CLINICAL REVIEW

Intravascular Radiographic Contrast Media: Issues for Family Physicians

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Background: **Family physicians frequently order and in some instances supervise diagnostic tests using intravascular radiographic contrast media.**

Methods: **MEDLINE database was searched from 1966 to the present using the key terms "contrast media," "adverse reaction," "anaphylaxis," "anaphylactoid," "nephropathy," "renal failure," "kidney failure," and "MRI" in combinations. Other sources were found by back referencing these articles and in recent texts.**

Results and Conclusions: **The adverse reactions likely to be encountered in most patients are acute anaphylactoid and cardiovascular reactions, delayed reactions, and renal effects. Mild acute reactions usually require no treatment, but if more severe reaction symptoms occur, emergency treatment is indicated. Acute reactions can be prevented or reduced by close attention to risk factors and pretreatment. Delayed reactions seldom require specific treatment. The type of contrast agent used might lessen the risk of immediate reactions. Contrast-associated nephropathy is most likely to occur in patients who have preexisting renal disease, heart failure, and volume depletion. Optimization of precontrast hydration can lessen the renal effects of contrast material. Magnetic resonance imaging contrast agents might be safer, because of smaller volumes administered, but adverse reactions have occurred. (J Am Board Fam Pract 1999;12:32-42.)**

Family physicians frequently request radiographic studies that use intravascular radiographic contrast media in the course of evaluation of a wide spectrum of illness. Examples include infusion pyelography, computed tomography, and venography. In many situations a radiologist is not available to supervise such studies, or family physicians are called upon to respond to patients with acute adverse reactions to the contrast medium. Physicians caring for patients must be aware of the potential for deterioration of renal function, because patients undergoing such studies often have coexisting diseases that increase the risk of adverse reaction. Family physicians who supervise the administration of intravascular radiographic contrast media should be able to anticipate and treat adverse reactions, advise patients about the risks of administration, and be aware of the different classes of radiographic contrast media and the issues involved in the proper selection and use of these agents. Family physicians who request studies using intravascular radiographic contrast media should be aware of the risks involved and council their patients accordingly.

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Methods

The MEDLINE database was searched from 1966 to the present using the key terms "contrast media," "adverse reaction," "anaphylaxis," "anaphylactoid," "nephropathy," "renal failure," "kidney failure," and "MRI" in combinations. Other sources were found by back referencing these articles as well as in recent texts.

Conventional Intravascular Radiographic Contrast Media

Intravascular radiographic contrast media commonly used for conventional ionizing radiation (x-ray) studies are iodinated benzoic acid derivatives.[1] They are categorized by osmolality (high or low), structure (monomeric or dimeric ring structure), and ion tendency (ionic or nonionic). Osmolality in solution is somewhat dependent on the concentration of iodine necessary to obtain radiographic attenuation relative to the particles in solution. Ion

tendency of these agents is principally due to the presence of carboxyl side chains and is reduced by hydroxylation of these side chains.

The high-osmolality contrast media (HOCM) are ionic monomers, with osmolality in solution ranging from 1200 to 2400 mOsm/kg H_2O.[2-4] The HOCM are among the most used drugs in the history of medicine. During peak use in the 1970s, annual consumption surpassed 2000 metric tons.[5]

The low-osmolality contrast media (LOCM) are represented structurally by the ionic dimers, nonionic monomers, and nonionic dimers. Ioxaglate is the only commonly used ionic dimer. In solution it forms two particle aggregates and does not readily ionize,[3] rendering an osmolality of about 600 mOsm/kg H_2O.[2,4]

The nonionic monomers, as a result of their lower toxicities, are rapidly becoming the contrast agents of choice.[6] In addition to nonionic tendencies and lower osmolalities, the newer nonionic monomers, such as ioversol and iohexal, are more hydrophilic and thus potentially less chemotoxic.[3,7] The approximate osmolality range of these agents is 290 to 860 mOsm/kg H_2O.[2,4]

The lower toxicity of LOCM is offset somewhat by higher cost. The pricing structure for intravascular radiographic contrast media is dependent on a number of factors, but typical hospital cost in the United States is $0.10 to $0.15/mL of HOCM, and $0.30 to $0.40/mL for LOCM (personal communication, with suppliers). For a study requiring 100 mL of radiographic contrast media, such as an intravenous pyelogram, using LOCM would result in an increased cost of $15 to $30 per study.

The nonionic dimers are largely in the developmental stages. Although the osmolality of these agents approaches that of plasma, they are highly viscous and thus of limited clinical usefulness.[1,2,5]

When evaluating the literature, one must note the potential differences in the terms ionic, nonionic, and low osmolality, high osmolality. Ioxaglate is an LOCM, but it also has some ionic tendencies.

Currently there is much controversy regarding the appropriate use of LOCM and HOCM, and the true benefits and ethical issues of LOCM versus HOCM use are the subject of debate in the medical literature.[3,7-14] Legal issues surrounding the selection of radiographic contrast media have surfaced in the courts and state legislative bodies.[9] Numerous local and national organization guidelines exist to guide the physician in the appropriate selection of radiographic contrast media, but there continues to be wide variation in the use of LOCM by individual physicians, institutions, and geographic location.[9]

Toxicity of Iodinated Radiographic Contrast Materials

The toxicity of iodinated radiographic contrast media is related to (1) chemotoxicity, (2) ion toxicity, and (3) osmotoxicity of the specific compound used. Chemotoxicity increases as the hydrophobic nature of the substance increases. Chemotoxicity can result in release of vasoactive substances, activation of the complement and fibrinolytic systems, blockage of platelet aggregation, direct neurotoxicity, and decreased myocardial contractility and conduction. Ion toxicity is due to the direct effects of the anionic contrast medium or its conjugated cation on cellular membranes or cellular function. Osmotoxicity can result in pain upon injection, blood-brain barrier disruption, vagal and emetic center stimulation, decreased myocardial contractility, lowering of the myocardial fibrillation threshold, renal vasoconstriction, erythrocyte cell wall rigidity, increased pulmonary artery pressure, and decreased peripheral vascular resistance and vasodilation.[2,7,15,16]

The effects likely to be problematic for the family physician are those that produce immediate anaphylactoid, cardiovascular symptoms and delayed reactions. Rarely will radiographic contrast media precipitate exacerbation of myasthenia gravis or thyroid storm.[4,16,17]

Anaphylactoid Reactions to Radiographic Contrast Media

The so-called allergic reaction to iodinated radiographic contrast media is, in fact, an anaphylactoid or pseudoallergic reaction. Numerous mediators typical of allergic reactions are released or activated, but the mechanism is not antigen-antibody mediated.[15,18] A true antibody-mediated reaction to iodinated radiographic contrast media is rare, with only three reported cases as of 1994.[15] The exact mechanisms of these anaphylactoid reactions are not known but probably include direct cellular effects, direct enzyme induction, and direct activation of the compliment, fibrinolytic, kinin, and other systems.[2,7,15] Symptoms usually

develop within minutes of administration and reflect the actions of the released or activated mediating substances.

The symptoms can be classified as mild, moderate, and severe.[19,20] Mild symptoms include a sensation of warmth, flushing, pruritus, rhinorrhea, scattered urticaria, brief retching, and diaphoresis.[2,15] Urticaria is the most commonly reported adverse reaction.[21] It is imperative that patients with mild symptoms be observed very closely for progression of symptoms that would indicate a more severe reaction, which would require immediate treatment. Moderate symptoms include persistent vomiting, diffuse urticaria, headache, facial edema, mild bronchospasm or dyspnea, palpitations, and abdominal cramps. Severe reactions are indicated by life-threatening arrhythmias (ie, ventricular tachycardia), hypotension, overt bronchospasm, laryngeal edema, pulmonary edema, seizures, and death.

Treatment of Acute Reactions to Radiographic Contrast Media

The primary dictum in treating adverse reactions to radiographic contrast media is to be prepared. A thorough history should be taken focusing on risk factors, previous exposure to radiographic contrast media and any reactions, and comorbidities. A history of an adverse reaction manifested by symptoms more severe than a few urticaria should, if possible, prompt consideration of delaying the study for pretreatment. Before administering intravascular radiographic contrast media, one must ensure that resuscitation medication, equipment, and trained personnel are on hand. An intravenous line of sufficient caliber to administer bolus medications should be secured before injection of the radiographic contrast medium, because most acute reactions occur within minutes of administration. The patient must be closely observed during and after contrast medium administration. Any symptoms should prompt a heightened readiness for rapid intervention.

Mild symptoms are usually self-limiting and require no specific treatment other than close observation for progression of more severe symptoms.[2,15,22] The first-line treatment of moderate anaphylactoid reactions is epinephrine, 1:1,000 dilution, at a dose of 0.1 to 0.3 mL given subcutaneously, or 1:10,000 dilution given intravenously at a dose of 1 to 3 mL. If hypotension or evidence of poor perfusion occurs, the intravenous route is preferred, as the subcutaneous dose might be poorly absorbed. Small frequent doses are preferred to minimize potentially dangerous cardiovascular side effects. Diphenhydramine at a dose of 25 to 50 mg intravenously is also effective for many symptoms, especially urticaria.

Mild bronchospasm often responds to inhaled bronchodilators, such as albuterol, which can be given by metered-dose inhalers at a dose of 4 puffs every 20 minutes as needed or by nebulized updraft therapy. Moderate bronchospasm also calls for subcutaneous epinephrine at the above-described dose, which may be repeated at 15-minute intervals. Severe bronchospasm can require intravenous epinephrine at the above-described dose and continuous nebulized bronchodilator therapy. Histamine (H_2) blockers, such as cimetidine, are effective additional treatment for persistent symptoms. Oxygen by mask or cannula should be administered as soon as possible while other therapies are initiated.[2,16,22]

Severe reaction symptoms call for rapid and aggressive intervention. The ABCs (airway, breathing, circulation) of resuscitation should be addressed rapidly in proper sequence. If available, a code team should be summoned. Epinephrine may be administered intravenously at a dose of 1 to 3 mL of 1:10,000 dilution in 2 to 3 minutes. Hypotension should be treated with rapid infusion of 1 to 2 L of crystalloid fluid solution. Dysrhythmias (both bradycardia and tachycardia) should be treated according to established protocol. Aggressive airway and ventilatory support might be necessary for pulmonary edema or laryngeal edema. Diphenhydramine and H_2 blockers are useful to counteract histamine-mediated symptoms.[2,16,22]

Corticosteroids are not useful in the initial emergency management of anaphylactoid reactions to radiographic contrast media because of their delayed onset of response.[16,22] They can be beneficial, however, in preventing or reducing the severity of delayed or prolonged symptoms.[2,19]

The medications used to treat anaphylactoid reactions are not without potentially serious side effects. Epinephrine can cause myocardial ischemia and arrhythmias. Fluid boluses must be given judiciously in persons with history of heart failure or other volume overload problems. Diphenhydramine can cause drowsiness and exacerbate respiratory depression and airway manage-

ment problems. Supplemental oxygen should be used with caution in patients with known carbon dioxide retention, but should not be withheld if the patient shows evidence of hypoxemia or respiratory compromise. Treatment should be individualized in patients at risk for complications, carefully weighing the risk of treatment against the severity and risks of the contrast reaction.

Risk of Immediate Adverse Reaction to Radiographic Contrast Media

Patient characteristics have a definite impact on risk of adverse reactions to radiographic contrast media. Patients who had an adverse reaction on a previous exposure appear to have an approximately four- to six-fold increase in the risk of adverse reaction on subsequent exposure.[23,24] Patients with advanced congestive heart failure have been found to be at increased risk in numerous studies. A history of asthma or environmental allergies is considered a risk factor for contrast media administration.[9,23-26]

β-Blocker use is associated with increased risk and severity of adverse reaction to radiographic contrast media.[25,26] The anaphylactoid symptoms in patients taking β-blocking agents can be particularly severe and prolonged.[27-29] The mediators of anaphylactoid reactions are inhibited by β-adrenergic mechanisms; thus, release of these mediators can be enhanced in patients taking β-blocking agents (either β_1 or β_2). Furthermore, treatment of adverse reactions in patients taking β-blockers can result in paradoxical vasotonic effect by means of uninhibited α-adrenergic feedback mechanisms. Treatment of anaphylactoid reactions in patients taking β-blockers can require unusually high doses of epinephrine. Glucagon might also be effective for hypotension refractory to other treatments.[27]

A number of factors found to be correlated with an increased risk of adverse reaction to radiographic contrast media are listed in Table 1. The use of nonionic contrast media is associated with a lower incidence of adverse reaction in those with risk factors.[2,8,23,24,30] Anxiety appears to play a role in the evolution of adverse reaction symptoms in some patients.[31] Medications that can cause unpleasant symptoms, such as antihistamines, can therefore exacerbate minor symptoms. Those who are very old might have an overall lower risk of adverse reaction to radiographic contrast media,[3,8,23] but the reactions tend to be more severe, probably because of multisystem disease states in the elderly and limited functional reserves.[3,22] Cohen[32] reviewed the available literature on reactions to radiographic contrast media in the pediatric age group and found no large difference in the incidence of major and minor reactions in children compared with adults. He also noted the problems of perception of symptoms and sedation in the pediatric population. Current or past treatment with interleukin-2 increases the risk for adverse reaction, which can be immediate or delayed.[33,34]

Table 1. Risk Factors for Immediate Reaction to Radiographic Contrast Material.

Previous immediate reaction to contrast
Environmental allergies (food allergies or hay fever)
Asthma
Congestive heart failure
β-Blocker use
Interleukin-2 (current or past use)
High-anxiety state

The risk of an anaphylactoid reaction to iodinated contrast media is somewhat dependent on the type of contrast agent used. There appears to be a reduced risk of serious reaction with LOCM, but no difference in the risk of death. Katayama et al,[23] in a study involving more than 300,000 cases of radiographic contrast media administration, found the overall risk of severe adverse drug reaction to be 0.04 percent for nonionic contrast media and 0.2 percent for ionic contrast media. Caro et al[30] performed a meta-analysis of the published data from 1980 through 1989 and concluded the overall risk of severe adverse reaction to be 0.031 percent for LOCM and 0.157 percent for HOCM. Katayama et al[23] noted two deaths but could not establish a causal relationship to the contrast media. Caro et al found the risk of death to be 1 in 100,000 with either type of agent.

The overall risk of adverse reaction to radiographic contrast media is also dependent on the definition of adverse event. Shehadi and Toniolo,[35] in a study involving more than 300,000 case reports, found the risk of any adverse reaction to be about 5 percent. Most patients with these reactions required no treatment. Katayama et al[23] found the overall risk of any adverse reaction to be 12.66 percent with ionic contrast media and 3.13 percent with nonionic contrast media. Wolf et al[24] found the overall rate of adverse reaction to radiographic

contrast media to be 4.4 percent with ionic agents and 0.6 percent with nonionic agents, with most patients in both groups requiring no treatment.

Most guidelines recommend the use of LOCM in patients who have had previous reactions, patients who have a history of asthma or allergies, and patients who have a history of cardiac dysfunction.[3,4,9,12] At this time there are insufficient data to support or reject the use of LOCM in patients taking β-blockers.[25,26]

Role of Pretreatment in Preventing Acute Reactions

Pretreatment can decrease the incidence of severe adverse reactions to ionic radiographic contrast media, particularly in the patient with the risk factors of asthma, allergies, or previous adverse reaction to contrast media.[14,23,36] Pretreatment regimens include corticosteroids alone or in combination with antihistamines and sympathomimetics.[4] A 32-mg dose of methylprednisolone can be given orally 12 and 2 hours before contrast media administration.[37] Another popular dosage regimen is 50 mg of prednisone given orally 13 hours, 7 hours, and 1 hour before administration of contrast media, combined with 50 mg of diphenhydramine, with or without 25 mg of ephedrine, given orally 1 hour before contrast media administration.[4]

In a survey of the members of the Society of Uroradiology, Cohan et al[13] found that most respondents used one of the above corticosteroid pretreatment protocols in high-risk patients, and approximately one third of the respondents pretreat patients with asthma. If the patient is unable to take oral medication, hydrocortisone 200 mg is given intravenously instead of prednisone.[36] There appears to be less risk with nonionic radiographic contrast media alone compared with ionic contrast media with pretreatment,[24] but pretreatment is indicated in all patients with history of adverse reaction regardless of the type of radiographic contrast media used. Craig[38] has recommended pretreatment for asthmatic patients receiving radiographic contrast media, but this recommendation is not universal. Zukiwski et al[34] recommend corticosteroid pretreatment in patients with current or past exposure to interleukin-2.

There is no role for pretesting for adverse reactions, as there is no predictive value of oral, intradermal, intravascular, or subcutaneous contrast test dosing for subsequent severe reactions.[20,39,40]

Cardiovascular Reactions to Radiographic Contrast Media

Radiographic contrast media can produce a strong vagal cardiovascular response, causing hypotension and bradycardia.[7,8] HOCM can lower the ventricular arrhythmia threshold and decrease contractility,[2] and peripheral vasodilatation can occur as a direct effect.[15] Fluid shifts from infusion of an osmotic load can precipitate volume overload,[3] and pulmonary edema could occur.[19] Cardiovascular symptoms and signs might also be caused by the release of vasoactive and cardioactive substances from a pseudoallergic-type reaction. The vagal response, in particular, can produce a transient vasodilation with vomiting. This response is generally self-limiting, but it can also be an indicator of a more severe evolving reaction. The overlap of findings and symptoms of cardiovascular and anaphylactoid reactions has led to difficulties in defining the true incidence of the types and severities of reactions to radiographic contrast media[8] and could lead to overtreatment or undertreatment of symptoms.

Delayed Reactions to Radiographic Contrast Media

Delayed reaction has not been strictly defined but generally implies an adverse reaction attributable to radiographic contrast media that occurs between 1 hour and several days after administration.[16,41] Delayed reactions have been reported to occur at a rate ranging from 2.1 percent to 31 percent.[41-44] Fortunately, most of the delayed reaction symptoms were mild and required no specific treatment.

Headache, itching, rash, and urticaria have been the most common symptoms, with most patients reporting the onset of symptoms within 6 hours of contrast media administration.[41,42] A flu-like syndrome with fever, malaise, arthralgias, and nausea can occur, as well as vomiting, abdominal pain, diarrhea, dizziness. Rare symptoms include wheezing, parotitis, and hypotension.[4,16,43,44] Most delayed reactions are mild and require no specific treatment. If therapy is indicated, symptom-directed treatment with analgesics, antipyretics, and antihistamines is usually sufficient.[16] Hypotension and wheezing require more aggressive therapy. Patients who have been treated with interleukin-2 appear to be particularly prone to delayed reactions.[33,34] Zukiwski et al[34] found that cortico-

steroids were effective in treating and preventing delayed reactions in patients with interleukin-2 exposure histories.

Renal Toxicity of Radiographic Contrast Media

Renal dysfunction has been long recognized to be associated with the use of radiographic contrast media. The spectrum of dysfunction ranges from a transient slight increase in serum creatinine levels to overt renal failure requiring transient or long-term dialysis. The term contrast-associated nephropathy (CAN) has been used to label this process.[45] CAN has been reported to be the third most common cause of renal insufficiency occurring in hospitalized patients,[46] and it might be a factor in up to 10 percent of all cases of acute renal failure.[47] CAN is broadly defined as a rise in serum creatinine levels in relation to the administration of contrast media, but a firm definition has not been established. Porter[45] has recommended defining CAN as an increase in serum creatinine levels of 25 percent or more if the baseline creatinine level is less than 1.5 mg/dL or an increase of 1.0 mg/dL if the baseline is greater than 1.5 mg/dL, occurring within 72 hours of the administration of radiographic contrast media.

The data regarding CAN are difficult to evaluate. Multiple definitions of CAN; variations in the length of time serum creatinine is monitored; the different types, doses, and routes of contrast media used; and varying study designs have all resulted in a wide range of results and often conflicting conclusions and recommendations.

Pathophysiology of Contrast-Associated Nephropathy

The mechanisms of CAN are not well understood. After injection of radiographic contrast media, transient vasodilatation is followed by a prolonged vasoconstriction of the renal vascular bed,[48-50] with return to normal flow within 1 to 2 hours.[51] The initial increased osmotic load of the contrast media triggers an intrarenal feedback resulting in renal arteriolar vasoconstriction. This phenomena is enhanced in salt-depleted or dehydrated animals.[48,51] The renin-angiotensin system, calcium, and adenosine have been identified as possible mediators of this vasoconstriction.[48,51] Some evidence also supports a role of direct tubular toxicity of the contrast media.[48-51]

Incidence of Contrast-Associated Nephropathy

The incidence of CAN is dependent upon its definition and the characteristics of the study population. For a healthy outpatient population, the incidence of CAN has been estimated at 1 percent or less.[2,49,52] Using a definition of an increase in serum creatinine levels of 1.0 mg/dL, D'Elia et al[53] found the incidence of CAN to range from 0.5 percent in nonazotemic nondiabetic patients to 33.0 percent in azotemic patients. Cramer et al[54] found the incidence of CAN to be 2.1 percent in their general hospitalized population, including patients with precontrast serum creatinine levels of 1.5 mg/dL or more, using a definition of an increase in serum creatinine levels of greater than 50 percent and rising to more than 1.2 mg/dL. The control group in their series (no radiographic contrast media) experienced similar renal dysfunction at an incidence of 1.3 percent. Lautin et al[55] found an incidence of CAN of 10 percent for nonazotemic patients and 38 percent for diabetic azotemic patients using a definition of an increase in serum creatinine levels of 0.3 mg/dL and 20 percent above baseline. In the same study the incidence of CAN in nonazotemic nondiabetic patients was 2 percent. Taliercio et al[56] defined CAN as a rise in the level of serum creatinine of 1 mg/dL, and found an incidence of 23 percent in patients with baseline creatinine levels of 2.0 mg/dL or higher. When advanced azotemia (serum creatinine > 4.5 mg/dL) and diabetes are both present, the rate of CAN has been stated to approach 100 percent.[57]

Risk Factors for Contrast-Associated Nephropathy

The risk factors for developing CAN are listed in Table 2. The single most important risk factor is preexisting renal insufficiency.[7,45,51-53] Diabetes mellitus does not appear to be a strong risk factor alone, unless renal disease is also evident.[49,58] The combination of diabetes and prestudy renal insufficiency or nephropathy appears to be a greater risk factor than renal disease alone.[45,55,57,59] Advanced heart failure with low cardiac output is a risk factor for CAN.[56] Dehydration has been implicated but has not been proved to be a risk factor in prospective studies.[52] Multiple myeloma, once thought to be a strong risk factor for CAN, does not appear to be a risk factor alone unless renal involvement from the disease is present.[47,49,52] Advanced age does not appear to be an independent risk factor.[55,56]

Table 2. Risk Factors for Contrast-Associated Nephropathy.

Preexisting renal insufficiency
Heart failure: New York Heart Association class 3 & 4
Volume depletion
Proteinuria
Diabetes with evidence of renal involvement
Contrast dose > 2 mL/kg
Repeated contrast administration within 72 hours, or before serum creatinine returns to baseline levels between studies
Other nephrotoxic drug use
Multiple myeloma, if renal involvement is present

In summary, renal insufficiency and volume depletion increase the risk for CAN. In healthy, well-hydrated patients who have no risk factors, the incidence of CAN is very low, and radiographic contrast media can be administered with little risk to the patient.

Prevention of Contrast-Associated Nephropathy

The best way to avoid CAN is to avoid using radiographic contrast media when possible, particularly in patients at risk and especially in those patients whose baseline serum creatinine level is greater than 1.5 mg/dL. Alternate imaging modalities such as sonography, radionucleotide imaging, and magnetic resonance imaging should be considered, with liberal consultation with a radiologist. If it is determined that exposure to radiographic contrast media is necessary, it is possible to reduce the severity of CAN or prevent it in at-risk populations. Adequate preprocedure hydration might lessen the effects of renal ischemia and is widely recommended.[1,45] Eisenberg et al[60] maintained "adequate hydration" and reported no cases of CAN in more than 500 consecutive cases of angiography in patients with known risk factors, although the definition of CAN was not as well defined in that study.

Prostaglandin inhibitors should be discontinued when possible before contrast media administration. Studies utilizing mannitol and loop diuretics during and immediately after constast media dosing have yielded conflicting results.[52] Weinstein et al[61] found the addition of furosemide to saline hydration to result in worsening of renal function after radiographic contrast media administration in patients with preexisting renal disease. Solomon et al[62] compared the administration of furosemide or mannitol given over 30 to 60 minutes with 0.45 percent saline or with administration of saline alone, and found less CAN with saline hydration alone. Barrett and Parfrey[63] recommend against using furosemide and mannitol to prevent CAN. If multiple studies are needed, when possible the creatinine level should be allowed to return to baseline before a radiographic contrast medium is readministered[49] or delayed at least 72 hours between studies.[47,56]

The dose of radiographic contrast media has been found to be a risk factor for CAN in some studies, but this finding is not universal.[57] Taliercio et al[56] found a significant increase in CAN in patients with abnormal renal function when the dose of ionic contrast media exceeded 125 mL. Cochran et al[64] found an increased incidence of CAN when the dose of ionic contrast media exceeded 2 mL/kg. Using a formula to calculate dose based on renal impairment (maximum dose = 5 mL/kg per 1 mg/dL serum creatinine), Cigarroa et al[65] were able to decrease significantly the incidence of CAN in azotemic patients. D'Elia et al,[53] however, found no correlation between contrast media dose and CAN in a hospitalized population.

Using LOCM or nonionic contrast media might decrease the incidence of CAN, although the data are not definitive. Several studies showed no clinically important or statistically significant differences in outcome between the different radiographic contrast media in general or high-risk populations.[56,66-68] Although Harris et al[66] found a significant difference of 14 percent compared with 2 percent in patients with impaired renal function, they found this difference to not be clinically significant. Barrett et al[59] and Gomes et al[69] found a difference that did not obtain statistical significance in high-risk patients. Of interest, all the high-risk patients who required dialysis in the Gomes et al study received ionic contrast media.

Schwab et al[70] found no significant difference in the incidence of CAN in high- or low-risk patients when comparing LOCM with HOCM. Lautin et al,[71] however, found that the risk of CAN was significantly less with LOCM compared with HOCM in both their general population and their high-risk population. The clinical impact and degree of CAN of their findings were not described. Golman and Almen[50] reported that CAN occurred less frequently in animals given nonionic versus ionic radiographic contrast media, but

noted a lack of convincing evidence in human studies. Dawson and Trewhella[72] reviewed the data on this subject and strongly recommended nonionic radiographic contrast media for all patients with impaired renal function.

A meta-analysis on the subject by Bartlett and Carlisle[68] found that LOCM offered no more benefit than HOCM for preventing CAN in patients with normal renal function, and LOCM provided some benefit for reducing the incidence and severity of CAN in patients with preexisting renal dysfunction. The conclusion of Lawrence et al[10] in a study of the available evidence was that there is no difference in the incidence of CAN when comparing LOCM with HOCM. Nonetheless, most uroradiologists surveyed by Cohan et al[13] use LOCM in patients with elevated serum creatinine levels.

In summary, the best way to prevent CAN, especially in patients with preexisting renal compromise, is to avoid exposure to radiographic contrast media. If a contrast medium must be administered, optimize and maintain hydration throughout the study period. Minimize the dose necessary to yield an adequate study. Although definitive evidence is lacking, many experts recommend using LOCM in patients with preexisting renal compromise.

Treatment of Contrast-Associated Nephropathy

CAN usually causes a rise in serum creatinine levels within 24 hours after the radiographic contrast media is administered, typically reaching a peak in 2 to 7 days. Creatinine levels usually return to baseline in 7 to 14 days. Most patients remain nonoliguric,[4,49,50] but oliguria could indicate a more severe insult.[1,51] Progression to dialysis is rare but is more likely in the patient whose baseline serum creatinine level exceeds 4 mg/dL.[49] Treatment is supportive and consistent with the treatment of other forms of acute renal failure. Close monitoring of electrolytes, volume status, and medications will eliminate serious complications in most patients.[52] Porter's analysis[51] of post-CAN follow-up studies showed a return to baseline serum creatinine levels in 75 percent of patients.

Contrast Agents For Magnetic Resonance Imaging

Although the main purpose of this discussion is to review the use of conventional radiographic contrast media, it is appropriate to mention the potential for adverse reactions to contrast agents used for magnetic resonance imaging (MRI). Contrast agents used for MRI are quite different from conventional radiographic contrast media in structure and function. The effectiveness of a contrast agent for MRI is dependent upon the ability of the agent to affect the relaxation rates (T1 and T2) in the target tissues, thereby inducing contrast relative to the surrounding tissues.

Common MRI contrast materials use metals (gadolinium or manganese) complexed with organic molecules or iron oxides. These compounds can be modified or further complexed to create nonionic agents. Several substances, such as porphyrins and tissue-specific antibodies, are currently under investigation to provide specific tissue contrast when complexed with metal molecules. Although the osmolality of MRI contrast agents can be quite high (up to 1940 mOsm/kg H_2O) relative to plasma, the doses usually required are small (10 mL).[73,74] A postmarketing surveillance of adverse reactions to gadopentetate dimeglumine revealed a reported drug-related incidence of less than 0.03 percent. Most reported adverse events were mild, but anaphylactoid reactions and one death have been reported.[75] For this reason, personnel and equipment for dealing with adverse events must be available whenever MRI contrast is administered. Gadolinium does not appear to be nephrotoxic at MRI contrast doses in patients who have normal renal function or renal insufficiency.[75,76]

Medicolegal Issues

Physicians involved with the use of radiographic contrast media should be aware of the medicolegal issues surrounding their use. Obtaining informed consent for use of radiographic contrast media is not a universal practice. Whether informed consent is requested and the actual risks and alternatives are disclosed vary by institution, medical community, and geographic location. Case law has been established to support reasonable physician-oriented disclosure, reasonable patient-oriented disclosure, and hybrids. At least one state (Georgia) mandates by law that informed consent be obtained and specific risks disclosed. The selection of and disclosure issues surrounding the use of LOCM and HOCM will certainly become issues in the courts and might possibly become regulatory issues for state governing bodies.[9]

Family physicians should discuss the risks of ra-

diographic contrast media and diagnostic alternatives with their patients, and the nature of the discussion should be documented in the record. Institutional or organizational guidelines should be followed for consent and selection of contrast. Where no guidelines exist, it would seem prudent to obtain documented informed consent and use LOCM in high-risk patients.

Conclusion

Radiographic contrast media are generally well tolerated and safe, with a low incidence of acute reactions in a general population. Whenever contrast media are administered, personnel and equipment for treating acute reactions should be immediately available. Most reactions are mild and require little or no treatment, but moderate or severe reactions should be treated promptly. Severe life-threatening reactions are rare but require immediate and aggressive treatment. Pretreatment and LOCM should be given to patients with a previous adverse reaction to radiographic contrast media, and LOCM should be considered in patients with other risk factors for adverse reactions.

Nephrotoxicity from contrast media appears to have a low incidence in the general population, though preexisting renal disease increases this risk. Optimizing hydration can afford some protection from CAN. Furosemide and mannitol are not recommended to prevent CAN. LOCM or nonionic contrast media appear to pose less risk for acute adverse reactions and possibly for nephrotoxicity but at higher cost. In patients with risk factors for adverse reactions or CAN, the use of alternate imaging modalities, such as sonography, radionucleotide imaging, and magnetic resonance imaging, should be considered, if possible. Agents used for contrast in MRI studies appear to have an excellent safety profile, but adverse reactions to these MRI contrast agents can occur. Patients should be informed about the risks of radiographic contrast media administration, and informed consent should be obtained in keeping with existing community standards of care.

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