

A Novel Pretreatment Regimen for Breakthrough Radiocontrast Media Anaphylaxis in Cardiac Patients

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Background: Radiocontrast media allergy is a severe and potentially life-threatening condition. This creates a clinical dilemma for cardiac patients who require urgent interventions with radiocontrast media. Several pretreatment regimens have been suggested for patients with prior immediate hypersensitivity reactions to radiocontrast media. Despite using pretreatment regimens, breakthrough reactions have been reported in 2.1%–18% of patients with radiocontrast media allergy. Little is known about management of patients with a history of breakthrough radiocontrast media anaphylaxis who require urgent lifesaving procedures.

Methods: We report a retrospective analysis of 2 cardiac cases with a history of breakthrough radiocontrast media anaphylaxis despite standard pretreatment. These patients required urgent cardiac intervention with the use of radiocontrast media.

Results: We present a novel pretreatment regimen for high-risk cardiac patients with breakthrough radiocontrast media anaphylaxis despite prior pretreatment who need urgent coronary interventions.

Conclusion: This protocol is both safe and effective in mitigating anaphylaxis in cardiac patients.

Key Words: radiocontrast media allergy, radiocontrast media anaphylaxis, radiocontrast media hypersensitivity, IV contrast dye allergy, cardiac disease (*Crit Pathways in Cardiol* 2016;15: 161–164)

Adverse drug reactions, as defined by the World Health Organization, are unpredictable, noxious, unintended, and dose-independent reactions occurring after the administration of normal medication treatment doses.¹ They can be predictable, such as a known side effect of the medication, or unpredictable, ranging from allergic to idiosyncratic reactions. Systemic allergic reactions can be divided into IgE-mediated anaphylaxis or systemic non-IgE-mediated anaphylaxis, previously referred to as anaphylactoid reactions.^{2,3}

Radiocontrast media (RCM) allergy is a severe and potentially life-threatening condition. Non-IgE-mediated anaphylaxis has been reported in up to 3% of patients receiving RCM.⁴ Severe life-threatening reactions occur in 0.04%–0.22% of patients depending on the type of contrast used.^{3,4} In patients with prior RCM allergy, studies have suggested that the risk of reaction on repeat RCM exposure ranges from 16% to 35%.^{5,6} Although no prophylactic regimen is completely protective,^{3,7,8} pretreatment regimens are commonly used in patients with prior RCM anaphylaxis. These protocols use prednisone, diphenhydramine, and occasionally cimetidine and ephedrine, thereby reducing the risk of repeat reactions to 3.1%–9%.^{5,6} Despite using pretreatment regimens, breakthrough allergic reactions have been reported in 2.1%–18% of patients with

RCM hypersensitivity.^{9–12} This creates a therapeutic dilemma when patients with a history of RCM allergy need urgent lifesaving therapies that require the use of RCM.

Cardiac catheterizations use RCM as an integral part of anatomic visualization. While over 1 million cardiac catheterizations were performed in 2010 according to the American Heart Association, almost 500,000 were percutaneous coronary interventions (PCIs).¹³ The current practice guidelines from the American College of Cardiology Foundation/American Heart Association Task Force recommend pretreatment with steroids and antihistamines in patients with a history of RCM anaphylaxis prior to undergoing cardiac catheterization and/or PCI.¹⁴

Data on additional pretreatment regimens for breakthrough RCM allergic reactions are lacking. We present a novel pretreatment regimen in 2 high-risk patients with coronary artery disease (CAD) and history of coronary artery bypass grafting (CABG) who had a history of both RCM anaphylaxis and breakthrough RCM anaphylaxis despite standard pretreatment regimens. This protocol is both safe and effective in preventing anaphylaxis in cardiac patients.

METHODS

Study Design

We conducted a retrospective analysis of consultations performed by a university allergy-immunology service from October 2014 to October 2015 for breakthrough RCM allergic reactions in cardiac patients. Patients were identified based on the International Classification of Diseases—ninth revision codes of 995.27 (Drug Allergy, Not Elsewhere Classified) and/or V15.08 (Contrast Media Allergy). We present 2 cases that met these criteria and required urgent cardiac intervention with the use of RCM. This study was approved by the Institutional Review Board at our facility.

Pretreatment Protocol

Our novel protocol is tailored for patients undergoing cardiac procedures with a history of breakthrough RCM anaphylaxis despite standard pretreatment regimens. This multi-day protocol uses systemic corticosteroids, antihistamines, and leukotriene receptor antagonists (LTRAs; Table 1). The duration of pretreatment is determined by extending medication dosing 2 days longer ($N + 2$) than the prior failed length (N) of RCM allergy pretreatment. For the entire duration of pretreatment, the patient receives systemic corticosteroids, H1 and H2 antihistamines, and an LTRA. For the last 24 hours of the protocol, the systemic corticosteroid is transitioned from oral prednisone 40 mg every 8 hours to intravenous (IV) methylprednisolone 40 mg every 4 hours prior to the RCM exposure.

RESULTS

Case 1

A 66-year-old male presented to an outside hospital with increased shortness of breath, chest pain, and lightheadedness. His relevant cardiac history included diabetes mellitus type II, hypertension, CAD with prior 3-vessel CABG, and 2 subsequent PCIs with stent placement (Table 2). He also had multiple medication, food,

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TABLE 1. Breakthrough RCM Pretreatment Regimen

Days Prior to Procedure	Systemic Corticosteroid	H1 Antihistamine	H2 Antihistamine	LTRA
N + 2	Prednisone 40 mg q8h*	Fexofenadine 180 mg q24h†	Famotidine 20 mg q12h	Montelukast 10 mg q24h
1	Methylprednisolone 40 mg IV q4h	Fexofenadine 180 mg q24h†	Famotidine 20 mg q12h	Montelukast 10 mg q24h
1 h		Diphenhydramine 50 mg IV		

*In patients with diabetes mellitus, steroid dose may be decreased to 40 mg prednisone daily.

†If inpatient or unable to tolerate oral medications, diphenhydramine 50 mg q6h may be substituted for fexofenadine.

N, number of previous pretreatment days.

and environmental allergies for which he was not receiving any specific medical therapy other than avoidance. On current presentation for unstable angina, he was noted to have a negative serum troponin but a positive Lexiscan (regadenoson) nuclear stress test, necessitating transfer to a tertiary care center. An urgent cardiac catheterization was indicated; however, it was noted that the patient had a history of flushing, slurred speech, and confusion during a prior cardiac catheterization thought to be due to RCM allergy. Therefore, he was premedicated with prednisone 40 mg at 12 and 2 hours and oral diphenhydramine 50 mg 4 hours prior to the procedure per the local treating physician. Twenty minutes after IV injection of Isovue 370 (iopamidol), he developed diffuse urticaria, difficulty breathing, and copious oral secretions followed by bradycardia (heart rate = 44) and hypotension (blood pressure = 88/22 mm Hg). The procedure was aborted and he received 1 dose of epinephrine 0.5 mg intramuscularly followed by epinephrine 1 mg IV, famotidine 20 mg IV, diphenhydramine 50 mg IV, and hydrocortisone 100 mg IV. Because of persistent bradycardia and hypotension, he was treated with atropine 1 mg IV, a continuous dopamine infusion, and transferred to the intensive care unit for further monitoring. While his hypotension improved, his chest pain persisted and he was transitioned from the dopamine infusion to a nitroglycerin infusion, which resolved his chest pain. As repeat cardiac catheterization was required, the allergy service was consulted.

On review of his records, he failed 1 day of prior pretreatment; therefore, he was pretreated for 3 days (N + 2) with our novel protocol for refractory RCM allergy (Table 1). Because of his uncontrolled diabetes mellitus type II, we elected to dose his prednisone at 40 mg every 24 hours instead of every 8 hours. In addition, he received diphenhydramine 50 mg IV every 6 hours, famotidine 20 mg every 12 hours, and montelukast 10 mg every 24 hours. The prednisone was stopped 24 hours prior to his cardiac catheterization, and he was transitioned to methylprednisolone 40 mg IV every 4 hours until the time of his procedure. The diphenhydramine, famotidine, and montelukast were continued for the remaining 24 hours. One hour prior to his RCM exposure, he was given an additional dose of diphenhydramine 50 mg IV. We also recommended use of an iso-osmolar RCM agent. He subsequently underwent successful PCI

using Visipaque 320 (iodixanol) with angioplasty and stenting of 5 critical lesions. On completion of his procedure, he had no symptoms of anaphylaxis and no recurrence of chest pain.

Case 2

A 63-year-old male presented with fatigue, dyspnea on exertion, and progressive chest heaviness at rest over the past several months. His relevant cardiac history included rheumatic heart disease with St. Jude aortic valve replacement, CAD with single vessel CABG, mitral stenosis, and hypertension (Table 2). He had multiple medication and environmental allergies for which he was not receiving any specific medical therapy other than avoidance. Echocardiogram was obtained and revealed severe mitral stenosis (0.9 cm² mitral valve area) and an ejection fraction of 50%–55%. He had a history of multiple prior anaphylactic reactions to RCM with symptoms including sneezing, throat tightness, and hypotension despite using 2 different pretreatment regimens. The first failed protocol included prednisone, diphenhydramine, and famotidine administered 24 hours prior to cardiac catheterization, and the second failed protocol administered prednisone for 3 days prior to cardiac catheterization. Because of his unstable angina and severe mitral stenosis, left and right cardiac catheterizations were indicated.

The patient was seen for outpatient allergy consultation, and based on his prior treatment failure of 3 days, a 5-day (N + 2) pretreatment protocol was implemented (Table 1). His pretreatment regimen included 4 days of prednisone 40 mg every 8 hours, fexofenadine 180 mg every 24 hours, famotidine 20 mg every 12 hours, and montelukast 10 mg every 24 hours. The patient was admitted to the hospital 24 hours prior to his cardiac catheterization and transitioned from prednisone to methylprednisolone 40 mg IV every 4 hours until the time of his RCM exposure. The fexofenadine, famotidine, and montelukast were continued. In addition, 1 hour prior to the procedure, he was given diphenhydramine 50 mg IV. He subsequently underwent successful left and right diagnostic cardiac catheterization with Isovue 370 without any sign of allergic reaction. As the patient also required a computed tomography angiogram of the coronary arteries for perioperative assessment after catheterization,

TABLE 2. Baseline Characteristics of Patients Undergoing Pretreatment

Patient #	Sex	Age (Years)	Comorbid Diseases	Clinical Indication for RCM	Symptoms of Prior RCM HSR	Time from Last HSR to Pretreatment Protocol
1	M	66	HTN, CAD, HLD, DM, OSA	UA	Hives, SOB, increased secretions, bradycardia, slurred speech	Reaction #1 was 6 months prior Reaction #2 was 5 days prior
2	M	63	HTN, HLD, OSA, AFib, AVR, MS	UA, MS	Sneezing, throat tightness, hypotension	19 years prior

AFib, atrial fibrillation; AVR, aortic valve replacement; DM, diabetes mellitus; HLD, hyperlipidemia; HSR, hypersensitivity reaction; HTN, hypertension; M, male; MS, mitral stenosis; OSA, obstructive sleep apnea; SOB, shortness of breath; UA, unstable angina.

the methylprednisolone 40 mg IV was continued every 4 hours and fexofenadine 180 mg every 24 hours, montelukast 10 mg every 24 hours, and famotidine 20 mg every 12 hours. Twenty-four hours after cardiac catheterization, he underwent successful computed tomography angiogram using Isovue 370 without any sign of hypersensitivity reaction.

DISCUSSION

Management of cardiac patients with a history of RCM anaphylaxis can be complex. Little is known about managing a patient with a history of breakthrough RCM anaphylaxis who has failed standard pretreatment regimens. We present a novel pretreatment regimen for high-risk cardiac patients with breakthrough RCM anaphylaxis who need urgent coronary interventions.

Previously identified risk factors for severe RCM allergic reactions include prior severe reactions to RCM, older than 60 years, the presence of cardiovascular disease, use of β -blocker medications, history of other allergy (food, medication, or environmental), history of severe asthma, the presence of hematologic conditions, and female sex.^{8,15,16} Furthermore, risk factors for severe breakthrough RCM allergic reactions despite standard pretreatment regimens include history of severe RCM reaction, drug allergy, allergy to 4 or more allergens, and chronic oral corticosteroid use.^{9,17} Our 2 patients were high risk for both severe initial and breakthrough RCM anaphylaxis as they were older than 60 years, had CAD, were on β -blocker therapy, had prior severe RCM allergic reactions, and had multiple other medication and environmental allergies. Although both patients had underlying allergic disease, neither patient was using any medication therapies on a chronic basis to treat their allergies. If a patient who required this protocol was on baseline allergy medications, such as H1 or H2 antihistamines, or LTRAs, we recommend continuing/adjusting these allergy medications to reflect what is recommended in this pretreatment protocol.

Two primary pretreatment regimens have been used for patients with a history of RCM anaphylaxis undergoing cardiac procedures. The first consists of prednisone 50 mg orally given at 13, 7, and 1 hour prior to the procedure and diphenhydramine 50 mg orally 1 hour prior to the procedure.^{5,6} The second pretreatment regimen has been successfully used in 9 patients for emergent situations: hydrocortisone 200 mg IV every 4 hours until procedure completion and diphenhydramine 50 mg 1 hour prior to the procedure.¹⁸ Neither of these studies addressed the treatment of patients who required urgent intervention and had a history of severe breakthrough RCM anaphylaxis despite standard pretreatment. Thus, we developed a flexible and unique protocol to address this unmet clinical need. In coordination with the treating cardiologist, the initial days of our pretreatment regimen can be administered on an outpatient basis with the patient admitted only 24 hours before the planned cardiac intervention and RCM exposure.

Reactions to RCM are believed to result from direct stimulation of mast cells and basophils leading to degranulation and a release of systemic mediators, causing anaphylaxis.³ The mechanism by which systemic corticosteroids prevent anaphylaxis is not completely understood. It is hypothesized that steroids may stabilize cell membranes and inhibit mediator generation and release.^{7,17} We speculated that a prolonged course of steroids would confer a greater stability of the mast cell and basophil membranes and elected to prolong the systemic corticosteroid course ($N + 2$, where N represents the prior number of days of failed steroid pretreatment). H1 antihistamines bind to the histamine receptor and act as inverse agonists, therefore inactivating and stabilizing the receptor.¹⁹ As H1 and H2 antihistamines are used as adjunctive therapy for acute anaphylaxis and for prevention of anaphylaxis in allergen immunotherapy pretreatment protocols,^{20,21} we elected to use this therapeutic approach

in these patients as they had failed the standard pretreatment regimen with systemic corticosteroids and H1 antihistamines. The use of the H2 antihistamine, cimetidine, is controversial in RCM prophylaxis as one study showed a higher incidence of RCM anaphylaxis in the group pretreated with prednisone–diphenhydramine–ephedrine–cimetidine compared to the prednisone–diphenhydramine–ephedrine pretreatment group. Interestingly, this increase in RCM anaphylaxis was not seen when comparing the group pretreated with prednisone–diphenhydramine–ephedrine–cimetidine to the prednisone–diphenhydramine pretreatment group.²² The mechanism underlying this observation is unknown. Because of its safety profile in cardiac patients, we opted to use famotidine as our H2 antihistamine.²³ Cysteinyl leukotrienes may also contribute to RCM allergic reactions.²⁴ Two prior studies successfully used montelukast in pretreatment protocols: one for emergent PCI in ST-elevation myocardial infarction patients with a history of RCM allergy and another for patients undergoing rush venom immunotherapy.^{25,26} Therefore, we elected to add montelukast to our novel pretreatment regimen.

There are 3 main categories of contrast media used for cardiac catheterizations: high-osmolar, low-osmolar, and iso-osmolar agents. Out of these, iso-osmolar agents have the lowest osmolality, approximating that of blood (290 mOsm).²⁷ Prior studies have identified a higher risk of immediate hypersensitivity reactions with high-osmolar contrast media and have shown a decrease in reactions by switching to low-osmolar contrast.^{4,7,27} In case 2, it was recommended that the patient receive a low-osmolar agent (Isovue 370) in addition to our pretreatment regimen. In case 1, as the patient had already experienced anaphylaxis despite a standard pretreatment regimen and use of a low-osmolar contrast agent (Isovue 370), we recommended switching to the iso-osmolar agent, Visipaque 320. In conjunction with our novel protocol and this agent, the patients tolerated their procedures without complication.

This case series has several limitations including the limited sample size and the retrospective nature of the analysis. Additionally, the use of prednisone 40 mg every 24 hours (case 1) did not seem to reduce the efficacy of the protocol compared to prednisone 40 mg every 8 hours (case 2). Therefore, in future protocols a lower prednisone dose may be considered as an acceptable alternative. Further validation of this protocol will require a larger patient series.

CONCLUSION

Our novel pretreatment protocol successfully prevented anaphylaxis in 2 high-risk cardiac patients with a history of breakthrough RCM anaphylaxis. In using systemic corticosteroids, H1 and H2 antihistamines and an LTRA for 2 days longer than the prior failed length of pretreatment ($N + 2$), we mitigated hypersensitivity reactions to RCM. In addition, we recommend this treatment regimen be used in conjunction with administration of the lowest osmolality RCM agent available. We are hopeful that this flexible protocol presented in this study will provide an effective therapeutic option for high-risk patients in need of lifesaving procedures such as cardiac catheterization and PCI despite their history of breakthrough RCM anaphylaxis.

DISCLOSURES

Nothing to declare.

REFERENCES

1. World Health Organization. International drug monitoring: the role of national centres. Report of a WHO meeting. *World Health Organ Tech Rep Ser.* 1972;498:1–48.
2. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy.* 2014;69:420–437.
3. Solensky R, Khan DA. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010;105(4):259–273.

4. Wolf GL, Mishkin MM, Roux SG, et al. Comparison of the rates of adverse drug reactions. Ionic contrast agents, ionic agents combined with steroids, and nonionic agents. *Invest Radiol*. 1991;26:404–410.
5. Greenberger PA, Patterson R, Radin RC. Two pretreatment regimens for high-risk patients receiving radiographic contrast media. *J Allergy Clin Immunol*. 1984;74:540–543.
6. Marshall GD Jr, Lieberman PL. Comparison of three pretreatment protocols to prevent anaphylactoid reactions to radiocontrast media. *Ann Allergy*. 1991;67:70–74.
7. Goss JE, Chambers CE, Heupler FA; Members of the Laboratory Performance Standards Committee of the Society for Cardiac Angiography and Interventions. Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedures: Guidelines for prevention, diagnosis, and treatment. *Cathet Cardiovasc Diagn*. 1995;34:99–104.
8. Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S126–S137.
9. Davenport MS, Cohan RH, Caoili EM, et al. Repeat contrast medium reactions in premedicated patients: frequency and severity. *Radiology*. 2009;253:372–379.
10. Freed KS, Leder RA, Alexander C, et al. Breakthrough adverse reactions to low-osmolar contrast media after steroid premedication. *AJR Am J Roentgenol*. 2001;176:1389–1392.
11. Jingu A, Fukuda J, Taketomi-Takahashi A, et al. Breakthrough reactions of iodinated and gadolinium contrast media after oral steroid premedication protocol. *BMC Med Imaging*. 2014;14:34.
12. Mervak BM, Davenport MS, Ellis JH, et al. Rates of breakthrough reactions in inpatients at high risk receiving premedication before contrast-enhanced CT. *AJR Am J Roentgenol*. 2015;205:77–84.
13. Mozaffarian D, Benjamin EJ, Go AS, et al; the writing group members. Heart disease and stroke statistics – 2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38–e360.
14. Levine GN, Bates ER, Blankenship JC, et al; Writing Committee Members and the ACC/AHA Task Force Members. 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:2574–2609.
15. Bottinor W, Polkampally P, Jovin I. Adverse reactions to iodinated contrast media. *Int J Angiol*. 2013;22:149–154.
16. Nayak KR, White AA, Cavendish JJ, et al. Anaphylactoid reactions to radiocontrast agents: prevention and treatment in the cardiac catheterization laboratory. *J Invasive Cardiol*. 2009;21:548–551.
17. Schopp JG, Iyer RS, Wang CL, et al. Allergic reactions to iodinated contrast media: premedication considerations for patients at risk. *Emerg Radiol*. 2013;20:299–306.
18. Greenberger PA, Halwig JM, Patterson R, et al. Emergency administration of radiocontrast media in high-risk patients. *J Allergy Clin Immunol*. 1986;77:630–634.
19. Church DS, Church MK. Pharmacology of antihistamines. *World Allergy Organ J*. 2011;4(3 suppl):S22–S27.
20. Portnoy J, Bagstad K, Kanarek H, et al. Premedication reduces the incidence of systemic reactions during inhalant rush immunotherapy with mixtures of allergenic extracts. *Ann Allergy*. 1994;73:409–418.
21. Lieberman P, Nicklas RA, Oppenheimer J, et al. Anaphylaxis – a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115:341–384.
22. Greenberger PA, Patterson R, Tapio CM. Prophylaxis against repeated radiocontrast media reactions in 857 cases. Adverse experience with cimetidine and safety of β -adrenergic antagonists. *Arch Int Med*. 1985;145:2197–2200.
23. PEPCID® (Famotidine). US prescribing information. 2011. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2011/019462s0371bl.pdf. Accessed April 29, 2016.
24. Böhm I, Speck U, Schild H. A possible role for cysteinyl-leukotrienes in non-ionic contrast media induced adverse reactions. *Eur J Radiol*. 2005;55:431–436.
25. Hubbard CR, Blankenship JC, Scott TD, et al. Emergency pretreatment for contrast allergy before direct percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiol*. 2008;102:1469–1472.
26. Wöhrl S, Gamper S, Hemmer W, et al. Premedication with montelukast reduces local reactions of allergen immunotherapy. *Int Arch Allergy Immunol*. 2007;144:137–142.
27. Klein LW, Sheldon MW, Brinker J, et al; Interventional Committee of the Society for Cardiovascular Angiography and Interventions. The use of radiographic contrast media during PCI: a focused review: a position statement of the Society of Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2009;74:728–746.