

# Current Epidemiology and Management of Radiocontrast-Associated Acute- and Delayed-Onset Hypersensitivity: A Review of the Literature

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## ABSTRACT

Radiocontrast-associated acute-onset hypersensitivity reactions now occur less frequently than before 1990, when high-osmolar, ionic, radiocontrast agents were widely used. Premedication with corticosteroids and antihistamines does not reliably prevent recurrent low-osmolar radiocontrast-associated acute hypersensitivity reactions. Corticosteroid prophylaxis for acute hypersensitivity currently causes more morbidity than benefit. The specific radiocontrast agent that is associated with a patient's adverse reaction must be displayed in the drug intolerance or drug "allergy" field of their electronic health record to enable effective management and prevention of future reactions. The term *iodine allergy* should never be used in the context of radiocontrast-associated adverse reactions because it leads to poorer clinical outcomes. The time to onset of the reaction and the nature of the reaction must be noted in enough detail in the drug intolerance comment fields in the electronic health record to determine the potential mechanism for the reaction and to enable selection of the appropriate radiocontrast material for future exposures. Most individuals with a history of radiocontrast agent hypersensitivity can be effectively managed by selecting an alternative radiocontrast agent, without any premedication. Radiology Departments, catheterization laboratories, and all physicians who use parenteral radiocontrast media must have management plans in place to treat severe acute reactions when they occur. Patients should be informed that delayed-onset reactions, mostly benign rashes within one week of exposure, are as common or more common than acute reactions. Future radiocontrast-associated acute and delayed-onset reactions can be minimized, but never completely avoided, by using an appropriate alternative agent.

China. They prospectively collected data on all cases. They identified 506 (0.4%) hypersensitivity reactions, of which 90.0% were mild, 7.7% were moderate, and 1.4% were considered severe. Hypersensitivity reactions were more common with iso-osmolar agents than with hypo-osmolar radiocontrast media. Risk factors for acute reactions included previous acute reactions, asthma, doses higher than 100 mL, and injection rates higher than 5 mL/s. The authors were unable to reliably collect delayed-onset reaction data because many patients were in the facility only for the procedure.

We reported in 2012 that of 2,375,424 Kaiser Permanente Southern California (KPSC) Health Plan members who had a health care visit and at least 11 months of health care coverage during 2009, a total of 0.5% of females and 0.3% of males had a radiocontrast agent "allergy."<sup>7</sup> During 2009 a new radiocontrast "allergy" was reported in 0.1% of females who had at least 1 other drug "allergy," in 0.1% of males who had at least 1 other drug "allergy," 0.04% of females who had no other drug "allergy," and in 0.02% of males who had no other drug "allergy." Individuals with any drug "allergies" were more likely to use more health care services and thus might be more likely to be exposed to radiocontrast media. Between January 1, 2014, and April 30, 2017, there were 372 serious, acute-onset, radiocontrast-associated reactions reported by KPSC Radiology Departments, 335 (90.1%) associated with iohexol, 19 (5.1%) associated with iodixanol, 1 (0.3%) associated with diatrizoate, and 17 (4.6%) with the associated radiocontrast agent not reported. It is currently not possible to accurately identify all exposures to radiocontrast agents throughout the entire KPSC health care

## INTRODUCTION

The epidemiology and optimal management of radiocontrast-associated adverse reactions have changed dramatically since 1985, with the almost exclusive current use of low-osmolality nonionic radiocontrast agents and very low rates of use of high-osmolality ionic radiocontrast agents.<sup>1</sup> This review will concentrate on reports published since 2010. The goal of this review is to add clarity and specificity to the general suggestions given in the American College of Radiology's *ACR Manual on Contrast Media, Version 10.3*, last updated on May 31, 2017.<sup>2</sup>

benign delayed-onset, and severe delayed-onset. *Acute onset*, which occurs less than one hour after exposure, is typically caused by mast cell activation, either directly or, rarely, is immunoglobulin E (IgE) mediated.<sup>3</sup> *Delayed onset* is defined as starting more than one hour but typically starting more than three hours and up to two to five days after exposure; these reactions are thought to be T-cell-mediated, delayed-type hypersensitivity.<sup>4</sup> These reactions rarely rise to the level of a serious cutaneous adverse reaction, such as toxic epidermal necrolysis or Stevens-Johnson syndrome.<sup>5</sup>

## REVIEW OF THE LITERATURE Radiocontrast Agent Hypersensitivity Mechanisms

There are four general categories of radiocontrast-associated hypersensitivity reactions: benign acute-onset, anaphylaxis,

### Epidemiology

Li and coworkers<sup>6</sup> in 2016 reported on 120,822 individuals receiving iopromide, iodixanol, iopamidol, ioversol, iobitridol, or iohexol between January 2014 and March 2016 at a single institution in Chongqing,

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system or to capture all new acute and delayed-onset reactions because of the poor quality of the adverse drug reaction reporting in the electronic health record (EHR). Even when reported, the specific radiocontrast agent implicated is virtually never noted in the EHR, nor are the symptoms described in enough detail to confidently determine a mechanism. It was, however, possible to identify how much radiocontrast medium was purchased each year for KPSC and then estimate annual exposures. The amount of iohexol and iodixanol used annually in KPSC in 2014 through 2016 is displayed in Table 1. In KPSC we annually used about 11.5 to 16 times as much iohexol as iodixanol. We had approximately 1 reported severe acute reaction for every 183,697 mL (about 3674 exposures [range, 1837-18,370]) of iohexol and 1 reported severe acute reaction for every 229,684 mL (about 4594 exposures [range 1199-22,968]) of iodixanol.

Scheinfeld and colleagues<sup>8</sup> at Albert Einstein College of Medicine in New York, NY, reported in 2014 that of 927,000 total “allergies” documented during a 10-year period in their EHR, virtually none of the more than 7000 patients with “allergies” reported to “contrasts” or “iodine” had a specific radiocontrast agent listed.

Dean et al<sup>9</sup> reported in 2015 that adverse reactions after radiocontrast-enhanced computed tomography (CT) scans were reported at a lower overall rate in inpatients compared with outpatients, but the reactions reported were more severe. Less than 10% of the reported reactions were delayed onset. Most patients were exposed to iohexol; only a small minority were exposed to iodixanol. There were 86 (0.23%) of 34,508 reactions reported after outpatient CT scans vs 10 (0.03%) of 38,066 reactions reported after inpatient CT scans. The overall use of adrenaline was the same in both groups—4 uses in inpatients (1 in 9516 exposures), and 4 uses in outpatients (1 in 8627 exposures).

Palmiere and Reggiani Bonetti<sup>10</sup> reviewed radiocontrast-associated anaphylaxis fatalities in 2014. They identified 24 cases, initially reported between 1972 and 2012. Only a minority of the

**Table 1. Radiocontrast agent use in Kaiser Permanente Southern California, 2014 through 2016**

Agent	2014	2015	2016	Total
Iohexol <sup>a</sup> (mL)	19,088,565	20,385,128	22,064,825	61,538,518
Iodixanol <sup>b</sup> (mL)	1,650,500	1,361,000	1,352,500	4,364,000
Total (mL)	20,739,065	21,746,128	23,417,325	65,902,518
Approximate exposures at 50 mL per exposure	414,782	434,922	468,346	1,318,050

<sup>a</sup> Typically used at 10 mL to 100 mL per exposure.

<sup>b</sup> Typically used at 10 mL to 250 mL per exposure.

cases had any previous exposure to radiocontrast agents. The authors concluded that “risk” factors for fatal anaphylaxis included any history of asthma, allergic rhinitis, atopic dermatitis, multiple allergies, drug allergy, food allergy, previous radiocontrast exposure,  $\beta$ -blocker or nonsteroidal anti-inflammatory drug use, and any preexisting condition including any cardiovascular, renal, hematologic, autoimmune, or metabolic disease. This list is of questionable utility, with almost as many “risk” factors as reported cases.

There have been only rare reported cases of radiocontrast-associated serious cutaneous adverse reactions, specifically Stevens-Johnson syndrome or toxic epidermal necrolysis.<sup>5</sup> There has been one case of recurrent iopromide-associated Stevens-Johnson syndrome reported, with three distinct episodes.<sup>11</sup>

### Prevention of Recurrent Radiocontrast-Associated Reactions

Kolbe and coworkers<sup>12</sup> at the Mayo Clinic in Rochester, MN, reported in 2014 data from 245 individuals with reactions (0.08%, or 1 in 1222), of 299,413 total individuals exposed to low-osmolality contrast media between 2002 and 2008. All affected individuals noted only acute-onset hives associated with their radiocontrast agent exposure. Seventy-three of these 245 individuals then had at least 1 additional radiocontrast exposure through 2009. The authors excluded 8 patients who were receiving long-term corticosteroid therapy and 15 additional patients who had their index radiocontrast-associated reaction before 2002, to avoid individuals with their index reaction occurring after high-osmolar ionic radiocontrast agent exposure. The remaining 50 study subjects had 133

subsequent radiocontrast exposures, with a median of 2 exposures and a range of 1 to 11. There were 19 individuals (38.0%) who had at least 1 additional episode of radiocontrast-associated hives, for a total of 26 events (19.5%) in the 133 imaging studies. Paradoxically, individuals who were premedicated were more likely to have hives with subsequent exposures. There was no premedication given before 89 (66.9%) of the scans. Those premedicated with diphenhydramine had an adjusted odds ratio of 1.2 (95% confidence interval = 0.2-7.3,  $p = 0.85$ ). Those premedicated with corticosteroids had an adjusted odds ratio of 14.3 (95% confidence interval = 4.1-50.4,  $p < 0.0001$ ). Those premedicated with corticosteroids and diphenhydramine had an adjusted odds ratio of 8.3 (95% confidence interval = 1.8-37.9,  $p = 0.006$ ). The authors concluded that premedication may not be necessary, but radiology personnel need to be aware of prior reaction history and be knowledgeable in recognition and treatment of these reactions.

Mervak and coworkers<sup>13</sup> in 2015 reported on 626 inpatients with a history of acute-onset radiocontrast-associated hypersensitivity who received a 13-hour corticosteroid and diphenhydramine premedication regimen before reexposure to low-osmolar radiocontrast materials between January 2010 and December 2013. Breakthrough reactions occurred in 13 (1.2%). This is about 3 or 4 times the ordinary reaction rate in the general population.<sup>13</sup>

Jung et al<sup>14</sup> in 2016 retrospectively reported on 322 patients with a history of acute-onset radiocontrast agent reactions, seen between June 2010 through May 2012, who were reexposed to low-osmolar contrast media after premedication with

antihistamines, corticosteroids, or both. Breakthrough reactions occurred in 3.4% of all patients and in 14.3% of patients with severe index reactions.

Abe and coworkers<sup>15</sup> from Japan reported in 2016 data from 771 individuals seen between January 2006 and September 2014 with a history of a previous radiocontrast-associated adverse reaction who were reexposed to a nonionic radiocontrast agent. The same radiocontrast medium was used in 220 individuals (28.5%) without premedication (Group 1) and in 271 (35.1%) with premedication (Group 2). A different radiocontrast agent was used in 58 (7.5%) without any premedication (Group 3) and in 222 (28.8%) with premedication (Group 4). Group 1 had 61 (27.7%) repeated reactions. Group 2 had 47 repeated reactions (17.3%,  $p < 0.01$ ). Group 3 had only 3 repeated reactions (5.2%,  $p < 0.001$ ). Group 4 had 6 repeated reactions (2.7%,  $p < 0.001$ ). The authors concluded that changing the radiocontrast agent was more effective than premedication for subsequent exposures. Premedication was also not helpful in preventing reactions to nonionic radiocontrast agents in individuals with a history of an ionic radiocontrast-associated reaction.<sup>15</sup>

Mammarappallil and coworkers<sup>16</sup> from Wake Forest University and Duke University in NC reported in 2016 on the first 500 patients newly labeled as “allergic” to iodinated contrast agents between 1999 and 2009 at a single academic tertiary care hospital. They found that only 83 (16.6%) had both evidence of radiocontrast exposure and documentation compatible with a hypersensitivity reaction noted in the EHR. There were 69 (13.8%) who had evidence of radiocontrast exposure and did have nonhypersensitivity reactions documented, 19 (27.5%) with benign isolated swelling, 38 (55.1%) with “concerns about renal insufficiency,” and 12 (17.4%) with various benign isolated symptoms such as warmth, flushing, nausea, or taste perversion. The authors found that 224 (44.8%) had evidence of radiocontrast exposure but no documentation supporting any hypersensitivity or nonhypersensitivity reaction. The

final 124 individuals (24.8%) had no evidence of any radiocontrast exposure or reaction. Mammarappallil et al<sup>16</sup> also found that asking the patient was often not helpful because the patient was unsure of what, if anything, happened and were just told they were “allergic” to radiocontrast material, even if they had no documented exposure. The authors concluded that it is necessary to train the medical community to document accurately and completely when radiocontrast-associated reactions occur.

Berti and coworkers<sup>17</sup> from Italy reported in 2016 that 35 patients with breakthrough reactions to radiocontrast agents had a lower incidence of positive skin test reactions than 28 patients with an initial hypersensitivity reaction. This is evidence that most breakthrough reactions are not IgE mediated.

Lee and coworkers<sup>18</sup> from Korea reported in 2016 on a group of 453 (3.0%) individuals (of 14,785 seen between January 2014 and December 2015) with a history of mild radiocontrast-associated acute-onset hypersensitivity who had another nonionic radiocontrast study. The authors retrospectively identified 273 individuals (60.3%) who had been pretreated with chlorpheniramine maleate 4 mg, 30 to 60 minutes before their repeated radiocontrast exposure. There was no randomization, and the decision to pretreat was made by the physician using his or her judgment. There was no difference in the recurrence of an acute hypersensitivity reaction between the pretreated and the nonpretreated groups (10.6% vs 11.7%,  $p = 0.729$ ). There was also no difference in the time to recurrent reaction or reaction severity. There was no effort made to change the specific nonionic radiocontrast material used.

Lerondeau and coworkers<sup>19</sup> from France reported in 2016 on 340 patients referred for evaluation of radiocontrast agent hypersensitivity. Of these, 234 (71.5%) had normal (“negative”) test and rechallenge results. Another 97 (28.5%) had abnormal (“positive”) test or rechallenge results. Of those with abnormal results, there were 55 (56.7%) whose test or rechallenge was positive to the index radiocontrast agent. There were 33 (34.0%) whose test was negative to

the index radiocontrast material, but of these, 3 (9.1%) uniquely tested positive to an excipient and 30 (90.9%) were test or challenge positive to 1 or more other radiocontrast agents. Finally, there were 9 (9.3%) in the abnormal results group who had an unknown index radiocontrast medium, but who were test or challenge positive to an excipient or to 1 or more radiocontrast agents. The authors concluded that their data were only useful in evaluating the risks of recurrent delayed-onset reactions.<sup>19</sup> They identified 3 groups of radiocontrast agents that were very unlikely to cross-react for presumed T-cell-mediated, delayed-type hypersensitivity. Group A included ioxitalamate, iopamidol, iodixanol, iomeprol, ioversol, and iohexol. Group B included iobitridol and ioxaglate. Group C included only amidotrizoate/diatrizoate.<sup>19</sup> Unfortunately, iobitridol and ioxaglate are not currently approved for use in the US, and amidotrizoate/diatrizoate is an old-style ionic high-osmolality radiocontrast agent.

Davenport and Cohan<sup>20</sup> reported in 2017 that the morbidity associated with corticosteroid prophylaxis for acute-onset radiocontrast agent hypersensitivity currently outweighs any population benefit in hospitalized patients. They noted that the number needed to treat to prevent 1 severe acute reaction was approximately 569, and to prevent 1 lethal acute reaction was likely greater than 50,000. The authors concluded that corticosteroid prophylaxis, with the goal of preventing recurrent severe acute-onset reactions in high-risk inpatients, is likely associated with substantial costs and indirect harm related to longer hospital stay.

Böhm and coworkers<sup>21</sup> reported in 2017 on 300 patients with a history of “iodine allergy” entered into their medical record, compared with 2 age-, sex-, and procedure-matched groups with a nonspecific or specific radiocontrast agent “allergy.” Patients with the “iodine allergy” were more likely to get a suboptimal unenhanced CT scan when an enhanced CT image was clinically indicated. They also experienced higher rates of recurrent radiocontrast-associated reactions.

The radiocontrast materials that are non-cross-reacting for delayed-onset hypersensitivity are displayed in Table 2. The other nongrouped radiocontrast agents available

in the US are displayed in Table 3. Most of the agents are monomers. They all have very similar core structures, have a tri-iodinated benzene ring, and vary only by their

hydrophilic side chains. They all have very low protein binding; thus, they are unable to haptenate serum proteins and induce IgE-mediated acute-onset hypersensitivity.

**Table 2. Noncross-reacting radiocontrast agent groups for presumed T-cell-mediated, delayed-onset reactions**

Group	Radiocontrast material	Group	Radiocontrast material
<b>Group A</b>		<b>Group B</b>	
	loxitalamate (high-osmolar ionic monomer) 		lobitridol (low-osmolar nonionic monomer) 
	lopamidol (low-osmolar nonionic monomer) 		loxaglate (low-osmolar ionic dimer) 
	lodixanol <sup>a</sup> (low-osmolar nonionic dimer) 	<b>Group C</b>	
	lomeprol (low-osmolar nonionic monomer) 	Amidotrizoate/diatrizoate (high-osmolar ionic monomer) 	
	loversol (low-osmolar nonionic monomer) 		
	lohexol <sup>a</sup> (low-osmolar nonionic monomer) 		

<sup>a</sup> Used in Kaiser Permanente Southern California.

**Table 3. Other ungrouped nonionic radiocontrast materials available in the US**

Radiocontrast material
Iopromide (low-osmolar nonionic monomer) 
Iopamidol (low-osmolar nonionic monomer) 
Iothalamate (high-osmolar ionic monomer) 

Kelly and coworkers<sup>22</sup> in 2010 reported on the processing-dependent and processing-independent pathways for recognition of radiocontrast agents by specific human T cells. They concluded that radiocontrast media can activate T cells by direct binding to the major histocompatibility-T-cell receptor complex or by binding after uptake and processing by antigen-presenting cells. This calls into question the assumed inert nature of current radiocontrast agents.

### HOW TO MANAGE SPECIFIC CLINICAL SCENARIOS

Specific clinical scenarios of radiocontrast-associated hypersensitivity and their management are displayed in Table 4. Additional detail is provided beyond the general recommendation in the American College of Radiology's *ACR Manual on Contrast Media, Version 10.3*.<sup>2</sup>

If either iobitridol or ioxaglate is ever approved for use in the US, they would be the agents of first choice over amidotrizoate/diatrizoate in patients with a history of a severe delayed-onset reaction to iohexol or iodixanol. If corticosteroids are used to help prevent delayed-onset reactions, clinicians

should consider starting the dosing at least 24 hours before the radiocontrast exposure, to allow enough time for the corticosteroids to induce new regulatory proteins, and use a several-day course, such as prednisone at 40 mg/d for 5 days.

If the patient had a severe acute-onset reaction to an unknown contrast agent before 1990 and only amidotrizoate/diatrizoate is now available, then pre-treatment with oral prednisone 40 mg, 16 hours, 6 hours, and 1 hour prior, and oral diphenhydramine 50 mg, 1 hour before exposure, has been shown to reduce recurrent severe acute reactions.<sup>22</sup>

If any mild acute reaction occurs, such as flushing or hives, treat with diphenhydramine 50 mg. If there are any signs or symptoms of anaphylaxis, immediately use adrenaline, 0.3 mL of 1:1000 concentration intramuscularly. This can be easily performed by having adrenaline autoinjectors available and all radiology staff trained in their use.<sup>23</sup> If adrenaline is used, check the patient's acute serum tryptase level.

Tell patients to report all delayed-onset rashes. Always list the exact radiocontrast agent used and supply enough detail in the drug "allergy" field of the EHR to allow other medical professionals treating the patient in the future to determine time of onset and severity.<sup>24</sup>

### CONCLUSION

Radiocontrast-associated acute-onset hypersensitivity reactions occur after about 0.4% of all exposures. Delayed-onset

reactions are probably as common or more common than acute-onset reactions, but are underreported. Most acute and delayed-onset reactions are mild. Premedication with corticosteroids and antihistamines fails to prevent many, if not most, recurrent acute or delayed-onset reactions. Corticosteroid prophylaxis for prevention of acute hypersensitivity currently appears to result in more morbidity than benefit. The specific radiocontrast agent associated with the adverse reaction must be displayed in the drug intolerance or drug "allergy" field of the EHR to enable effective management and prevention of future reactions. The time to onset of the reaction and the nature of the reaction should be noted in enough detail in the comment fields to determine the potential mechanism for the reaction, and to enable selection of an alternative radiocontrast medium for future exposures. The term *iodine allergy* should never be used in the context of radiocontrast-associated adverse reactions because it leads to poorer clinical outcomes. Most acute and delayed-onset reactions can be effectively managed by selecting an alternative radiocontrast material, without any premedication. Radiology Departments, catheterization laboratories, and all physicians who use parenteral radiocontrast agents must have management plans in place to treat serious acute reactions when they occur. Patients must be informed that delayed-onset reactions, mostly rashes occurring within one week of exposure, are as common or more common than acute

**Table 4. Management of future contrast exposures in individuals with previous radiocontrast-associated hypersensitivity**

Clinical history	Preferred radiocontrast material
Severe acute-onset reaction to an unknown radiocontrast agent before 1990	Iohexol or iodixanol without any premedication
Severe delayed-onset reaction to an unknown radiocontrast agent before 1990	Iohexol or iodixanol without any premedication
Acute-onset reaction to an unknown radiocontrast agent after 1990, assumed to be iohexol	Iodixanol without any premedication
Acute-onset reaction to iohexol	Iodixanol without any premedication
Acute-onset reaction to iodixanol	Iohexol without any premedication
Mild delayed-onset reaction to iohexol	Iodixanol without any premedication
Mild delayed-onset reaction to iodixanol	Iohexol without any premedication
Severe delayed-onset reaction to iohexol or iodixanol	Amidotrizoate/diatrizoate or consider iopromide or iopamidol and prednisone (40 mg/d for 5 d starting 1 d before exposure)

reactions. Future radiocontrast-associated acute- and delayed-onset reactions can be minimized, but probably never completely avoided, by using an appropriate alternative agent. ❖

#### Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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## What Would It Be Like In A Radiologist's Shoes?

To spend most of my day dealing with images of people: Plain black-and-white x-ray images, or speckled images caused by sound waves bouncing off organs, or images caused by dyes outlining arteries and veins, or contrast medium filling loops of bowel, or images reconstructed by computers into cross sections of the body ...

— *My Own Country*, Abraham Verghese, MBBS, b 1955, Indian-American physician-author