

Hypersensitivity Reactions to Iodinated Radiocontrast Media: To Skin Test or Not to Skin Test



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Low-osmolality iodinated radiographic contrast media (RCM) are subdivided into either those that are twice human serum osmolality (eg, iopamidol 612 at 616 mOsm/kg/H₂O) or iso-osmolality (eg, iodixanol 550 at 290 mOsm/kg/H₂O or iopromide at 328 mOsm/kg/H₂O).¹ High-osmolality RCM can have serum osmolality of 1,000 mOsm/kg/H₂O or greater. The RCM also can be classified into ionic or nonionic agents. Immediate hypersensitivity reactions, such as acute urticaria, acute massive angioedema of the tongue, or anaphylactic shock, usually occur within minutes of injection of RCM, but “immediate” includes reactions occurring in the first hour after administration of RCM.² Delayed hypersensitivity reactions, such as acute urticaria or an erythematous or morbilliform rash, have onset between 1 hour and 1 week.² Fortunately, RCM are very safe from the perspective of immediate and delayed reactions. It was estimated that severe reactions occurred in 1:3,674 exposures to iohexol (0.03%) and 1:4,594 exposures to iodixanol (0.02%) at the Kaiser Permanente Southern California Health Plan facilities.³ From a series of 120,822 people who received RCM at a single institution in Chongqing, China, 506 (0.4%) experienced immediate reactions of which 1.4% were considered severe, with 7.7% labeled moderate and 90.0% mild.⁴ Stated differently, just 7 of 120,822 people developed a severe reaction, implying a probability of 1:17,260 (0.006%).⁴ There were no fatalities. Patients with a history of a reaction to RCM had a 22-fold greater incidence of reaction at 7.2%, compared with the incidence of immediate reaction of 0.32% in patients with a previous exposure to RCM without any untoward reaction.⁴ Some 5,128 of 18,934 patients underwent coronary artery angiography in the setting of a beta-adrenergic receptor antagonist, and 10 (0.2%) patients experienced an adverse reaction (1 serious). This incidence was one-third lower than in the patients who did not receive beta-adrenergic receptor antagonists (0.61%).⁴ This observation is analogous to the

previously reported lack of significant increase in immediate reactions to RCM in patients receiving beta-adrenergic receptor antagonists and undergoing coronary arteriography.⁵

Patients who have experienced immediate hypersensitivity (anaphylactic) reactions to RCM have evidence for mast cell activation, and serum tryptase level can be elevated. When fatalities occur, it has been suggested that a useful discriminatory concentration for serum tryptase, obtained postmortem, be 44.3 ng/mL or more instead of 11.4 ng/mL in surviving patients.⁶ A supporting and tragic example is that of a fatality from RCM in a 23-year-old woman who had undergone 3 previous procedures with RCM uneventfully.⁷ After administration of 100 mL of ioversol, she developed shortness of breath, felt hot, and then hypoventilated and became unresponsive with pulseless asystole. The postmortem serum tryptase concentration was 211 ng/mL.⁷ In another report of 8 cases of fatal anaphylaxis, the arterial blood pressure declined from 3 to 10 minutes after injection of RCM.⁸ The autopsy examinations did not reveal anatomic explanations for the deaths, but the postmortem serum tryptase concentrations ranged from 51 to 979 ng/mL.⁸ Degranulated mast cells were present in the spleen in all 8 cases.⁸ From an investigation of 27 adult patients who had experienced non-life-endangering immediate hypersensitivity reactions to RCM, measures of serum chymase and carboxypeptidase 3 proved to provide greater discrimination from controls than serum tryptase and prostaglandin D₂.⁹ It can be summarized from laboratory investigations over many years that mast cell activation could occur by (1) direct effects of RCM on mast cells and basophils, (2) activation of the coagulation-contact system, (3) activation of the complement system, (4) IgE-mediated processes, and (5) generation of nitric oxide from L-arginine.^{1,9}

RCM are based on the core tri-iodinated benzene ring and have hydrophilic side chains. The molecular weights range from 600 to 1,600 Da. Scientific studies have not been persuasive that RCM haptenate proteins to cause IgE-mediated hypersensitivity reactions. There has been considerable scientific disagreement across the Atlantic Ocean on the strength of evidence for IgE-mediated processes to explain immediate hypersensitivity reactions to RCM.² The 2010 practice parameters of the American Academy of Allergy Asthma and Immunology, the American College of Allergy Asthma and Immunology, and the Joint Council of Allergy Asthma and Immunology¹⁰ and the American College of Radiology Contrast Media Manual¹ do not support skin testing, whereas there has been support based on a 2009 European multicenter study (“For tests conducted within the time period from 2 to 6 months after the reaction, up to 50% of immediate reactors and up to 47% of nonimmediate reactors were skin test positive”),¹¹ an international consensus² of which I am a coauthor, and a report in this issue of the *Journal of Allergy*

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and *Clinical Immunology: In Practice*.¹² In particular, skin prick testing was conducted with undiluted RCM and if negative, intradermal tests with undiluted (initially) or 1:10 dilutions thereafter.¹² From a cohort of 423 patients experiencing immediate hypersensitivity reactions, 118 patients with nonimmediate reactions and 56 patients with unknown reactions to RCM, 80 (13.4%) patients were found to be skin test positive.¹² Upon readministration of RCM, 16 of 17 (94.1%) patients with positive skin test results tolerated the procedure without reaction compared with 201 of 216 (93.1%) patients with negative skin test results.¹² The investigators painstakingly carried out skin testing with up to 10 RCM to explore potential cross-reactivity and concluded that skin prick testing can identify safe alternatives. Curiously, the skin test results were most likely to be positive if testing was performed from 1 to 6 months after the reaction to RCM. This finding extends what has been reported previously with RCM.¹¹ It is unclear why if IgE-mediated, immunologic hypersensitivity is present, it would be so transient. Might there be similar transient production of anti-RCM IgE antibodies analogous to what occurs in a minority of patients who experience anaphylaxis to Hymenoptera stings and then lose skin test reactivity or *in vitro* anti-Hymenoptera venom IgE within months of the immediate reaction? For a potential explanation, during rush immunotherapy with Hymenoptera venom, there are increases in serum IL-10 by day 3 and in CD3+ IL-10 and CD14+ IL-10 secreting cells by day 5.¹³ Another question is why intradermal testing with undiluted or 1:10 dilutions of RCM did not cause anaphylaxis as would be expected with similar intradermal testing of aeroallergens, foods, Hymenoptera venoms, or penicillin and its determinants? What would the results of skin testing be if much fewer than 29% of the patients were atopic? It is appropriate to ask whether the investigators have overinterpreted their findings and that there will be little or no utility of skin testing to provide the most safety for patients on a prospective basis? To overcome the incomplete data, such as accurate identification of culprit RCM and

readministered RCM, it will be informative to explore the “skin test first” approach prospectively before practice should be changed.

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