

ANAPHYLACTOID REACTIONS TO RADIOCONTRAST AGENTS

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Systemic reactions to radiocontrast media (RCM) administration are not a rare clinical occurrence. Most of these reactions involve some combination of pulmonary, cardiovascular, gastrointestinal, and cutaneous symptoms that can be life-threatening if not promptly and properly treated. These reactions involve systemic mast cell activation, histamine release, but not specific IgE, and are most accurately termed *anaphylactoid*.²⁹ It is estimated that up to 1% of all subjects receiving standard RCM (i.e., ionic, hyperosmolar solutions) experience clinically significant anaphylactoid reactions. Such reactions should be distinguished from vasomotor reactions, which occur in 5% to 8% of patients undergoing RCM-based procedures, and consist of nausea (with or without vomiting), flushing and warmth but no hypotension, urticaria, or airway obstruction.¹⁵ Life-threatening RCM reactions occur less frequently (rate less than 0.1%), and actual fatalities are fortunately rare (0.03% to 0.001%, depending on the specific procedure). Even with the development of less hypertonic agents, RCM reactions still occur and can have alarming, even fatal, consequences. This article reviews the pathophysiology, clinical presentations, and management of RCM reactions.

PATHOPHYSIOLOGY OF RADIOCONTRAST MEDIA REACTIONS

RCM have been developed to achieve appropriately radiodense contrast for diagnostic imaging. The standard agent used consists of a tri-iodinated benzoic acid compound whose osmolality is sixfold greater than human plasma. More recently developed RCM are less hypertonic (often accomplished through the

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conjugation of identical molecules into dimers), and have lessened the incidence of severe adverse reactions.³⁵ Reactions still occur, however, with these preparations and they are significantly more expensive, bringing into question the overall cost effectiveness of switching to them.

Because the clinical presentation was noted to be similar to other conditions, such as bee sting reactions, well before the discovery of allergen-specific IgE, RCM reactions were initially thought to be allergic, most likely to iodine. Indeed, RCM-reactive patients were instructed to avoid iodine-rich foods, such as fish and other seafood. Even with selective case reports of what may be iodine-specific IgE,²¹ information supports a non-IgE-mediated mechanism as the cause of RCM-induced, life-threatening reactions.^{1, 3, 13, 21, 26, 45, 50} Based on the clinical syndrome, RCM anaphylactoid reactions are mast cell-mediated. Histamine and other mediators released by activated mast cells cause the physiologic changes characteristic of RCM anaphylactoid reactions. Although a definitive mechanism explaining how RCM activates mast cells has never been established, the most important factors suspected to influence the likelihood of a reaction are tonicity of the solution and the ionic nature of the compound. Tonicity likely is more important because nonionic dimers still can cause reactions.

Research suggests a direct effect of RCM on mast cell activation. Indeed, plasma histamine levels can rise after RCM infusion.¹⁵ In vitro studies demonstrate the ability of hyperosmolar buffer solutions to induce histamine release from blood basophils, particularly from individuals with allergic histories.³ Further, various RCM (i.e., ionic and nonionic) preparations have similar capabilities of direct basophil and mast cell release of preformed histamine, but do not activate the cells to produce additional mediators.¹³ Finally, multiple epidemiologic studies comparing high and low osmolarity RCM reaction rates indicate a clearly lower reaction rate with low osmolarity compounds.^{26, 27}

Other mechanisms implicated for RCM effects include complement activation (i.e., classical and alternative pathways), inhibition of various enzyme systems and binding to plasma proteins with resulting conformational changes, and possible immune complex formation (i.e., conventional RCM can activate the classical complement pathway through the cleavage of C3 and C5 to produce anaphylatoxins [C3a, C5a], which bind to and activate mast cells to degranulate).¹¹ Newer agents also activate complement through inhibition of factors H and I of the alternative pathway. Hypocomplementemia was reported after RCM infusion in association with anaphylactoid⁴⁸ and hemolytic episodes.³⁶ Several potential physiologically important enzyme levels are altered by experimental exposure of mast cells to various RCMs or in patients who had reactions. In vitro exposure of mast cells to various RCM inhibited the enzyme systems urokinase, streptokinase, collagenase, tissue plasminogen activator, and lysozyme.²² In contrast, plasma prekallikrein and α_2 -macroglobulin activities were elevated in patients with previous RCM reactions compared with age-matched controls.³²

Finally, the issue of protein binding and potential immunogenicity remains controversial. Although studies looking for RCM-reactive IgE yielded little evidence of allergenicity, experimental⁵ and clinical⁴⁸ data suggest the potential for RCM to induce IgM formation in selected cases or for RCM-reactive IgM to be present in individuals experiencing RCM-induced adverse reactions; the overall clinical implication of this remains unclear.

Thus, although RCM can induce potentially life-threatening, anaphylactoid reactions, the mechanism is unknown. There may be multiple mechanisms resulting in similar clinical manifestations. RCM reactions may be better termed

a syndrome rather than a specific clinical entity, which may explain the diversity of clinical outcomes associated with the administration of this class of agents.

CLINICAL PRESENTATIONS OF RCM REACTIONS

Anaphylactoid reactions involve some combination of a cutaneous (e.g., urticaria or angioedema), respiratory (e.g., bronchospasm or laryngospasm), cardiovascular (e.g., hypotension or tachyarrhythmias), or gastrointestinal (e.g., nausea, vomiting, diarrhea, or cramping) symptoms. Vasovagal reactions to RCM may include gastrointestinal symptoms, syncope, bradycardia, and flushing but not sustained cardiovascular or respiratory compromise.¹⁵ Although vasovagal reactions are not life-threatening, it is not always possible to discern them from early mast cell-mediated reactions that have not yet involved the cardiorespiratory systems.

Because RCM most often is given intravenously, little formal data are available that compare the risks of reactions using routes of administration. Intracystic administration for urologic imaging procedures was reported to cause anaphylactoid reactions.⁴⁶ The proposed mechanisms were absorption of RCM across the urothelium or vagal reaction, perhaps from bladder distention. Additionally, oral administration of diatrizoate was reported to induce an anaphylactoid reaction in a single patient, which occurred again after rechallenge.³⁴ Finally, intracoronary arterial administration of RCM during cardiac catheterization was reported to induce systemic reactions,⁴¹ as well as coronary spasm resulting in cardiogenic shock.³⁸

Other nonanaphylactoid, potentially life-threatening reactions to RCM administration were reported. These included hemolytic anemia,^{40, 48} disseminated intravascular coagulation,³¹ and noncardiogenic pulmonary edema.^{6, 14, 18, 39} Pulmonary edema occurred using ionic and nonionic agents during intravenous and intra-arterial procedures. No specific mechanisms for the reactions were established in these unusual cases.

RISK FACTORS FOR RCM REACTIONS

Because the overall incidence of RCM reactions is so low, many underestimate the importance of identifying patients at high risk for potentially life-threatening reactions so that appropriate preventative or therapeutic measures can be taken. Indeed, although only 1% of all RCM-based procedures result in a reaction, up to 33% of previous reactors have subsequent reactions of equal or greater severity. Many patients undergoing RCM-based imaging procedures have underlying illnesses that compromise their ability to tolerate anaphylactoid reactions. Prospective identification of specific risk factors has clinical utility in the cost effective care of patients undergoing these procedures (Table 1). Because low osmolality agents have lower risk and higher cost, risk assessments would help identify appropriate patients.

Gender

In a study involving more than 5000 patients who received RCM-based procedures (51% men, 49% women), women were more than twice as likely to experience anaphylactoid reactions as men.²⁵ Of the 22 patients who experienced

Table 1. FACTORS THAT INCREASE RISK FOR RCM-INDUCED ANAPHYLACTOID REACTIONS

Physiologic	Concomitant Medications
Gender (female)	β -blockers
Asthma/allergy	Biological response modifiers (rIL-2)
Previous reaction to RCM	

life-threatening symptoms, 21 were women. The reason for this gender difference is not known, and this pattern is not typical of other mast cell diseases.

Atopy

Previous reports have established that the main risk factor for developing an IgE-mediated drug allergy is a history of previous drug allergy.³⁷ The explanation for this observation has supposed a genetic predisposition to make IgE rather than other isotypes when repeatedly exposed to drug antigens. The same observation is true for other forms of anaphylaxis. Because RCM anaphylactoid reactions appear not to be IgE-mediated, it would seem that previous atopic history would not be a contributing risk factor. Increased incidence of RCM reactions in a series of allergic or asthmatic patients, however, has been reported.⁴³ Increased incidence of RCM reactions may be related to a direct difference in mast cell degranulation potential from allergic versus nonallergic patients.

Concomitant Medication Use

Not all RCM reactions occur with the first dose, and among those who have had previous reactions, two thirds do not experience subsequent reactions whether pretreated or not. Concurrent medication use is a common factor that may influence RCM reactions. β -blockers are known to worsen mast cell-mediated reactions, regardless of the cause. A retrospective study of 34,000 RCM procedures, including 122 resulting in anaphylactoid reactions, however, suggested that the presence of β -blockers (usually for hypertension or cardiac disorders) was a risk factor for increased reaction severity, although β -blockers were not associated with an increased frequency of reactions.

The therapeutic use of modern biological agents with direct effects on mast cells may potentiate anaphylactoid reactions. Recombinant interleukin-2 (rIL-2), a potent T-cell cytokine, has been used for more than a decade in many cancer and HIV treatment protocols. Hypotension is one of the well-recognized side effects of rIL-2 administration, which is thought to involve increased vascular permeability and decreased systemic vascular tone, properties shared with mast cell mediators, such as histamine. Reports have suggested that rIL-2 administration was associated with an increased risk of adverse reactions after RCM exposure.⁴² The postulated mechanisms included an additive adverse effect of rIL-2 and RCM on the various common target organs, increased basophil-derived histamine release after IL-2 exposure and a possible increased production of natural IL-2 in situ by sensitive patients with RCM exposure. These reports add information regarding possible mechanisms of action for RCM-mediated reactions, and provide a rationale for the cautious, concomitant use of RCM and agents known to have similar systemic side effects.

Choice of RCM

As previously mentioned, the standard radiocontrast agent is a hypertonic, ionic, iodide-based solution. Replacement of the standard reagents with low osmolality RCM has significantly lessened serious adverse reactions in many studies.^{9, 17, 49} As a result, low osmolality RCM is often considered preferable but has been challenged on a cost- and biological basis.²⁸ The incidence of adverse reaction to RCM is still low and the cost of the low osmolar agents is considerably higher than the standard agents. Additionally, other reports comparing high versus low osmolality and ionic versus nonionic RCM did not see a significant difference in serious reaction rates between the groups.⁴ Meta-analysis of available studies comparing use of high versus low osmolality RCM in terms of risk of death or serious reactions failed to show significant differences in mortality between the two categories.⁷ Risk of death was 0.9 per 100,000 in the high osmolality group and 0 in the low osmolality group, whereas risk of serious adverse reaction was 157 per 100,000 in the high osmolality group and 126 per 100,000 in the low osmolality group. These data, as well as pragmatic cost considerations, motivated the American College of Radiology's Committee on Drugs and Contrast Media to issue a policy statement outlining the criteria for appropriate use of low osmolar RCM in specific risk categories (Table 2).¹ This statement reflects risk factors for experiencing a reaction (e.g., previous adverse event with RCM, asthma, atopy, sickle cell anemia, or aspirin sensitivity) and for having a poor outcome should a reaction occur (e.g., cardiac dysfunction, severe debilitation, or a poor historian making the presence of other risk categories uncertain).

TREATMENT AND PREVENTION OF RCM ANAPHYLACTOID REACTIONS

Acute Therapy

The treatment for acute anaphylactoid RCM reactions is the same for any other systemic mast cell-mediated reaction. The key is early recognition and initiation of treatment to avoid the poorer outcomes associated with more severe

Table 2. AMERICAN COLLEGE OF RADIOLOGY RECOMMENDATIONS FOR ROUTINE USE OF LOW OSMOLARITY RADIOCONTRAST AGENTS

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manifestations (e.g., hypotension or respiratory compromise). Distinguishing anaphylactoid reactions from vagal reactions, however, is sometimes difficult. Vagal reactions most often manifest as gastrointestinal distress with or without a sensation of heat or flushing,⁴⁵ and patients with these isolated symptoms may be carefully observed without initiating other treatment. The onset of any respiratory symptoms or cardiovascular compromise (i.e., dysrhythmias or hypotension) warrants immediate intervention with a combination of H₁ and H₂ antihistamines, intravenous fluids (if hypotensive), and subcutaneous epinephrine (for hypotension or respiratory compromise). The use of corticosteroids to prevent a late-phase reaction has been questioned because RCM anaphylactoid reactions may not activate mast cell mediators other than late-phase histamine (e.g., ecosanoids, cytokines, and chenokines).¹³ Because there are reports of delayed reactions to RCM,^{33,45} however, the use of short-term systemic corticosteroids is prudent in patients for whom there is no contraindication. As previously mentioned, the use of β -blockers is associated with increased reaction severity. One report of RCM-induced anaphylactoid reaction unresponsive to routine anaphylaxis treatment did respond well to intravenous glucagon infusion.²⁰

Prophylaxis

In all cases, prevention is preferable to therapy. Patients at high risk who require any diagnostic procedure involving RCM should receive prophylaxis (Table 3). High-risk patients are those who have a previously documented clinically significant RCM reaction or those who had a questionable reaction but whose underlying clinical condition (e.g., cardiac, pulmonary, neurologic, and so forth) would make surviving any significant reaction questionable. Although the specific regimens vary somewhat,^{8, 16, 30} the basic categories have a common rationale. First, low osmolar, nonionic RCM should be used. Although some suggest that regular RCM combined with prednisone pretreatment is safe,¹⁰ most still recommend the use of low osmolar agents. Second, corticosteroids should be administered, preferably beginning 24 hours before the anticipated procedure. This steroid presumably stabilizes mast cell membranes, thereby resisting the effects of the RCM.² Systemic corticosteroids also inhibit many inflammatory networks and mediators previously described that may be active in these reactions.⁴⁷ A combination of H₁ and H₂ antagonists should also be given in advance to block effects of any histamine that is released. Finally, some studies recommend the use of an adrenergic agent, such as ephedrine, when no cardiovascular contraindication exists.³⁰

For some time, identification of the patient at high risk for major reactions has been attempted. Early attempts using intravenous challenge with a test dose

Table 3. THERAPY FOR RCM-INDUCED ANAPHYLACTOID REACTIONS

Acute	Prophylaxis
Adrenergic agents (e.g., epinephrine, albuterol)	Low osmolar, nonionic RCM
Fluid replacement/expansion	Prednisone
H ₁ blockers (diphenhydramine)	H ₁ blocker
H ₂ blockers	H ₂ blocker
Systemic corticosteroids	Adrenergic agent (e.g., ephedrine)
Glucagon*	

*May be useful in patients who were taking β -blockers.

of 1 cc RCM was abandoned because of reported deaths with the procedure¹²; however, a graded challenge procedure in 204 previous RCM reactors—categorized according to their history of reaction (vague versus specific), their challenge result (positive versus negative), and pretreatment (diphenhydramine versus none)—demonstrated a clear use of the procedure to identify high-risk patients likely to have repeat reactions with subsequent RCM exposure.⁵⁰ Such patients would require pretreatment and careful monitoring.

CONCLUSION

Although the use of RCM is generally safe, clinically significant reactions occur in a small but significant percentage of patients undergoing radiocontrast procedures. Risk factors—such as gender, concurrent asthma or allergic diseases, concomitant use of medications such as β -blockers and rIL-2 and, most importantly, previous reactions to RCM—identify patients at greatest risk for severe RCM anaphylactoid reactions. The use of low osmolar, nonionic reagents and pretreatment protocols have reduced, but have not eliminated the incidence of severe reactions. Better techniques of predicting RCM reactions in patients, as well as a better understanding of the mechanisms associated with the reactions, are desirable. Such information will contribute to the development of a more effective pretreatment for or even prevention of the adverse effects of this commonly used class of agents.

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