Rapid Desensitization to Overcome Contrast Allergy Prior to Urgent Coronary Angiography

Saurav Uppal,1 MD, Anthony E. DeCicco,2 MD, Anselma Intini,2,3 MD and Richard A. Josephson,2 MD

Summary

Allergic reactions to contrast media are a frequently reported complication of coronary angiography. The majority of patients experience mild, self-limited episodes, but in rare cases patients may experience severe, persistent symptoms. A strategy of premedication with corticosteroids and anti-histamines and an optimal selection of contrast agent is almost always successful in averting contrast reactions, yet a select few patients will continue to have breakthrough events. This is a case of recurrent, severe allergy to contrast media despite standard precautions complicating the treatment of non-ST elevation myocardial infarction (NSTEMI). Our patient was successfully managed with a strategy of rapid desensitization to iodinated contrast media achieved by administering progressively incremental doses of the media.

Key words: Coronary artery disease, Chemotoxic reaction, Anaphylactoid reaction

Minor allergic reactions to contrast media are a frequently reported complication of coronary angiography though severe allergic reactions are much less common. Such events are typically prevented with premedication and selection of appropriate contrast media prior to the procedure. Here we present a case of refractory, severe allergic reaction to contrast media during coronary angiography that was successfully managed with a desensitization protocol.

Case Report

The patient was a 67-year-old man with a history of non-obstructive coronary artery disease (CAD) diagnosed 3 years previously on a coronary angiogram that demonstrated a 50% stenosis in the mid left anterior descending artery (LAD), pacemaker placement for complete heart block (CHB), asthma and bladder cancer whom was initially admitted to our affiliated Veterans Hospital for a planned cystoscopy/retrograde pyelogram. While in recovery in the post-anesthesia care unit he informed his nurse of intra-operative chest pain that had since resolved. An electrocardiogram (ECG) was unchanged from baseline. His first troponin was 0.18. He was started on dual anti-platelet therapy and anticoagulation and continued on his beta-blocker and statin. His troponin peaked at 0.20 the following day. Urgent revascularization for NSTEMI was scheduled for the following morning.

Pre-catheterization evaluation revealed a significant history of allergic reaction to contrast media. In early 2013 the patient developed nausea and an erythematous, pruritic rash following a contrast-enhanced CT scan of the abdomen and pelvis. A contrast allergy was added to his medical record. He was scheduled for coronary angiography later that year, and was pretreated with oral prednisone 50 mg (13 hours, 7 hours and 1 hour pre-procedure), as well as oral diphenhydramine (1 hour pre-procedure). Despite pretreatment he developed severe nausea and pruritus, with scattered erythema and bullae noted on exam. He was treated with intravenous methylprednisolone, famotidine, and diphenhydramine, and monitored in the ICU for 2 days. He was hospitalized again in 2014 after developing similar symptoms following another CT scan of the abdomen and pelvis.

Given his extensive history of allergic reaction our Allergy and Immunology team was consulted. Their recommendations were to use non-ionic iso-osmolar contrast media (Visipaque, GE Healthcare Cork, Ireland), and to pretreat with prednisone, diphenhydramine, and ranitidine. In addition, they recommended a desensitization protocol prior to catheterization. Desensitization was performed in our cardiac intensive care unit (CICU). Serial dilutions of contrast were prepared and then the patient was given escalating doses of Visipaque, administered intravenously every 10 minutes as shown in the Table. Epinephrine, diphenhydramine, methylprednisolone, glucagon, and emergency equipment were available at bedside in case of an adverse reaction. Catheterization was originally sched-
Rapid desensitization to overcome contrast allergy

Table. Visipaque Contrast Desensitization

<table>
<thead>
<tr>
<th>Dose #</th>
<th>Dilution</th>
<th>Concentration (mg/mL)</th>
<th>Dose (mg)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:10,000</td>
<td>0.032</td>
<td>0.160</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1:5,000</td>
<td>0.064</td>
<td>0.320</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1:1,000</td>
<td>0.320</td>
<td>1.600</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>1:500</td>
<td>0.625</td>
<td>3.125</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>1:250</td>
<td>1.250</td>
<td>6.250</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>1:125</td>
<td>2.500</td>
<td>12.50</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>1:62.5</td>
<td>5.000</td>
<td>25.00</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>1:32</td>
<td>10.00</td>
<td>50.00</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>1:16</td>
<td>20.00</td>
<td>100.0</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>1:8</td>
<td>40.00</td>
<td>200.0</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>1:4</td>
<td>80.00</td>
<td>400.0</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>1:2</td>
<td>160.0</td>
<td>800.0</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>1:1</td>
<td>320.0</td>
<td>1600.0</td>
<td>5</td>
</tr>
</tbody>
</table>

Due to exigent circumstances in the catheterization lab, our patient’s scheduled procedure was delayed 1 hour, and our protocol was subsequently extended. To ensure that our patient remained fully desensitized during the delay, and as the half-life of Visipaque is approximately 2 hours, doses numbered 4 through 8 were repeated at intervals of 15 minutes after dose number 12 was administered. Dose number 13 was administered as our patient was being draped on the cath lab, and the procedure was completed less than 30 minutes after his last dose of Visipaque.

Notably, our patient was found to have a severe stenosis in the mid-LAD. He underwent successful PCI with a drug eluting stent (DES) immediately following his diagnostic angiography. He tolerated both procedures without any complications. During follow-up he remained asymptomatic, and was discharged without incident the following day.

Discussion

Cardiac angiography and PCI are central to the evaluation and treatment of CAD, procedures that rely on contrast media to accurately evaluate anatomy. Available contrast media differ in three specific properties. Contrast agents can be iodinated or noniodinated; however, there is a limited role for non-iodinated contrast in angiography, and we will therefore focus on iodinated media. These are available in ionic or nonionic preparations. Ionic contrast media can be prepared at hyperosmolar or low-osmolar concentrations, while nonionic media can be prepared at low-osmolar or iso-osmolar concentrations (Figure).

The rate of adverse reactions generally decreases in concert with osmolality. Thus ionic, high-osmolar contrast is associated with a 15% incidence of adverse events, whereas low-osmolar contrast is associated with a 3% incidence. Adverse reactions related to nonionic contrast media are estimated at 5-10%. These incidence rates are consistent with available data on adverse reactions for non-invasive radiologic procedures. Renal injury from contrast media is widely established and there are a few proposed risk models to predict the risk of renal injury. The rate of severe or prolonged reactions during catheterization...
zation is estimated at 0.23-2.8%, translating to a risk of 1 death per 55,000 procedures. Patients with a known previous history of adverse reaction to contrast media are at the highest risk of repeat reaction on subsequent procedures. Other risk factors thought to increase the risk include persistent asthma, female sex, and prior atopy.

The pathophysiology of adverse reactions can be broadly characterized as chemotoxic or anaphylactoid (but not anaphylactic). Chemotoxic reactions are the direct result of injury from the contrast media itself. Common symptoms associated with these reactions include warmth, flushing, vasovagal changes, and renal toxicity. Properties like osmolality and the infusion rate of the media highly influence these reactions. Unlike non-IgE mediated reactions, the chemotoxic reactions are directly dependent on dose and concentration of the administered agent.

Anaphylactoid reactions, as their name suggests, mimic true allergic reactions. Associated symptoms include generalized rash, hives, bronchial or laryngeal spasms, nausea/vomiting, hypotension and, rarely shock. Importantly, these manifestations seem to occur independent of the IgE pathway that is common to true allergic reactions. As the IgE pathway is avoided, these reactions do not require prior exposure and can occur on the 1st administration.

The appropriate management of anaphylactoid reactions begins with prevention. All efforts should be made to use nonionic, low- or iso-osmolar contrast. Patients with a history of prior reactions should be pre-medicated with one of two now standardized regimens, both involving corticosteroids and one using antihistamines along with ephedrine. Lasser, et al. demonstrated the efficacy of this intervention. The authors randomized 1155 patients to treatment with corticosteroids or placebo prior to exposure to contrast media either for urography or contrast-enhanced CT. Treatment with corticosteroids significantly reduced the rate of allergic reaction (1.7% versus 4.9%, \( P = 0.05 \)). However, as the efficacy of corticosteroids is not 100%, a limited number of patients will continue to have breakthrough reactions.

Desensitization has long been used for refractory allergic reactions to common allergens such as bee venom or penicillin. It is defined as the graduated exposure of an allergen to a patient, in order to create a temporary state of tolerance to that agent. Desensitization has been shown to have 95-100% efficacy in the prevention of recurrent adverse reactions in patients with histories of such reactions from drugs as variable as chemotherapy and anti-platelet agents. Data regarding the efficacy of contrast desensitization at the time of coronary angiography are more limited consisting of two prior case reports. Both used a similar non-catheterization laboratory protocol that had been modified for contrast agents. Hong, et al. presented a case of cardiac arrest and NSTEMI complicating contrast administration for chest CT. They administered 2 days of prophylactic glucocorticoids and diphenhydramine before using the desensitization protocol outlined in the Table. The patient tolerated subsequent coronary angiography and PCI (iodixanol, 190 mL total) without complication.

Gandhi, et al. described a case of progressive anaphylactoid reactions complicating successive percutaneous interventions for a woman with severe CAD and left main (LM) involvement. They administered prednisone 100 mg (1 mg/kg) at 13 hours, 7 hours, and 1 hour before desensitization; diphenhydramine 50 mg intramuscular 1 hour before desensitization; and ranitidine 300 mg orally 1 hour prior to desensitization. They then initiated desensitization using the protocol adapted from Hong, et al. The patient tolerated subsequent coronary angiography and LM PCI (iodixanol, 300 mL total) without complication.

The protocol we used for our patient was adopted from the above-mentioned studies. Due to unexpected delays in the procedure for our patient, repeated administration of doses 4 through 8 was performed to maintain his state of tolerance to the contrast media and to avoid any complications during the procedure. Our patient received his final dose of the protocol while he was being prepped in the catheterization lab. He tolerated the procedure without any complications and it seems the repeated doses to compensate for the delay maintained his tolerant state.

Conclusion

Awareness that contrast reactions are common, and are not universally preventable with widely used premedication regimens and contrast selection is needed. Desensitization to intravascular iodinated contrast is feasible, may be accomplished within a time frame suitable for many clinical situations, and thus allows optimal and safe diagnostic and therapeutic use of contrast in patients where it may otherwise be avoided or dangerous. In conclusion, rapid desensitization is an effective and safe strategy for the management of patients with refractory anaphylactoid reactions to contrast media.

Acknowledgment

The authors would like to thank Yoon Kim, MD (University Hospitals Cleveland Medical Center, Department of Allergy, Asthma and Immunology) for her help in the preparation of this manuscript.

Disclosures

Conflicts of interest: None.

References

4. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media: a report from the Japanese Committee on the safety of