

Frequency, Outcome, and Appropriateness of Treatment of Nonionic Iodinated Contrast Media Reactions

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OBJECTIVE. The objective of our study was to evaluate the frequency, outcome, and appropriateness of treatment of adults with acute allergiclike reactions related to IV-administered nonionic iodinated contrast media.

MATERIALS AND METHODS. For IV injections of nonionic iodinated contrast media between January 1, 1999, and December 31, 2005, contrast reaction reports and medical records of patients in whom contrast reactions occurred were reviewed. Data collected included patient sex and age, symptoms, reaction manifestations, treatment, and long-term sequelae. The appropriateness and efficacy of patient management were assessed.

RESULTS. Allergic-type reactions occurred in 545 (0.6%) of patients injected with nonionic iodinated contrast media: 418 (77%) reactions were mild, 116 (21%) were moderate, and 11 (2%) were severe. Two hundred twenty-one patients (41%) received treatment. The most commonly administered medication was diphenhydramine (145 patients or 27%). Corticosteroids were administered to 17 patients, nebulized albuterol to 16, and epinephrine to 15. Although 99% of the treatments did not result in any complication, three patients may have had short-term sequelae as a result of receiving a nonrecommended treatment.

CONCLUSION. Patients usually do well after developing acute allergiclike reactions to nonionic iodinated contrast media. Fortunately, in our series, this was true even in the rare cases in which the instituted treatment was considered to be inappropriate. Reacting patients rarely develop serious long-term sequelae.

Acute allergiclike reactions are a well-known complication of IV nonionic iodinated contrast media injections and range from mild symptoms such as urticaria and itching to more severe reactions such as cardiopulmonary arrest and death. Although the symptoms of allergiclike reactions resemble hypersensitivity reactions, the exact mechanism is unknown and does not appear to result from an antigen–antibody interaction in most cases. Patients not previously exposed to nonionic iodinated contrast media can have the same reactions as those who had been previously exposed [1]. In their landmark article, Katayama and associates [2] reported that 3.13% of patients injected with nonionic contrast media had an adverse reaction. In more recent studies, Mortelé et al. [3] and Cochran and associates [4] reported adult adverse reaction rates of 0.7% and 0.3%, respectively, for nonionic iodinated contrast media IV injections, although not all of those reactions were allergiclike.

CT use—and, therefore, IV contrast material administration—has increased dramatically at our institution, from 7,010 injections in 1999 to 20,491 in 2005. This increased use has led to an increased number of allergiclike reactions, from 45 reactions in 1999 to 179 in 2005.

Although several reports discuss treatment algorithms for various contrast reactions [5–9], contrast reaction treatment and the short- or long-term sequelae from the reactions and the treatment have not been evaluated, to our knowledge. We designed our study to examine the outcome in patients having reactions to nonionic iodinated contrast media and the appropriateness of any instituted treatment.

Materials and Methods

Injection Technique and Contrast Reaction Management

At our institution, IV injections for CT examinations are performed and monitored by the radiology technologists, all of whom have received

Keywords: allergic reactions, contrast media, nonionic iodinated contrast media, treatment of contrast reactions

DOI:10.2214/AJR.07.3421

Received November 13, 2007; accepted after revision March 4, 2008.

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AJR 2008; 191:409–415

0361–803X/08/1912–409

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training in IV injection technique and in-services on assessing patients for adverse reactions to contrast material. The technologists are trained to discuss possible contrast reaction symptoms with the patient before the study, and the patient is instructed to inform the technologist immediately if any symptoms occur during or shortly after the contrast material is injected, such as flushing or redness, pruritus, urticaria, stuffy nose, sneezing, difficulty breathing, scratchy throat, swelling, or chest pain. All the radiology staff, including technologists, faculty, fellows, and residents, are certified in Basic Life Support for Health Care Providers (American Heart Association). Also, a 1-week departmental course about recognizing and treating contrast reactions is held once a year and includes didactic lectures and hands-on simulated patient events. Attendance at this course is optional for faculty members but is required for all fellows and residents.

If a contrast reaction occurs, the technologists have been trained to request physician presence, and the resident, fellow, or attending radiologist is called to examine the patient immediately. The patient is asked to describe his or her symptoms, when possible, and to provide a brief history. Vital signs are obtained and treatment instituted if deemed necessary. After each reaction and its treatment, the radiologist is required to complete a contrast reaction incident data form after treatment is completed or the patient has been sent to an appropriate consulting service. This form is filed in the radiology department for quality assurance monitoring and to facilitate follow-up. Contrast reaction form completion is not required for manifestations that are considered to be purely physiologic, such as isolated nausea or warmth.

Study Group

Institutional review board (IRB) approval was obtained for permission to access the medical records of the patients involved in this study. The submitted IRB proposal was deemed to be compliant with both institution and federal government (HIPAA) guidelines. Waiver of informed consent was granted for this retrospective review.

During the study period (January 1, 1999–December 31, 2005), nonionic iodinated contrast material was used for all contrast-enhanced CT examinations. From January 1999 to September 2004, iohexol 300 (Omnipaque 300, GE Healthcare) was used, and from October 2004 to December 2005, iopromide 300 or 370 was used (Ultravist 300 or 370, Bayer HealthCare). Over the duration of the study, iodixanol 320 (Visipaque 320, GE Healthcare) was used for selected patients (e.g., patients with renal insufficiency and, as has been suggested by the American College of Radi-

ology's (ACR) Committee on Drugs and Contrast Media [10], patients with severe prior reactions to monomeric nonionic contrast media).

All contrast reaction incident data forms completed for adult patients (age ≥ 18 years) between January 1, 1999, and December 31, 2005, were reviewed. Data obtained from the forms included patient sex and age; inpatient, outpatient, or emergency department status; symptoms; vital signs; physical findings; and the nature of any instituted treatment. Using our institution's electronic medical records, progress notes generated on the day of the contrast reaction and thereafter were reviewed, when available, for mention of any adverse sequelae or treatment related to the contrast reaction. When adverse sequelae were present, additional progress notes were reviewed until patient symptoms had resolved or until any instituted treatment was completed.

No patients with adverse reactions consisting entirely of physiologic manifestations were included. Each reaction was graded retrospectively by consensus of two authors as mild, moderate, or severe based on the most severe clinical symptom or sign. The classification system was similar to that used in the ACR's *Manual on Contrast Media* [10]. Specifically, contrast reactions that involved cutaneous symptoms only, such as mild flushing or redness, urticaria, or pruritus, were categorized as mild. Reactions consisting of nasal congestion, sneezing, mild eye swelling, or other minimal facial swelling and minimal throat scratchiness were also considered to be mild. Moderate reactions included many respiratory symptoms, such as subjective throat tightness, hoarseness, bronchospasm, shortness of breath, facial edema, transient chest pain, hypotension or hypertension, and symptomatic bradycardia or tachycardia. Severe reactions included severe respiratory distress, progressive angioedema, convulsions, unresponsiveness, and cardiopulmonary arrest. Although contrast reaction grading systems such as these are subjective and vary somewhat from one reviewer and one institution to the next, we believe that it is important to classify reactions in some fashion to better understand patient outcome.

After reviewing the symptoms, reported vital signs, findings on physical examination, and treatments, two authors determined by consensus whether subsequent patient management was appropriate and if it was not appropriate whether the treatment was potentially harmful. An example of management classified as not appropriate, although not harmful to a patient, was administering 2 L/min of oxygen by nasal cannula to a patient with mild transient tightness in the throat. If oxygen is administered to a patient having a respiratory reaction to contrast material, patients

should receive oxygen at a rate of at least 6 L/min and the oxygen should be delivered by face mask [7, 9, 10]. Examples of management considered not appropriate as well as potentially harmful to a patient include administering diphenhydramine for the treatment of hypotension, failure to administer IV fluid to a hypotensive patient, or injecting an improper dose of epinephrine. The effects of patient treatment and patient outcome were assessed by reviewing follow-up progress notes in the patients' electronic medical records.

Results

Total Patient Population

During the time period from January 1, 1999, through December 31, 2005, there were 84,928 IV injections of nonionic iodinated contrast media in adults. Five hundred forty-five contrast reaction report data forms, representing 0.6% of the injections, were completed for 507 different patients. There were 318 women (63%) and 189 men (37%) with a mean age of 49 years (range, 18–96 years). A single reaction was observed in 473 patients. Thirty-one patients had two reactions, two had three, and one had four. Of the 545 reactions, 432 (79%) were seen in outpatients, 61 (11%) in inpatients, and 52 (10%) in patients who were being seen in the emergency department. Of the 545 contrast reactions, 519 had follow-up documented in the electronic medical record system and 26 did not (mean and median follow-up of 24.3 and 19 months, respectively; range, 0–89 months).

Classification of Contrast Material Reactions

Four hundred eighteen (77%) of the contrast reactions were classified as mild, 116 (21%) as moderate, and 11 (2%) as severe. Manifestations of the different types of contrast reactions and patient outcomes are summarized here.

Mild reactions—Manifestations of mild reactions are summarized in Table 1. The 418 mild reactions included a wide variety of manifestations, most of which were cutaneous, with the most common cutaneous reaction being urticaria (286 reactions or 68%). Two hundred one mild reactions had a single manifestation, and 215 had more than one manifestation. In two instances, the manifestations, although mentioned as being mild, were not described specifically on the reaction forms.

There was sufficient follow-up to determine the time until symptom resolution for 402 of the 418 mild reactions. Two hundred five (51%) of these 402 reactions resolved

Treatment of Nonionic Iodinated Contrast Media Reactions

TABLE 1: Mild Allergiclike Manifestations: 658 Manifestations in 418 Reactions

Mild Manifestations	No. of Reactions
Urticaria	286
Pruritus	131
Erythema or rash	114
Scratchy throat	28
Nasal congestion	25
Sneezing	24
Localized facial swelling	15
Chest discomfort ^a	14
Transient cough	8
Rigors or chills	5
Tachycardia or palpitations	5
Thickened tongue ^b	2
Injected eye	1

^aThought to not be cardiac.

^bPatient reported a subjective sensation.

within 1 hour and 194 (48%) resolved between 1 and 24 hours after injection. Three (0.7%) patients' symptoms required more than 24 hours to resolve. These three mild reactions initially consisted of urticaria and erythema in two patients and isolated urticaria in one; ongoing symptoms were noted more than 24 hours after contrast material injection in each. These three patients developed full-body urticaria: one beginning shortly after the study, one starting the day after the CT, and one 4 days later, although it was unclear whether the urticaria in this last patient represented a delayed contrast reaction or a reaction to newly administered antibiotics.

Moderate reactions—The breakdown of moderate allergiclike manifestations is listed in Table 2. Ninety-one (78%) of the 116 moderate reactions were classified as such due to the presence of respiratory symptoms, facial edema, or both. Twenty-four other reactions (21%) resulted in chest pain without a respiratory component, and the remaining reaction consisted of symptomatic tachycardia. Eighteen reactions (16%) consisted of a single and 98 (84%) of more than one manifestation.

Symptoms were reported to resolve within 1 hour in 62 (53%) of the 116 moderate reactions. In the remaining 54 moderate reactions (47%), symptoms lasted more than 1 hour but resolved within 24 hours of contrast material injection. None of the 116 moderate reactions had manifestations lasting more than 24 hours.

TABLE 2: Moderate Allergiclike Manifestations: 181 Manifestations in 116 Reactions

Moderate Manifestations	No. of Reactions
Shortness of breath	55
Cardiaclike symptoms ^a	48
Laryngeal edema	38
Facial edema	14
Bronchospasm	10
Rigors	7
Hypotension	4
Diaphoresis	2
Tongue swelling	2
Hypertension	1

Note—Many patients had more than one manifestation. Many patients also had mild manifestations, including cutaneous symptoms ($n = 66$), as well as moderate manifestations.

^aChest pain or pressure, jaw pain, left arm numbness, or a combination of these symptoms.

Severe reactions—The 11 severe reactions are summarized in Table 3. They occurred in eight women and three men, with a mean age of 55 years (range, 30–96 years). Three patients became unresponsive or semiresponsive, and frank cardiopulmonary arrest occurred in one of these three patients.

In one instance (a 61-year-old woman who had a seizure), there was no indication in the electronic medical record that additional help was sought in treating the reaction, although this patient was an inpatient who would therefore be closely followed by the referring clinical service. For the other 10 severe reactions, there is documentation that the radiologist sought assistance by transferring nine outpatients to the emergency department and by contacting the clinical service for the remaining inpatient. Of the 10 patients for whom medical records were available, two returned to their normal baseline conditions within 1 hour. In six patients, manifestations resolved completely within 24 hours, despite their severe symptoms and often extensive treatment.

Only two patients with severe reactions had documented sequelae lasting more than 24 hours. One was a 69-year-old female outpatient with metastatic renal cancer who rapidly developed erythema, urticaria, unresponsiveness, and then cardiopulmonary arrest. The cardiac arrest team was called and aggressive resuscitation ensued; however, the patient developed transient pulseless elec-

trical activity, an anterior wall myocardial infarction, and hypoxic encephalopathy, the latter resulting from hypoxia that occurred during the cardiac arrest. Initially, she had cognitive defects and required 6 weeks of speech and occupational therapy; however, she was deemed fully recovered at a follow-up appointment in the neurology clinic 4 months later.

The second patient was a 32-year-old female outpatient with a history of Crohn's disease who was being assessed for disease activity. She developed erythema, hypotension with tachycardia, and shortness of breath and became semiresponsive. The patient was treated with oxygen by face mask and 1 mg of 1:10,000 epinephrine IV. Subsequently, the patient developed chest pain, likely as a result of the epinephrine administration, requiring admission to the ICU. She was found to have a troponin leak but no evidence of frank myocardial infarction. Her troponin levels gradually returned to normal and she was at baseline condition at discharge 6 days later.

Management of Contrast Reactions

No treatment was administered during 324 (59%) of the 545 reactions. A variety of therapies were used for the remaining 221 reactions. Specific interventions are described in the paragraphs that follow.

Oxygen—In 82 (15%) of the reactions, oxygen was administered for treatment of a variety of described symptoms, 60 of which had a respiratory component. Respiratory manifestations consisted of shortness of breath, bronchospasm, laryngeal edema, facial edema, or some combination of these. Twelve of these 60 reactions also consisted of chest pain and three of the reactions also included hypotension. Twenty-two reactions were nonrespiratory, with manifestations including chest pain, erythema, hypotension, rigors, urticaria, and palpitations.

For 38 reactions, the method of oxygen administration was not recorded. Twenty-four times oxygen was recorded as being administered by nasal cannula at a variety of rates, ranging from 1 to 10 L/min. In all 24 of these instances, the route of administration was deemed to be insufficient for oxygen delivery by the retrospective reviewers. Of the 20 reactions in which oxygen was administered by face mask, delivery rates were deemed appropriate for all 13 instances in which this information was available (10–15 L/min).

TABLE 3: Severe Allergiclike Manifestations in Approximate Order of Decreasing Severity

Patient		Symptoms	Treatment	Outcome (h)	Sequelae
Sex	Age (y)				
F	69	Erythema, hypotension, tachycardia, unresponsiveness, arrhythmia, ^a cardiopulmonary arrest	CPR, 1 mg of epinephrine IV, 1 mg of atropine IV, 50 mEq of sodium bicarbonate, 1 g 10% calcium chloride	> 24	Myocardial infarction, hypoxic encephalopathy, full recovery by 4 mo
F	32	Erythema, shortness of breath, hypotension, semiresponsiveness	10 L of O ₂ by face mask, 1 mg of IV epinephrine, 100 mg of diphenhydramine, 200 mg of IV hydrocortisone	> 24	Troponin leak (returned to normal within 6 days)
F	58	Nausea, diaphoresis, rash, hypotension, semiresponsiveness	1 mg of epinephrine IV, 50 mg of diphenhydramine IV	< 24	Chest pain
M	54	Urticaria, shortness of breath, dizziness, hypotension, transient ischemic attack	O ₂ by face mask, 0.3 mg of epinephrine SQ, 50 mg of diphenhydramine IV	< 24	None
F	96	Shortness of breath, laryngeal edema, gagging and difficulty speaking	10 L of O ₂ by face mask, 0.1 mg of epinephrine IV, 50 mg of diphenhydramine IV	< 24	None
M	76	Sneezing, scratchy throat, shortness of breath, bronchospasm, chest pain, generalized seizure	12 L of O ₂ by face mask, normal saline, 0.5 mg of epinephrine IV, 50 mg of diphenhydramine IV	< 24	None
M	44	Urticaria, erythema, hypotension, tachycardia, lightheaded and dizzy	6 L of O ₂ by face mask, normal saline, 50% dextrose, 50 mg of diphenhydramine IV, 120 mg of methylprednisolone	< 1	None
F	30	Urticaria, scratchy throat, laryngeal edema, bronchospasm, chest pain	12 L of O ₂ by face mask, 0.1 mg of epinephrine IV	< 24	None
F	37	Urticaria, erythema, facial edema, hypotension, tachycardia	O ₂ by face mask, normal saline, 50 mg of diphenhydramine IV	< 24	None
F	61	Seizure	None	< 24	None
F	53	Seizure	None	< 1	None

Note—CPR = cardiopulmonary resuscitation, SQ = subcutaneous.

^aPulseless electrical activity.

In all, there were 17 reactions during which oxygen saturations were recorded at < 92%. Five of these 17 reactions were treated with oxygen, but the delivery rate and route of administration were not recorded. Seven of these reactions were treated appropriately—that is, using high flow rates of oxygen delivered by a face mask. The five remaining reactions were deemed retrospectively to have been treated with insufficient amounts of oxygen: four because the oxygen was delivered by a nasal cannula rather than a face mask and one because a rate of only 4 L/min was used.

Fortunately, no adverse sequelae were attributed retrospectively to inappropriate oxygen administration.

Hydration—The treating radiologist reported administering fluids for treatment of 23 reactions and to raising the patient's legs during another two reactions. Normal saline (0.9%) was administered IV in 20 instances and oral hydration in three, with the amount of fluid only specified twice (as 250 and 500 mL, IV). Only four of these reactions were

documented as being hypotensive (systolic blood pressure < 100 mm Hg), and all were treated with IV fluids. The use of hydration was deemed appropriate for all 23 reactions.

Fluid administration was not documented for 10 other reactions that were clinically diagnosed as being hypotensive. There were no short-term adverse sequelae in nine of these reactions. The last reacting patient, who had systolic blood pressure in the 80s, was given 1 mg of epinephrine and 100 mg of diphenhydramine but no IV fluid. This patient subsequently developed a troponin leak, which was likely due to epinephrine, but had no long-term sequelae.

Diphenhydramine—One hundred thirty (90%) of the 145 reactions treated with diphenhydramine had cutaneous manifestations. One hundred two of the cutaneous reactions were isolated, consisting of urticaria alone (64 reactions), urticaria and erythema (21 reactions), erythema alone (13 reactions), and pruritus alone (four reactions). The remaining 28 cutaneous reactions also showed a variety of noncutaneous manifestations: facial

or laryngeal edema (13 reactions), shortness of breath (seven reactions), hypotension (six reactions), and bronchospasm (two reactions).

Diphenhydramine was administered for treatment of 15 reactions that did not have cutaneous manifestations. Ten reactions were characterized by isolated respiratory symptoms. The five other reactions were composed of one each with isolated hypotension, sneezing with nasal congestion, sneezing alone, nasal congestion alone, and rigors.

Diphenhydramine was administered orally in 65 instances, IV in 53, by an unknown route in 26, and intramuscularly in one instance. Doses used were 50 mg (97 patients), 25 mg (38 patients), unknown (nine patients), and 100 mg (one patient). The contrast reactions treated with diphenhydramine resolved within 1 hour in 54 patients, between 1 and 24 hours in 87 patients, and after 24 hours in three patients. In the remaining one patient, the time to reaction resolution was not known.

In seven of 145 administrations, diphenhydramine was judged to have been given

Treatment of Nonionic Iodinated Contrast Media Reactions

inappropriately because, in all seven cases, the reacting patient was hypotensive; it is known that diphenhydramine can exacerbate hypotension [10]. One of these patients was a 54-year-old man, whose contrast reaction consisted of hypotension (with systolic blood pressures in the 80s), shortness of breath, and urticaria. He received 50 mg of diphenhydramine IV. The patient subsequently had a transient ischemic attack thought to be due to hypoperfusion. The relative contributions to this event from the diphenhydramine and from the preexisting hypotension are unknown.

Corticosteroids—Corticosteroids were administered to treat 17 reactions, 15 of which had multiple allergiclike manifestations. Cutaneous manifestations (urticaria, erythema or flushing, pruritus, or a combination of these manifestations) were present in 15 reactions treated with corticosteroids, 12 of which also had other more concerning manifestations, including facial or laryngeal edema or hypotension. The other two reactions resulted in facial edema and respiratory symptoms without cutaneous manifestations. Most of these reactions were treated with other interventions in addition to corticosteroids. Thirteen of these reactions were also treated with diphenhydramine, two of which were also treated with epinephrine. In only four instances were corticosteroids used as the sole method of treatment. Three of these reactions had only cutaneous manifestations. The fourth reaction consisted of flushing and redness and shortness of breath and was treated with 125 mg of IV methylprednisolone. This patient's symptoms resolved before discharge from the radiology department.

Corticosteroids were administered IV to treat 13 reactions and orally to treat one reaction at doses of 125 mg of methylprednisolone (eight reactions), 100 mg of hydrocortisone (four reactions), 200 mg of hydrocortisone (one reaction), and 50 mg of prednisone (one reaction). In three instances, the route, type, and dose of corticosteroid were not provided.

Symptoms resolved within 1 hour in four instances, between 1 and 24 hours in 10 instances, and after 24 hours in the remaining three patients (who had persistent or recurrent urticaria). These three patients were placed on tapering doses of steroids.

Although corticosteroids are believed to have no efficacy in modifying the acute symptoms in a reacting patient, they may have a role in preventing symptoms from recurring. Thus, corticosteroid administration in isolation was considered either appropri-

ate or not necessary but not harmful in 16 of the 17 instances in which it was used. Use of corticosteroids alone was considered inappropriate and potentially harmful in the sense that the appropriate treatment was not administered in the one patient who developed shortness of breath. Fortunately, the patient did well and returned to baseline before leaving the radiology department.

Albuterol—Sixteen reactions were treated with albuterol for symptoms of shortness of breath without obvious wheezing (seven reactions), wheezing (six reactions, five of which also were characterized by shortness of breath), isolated chest pain or tightness (two reactions), and respiratory congestion (one reaction). Three of the reactions were also thought to have a component of laryngeal edema (i.e., a tight or scratchy throat or choking sensation).

Reaction manifestations resolved in 10 instances within less than 1 hour and within more than 1 hour but fewer than 24 hours in the remaining six instances. In no reacting patient who received albuterol was there judged to be any adverse outcome. The choice of albuterol treatment was deemed either as appropriate or as not necessary but not harmful for all 16 reactions.

Epinephrine—Fifteen reactions were treated with epinephrine. Six of these reactions had manifestations suggesting laryngeal edema, with three producing shortness of breath, one of which also resulted in semiresponsiveness, and one also resulting in bronchospasm. Four reactions produced shortness of breath but without the reacting patients being able to localize their symptoms, with two of these four dyspneic patients also being hypotensive and a third also having chest pain. Two reactions resulted in facial edema; one in shortness of breath and bronchospasm; and one in hypotension without respiratory symptoms but with eventual semiresponsiveness. The final reaction consisted of unresponsiveness followed by cardiopulmonary arrest. The cardiac arrest team was summoned for three semiresponsive or unresponsive patients, although cardiopulmonary resuscitation was needed for only one patient.

Epinephrine was administered IV to treat 12 reactions and subcutaneously to treat three of these 15 reactions. Ten of the 12 reacting patients treated with IV injections of epinephrine appropriately received a 1:10,000 dilution; however, two patients were injected IV with 1:1,000 dilutions. All three patients who

received subcutaneous epinephrine were injected with the 1:1,000 concentration.

Epinephrine administration was deemed appropriate for treatment of eight of the contrast reactions: six IV injections of 0.1 or 0.2 mg of the 1:10,000 concentration, one subcutaneous injection of 0.2 mg of the 1:1,000 concentration, and one IV injection of 1 mg of the 1:10,000 concentration in the patient who had a cardiopulmonary arrest.

Administration was considered inappropriate for six reactions because of excessive dosing. Four of these six reacting patients received 0.5 mg (three, IV, one of whom was injected with the 1:1,000 dilution, and one subcutaneously) and two patients received 1 mg IV in the absence of cardiopulmonary arrest, one of whom was injected with the 1:1,000 dilution. One of the patients, regarded as having received a 1-mg dose inappropriately, had become transiently semiresponsive. It is possible that the treating radiologist in this instance believed that cardiopulmonary arrest was imminent in this patient and that is why such a large dose of epinephrine was administered.

The remaining patient who received epinephrine was judged to have been treated inappropriately because the wrong route of administration was chosen: This patient was hypotensive and was given 0.3 mg of a 1:1,000 dilution subcutaneously. The reviewers determined that IV administration of the same dose (0.3 mg) using the 1:10,000 concentration would have been preferred in this instance because systemic absorption of subcutaneous epinephrine may be unreliable in a hypotensive patient.

Follow-up information was available in the medical records for all 15 reactions treated with epinephrine. All seven patients having reactions that were judged to have been treated with appropriate low doses of epinephrine via an appropriate route responded and had no adverse sequelae, once their initial manifestations had resolved (which was within 24 hours of contrast material injection in every case). An eighth low-dose patient, who was hypotensive but who received 0.3 mg of epinephrine subcutaneously (an appropriate dose given via a nonrecommended route), developed a transient ischemic attack, although his symptoms resolved completely within 24 hours.

There were no adverse sequelae directly attributable to epinephrine administration in the four reacting patients who were injected with 0.5 mg of epinephrine. In each of these

patients, all contrast reaction manifestations resolved completely in more than 1 hour but less than 24 hours.

Each of the three patients who received 1 mg of epinephrine, all via an IV route, had cardiac sequelae. This included the one patient who received the correct dose during a full cardiopulmonary arrest. She had a myocardial infarction, which is a recognized and acceptable complication of cardiopulmonary arrest and vigorous resuscitation. The other two patients received inappropriately excessive doses. A 32-year-old woman who developed hypotension, shortness of breath, erythema, and semiresponsiveness was treated with 1 mg of 1:10,000 epinephrine IV and developed a troponin leak without frank myocardial infarction. This patient was monitored in the hospital for more than 24 hours. A 58-year-old woman who developed hypotension, tachycardia, and urticaria was treated with 1 mg of 1:1,000 epinephrine IV and developed chest pain. This represented both an excessive dose of epinephrine and inappropriate IV administration of a concentrated solution intended for subcutaneous use. She was transferred to and then eventually discharged from the emergency department with a diagnosis of transient cardiac ischemia but no myocardial infarction. Her symptoms resolved within 24 hours.

Nitroglycerin—Sublingual nitroglycerin was administered to treat eight reactions, with seven patients receiving one tablet and one patient receiving two tablets. Five of the eight reactions occurred in patients who had a known history of coronary artery disease. Six reacting patients complained of chest pain, one had jaw pain and left arm numbness, and one had shortness of breath and right shoulder heaviness. The symptoms resolved in less than 1 hour in four instances and between 1 and 24 hours in four instances. Treatment was deemed appropriate for all eight of these reactions.

Other interventions—A number of other medications were administered to a few patients. These less commonly used medications, each administered to treat only one reaction, included ipratropium (an anticholinergic medication), meperidine, cetirizine (an antihistamine), IV 50% dextrose, atropine, bicarbonate, and calcium carbonate (with the last three agents used in the same one patient in whom cardiopulmonary resuscitation was required). Of note, atropine was not administered to the one hypotensive and bradycardic patient in this series. The patient,

who was transferred promptly to the emergency department, had normal vital signs by the time he arrived there and was discharged in baseline condition within 24 hours.

Discussion

In our study of 84,928 IV injections of nonionic contrast media, there was a 0.6% reaction rate, with 77% of the reactions being mild, 21% moderate, and 2% severe. There were no deaths. Our observed reaction rate of 0.6% to nonionic iodinated contrast medium injections is comparable to those previously reported by Mortel  et al. [3] in 29,508 patients and by Cochran et al. [4] in 73,039 patients. As in those prior studies, we found that the most common manifestations of such reactions were urticaria and pruritus.

In the study by Mortel  et al. [3], the percentage of reactions considered mild was slightly higher than that noted in our study (89.5% rather than 77%). This difference is almost certainly due to variations in the subjective criteria used to define mild and moderate reactions in the two studies. One of the requisite criteria used to define a moderate reaction in the Mortel  et al. series was the need to transfer patients to the emergency department for prolonged observation, whereas our inclusion criteria for moderate reactions were broader and included patients with respiratory symptoms and chest pain even when referral to the emergency department did not occur. In our series, only 58 patients were transferred to the emergency department. Thus, more than half of the patients with reactions that we classified as moderate were treated solely by radiologists. These reactions would have been classified by Mortel  et al. as mild reactions. If we had limited our moderate reactions to only the 58 patients transferred to the emergency department, we would have had 58 more mild reactions and we would have classified 476 (rather than 418) or 87% (rather than 77%) of our reactions as mild, results that are much closer to those of Mortel  and associates. In comparison, our 2% incidence of severe nonionic iodinated contrast media reactions is identical to that observed by Mortel  and colleagues [3], presumably because of the similarity of the criteria used to define severe contrast reactions.

Our study, like others, found that moderate and severe nonionic iodinated contrast media reactions are rare, occurring in only 116 (0.1%) and 11 (0.01%), respectively, of 84,928 contrast material injections in our se-

ries. Although there were no deaths in our study as a result of nonionic iodinated contrast media injection, Mortel  and associates [3] reported one death and Cochran and colleagues [4] reported two deaths.

The results of our study show that when a nonionic iodinated contrast media reaction does occur, it rarely results in long-term sequelae. Ninety-nine percent ($n = 540$) of the adverse reactions encountered in our study resolved within 24 hours. Only two patients whose symptoms resolved within 24 hours were deemed to have suffered significant short-term sequelae, one who had a transient ischemic attack and one who experienced chest pain due to cardiac ischemia. Even in these patients, the short-term sequelae resolved without any further patient morbidity.

Only five (0.9%) of 545 contrast material reactions to nonionic iodinated contrast media resulted in sequelae that lasted more than 24 hours. Three of these patients developed persistent or delayed urticaria that was treated with corticosteroids, and none of these three had any long-term sequelae as a result of their reactions. Of the two remaining patients with symptoms lasting longer than 24 hours, one patient had a troponin leak that resolved by discharge 6 days later. The other patient had severe long-term adverse sequelae (myocardial infarction and hypoxic encephalopathy after cardiopulmonary arrest), although even this patient returned to baseline status when evaluated 4 months later. Overall, in our study, none of the 545 contrast reactions produced any definite permanent patient morbidity.

Although many articles have reviewed the treatment of contrast reactions [5–9], little prospective or even retrospective data about the outcome of such treatment are available. In 1990 vanSonnenberg et al. [11], in a small series of 30 patients, reviewed the efficacy of pharmacologic and fluid therapy specifically for treatment of hypotensive reactions. We are unaware of any large study that has evaluated the appropriateness of other methods of treatment and for all types of contrast reactions or of any study that has correlated appropriateness of treatment with patient outcome.

The results of our study show that most patients who have respiratory reactions to contrast material and who are thought to require treatment do well with such treatment especially when appropriate doses of medication are administered. In this series, all patients whose initial reaction was anything except severe and life-threatening recovered

completely, usually within a short period of time. This includes patients in whom the radiologist instituted treatment with oxygen, hydration, diphenhydramine, albuterol, epinephrine, nitroglycerin, or corticosteroids.

Radiologists are known to make decision errors when treating contrast reactions. In one report [12], for example, 42 questionnaires were completed by radiology residents and attending radiologists. Only 18 respondents were able to provide the appropriate initial dose of epinephrine to be administered to a patient having a contrast reaction. In another series [13], only one of 19 participating residents was able to perform the correct sequence of interventions during two simulated pediatric contrast reactions (for a total of 38 simulations). Although written material containing appropriate dosing information was distributed to each resident during one of these simulations, nearly half of the participating residents ordered incorrect doses of epinephrine anyway.

To our disappointment, our study also has revealed that despite the annual instruction of our residents and fellows on treatment of contrast reactions at our institution, many errors occurred and there were potential consequences to some of these errors. Of course, we do not know how many more errors might have been made if our residents and fellows were not exposed to such regular instruction.

At our institution, oxygen was administered to 82 patients; however, in at least 24 instances a nasal cannula was used rather than a face mask. Thus, at least 30% of the time an insufficient delivery system was used. Diphenhydramine was the most frequently administered medication, even though its efficacy in treating many manifestations, especially those that are not cutaneous, is uncertain. Further, vanSonnenberg and colleagues [11] have shown that diphenhydramine can exacerbate hypotension and those authors advise against the use of diphenhydramine in patients with hypotension. In our series, diphenhydramine was administered to six patients who had cutaneous reactions and who were also hypotensive, as well as to one patient with isolated hypotension. One of these patients developed a transient ischemic attack thought to be due to hypoperfusion; we cannot be certain but the hypotension might have been made worse as a result of diphenhydramine use.

Administration of large doses (0.5–1 mg) of epinephrine can produce serious cardiac complications, even in young healthy pa-

tients [14, 15]. In our series, seven patients were administered large doses of epinephrine, four of whom received 0.5 mg and three of whom received 1 mg. Fortunately, no adverse sequelae occurred in the patients who received 0.5 mg of epinephrine; however, all three patients who received 1 mg of epinephrine developed cardiac complications. The patient who had a cardiac arrest, in whom the large epinephrine dose was appropriate, had a myocardial infarction that could have resulted from the arrest rather than the epinephrine. In the two other patients whose reactions were less severe, excessive epinephrine doses may have caused a troponin leak in one and chest pain in the other.

The main limitation of our study is that it is retrospective and dependent on the accuracy of the contrast reaction data forms, some of which were clearly incomplete. This limits our ability to assess patient treatment. For example, IV hydration or other therapies likely were administered to some patients but not recorded. It is also possible that there was underreporting of some minor reactions, most of which did not require treatment. Finally, any retrospectively used system for classifying reaction severity, such as was used in this study, is subject to inherent biases of the reviewers and limitations in the clinical information that is available. Despite these limitations, we believe that some type of classification is necessary so that the duration of symptoms and appropriateness of treatment can be understood more thoroughly.

In summary, adverse reactions to nonionic iodinated contrast material are rare, and moderate and severe reactions are even less common. Most patients recover from their reactions without any long-term morbidity. Long-term morbidity is exceedingly unlikely in patients who do not have initially evident severe reactions that promptly lead to cardiopulmonary arrest. Commonly used medications can be administered safely; however, when given incorrectly, these medications can cause patient morbidity. Even when extensive effort is made to train radiologists in contrast reaction management, there is a substantial risk of error in the anxiety-producing situation of treating a reacting patient. More frequent instruction and reinforcement, perhaps at 6-month intervals, is probably necessary. Alternatively, some radiology departments have responded to the risk of administering epinephrine incorrectly by having standardized preloaded syringes available in their contrast reaction kits.

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