolone, aspirin, or nonsteroidal anti-inflammatory drugs	Least desirable; used when there is inadequate time to achieve corticosteroid effect
Steroid	IV methylprednisolone sodium succinate, 40 mg, or IV hydrocortisone sodium succinate 200 mg every 4 h until study performed	IV dexamethasone sodium sulfate 7.5 mg or betamethasone 6.0 mg every 4 h until study performed	Omit steroid; IV steroids have not been shown to be effective when administered less than 4–6 h before injection of contrast material
Antihistamine*	Diphenhydramine 50 mg IV 1 h before injection of contrast material	Diphenhydramine 50 mg IV 1 h before injection of contrast material	Diphenhydramine 50 mg IV 1 h before injection of contrast material

Sources.—References 46, 47.
Note.—IM = intramuscular, IV = intravenous.
*Antihistamines alone have not been proven to reduce occurrence of reactions.

Breakthrough Reactions

Sometimes a breakthrough reaction occurs with injection of iodinated contrast agents despite adequate premedication with corticosteroids. These are rare in premedicated patients who are given injections of a low-osmolar contrast agent and usually develop in those already identified as being at high risk. Reaction severity, signs, and symptoms are often reported to be similar to those of the initial reaction (6). Patients at the greatest risk for moderate or severe breakthrough reactions include those with severe allergies to any substance or drug including iodinated contrast material, those who have more than four allergies, and those with chronic use of oral corticosteroids (49). Patients who experience a breakthrough reaction should be evaluated and treated according to the recommendations previously discussed. These patients also should be counseled that they are likely to be at increased risk for more severe reactions if iodinated contrast material is administered in the future.

Extravasation

Intravenous access should be evaluated before the administration of contrast media. This includes verifying that the catheter is appropriate for the injection, confirming venous return, performing a saline flush, and performing a test injection with a power injector (50). Use of a 20-gauge or larger catheter in an antecubital or other large forearm vein is recommended for flow rates of at least 3 mL/sec, with flow rates no greater than 1.5 mL/sec for peripherally placed or 22-gauge catheters (6). The use of deep brachial intravenous catheters should be avoided because of the markedly higher relative risk of extravasation (51). Central venous (52) and peripherally inserted central catheters (53) also can be used safely, after verifying that they are power injector compatible to the manufacturer-recommended pressure limits.

Extravasation occurs when contrast material escapes the vascular lumen and infiltrates the interstitial tissue during injection. The most effective methods for identifying extravasation are *(a)* directly palpating the catheter venipuncture site during the initial seconds of injection, and *(b)* asking the patient to report any sensation of pain or swelling at the injection site. The incidence of intravenous contrast material extravasation usually is reported as less than 1% and is not directly correlated with injection

flow rate (54). Some patients are asymptomatic, while others report swelling, tightness, stinging, or burning pain and may demonstrate edema, erythema, or tenderness at the injection site (55). Prompt recognition and evaluation by a physician are required to reduce the chance and severity of injury.

Currently, there is no agreement among physicians on the best treatment of intravenous contrast agent extravasation. Physicians may recommend elevating the affected extremity or site and applying a warm or cold compress (56). Severe complications of extravasation include compartment syndrome, skin ulceration, and tissue necrosis; however, these are uncommon (54). Conservative treatment is recommended in most cases, with surgical consultation reserved for patients who develop progressive pain or swelling, decreased capillary refill, change in sensation (eg, paresthesia), skin ulceration, or blistering (57). Few patients require surgical intervention (57,58). All patients with extravasation should be monitored for a period as long as the responsible physician considers sufficient and should be discharged with instructions to watch for symptoms indicating a need for surgical evaluation.

Contrast Material–induced Nephrotoxicity

CIN is described as "a sudden deterioration in renal function (ie, acute kidney injury) following the recent intravascular administration of contrast media in the absence of another nephrotoxic event" (59). However, the validity of this condition and the potential clinical effects are unknown (60,61). Newhouse et al (62) showed that controlling for potentially confounding medical conditions that may cause acute kidney injury is difficult and that patients who were not exposed to iodinated contrast material showed rates of acute kidney injury similar to those of patients with CIN after CT (63). Authors of several large studies (44,64,65) have concluded that CIN and contrast agent–independent acute kidney injury are not significantly different and may be clinically indistinguishable when adjusted for patient risk factors. This suggests that greater latitude can be considered when using renal function estimates to determine the appropriateness of iodinated contrast agents; however, the effect of correcting hypovolemic states before injection of contrast material and the adverse effects of its absence have not been studied.

However, the validity of CIN is clinical dogma in many practices, and radiologists should well understand the issue. The Acute Kidney Injury Network has outlined the following criteria for intrinsic acute kidney injury, regardless of cause (66): *(a)* absolute serum creatinine increase of greater than or equal to 0.3 mg/dL (>26.4 μmol/L), *(b)* an increase in the percentage of serum creatinine of greater than or equal to 50% (1.5-fold higher than the baseline percentage), and *(c)* urine output reduced to less than or equal to 0.5 mL/kg per hour for at least 6 hours.

These risk factors and others such as hypertension, proteinuria, gout, and previous renal surgery, to our knowledge, have not been studied specifically with regard to CIN (20). The risk for CIN is considered low in patients with stable renal function, especially in the absence of risk factors and serum creatinine levels less than 1.8 mg/dL (159.12 μmol/L) at baseline (67). Because changes in serum creatinine levels are delayed during acute kidney injury, measurements are less reliable and should not be used for treatment decisions (68); however, use of any potentially nephrotoxic agent in such patients should be avoided. Patients with end-stage renal disease who are anuric can receive routine volumes of intravenous contrast material without risk for further renal damage or the need for urgent dialysis (69). It is unclear if patients with end-stage renal disease who are still producing urine may be able to preserve some renal function with dialysis after administration of iodinated contrast material.

Appropriate patient selection should include a risk-benefit analysis by a physician knowledgeable on the subject before administration of contrast media (64). Indicated examinations should be tailored to allow the clinical question to be answered and to avoid unnecessary or repeated administration of iodinated contrast material. Intravenous hydration has been studied in patients undergoing cardiac angiography, but to our knowledge, it has not been studied for administration of iodinated contrast material in patients with abnormal baseline renal function who are at moderate risk for CIN. To our knowledge, no proven benefit has been found for the use of other renal protective agents such as N-acetylcysteine, sodium bicarbonate, diuretics, and theophylline.

Nephrogenic Systemic Fibrosis

NSF is a serious, sometimes-fatal disease that occurs in patients receiving GBCAs who have severe chronic or acute renal failure. NSF primarily affects the skin but also can affect other organs including the lungs, pleura, skeletal muscle, heart, pericardium, and kidneys (70). Typical findings include rapidly progressive thickening of the skin, tethering, and hyperpigmentation mainly involving the extremities, progressing cephalad from the legs and feet (71). NSF is a clinical-pathologic diagnosis

Table 6: Association of GBCAs with NSF

Group 1: High-risk agents (associated with greatest number of NSF cases)
Gadodiamide (Omniscan)
Gadopentetate dimeglumine (Magnevist)
Gadoversetamide (OptiMARK)
Group 2: Intermediate-risk agents (associated with few, if any, unconfounded cases of NSF)
Gadoenate dimeglumine (MultiHance)
Gadofosveset (Ablavar)
Gadoxetate disodium (Eovist)
Group 3: Low-risk agents (no renal function evaluation required before examination)
Gadobutrol (Gadavist)
Gadoterate meglumine (Dotarem)
Gadoteridol (ProHance)

Source.—Reference 81.

Table 7: Strategies to Reduce Risk for NSF

Identify patients at risk (those dependent on dialysis, with severe chronic renal failure without dialysis, or with acute renal failure)
Consider alternative diagnostic study, such as CT or ultrasonography
Avoid use of GBCA whenever possible; if use of GBCA is unavoidable, use group 2 agent followed by prompt dialysis, but only if patient is already undergoing dialysis
Use lowest possible dose of GBCA
Do not readminister GBCA for several days to 1 week after initial dose

Source.—Reference 81.

without specific imaging findings. Major criteria used in the clinical diagnosis are patterned skin plaques; cobblestone, marked induration, or peau d'orange appearance of the skin; and joint contractures (72).

The association of NSF with GBCA was discovered in 2006 (73), but the relationship remains incompletely understood. Some practitioners speculate that it is related to the dissociation of gadolinium from the chelate in patients with renal dysfunction and prolonged circulation time related to impaired clearance of contrast material (74). The free gadolinium binds to anions, becoming an insoluble precipitate that is deposited in tissue, inciting a fibrotic reaction (75). NSF usually occurs days to months (average time, 2–10 weeks) after administration of GBCA, but authors of some studies have shown onset as long as 8 years after exposure, with an equal incidence between the sexes (76).

The most important risk factor for development of NSF is the degree of renal dysfunction (77). The highest risk for development of NSF is seen in patients undergoing dialysis and those with severe (stage 4; glomerular filtration rate, 30–40 mL/min per 1.73 m^2) or end-stage (stage 5, glomerular filtration rate < 30 mL/min per 1.73 m^2) chronic kidney disease without dialysis or acute kidney injury (76). However, the development of NSF is not related to the cause or duration of renal failure (76). Hepatic disease is no longer thought to be an independent risk factor for development of NSF (78,79).

The risk for NSF may be related to the type of GBCA chelate, cumulative dose, and residual renal function of the patient (76). Differences in the chelate structure and charge determine the ease with which free gadolinium can dissociate from its gadolinium-chelate complex. Macrocyclic and ionic chelates tend to be more stable than other gadolinium compounds, and therefore, have a decreased risk for causing NSF (80,81). GBCAs have been categorized on the basis of their risk of dissociation, with almost all reported cases associated with linear nonionic agents such as gadodiamide (Omniscan; GE Healthcare, Milwaukee, Wis), gadoversetamide (Optimark; Mallinckrodt, St Louis, Mo), and gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ) (82,83) (Table 6). Doses of GBCA higher than the standard 0.1 nmol/kg are associated with an increased risk for NSF with a single administration or multiple cumulative doses (76).

Outpatients at risk for NSF can be screened by using guidelines similar to those used with iodinated contrast agents (Table 2). Serum creatinine levels and estimated glomerular filtration rates should be obtained before administration of GBCA in patients with one or more risk factors. For patients undergoing dialysis, calculation of the glomerular filtration rate is not considered useful (76). For other inpatients, obtaining a glomerular filtration rate (within 2 days) and assessing for acute kidney injury should occur before administering any GBCA because glomerular filtration rate shows limited sensitivity for diagnosis of acute kidney injury (76).

There are several strategies for reducing risk for NSF (Table 7). For example, if a patient is anuric, consider CT with iodinated contrast material. If a GBCA must be used, consider avoiding gadodiamide, gadoversetamide, and gadopentetate dimeglumine and initiating dialysis within 2 hours of exposure and performing several prolonged dialysis treatments. One recommended protocol is performing 3-hour dialysis sessions, three times daily for 3 consecutive days (78).

However, prompt dialysis has not been proven to prevent NSF, and therefore, initiating dialysis in those who are not already receiving it is not recommended (78).

Other attempted therapies for NSF include extracorporeal photopheresis, plasmapheresis, ultraviolet A phototherapy, sodium thiosulfate, alefacept, and imatinib mesylate; however, none have shown consistent clinical improvement in patients (76). At this time, restoring renal function remains the most effective means of slowing the progression of NSF.

Miscellaneous Considerations

Enteric Contrast Agents

Barium sulfate is the preferred agent for opacification of the gastrointestinal tract. The most serious complication is the leaking of contrast material into the mediastinal or peritoneal cavity, which causes mediastinitis or peritonitis, so barium sulfate should not be used if bowel perforation is suspected. Aspiration of high volumes of barium may result in pneumonia or acute respiratory distress. Adverse physiologic or allergic-like reactions to a barium enteric contrast agent are rare, are almost always mild when they occur, and typically require no treatment (84). Iodinated water-soluble contrast media can be used in patients suspected of having bowel perforation or to confirm the position of percutaneous feeding tubes. They also can be used before anticipated endoscopic or surgical procedures. Aspiration of high-osmolar water-soluble contrast agents can lead to severe pulmonary edema. Therefore, iso-osmolar or low-osmolar agents should be used in patients at increased risk for aspiration (85).

A small amount (approximately 1%–2%) of ingested iodinated contrast material normally is absorbed (86). This absorption is increased in patients with mucosal inflammation or infection (87), and even these small volumes of contrast material absorption theoretically can cause dose-independent anaphylactoid reactions. Moderate-to-severe allergic-like reactions to iodinated enteric contrast material administered orally or rectally are rare but have been reported (87) and are more likely in patients with prior reactions to intravascular contrast media and in those with active inflammatory bowel disease because of reduced active mucosal protection against contrast material absorption (86).

Pregnant and Lactating Patients

Iodinated contrast material crosses the human placenta and has been demonstrated in fetal tissues; however, to our knowledge, teratogenic effects and hypothyroidism have not been reported (88). Despite these low theoretical risks, mostly regarding fetal thyroid development, avoiding intravenous contrast agents in pregnant patients is prudent when possible. GBCA crosses the primate placenta (89) and is assumed to cross the placenta in humans. After they enter the fetal bloodstream, these agents are excreted via the urinary tract into the amniotic fluid and are not removed effectively from the fetal environment (89). To our knowledge, there are currently no reported adverse effects in humans when the clinically recommended doses of GBCA are used in pregnant patients. Authors of one study of 26 women administered GBCA during the first trimester found no subsequent evidence of teratogenesis or mutagenesis (90).

Only a small percentage of iodinated contrast material or GBCA is excreted in breast milk and absorbed by the infant (17), and to our knowledge, there have been no reported cases of direct toxicity, allergic sensitivity, or reaction to these agents (88). Although it is therefore not necessary to stop breast-feeding, depending on personal preference mothers may still choose to express and discard breast milk for 12–24 hours after they are given contrast agents.

Children

Estimating the incidence of reactions to contrast media in children is difficult because of the lack of controlled prospective studies and consensus regarding what constitutes a true allergic reaction. The estimated incidence of allergic reactions after administration of iodinated contrast media in children (0.18%, of which 80% were mild in one study [91] of more than 11,000 pediatric injections) seems to be lower than that in adults. Guidelines for prevention and treatment of allergic reactions in children are similar to those for adults (6). Although few cases of NSF in children have been reported, and all of those patients had severe renal dysfunction, GBCAs should be used only when necessary because of the renal immaturity and lower glomerular filtration rates in pediatric patients (92).

Metformin

Metformin is an oral antihyperglycemic agent used to treat patients with non–insulin-dependent diabetes mellitus with the potential to precipitate lactic acidosis, which is seen most often in patients with several comorbid factors such as renal and cardiovascular disease (93). Use of contrast media is not an independent risk factor for patients taking metformin; however, as stated in the product package insert approved by the U.S. Food and Drug Administration, it should

be discontinued 48 hours after intravenous administration. Any reduction in renal function including acute renal failure that is a result of administration of contrast media could result in an accumulation of lactate and subsequent lactic acidosis. Discontinuation of metformin is not necessary after administration of GBCA in the recommended dose range (0.1–0.3 mmol/kg of body weight) (6).

Thyroid Disease

Patients with untreated Graves disease and/or multinodular goiter and thyroid autonomy, the elderly, and those living in areas where dietary iodine deficiency is common should be identified, and the risk of inducing thyrotoxicosis through excess iodine absorption should be reduced (7). Use of iodinated contrast agents should be avoided immediately before planned radioactive iodine imaging or therapy, because the iodine may reduce radioactive iodine uptake. Consultation with an endocrinologist may be beneficial before administration of an intravenous contrast agent.

Conclusion

Although it is generally considered to be safe and beneficial in medical imaging, use of contrast media occasionally results in adverse events in patients. Proper patient screening and adequate prophylactic measures can prevent some adverse reactions. Radiologists should be familiar with potential adverse renal events including contrast-induced nephropathy and NSF and with strategies to lower their incidence. Immediate recognition and treatment are invaluable to mitigate acute nonrenal reactions to contrast media and prevent escalation to severe or even life-threatening events. Knowledge, familiarity, and practice are crucial for an appropriate and effective response to these events. Every faculty and staff member should know the proper dosage of epinephrine, the phone number for the institution's emergency response team, and the location of emergency monitoring equipment and medications. Radiologists and their staff members should review regularly the treatment algorithms to accomplish their individual roles efficiently and correctly.

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