

Anaphylactoid Reactions to the Nonvascular Administration of Water-Soluble Iodinated Contrast Media

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OBJECTIVE. Anaphylactoidlike reactions occur during the nonvascular administration of iodinated contrast media. Many of these reactions have been severe. These reactions have occurred with many procedures, including gastrointestinal imaging, cystography, sialography, and hysterosalpingography.

CONCLUSION. This article reviews reports of these reactions. It also reviews what the literature recommends concerning how to deal with individuals undergoing these procedures who are at a higher risk for anaphylactoidlike reactions.

Although most iodinated contrast media are administered vascularly, several of these agents are administered via nonvascular routes during such procedures as gastrointestinal imaging, cystography, sialography, cystography, and hysterosalpingography. Although anaphylactoidlike reactions are well known to occur with vascular iodinated contrast media injections, anaphylactoidlike reactions have been reported for nonvascular administration also. Although these reactions occur less frequently with nonvascular administration than with vascular administration, life-threatening anaphylactoidlike reactions have occurred with nonvascular administration of iodinated contrast media.

This article reviews reported anaphylactoidlike reactions due to the nonvascular administration of water-soluble iodinated contrast media. This is important because their nonvascular applications continue to increase, such as the use of iodinated contrast media to diagnose postoperative gastrointestinal leaks and dilute oral iodinated contrast media for CT and CT colonography.

Contrast Media Reaction Types

Contrast media reactions have been divided into two groups: physiologic and allergiclike reactions [1]. Physiologic reactions to iodinated contrast media are most likely due to chemical characteristics of the iodinated contrast media, such as hyperosmolality, binding characteristics, and direct chemotoxicity. These may cause reactions such as

pain and warmth as well as cardiovascular effects, such as pulmonary edema, arrhythmias, and vasovagal reactions.

Anaphylactoidlike reactions are allergiclike reactions but because not all the immunologic factors of true allergic reactions are found, these reactions have been labeled anaphylactoidlike reactions. The American College of Radiology (ACR) guidelines [1] divide these reactions into three degrees of severity. Mild anaphylactoidlike reactions are self-limited. These include limited urticaria, pruritus, cutaneous edema, and itchy or scratchy throat; nasal congestion; sneezing; conjunctivitis; and rhinorrhea. Moderate anaphylactoidlike reactions are more pronounced and commonly require medical management. These include diffuse urticaria, pruritus, and erythema with stable vital signs; facial edema without dyspnea; and wheezing or bronchospasm with mild or no hypoxia. Severe anaphylactoidlike reactions are typically life threatening. These include diffuse edema or facial edema with dyspnea; diffuse erythema with hypotension; laryngeal edema with stridor or hypoxia; wheezing or bronchospasm with significant hypoxia; and anaphylactic shock. However, other groups, especially allergists, have different classification systems [2].

Gastrointestinal Reactions

One of the earliest nonvascular uses of iodinated contrast media was oral administration [3]. Although the early articles about its use described the oral contrast media as non-absorbable, one such article measured renal

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excretion of iodine both from humans and dogs [4]. Later, renal enhancement seen on abdominal radiographs after oral administration of iodinated contrast media was interpreted as a sign of bowel perforation [5, 6]. Soon, however, it was observed that bowel perforation was not necessary for renal excretion to occur but that renal excretion occurred more frequently with pathologic abnormalities due to bowel inflammation, bowel stasis due to obstruction, or postoperative ileus [7, 8]. Eventually, it was noted that renal excretion was even visualized in individuals with no known bowel abnormalities [9]. Such vicarious renal excretion has been misinterpreted as evidence for a rectovesical fistula [10].

Several reports of anaphylactoidlike reactions to the oral administration of iodinated contrast media are in the literature. Miller [11] described an anaphylactoidlike reaction to diatrizoate meglumine and diatrizoate sodium (Gastrografin, Bracco Diagnostics). The 64-year-old woman was given oral Gastrografin for a CT scan of the abdomen and pelvis to evaluate for pseudomembranous colitis. She had no known drug allergies or previous Gastrografin exposure. She went into severe respiratory distress with audible inspiratory and expiratory wheezing. She responded to subcutaneous epinephrine, oxygen, and IV steroids. Dismissing the reaction as being most likely due to aspiration, she was given more Gastrografin by nasogastric tube that shortly produced similar symptoms that were again treated successfully. She later received a diagnosis of pseudomembranous colitis.

Of note, although Davis et al. [4] reported the early use of oral iodinated contrast media in 1956, the reaction described by Miller [11] was not reported until 1997. Therefore, for nearly 40 years, to my knowledge, there was no reported case of anaphylactoidlike reaction to gastrointestinal administration of iodinated contrast media. Alternatively, any reactions may have been considered to be due to aspiration instead, as Miller's case initially was.

Similarly, Marik and Patel [12] described an 82-year-old woman who developed tachycardia, tachypnea, and expiratory wheezing each time after being given Gastrografin, twice in 6 hours. Again, treatment of anaphylactoidlike reaction was successful.

Seymour et al. [13] described a 58-year-old man with blunt abdominal trauma who developed severe respiratory distress after the oral administration of 10 mL of diatrizoate meglumine and diatrizoate sodium solution (MD-Gastroview, GE Healthcare) di-

luted in water. Emergent cricothyroidotomy was required when intubation was unsuccessful because of marked airway edema. Chest x-ray did not reveal any abnormalities suggestive of aspiration. Review of a videotape of the patient drinking the contrast agent (part of a performance improvement system) did not show aspiration.

Ridley [14] reported three cases of mild anaphylactoidlike reactions (primarily rashes, both immediate and delayed), to oral iodinated contrast media administered as a bowel CT scan contrast agent. His review of the Australian Adverse Drug Reactions Advisory Committee database at that time raised the possibility of at least four other patients who had had allergic symptoms to oral iodinated contrast media.

Schmidt et al. [15] described toxic epidermal necrolysis developing acutely in a 36-year-old man given diluted Gastrografin for a CT scan. The man had a history of skin rash and erythema from prior IV administration of iodinated contrast media for CT scan.

Interestingly, no reports of anaphylactoidlike reactions from iodinated contrast media enemas were found, even though it is well documented that iodinated contrast media are absorbed from enemas [16]. It is possible that the routine dilution of iodinated contrast media for enemas contributes to the lack of anaphylactoidlike reactions.

Urinary System Reactions

Iodinated contrast media are absorbed from the urinary system. Castellino and Marshall, Jr., [17, 18] showed iodinated contrast media absorption during retrograde pyelography in dogs, which occurred primarily from the pelvicalyceal systems and not the ureters. Currarino et al. [19] measured iodinated contrast media absorbed from the urinary bladder during cystourethrography in children. Seventeen of 18 children had increased blood iodine after cystourethrography. Half of the 12 children who retained contrast agent in the urinary bladder for longer than 15 minutes (range, 15–45 minutes) had pyelogram findings on delayed abdominal radiographs that could be confused with reflux.

Anaphylactoidlike reactions have been reported with retrograde cystography and retrograde ureterograms and pyelograms. Johanning [20] described a 38-year-old man who twice had severe anaphylactoidlike reactions with severe dyspnea, wheezing, and bronchospasms during retrograde pyelography without evidence of pyelovenous backflow. Weese

et al. [21] reported two cases of urinary-related anaphylactoidlike reactions. The first case was a 2-year-old girl who developed an urticarial skin rash as iohalamate meglumine was instilled into her bladder. The second case involved a 55-year-old man undergoing a videourodynamic study to look for bladder outlet obstruction. As the iohalamate meglumine was dripped into his bladder, spontaneous bilateral high-grade vesicoureteral reflux was observed. At that moment, he developed hypotension. McAlister et al. [22] described a 5-year-old child with bilateral ureteral reflux who developed urticaria during cystography 6 months after developing urticaria after her third excretory urogram. There are several other early reported cases of anaphylactoidlike reactions associated with retrograde pyelography, but they were confounded by the simultaneous administration of neomycin, which can also cause reactions.

Steroid premedication may not prevent anaphylactoidlike reactions with retrograde pyelography. Armstrong et al. [23] described a case of a 19-year-old woman with a history of dyspnea and urticarial rash associated with excretory urogram. In preparation for retrograde pyelography, she received 50 mg of prednisone at 13, 7, and 1 hour before the procedure and 50 mg of diphenhydramine 1 hour before the procedure. Immediately after the procedure, she developed an urticarial rash and then dyspnea that eventually resulted in reintubation.

More recently, Cartwright et al. [24] reported the anaphylactoidlike reaction outcome of 11,714 videourodynamic studies in women. The examinations used either iohexol (Omnipaque 140, GE Healthcare), a nonionic low-osmolality iodinated contrast media, or diluted sodium amidotrizoate and meglumine amidotrizoate (Urografin 370, Bayer), a high-osmolality ionic agent. No severe anaphylactoidlike reactions occurred. However, all women with histories of anaphylactoidlike reactions to IV infusion of iodinated contrast media were excluded. In addition, the authors did not record data concerning less-severe or delayed reactions.

Freed et al. [25] reported a case of a severe anaphylactoidlike reaction associated with an iodinated contrast media retrograde study into a bowel segment that was part of a urinary diversion.

Arthrography

There have been two large surveys of radiologists reporting the complications of arthrography with iodinated contrast me-

dia. The larger and more recent survey had 134 respondents reporting on approximately 248,680 career studies [26]. They reported 947 (0.4%) occurrences of hives, both immediate and delayed, and eight (0.003%) occurrences of severe anaphylaxis. However, if the patient had a known history of severe reaction to intravascular iodinated contrast media, 23% of the respondents would decline to do the study, and 51% of the respondents would premedicate the patient with a standard protocol and use nonionic contrast agent.

The earlier survey included 57 radiologist respondents who had performed or supervised more than 126,000 arthrograms [27]. They reported only 61 occurrences of hives, which is much lower than the rate in the later study, but five cases of severe anaphylaxis, which is a rate similar to that in the later study. Because the two surveys occurred approximately 13 years apart (1985 and 1998) and the respondents report all career occurrences, there may be overlap of cases.

Hysterosalpingography

Several anaphylactoidlike reactions to iodinated contrast media in hysterosalpingography have been reported. Capdeville and Rémy [28] discussed a 23-year-old woman who developed urticaria and anaphylactoid shock after the administration of ioxitalamate meglumine for hysterosalpingography. Stiris and Andrew [29] reported an instance of urticaria after using Ca-Na-methylglucamine metrizoate (Isopaque Cerebral, manufactured by Nyegaard in Norway and by Sterling-Winthrop in the United States). Elias [30] observed a case of generalized dermal erythema, facial angioedema, stridor, and wheezing in a 27-year-old woman who received diatrizoate meglumine and diatrizoate sodium injection (Renografin, Bracco) for hysterosalpingography. Her symptoms resolved after being treated with epinephrine and diphenhydramine. Although she had never received iodinated contrast media before, she was known to have asthma and seasonal allergic rhinitis.

Sanfilippo et al. [31], in a series of 505 hysterosalpingography examinations, reported one case of urticaria. La Fianza and Camilla [32], in a series of 1395 hysterosalpingography examinations, did not report any anaphylactoidlike reactions. There are several other reported cases of urticaria associated with hysterosalpingography in the literature, but they used oil-based iodinated contrast media.

Exposure to iodinated contrast media in hysterosalpingography can come from direct

exposure of the uterus and fallopian tubes, venous and lymphatic intravasation, and spillage into the peritoneal cavity [32].

Sialography

There have been few reports of anaphylactoidlike reactions with iodinated contrast media used for sialography. Salerno et al. [33] described a 33-year-old woman who developed swelling of the mouth and neck with respiratory impairment after undergoing sialography using the nonionic isoosmolar iodinated contrast media iodixanol (Visipaque 270, Nycomed Amersham). This was a delayed reaction that occurred 8 hours after the procedure.

Similarly, Cockrell and Rout [34] reported a delayed reaction in a 65-year-old woman that occurred approximately 24 hours after sialography using ioxaglate meglumine and ioxaglate sodium (Hexabrix 320, Mallinckrodt), a low-osmolar contrast agent. The reaction consisted of a macropapular rash affecting her axillae, groin, and elbows with marked edema of the right elbow in addition to severe shoulder and back pain.

Sialography of the rat has found that contrast medium extends into the adjacent connective tissues [35].

Discussion

This review shows that anaphylactoidlike reactions to the nonvascular administration of water-soluble iodinated contrast media are infrequent, but severe and life-threatening reactions do occur unpredictably with all types of administrations. The underlying pathophysiologic processes of the reactions are still debated. However, several facts can be deduced from the literature: First, contrast media can be absorbed from or cause an anaphylactoidlike reaction at just about any membrane surface (e.g., genitourinary, gastrointestinal, or synovial). Second, the reactions are infrequent enough that, unlike vascular administration trials, it will probably not be possible to acquire enough cases to determine the true incidence of anaphylactoidlike reactions to nonvascular administration of iodinated contrast media and what factors may predispose or prevent anaphylactoidlike reaction to nonvascular administrations. Therefore, the vascular administration data should be used to inform guidelines.

What guidelines should be followed concerning the nonvascular administration of iodinated contrast media? The ACR does not have any specific guidelines [1]. The European Society of Urogenital Radiology 2014

guidelines state [36], "Since contrast media administered into body cavities may reach the circulation in small amounts, take the same precautions as for intravascular administration." Of interest, the 2009 edition of the guidelines ended the same sentence with the condition [37], "in patients at increased risk of reaction." Therefore, the most recent European Society of Urogenital Radiology guidelines now recommend that precautions should be used for all patients irrespective of previous anaphylactoidlike reactions.

The Omnipaque package insert states under section III (Oral/Body Cavity Use) [38], "OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol." Under Precautions, the reader is referred to section II (Intravascular Precautions), which states the following [38]:

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

The Gastrografin package insert states [39], "Do not administer to patients with a known hypersensitivity to Gastrografin or any of its components." The MD-Gastroview package insert states [40], "Do not administer to patients with a known hypersensitivity to MD-GASTROVIEW or any of its components."

Therefore, it appears that for most nonvascular administration of iodinated contrast media, the same screening and premedication criteria as used for vascular administration should be used. This appears to be the procedure used by most of the physicians surveyed by Hugo 3rd et al. [26], who were performing arthrography, and by Cartwright et al. [24] for videourodynamic studies.

The ACR and others consider the enteric administration of iodinated contrast media a special case. The ACR guidelines include a chapter on the enteric administration of contrast media in adults, but they are ambiguous with respect to the administration of iodinat-

ed contrast media to patients with a history of anaphylactoidlike reactions, as follows [1]:

Because anaphylactoid reactions are not considered to be dose related and can occur with less than 1 ml of IV (IV) contrast media, it is generally accepted that allergiclike reactions can occur even from the small amounts of contrast medium absorbed from the gastrointestinal tract. Somewhat surprisingly, there are only very rare reports of moderate or severe allergiclike reactions to orally or rectally administered iodinated contrast media.

In addition, the ACR guidelines do not discuss anaphylactoidlike reactions to iodinated contrast media in the "Contraindications to [Gastrointestinal] administration of water soluble contrast agents" section. The European Society of Urogenital Radiology guidelines do not specifically discuss enteric administration of iodinated contrast media [41].

This ambiguity has created two conflicting clinical viewpoints based on the available data. The first view is that because iodinated contrast media are absorbed from the bowel and anaphylactoidlike reactions have occurred, some of which were severe, susceptible patients should be premedicated. The second view is that because the incidence of anaphylactoidlike reactions from enteric iodinated contrast media administration is very rare, susceptible patients do not need to be premedicated.

Therefore, centers adhering to the second view do not consider previous anaphylactoidlike reactions to iodinated contrast media a contraindication to the enteric administration of iodinated contrast media or the need to premedicate. For example, Pasternak and Williamson of the Mayo Clinic state the following [42]:

Although extremely rare, anaphylactoid-type contrast reactions have been reported after the oral administration of iodinated contrast. Typically, these reactions occur in the same time frame as reactions to intravascular contrast, can be similar in severity, and are treated using the same methods. Because of the rarity of these reactions, corticosteroid premedication before oral contrast administration is not considered the standard of care for patients with a history of a reaction to IV contrast.

However, other guidelines, including those published by the Department of Radiology, Yale Medical Center, take the first view that premedication is warranted before administering oral iodinated contrast media to patients with a history of moderate or severe reactions to iodinated contrast media administration [43], stating that, "Patients with a history of previous moderate or severe reaction to IV contrast should not get oral Omnipaque unless premedicated." (Please note that Yale's definitions of moderate and severe reactions are similar but not identical to the ACR definitions.)

Alternatives to Iodinated Contrast Media Administration

Barium may be used to evaluate for leaks in the mediastinum. In 1997, Gollub and Bains [44] showed that esophagrams could be performed safely with diluted barium to rule out postoperative anastomotic esophageal leaks when leaks were not suspected. In 11 patients, leaks of barium during postoperative esophagrams were calculated to range in volume from 0.25 to 375 mL (mean, 31 mL). No cases of mediastinitis were found after 7–448 days (mean, 226 days) of follow-up. Minimal barium was retained by radiograph at 4–48 days (mean, 10 days). However, if a leak was suspected, the authors recommended using iodinated contrast media first.

Swanson et al. [45] studied the usefulness of high-density barium to detect leaks after esophagogastrectomy, total gastrectomy, and total laryngectomy. In particular, their study included nine patients who had anastomotic leaks at esophagojejunostomies after total gastrectomies. In three of these patients, the leaks were seen only with high-density barium. Those authors also recommended that barium be used only after an iodinated contrast media study did not reveal a leak. They did not mention adverse effects of the barium that leaked. However, the leaks that were detected by barium administration only were small or blind ended.

Foley et al. [46] reported the detection of gastric and duodenal perforated ulcers and leakage from a gastrojejunostomy suture line using barium after no leakage was detected with iodinated contrast media. The peptic ulcer leak included minimal extravasation of barium around the liver and into the peritoneum. They also did not mention whether there were adverse effects of the barium that leaked.

The radiology literature states that iodinated contrast media should be used to rule out an intraperitoneal leak [1]. Barium granulomas have been detected from barium leaking

through gastric and duodenal ulcers into the peritoneal cavity [47]. By use of animal models, Almond et al. [48] showed that barium and feces in the peritoneum is a lethal mixture. In addition, they showed that even sterile administration of barium into the peritoneal cavity can cause marked peritoneal irritation and adhesion formation. However, Gordon et al. [49] described 10 patients with "substantial intraperitoneal leakage of barium due to gastrointestinal perforations" who did not have clinical adverse effects. All the patients underwent immediate laparotomy to repair the perforation and to perform peritoneal lavage to remove the barium. Despite peritoneal lavage, barium remained between peritoneal leaves and in peritoneal compartments. With follow-up of 3–10 years, there was no clinical evidence of adverse effects from the residual barium, including adhesive intestinal obstruction. Four of these patients had abdominal surgery for other reasons during this period. Although peritoneal adhesions and foreign body granulomas were found in all four patients, no bowel obstructions were found.

Others have considered using gadolinium-based MRI contrast agents as substitutes for several routes of nonvascular administration. Newport et al. [50] used gadolinium chelate mixed in saline to perform a CT cystogram. Taghizadeh et al. [51] used gadopentetate dimeglumine for retrograde urography. Bartolotta and Margulis [52] used gadopentetate dimeglumine as a rectal contrast agent to evaluate rectal colonic anastomoses for leaks in two patients with allergy to iodinated contrast media. Margulis et al. [53] reported using gadopentetate dimeglumine as an oral contrast agent to evaluate a patient for leaks after bariatric surgery. Williams et al. [54] injected gadolinium dimeglumine for contrast-enhanced sialography. No adverse effects were reported in any of these patients. However, since the time when most of those articles were published, the relationship between gadolinium-based contrast agents and nephrogenic systemic fibrosis has become known. Therefore, the use of gadolinium-based agents for most of these applications cannot be recommended until the risks are further evaluated. Nephrogenic systemic fibrosis is considered to be due to the dissociation of the gadolinium atom from its chelate. The rate of dissociation increases considerably in acidic milieus [55, 56], which may occur in gastric acid and possibly in acidic urine.

It has been observed that there have been less-frequent reports of iodinated contrast

TABLE 1: Recommendations for the Nonvascular Administration of Iodinated Contrast Media

General Guidelines	
1. Severe and life-threatening reactions can occur with the nonvascular administration of iodinated contrast media because some iodinated contrast media are absorbed from any body surface and cavity. Therefore, iodinated contrast media administered by any route should be administered only where there are properly trained and equipped staff to provide treatment of these reactions, including in children.	
2. People at higher risk for contrast agent reactions, especially those who have had an anaphylactoidlike reaction to iodinated contrast media, should be studied with iodinated contrast media only if it is not possible to obtain the same information more safely using a different contrast agent or test.	
3. Premedication does not prevent all anaphylactoidlike reactions. Therefore, premedication is not a substitute to being prepared for anaphylactoidlike reactions.	
Specific Guidelines for Nonvascular Administration of Iodinated Contrast Media	
1. Enteric administration of iodinated contrast media (esophagrams, upper gastrointestinal tract imaging, small-bowel follow-through, rectal enemas, and enterostomy enemas) to patients with a history of anaphylactoidlike reactions:	
a. Use low-osmolality contrast agent. (See exception for colonic enemas below.)	
b. Patients with a history of mild anaphylactoidlike reactions to iodinated contrast media do not need to be premedicated.	
c. Patients with a history of moderate or severe anaphylactoidlike reactions to iodinated contrast media or any other allergen by any route should be prepared using the institution's guidelines for IV administration of iodinated contrast media.	
d. Iodinated contrast media colonic enemas: A search of the literature found no reports of anaphylactoidlike reactions from ionic iodinated contrast media colonic enemas. Therefore, an exception to the use of low-osmolality contrast agent in this situation is applicable, but the other pretreatment guidelines (b and c above) for enteric contrast agent should be followed.	
2. Nonenteric iodinated contrast media administration (e.g., cystography, retrograde pyelography, fistulograms, cholecystograms, T-tube studies, and urinary diversion loops or neobladder): The patient should be screened and prepared using the institution's guidelines for IV administration of iodinated contrast media.	

media reactions recently. Possible explanations include the following: First, fewer mild-to-moderate reactions are occurring because of the advent of nonionic contrast agents, and severe reactions are infrequent. Second, the reactions are now considered common knowledge or incidental, and are no longer considered worthy of reporting, especially mild anaphylactoidlike reactions. The explanation is probably a combination of these because many of the initially reported reactions were mild or moderate, and new anaphylactoidlike reactions are reported after iodinated contrast media are used for a new application.

In addition, nonvascular anaphylactoidlike reactions may be underreported. Nonvascular iodinated contrast media absorption may be slower than vascular absorption. Therefore, mild reactions such as rashes and all delayed reactions may not occur until the patient has left the radiology department. Either the reactions will not be reported at all, or they may be reported to the primary or referring physician and go unknown to the radiologist. In addition, some reactions to oral CT contrast agents may be mistakenly attributed to IV iodinated contrast medium, even though the latter was not administered [14].

On the basis of this discussion, a set of recommendations for the nonvascular administration of iodinated contrast media is presented in Table 1. However, independent of these recommendations, any site administering iodinated contrast media by any route should be prepared to treat any anaphylactoidlike reaction, including in children. The use of premedication does not prevent new or repeat anaphylactoidlike re-

actions [25]. Unfortunately, as a recent survey has shown, because the rate of mild and moderate anaphylactoidlike reactions is decreasing, probably because of the use of nonionic iodinated contrast media, radiologists' knowledge of how to treat the serious anaphylactoidlike reactions has diminished [57]. Therefore, more frequent review of such treatments has been recommended [58]. Please see the ACR manual on contrast media [1] for free online access to the ACR treatment guidelines, and Bang et al. [59] for an excellent foldable pocket-, wallet-, or purse-sized summary. This may become more critical in the future because there are now reports that the incidence of anaphylactoidlike reactions may increase with serial iodinated contrast media exposure [60].

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