

Anaphylactoid Reactions to Radiocontrast Media

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ABSTRACT

As the role for diagnostic and therapeutic contrast-enhanced imaging increases, review of the epidemiology, mechanisms, risk factors, and pretreatment for radiocontrast-mediated anaphylactoid reactions becomes more and more pertinent. Ongoing research has failed to elucidate the precise mechanisms of both early and late reactions, though the current data point to a multifactorial pathogenesis. The risk of reactions has decreased over time as contrast media have evolved from ionic, high-osmolality to non-ionic, low-osmolality formulations; however, the expense of the low-osmolality agents limit their universal use. Today, 1–12% of patients exhibit adverse responses ranging from mild to severe, with individual risk depending on the type of contrast administered and certain baseline patient characteristics. For those high-risk patients who must receive contrast, effective pretreatment guidelines have been established. (Allergy and Asthma Proc 26:199–203, 2005)

In today's modern medical world, imaging plays a central role in patient diagnosis and management. Clinical decision making often hinges on findings documented by one or more of a vast array of available radiological exams. In the early 1920s, contrast-enhanced radiographic imaging emerged as an important technique that has continued to offer vital pathological and anatomic insight. Brooks initially described early angiography in live human subjects using a radiopaque sodium iodide solution, but the pain and toxicity of the contrast limited its use.¹ In 1929, a New York City medical intern,

Swick, created and tested a less toxic formulation while doing a fellowship in Germany.² Swick's early contrast, used initially for urography studies,³ is the basis for the current radiocontrast media (RCM) used today.

The radiopaque agent is an iodinated benzene ring and has undergone multiple structural revisions over time. The initial formulation, an ionic monomer, must be used at five times the osmolality of plasma, making it uncomfortable and occasionally injurious to inject. A nonionic monomer and an ionic dimer were developed in the 1970s; they required one-half the osmolality of their predecessor, reducing patient discomfort and risk of adverse reaction. Finally, the nonionic dimer has recently enabled effective contrast enhancement with an osmolality below that of plasma along with the most benign side effect profile to date.² In fact, it is now cost that is the hotly debated singular downside to this relatively new low-osmolar media.

As the field of radiology has grown and changed, so too has the role for RCM. Although urography and angiography have diminishing use in the setting of more advanced technology, computed tomography (CT) has increasingly put RCM to new use. The speed, ease, and usefulness of CT have contributed to an explosion in utilization, exposing many more patients to RCM and generating much data on its safety. Relative to many available drugs, all of the contrast products used today are exceptionally safe. Still, adverse and even fatal reactions do occur. These reactions can be classified based on their timing, severity, clinical features, or proposed pathogenesis.

Reactions that occur within 1 hour of contrast administration are considered immediate and, most commonly, secondary to "pseudoallergic" (non-immunoglobulin E [IgE] mediated) mechanisms. These acute reactions typically occur within minutes and can vary widely in their presentation. Between 1 and 24 hours after contrast injection, late reactions may include prolonged injection-site pain, gastrointestinal symptoms, angioedema, dyspnea, flush, rash, and fever.⁴ True contrast allergy (IgE-mediated type I hypersensitivity) is quite rare.

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In a purely clinical approach, the American College of Radiology (ACR) categorizes all acute adverse contrast reactions into three tiers of severity, irrespective of likely pathogenesis.⁵ The uncertain mechanisms behind RCM side effects and the ACR's practical goal of generating appropriate treatment guidelines support this method.

However, clinical observation and laboratory work have helped to elucidate several pathogenic possibilities that can aid in classification. Accordingly, another categorization designates acute symptoms as vasomotor, vagal type, or anaphylactoid. Vasomotor responses present with transient warmth, nausea, and emesis; vagal reactions manifest as bradycardia-associated hypotension. Anaphylactoid reactions range from minor to severe and occur within 30 minutes of contrast administration. They appear clinically identical to anaphylaxis but lack an IgE-dependent mechanism. Minor anaphylactoid reactions include transient nausea, vomiting, urticaria, pruritus, and diaphoresis. Moderate reactions present with faintness, prolonged vomiting and urticaria, facial and laryngeal edema, and mild bronchospasm. The hallmarks of a severe reaction include hypotensive shock, pulmonary edema, respiratory or cardiac arrest, and convulsions.⁶

EPIDEMIOLOGY

Adverse reactions to RCM occur with greatest frequency in those between 20 and 50 years of age, with relative rarity in the pediatric population.² The rate of adverse events varies from study to study but typically is reported between 5 and 12% for ionic high-osmolality contrast media (HOCM) and between 1 and 3% for nonionic low-osmolality contrast media (LOCM). Severe reactions occur far less frequently, with incidences well below 1% for both HOCM and LOCM.^{2,5-11} A Japanese study, one of the largest prospective studies to date, looked at the incidence and risk factors for developing adverse drug reactions to both HOCM and LOCM. In a study population of 337,647 patients, 12.66% of those who received ionic HOCM and 3.13% of those who received nonionic LOCM had adverse reactions of any kind. The most frequent symptoms were nausea, urticaria, pruritus, heat sensation, and emesis. Severe reactions occurred in 0.22 and 0.04% of those receiving ionic and nonionic contrast media, respectively. These severe reactions included dyspnea, sudden drop in blood pressure, loss of consciousness, and cardiac arrest.⁷

Although relatively few adverse events occur with either HOCM or LOCM, much research has focused on the relative benefits of using newer nonionic, low-osmolality media. All published data to date suggest a significantly increased risk of adverse reaction with ionic HOCM, but some debate exists as to whether or not the risk of severe adverse reactions is similarly elevated. Contrast-related deaths have been reported with about equal frequency in patients receiving both types of media.¹² Were it not for economics, most agree that the HOCM agents would be universally phased

out in favor of the more benign LOCM products. LOCM is several times more expensive than HOCM, and many authors have looked at safety data to determine whether safety benefits outweigh financial costs. The aforementioned Japanese study found statistically significant differences in overall and severe adverse event rates between the HOCM- and LOCM-infused patients, even though patients considered at greater risk likely received LOCM more frequently.⁷ A multidisciplinary working group reviewed the literature in 1992. They concluded that both HOCM and LOCM are safe but that the methodological shortcomings of the 10 observational studies done up to that point precluded any firm conclusion about their relative risks. The group did acknowledge a consistent pattern of lower rates of severe adverse reaction in patients receiving LOCM.⁹

A retrospective Australian review of 613,581 contrast injections looked specifically at mortality. Only eight deaths were reported, two of which were in patients given LOCM. Although the numbers were too small to give the study adequate statistical power, this difference did not represent significant improvement in mortality for patients receiving LOCM.¹³

In a more recent retrospective analysis of data reported to the U.S. Food and Drug Administration, Lasser *et al.* compared reported reactions in patients receiving ionic HOCM, ionic LOCM, and nonionic LOCM. Incidences of all reported reactions, severe reactions, and death (per million examinations) were greater with administration of HOCM than with nonionic LOCM (193.8 versus 44.4, 37.4 versus 10.5, and 3.9 versus 2.1, respectively). Notably, the incidence of severe reactions to total reactions was unexpectedly greater for the low-osmolar media as was the incidence of death to severe reactions. The authors attribute this to the increased risk of those patients chosen to receive LOCM, but similar results have not been borne out in other studies.¹⁴

Another prospective observational study conducted by Bettmann *et al.* looked at 75,616 angiography procedures and found a statistically significant decrease in overall adverse events in those patients receiving nonionic LOCM as compared with those receiving HOCM (4% versus 8%). The difference was most pronounced in patients undergoing cardiac procedures (2% versus 14%), while no significant difference was seen for patients undergoing noncardiac arterial interventional procedures. Notably, no significant difference in serious adverse events was identified overall or for any subgroup.¹⁵

Overall, the data comparing adverse reactions with low- and high-osmolar media suggest marked overall reduction in adverse events with the more costly low-osmolar agents, without definitive evidence of a reduction in serious events or deaths. Given economic constraints, many studies have sought to determine the highest risk patient population best suited to receiving the more costly LOCM. This work has done to characterize more accurately the epidemiology of the problem. Virtually all studies have established that sig-

nificant predisposing factors include prior adverse reaction to contrast medium (four to six times greater risk), asthma (eight times greater risk), and history of atopy (five times).⁷ One such case control study of 34,371 patients reported a significant increase in risk for asthma patients with or without atopy (odds ratio of 8.74).¹⁶ The risk in asthma is thought to relate to an exaggeration of the typical small, clinically insignificant bronchospasm caused by contrast agents.¹⁷ Notably, allergy specific to seafood does not impose increased risk of adverse reaction, because virtually no reactions to contrast media are truly allergic in nature or related to the media's iodine content. Additionally, few seafood allergies are in response to the iodine contained within the foods.²

Additional risk factors for radiocontrast reactions include cardiac disease, dehydration, hematologic conditions predisposing to thrombosis, renal disease, and anxiety.^{3,6} One study by Lang *et al.* points to β -blocker therapy as a statistically significant risk factor for anaphylactoid reaction, with an odds ratio of 2.67. In addition, the study showed that reactors receiving β -blockers more often required hospitalization for their reactions likely because of their reduced response to treatment.¹⁶

Although controversial early on, it now appears that women more frequently exhibit adverse reactions than do men. In 5264 consecutive patients receiving contrast-enhanced CTs, 70% of the 73 patients who experienced adverse reactions were women. Twenty-one of 22 severe anaphylactoid reactions occurred in women.¹⁸ Studies examining the overall incidence of anaphylaxis and anaphylactoid events have similarly shown an increased occurrence in women.²

Although trends in radiological technology have informed which specific RCM uses have been studied over the years, no consistent pattern of adverse reaction risk has emerged related to the type of exam being conducted. Arterial and venous administrations appear to yield the same risks,² as do contrast injections for CT and angiography.⁵

PATHOGENESIS

The pathogenesis of anaphylactoid responses to RCM remains poorly and incompletely understood. Lieberman *et al.* classify the proposed theories in four categories: direct histamine release, complement activation, antigen-antibody interactions, and multimediator recruitment. Some evidence supports each of the proposed hypotheses, and most presume that the true mechanism is multifactorial.

A number of human and animal studies have looked at the ability of RCM to directly trigger histamine release in mast cells and basophils. The release usually occurs slightly later than in IgE-mediated release,¹⁹ is enhanced by the presence of serum (suggesting the importance of anaphylatoxins), and may occur selectively in a few susceptible organs.²⁰ In animal models, measured histamine release correlates well with pathophysiological events, but such

clinical correlation has been shown less reliably in humans. RCM could cause non-IgE-mediated histamine release in several ways: *via* interaction with mast cell and basophil cell membranes, *via* its hyperosmolality, or *via* generation of anaphylatoxins. Much work has looked at the role of hypertonicity in generating adverse reactions.² *In vitro* experiments done in the 1980s showed that brief exposure to hyperosmolar solutions activates basophils so that they continue to release histamine even after returned to iso-osmolar buffers. In addition, basophils from atopic patients were far more sensitive to this osmolar trigger, releasing greater percentages of their contained histamine. This has been termed increased "releasability."²¹ Despite this and other early data supporting osmolality-mediated histamine release, several factors suggest that this mechanism does not fully explain the clinical response. Differences in time course, calcium dependence, and optimum temperature all imply that additional mechanisms are involved. In fact, both high- and low-osmolar contrast formulations have been shown to provoke histamine release.

Recently, focus has shifted toward a complement-mediated pathogenesis for anaphylactoid reactions to RCM.²² Observationally, the majority of patients receiving RCM exhibit brief decreases in serum complement levels, though patterns in these decreases do not correlate consistently with clinical reactions. *In vitro* studies also suggest that RCM activate complement outside of the classic and alternative pathways. Instead, an alternative lytic enzyme system appears to cause nonsequential complement activation, yielding unique cleavage products. The inciting event for complement activation appears to differ for ionic and nonionic contrast media. By any means, RCM-mediated complement activation yields several measurable biologically active cleavage products. These include both anaphylatoxins and chemotactic molecules.² Additional research should better characterize the degree to which complement-mediated pathways contribute to anaphylactoid reactions.

While most agree that the vast majority of RCM reactions are not IgE-mediated, there have been case reports of patients developing anti-RCM antibodies and possibly, therefore, true RCM anaphylaxis. One report describes a nonatopic patient who experienced anaphylaxis to iodinated contrast media twice within a 4-year period and had both positive intradermal and human basophil degranulation tests in the setting of negative controls. The latter test showed that passively sensitized basophils do not degranulate in the presence of RCM when the serum with which they are incubated is preheated. The test proves the heat sensitivity of the key element within the serum, suggesting that it could be IgE.²³ Other authors have directly reported anti-RCM IgE antibodies in the sera of patients who experienced severe adverse contrast reactions as well as positive skin testing in this group. Still, true IgE-mediated allergy likely represents a small subset of all adverse contrast reactions.²

A potpourri of effects on other physiological pathways makes up the fourth and final category of pathogenic mech-

anisms for immediate reactions. RCM appears to inhibit many enzymes, including cholinesterase. This leads to an increase in acetylcholine, which could contribute to symptoms of vagal stimulation such as bronchospasm and cardiovascular collapse.³ Other inhibited enzymes include urokinase, streptokinase, collagenase, tissue plasminogen activator, and lysozyme.² RCM appears to activate several physiological cascade systems in addition to the complement cascade described previously. Activation of the kinin system causes bradykinin release, stimulation of the coagulation cascade leads to disseminated intravascular coagulation, and the triggering of the fibrinolytic system causes fibrin degradation.²⁴

In the presence of RCM, platelets release serotonin, a substance that can enhance vasomotor collapse.³ Alterations in red blood cell structure can occur, along with granulocytosis. Hyperosmolarity, direct toxicity, and high injection pressures are the likely causes of damage to the vascular endothelium.² Although none of these individual effects is likely to be singularly responsible for the anaphylactoid reactions seen, they no doubt contribute to the clinical presentation of this phenomenon.

The pathogenesis of late reactions to RCM is even less well understood than that of immediate reactions. One case report proposes that late skin rashes might, in fact, be delayed-type hypersensitivity reactions. A nonatopic patient who underwent angioplasty developed a steroid-responsive rash 7 days after the procedure. The patient's history ruled out any other possible drug reaction. A second exposure to the contrast agent produced a similar rash within 1 day, despite aggressive steroid and antihistamine premedication. Patch testing was positive.⁴ Another case report describes a nonatopic patient who received RCM for CT examination and developed a pruritic, papular exanthema 4 days later. Patch testing was positive only for the specific contrast media used, and biopsy showed the presence of eosinophils and predominantly CD4⁺ lymphocytes. The authors suggest that delayed-type hypersensitivity or a late-phase reaction might be involved,²⁵ but more work in this area is warranted.

PREVENTION OF ADVERSE REACTIONS

Steps can be taken to minimize the risk of adverse reactions to RCM, ranging from informed decision making to pharmacologic prophylaxis. No radiological examination, particularly one requiring contrast, should be performed without clear clinical utility. This is particularly true in those at greatest risk for having a reaction. Based on much of the aforementioned data, the ACR has produced a list of patient groups whom they consider to be particularly predisposed to adverse reactions. The list includes those patients who have had severe reactions in the past, have a significant history of atopy or asthma, take β -blockers, have cardiac dysfunction, have renal insufficiency, or are severely debilitated.⁵ For these patients, noncontrast imaging

studies always should be considered as alternatives. When these less risky exams are deemed inappropriate or insufficient and clinical necessity of the contrast-enhanced exam has been confirmed, steps must be taken to achieve optimal risk reduction. Patients falling into the foregoing high-risk groups should preferentially receive LOCM in centers where financial considerations do not allow for universal administration of the low-osmolar agents, because this will significantly reduce the risk of adverse reactions. This was confirmed in a study by Barrett *et al.*, who randomly assigned 2113 high-risk patients (defined by prior RCM reaction, allergies, asthma, diabetes, cardiac or renal disease, anxiety, severe illness, or age >50 years) to receive either HOCM or LOCM. Adverse reactions occurred in 3.9% of patients receiving HOCM and in only 0.9% of patients receiving LOCM ($p < 0.000005$).¹⁰

A 2003 study also supports the selective use of LOCM in similarly defined high-risk patients as both safe and cost-effective. Although the low-risk patients receiving HOCM experienced mild adverse reactions with greater frequency than the high-risk patients receiving LOCM, no significant differences were found in terms of severe adverse reactions. Additionally, using the more expensive LOCM in the higher risk group saved approximately \$440,000 per 10,000 patients over using LOCM for all patients. Clearly, the cost-benefit analysis is in constant flux as the cost of contrast media changes and as financial arrangements between hospitals, physicians, and manufacturers vary. However, the study does confirm the safety and efficiency of the current LOCM criteria.²⁶

Pharmacologic pretreatment of high-risk patients has evolved over time since its inception in 1975. Diphenhydramine and corticosteroids were the first agents tried with success, and these continue to be the mainstays of the modern regimen. In 1985, H₂ blockers were introduced as potential risk-reducing agents when cimetidine was shown to have protective effects.²⁷ Ephedrine showed similar promise in a study conducted around the same time, but this same study showed increased risk of adverse reactions with the use of cimetidine.²⁸ A 1990 study compared three pretreatment regimens over 14 years in 149 patients who had prior anaphylactoid RCM reactions. Group I received prednisone (50 mg orally 13, 7, and 1 hour precontrast) and diphenhydramine (50 mg intramuscularly 1 hour precontrast); group II received prednisone, diphenhydramine, and cimetidine (300 mg orally 1 hour precontrast); and group III received prednisone, diphenhydramine, cimetidine, and ephedrine (24 mg orally 1 hour precontrast). Seven percent of the 149 pretreated patients had reactions, all of which consisted of urticaria and/or angioedema. The reaction rates and severity of reactions were equal across all three pretreatment groups, but the authors still recommended use of all four pretreatment agents when possible, given other more favorable data.¹¹

No pretreatment protocol has been shown to eliminate all repeat reactions. In fact, although several clinical trials have

shown a decrease in total adverse reactions with premedication, no study has been able to show a significant decrease in the incidence of severe events. Because of the conflicting and inadequate data, several pretreatment protocols have been proposed for current use. The two published by the ACR are

1. Prednisone, 50 mg by mouth at 13, 7, and 1 hour precontrast; diphenhydramine, 50 mg intravenously, intramuscularly, or by mouth 1 hour precontrast
2. Methylprednisolone, 32 mg by mouth 12 and 2 hours precontrast with or without diphenhydramine as aforementioned⁵

Given that adverse reactions occur even when every precaution is taken, preparedness on the part of the medical team is critical. Treatment for patients experiencing adverse reactions ranges from discontinuation of contrast injection and reassurance to aggressive resuscitative measures. The ACR publishes treatment protocols for each of the various symptoms exhibited by patients having acute reactions.⁵

CONCLUSION

Contrast-enhanced radiological imaging has proven its extreme safety even as it has faced the test of escalating use. However, the rare but occasionally serious reactions that do occur encourage prudent use of the available technology. Many patients who experience adverse reactions have no clear predisposing characteristics. For those with known risk factors, appropriate premedication, use of LOCM, and careful preparation help reduce adverse outcomes. Better elucidation of the pathogenetic mechanisms responsible for anaphylactoid adverse reactions will pave the way for future formulations of contrast media with improved side effect profiles.

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