
Letters

RADIOCONTRAST-INDUCED ANAPHYLAXIS DESPITE PRETREATMENT AND USE OF ISO- OSMOLAR CONTRAST

Patients may experience anaphylactic reactions with intravascular and nonvascular exposure to radiocontrast media (RCM).¹ Patients who have had anaphylactic reactions to RCM are at increased risk to have repeat reactions on subsequent exposure.¹ The mechanism responsible for RCM-induced anaphylactic reactions is unknown. Because use of low-osmolar contrast media has been associated with a decrease in the incidence of RCM-induced anaphylaxis,² it has been proposed that these reactions are triggered by hyperosmolality.³

We describe a 48-year-old woman for whom a computed tomographic scan of the abdomen and pelvis with contrast was ordered for the evaluation of unexplained abdominal pain. Fifteen years previously, she had developed an urticarial eruption within 10 minutes of the completion of a shoulder arthrogram. In light of this previous RCM reaction, she was referred to the Division of Allergy at Scripps Clinic for evaluation. Her medical history was notable for asthma. The patient received prednisone, 50 mg, orally at 20, 12, and 4 hours before the study and diphenhydramine, 50 mg, intramuscularly 1 hour before the study. Iso-osmolar RCM (iodixanol [Visipaque]) was administered intravenously. Within 5 minutes of completing the procedure, she developed an urticarial eruption involving her neck and chest. Over the next 10 minutes, she developed cough, wheeze, and chest tightness. She was treated with epinephrine, 0.3 mL (1:1,000) intramuscularly, levalbuterol, 1.25 mg nebulized, and cetirizine, 10 mg orally, with resolution of her symptoms over the next 60 minutes.

The pathophysiologic mechanisms of anaphylactic reactions to RCM are poorly understood. Although there is strong evidence that mast cell and basophil degranulation and resultant release of histamine, tryptase, and other mediators occur in immediate reactions to RCM, the precise stimulus for degranulation is unknown.³ Possibilities include chemical toxicity, complement activation, a nonspecific effect of hyperosmolar media, and IgE and non-IgE antibody-mediated mechanisms. Reports of patients with *in vitro* or *in vivo* evidence of RCM-specific IgE exist, but in most patients with anaphylactic reactions to RCM, evidence for medium-specific IgE is lacking.¹

Approaches to reduce the risk of recurrent anaphylactic reactions to RCM have involved the use of low-osmolar contrast media and pretreatment with antihistamines, corticosteroids, or both. A number of studies²⁻⁴ have demonstrated a significant reduction in the rate of initial and repeat anaphylactic reactions with the use of low-osmolar contrast media.

As a result, current guidelines for the prevention of recurrent anaphylactic reactions to RCM advocate the use of these agents.⁴

Since its release in 1996, iodixanol remains the only iso-osmolar contrast medium available in the United States. To the degree a hyperosmolar stimulus contributes to the mechanism of mast cell and basophil degranulation in RCM-induced anaphylactic reactions, there is a theoretical advantage of an iso-osmolar contrast medium. A randomized double-blind study⁵ comparing the effects of iodixanol to an ionic low-osmolar contrast medium, ioxaglate, on major adverse cardiac events in patients undergoing percutaneous transluminal coronary angioplasty demonstrated significantly fewer hypersensitivity reactions with iodixanol (0.7% vs 2.5%; $P = .007$). To our knowledge, no large-scale prospective studies evaluating the risk of repeat anaphylactic reaction to iso-osmolar contrast after a previous anaphylactic reaction to contrast media have been published. A prospective study⁶ involving 9 subjects with a prior reaction to high- or low-osmolar contrast media found no repeat reaction when iodixanol was used.

The administration of corticosteroids and/or antihistamines for the prevention of anaphylactic reactions to RCM in patients at increased risk is generally recommended.^{1,4} A recent systematic review⁷ examining the efficacy of corticosteroids and/or antihistamines for the prevention of immediate-type reactions to RCM identified 9 randomized controlled trials involving 10,011 adult patients. A significant reduction in respiratory symptoms, cutaneous symptoms, and potentially life-threatening reactions was found among treated patients.

We report a case of anaphylaxis induced by an iso-osmolar RCM (iodixanol) despite pretreatment with a corticosteroid and an antihistamine in a patient with a previous reaction to RCM. This raises the possibility of a nonosmolar mechanism of RCM-induced anaphylaxis. Physical properties other than osmolality may be involved. For example, iodixanol has a greater viscosity than a number of commonly used low-osmolar RCM.⁸

In patients with a previous reaction to RCM, pretreatment with corticosteroids and antihistamines and use of iso-osmolar contrast media effectively reduce the risk of repeat anaphylactic reactions but do not eliminate them. This case supports the need for continued vigilance and preparedness on the part of physicians involved in the care of patients undergoing imaging studies regardless of the pretreatment regimen or type of contrast media used.

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CARBOPLATIN DESENSITIZATION

We previously published in the *Annals* our experience using a slow desensitization infusion of carboplatin for patients who are allergic to this chemotherapeutic agent.¹ This protocol involved intravenous infusion of carboplatin with 1/1,000, 1/100, 1/10, and then the remainder of the total dose, each given over 24-hour periods, with a stepwise “exponential” increase in the infusion rate during each day. The reported protocol required that the initial 4-day regimen be decreased by 1 day at each subsequent 3-weekly infusion cycle by omitting the most dilute dose, eventually achieving a single 24-hour infusion. Despite the success of this approach, it was unlikely that the protocol would result in lasting drug tolerance because patients were not continuously exposed to carboplatin. This concern was strengthened by the observation that a single patient re-treated 1 year after a series of desensitization infusions had positive skin test results after her next desensitization infusion. Thus, it seemed that slow administration of the drug alone, with heavy premedication, was effecting acute drug desensitization but not lasting drug tolerance and, therefore, that the shortening of subsequent infusions could risk repeated anaphylaxis. This was of particular concern given a subsequent article² that suggested that regimens shorter than 24 hours had a significant repeated reaction rate. For these reasons, we adapted the original protocol to deliver the first 3 dilutions (1/1,000, 1/100, and 1/10 of the total dose) in 8 hours each, with the remainder administered over 24 hours, the same infusion protocol being followed at each 3-weekly cycle without omission of the most dilute dose (Table 1).

Authors have nothing to disclose.

Table 1. Adapted Carboplatin Infusion Protocol

Day	Hour	Bag No.	Bag dilution, in 1,000 mL	Rate, mL/h
Day 1	0	1	1/1,000 of total dose	43
	2			76
	4			136
	6			245
	8	2	1/100 of total dose	43
	10			76
	12			136
	14			245
	16	3	1/10 of total dose	43
	18			76
	20			136
	22			245
Day 2	24	4	Remainder (0.889 of total dose)	12
	27			17
	30			22
	33			30
	36			38
	39			52
	42			70
	45			93
	48	Stop		

Twelve consecutive women with ovarian cancer who had experienced anaphylactic reactions to carboplatin were referred to our department. Results of intradermal skin testing, performed as previously described,¹ were positive in 10 of these 12 women. The patients received a total of 33 infusion cycles using the modified protocol, along with the same regimen of corticosteroid and antihistamine cover as previously described.¹ All 12 patients tolerated the infusions without event. Cancer antigen 125 levels responded appropriately in 6 of 7 assessable patients; there was no significant change in 1 patient, possibly related to resistant disease. One patient had a normal cancer antigen 125 level at baseline but showed response on imaging, another declined further treatment after a single desensitization cycle, and the remaining 3 had received only a single infusion dose at the time of this writing.

Although some researchers have reported success using a 6-hour protocol,³ we found repeated allergic reactions in both patients in whom it was tried,¹ and, indeed, others have noted a significant repeated reaction rate even with infusions lasting 16.5 hours.² Our modified 2-day regimen is likely to be safer than and seems to be just as effective as our published protocol, and we, therefore, currently recommend it to carboplatin-allergic patients in whom carboplatin is the optimal agent.

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