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Current Understanding of Contrast Media Reactions and Implications for Clinical Management

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Contents

Abstract

Iodinated contrast media (CM) are an integral part of modern diagnostic medicine. Although these agents are considered to be relatively safe, adverse effects in the form of allergy-like reactions occur in a significant number of exposed patients. These reactions may be divided into immediate and delayed responses. Immediate (within 1 hour of administration) anaphylactic reactions range from urticaria and angioedema to laryngeal oedema, hypotension and even death. Delayed reactions to CM occur from 1 hour to 1 week after administration and usually have mostly cutaneous manifestations. History of prior CM reactions and atopy predispose patients to CM reactions. Despite intense research into the pathogenesis of the immediate anaphylactoid responses, new evidence shows that true IgE type I hypersensitivity mediation occurs only in rare, severe cases. The aetiology appears to be multifactorial in most individuals. There is strong evidence to conclude that type IV hypersensitivity is responsible for the delayed reactions to CM. Although switching to non-ionic agents significantly reduces the incidence of immediate reactions to CM, there is little consensus regarding corticosteroid prophylaxis in high-risk individuals. Skin testing and provocative challenges also provide little security. Therefore, physicians must be better prepared to treat immediate anaphylactoid responses. Preventing delayed CM reactions is best performed with patch and delayed intradermal testing in those with a history of prior reactions, although false-negative results have been reported. Corticosteroids and antihistamines may be required for treatment. Until newer agents are developed that negate these issues, healthcare providers must

strive to better understand the risk factors associated with CM reactions, as well as the available prophylactic and treatment options.

Iodinated contrast media (CM) are injected into human blood vessels more often than any other pharmacological agent.[1] In excess of 70 million injections are administered per year worldwide,[2] 15 million of which are undertaken in the US alone.[3] Although considered to be relatively safe, the sheer quantity of patients receiving these substances accounts for a significant number of adverse reactions ranging from simple cutaneous manifestations to life-threatening anaphylaxis. Minor adverse reactions are reported in 3–12%[4] of all recipients (depending on the agent), with mortality rates of <1 in 100 000 patients.[5]

CM is nevertheless an indispensable diagnostic aid that has revolutionised clinical practice since the late 1950s. That decade saw the breakthrough of the first relatively non-toxic iodinated CM with the introduction of sodium and meglumine salts of triiodinated benzoic acid derivatives.[6] These hyperosmolar (>1400 mOsm/kg) agents have an osmolality that is five to eight times that of blood.[7] Low-osmolality (600–850 mOsm/kg) CM arrived in the 1970s and was achieved by converting the triiodinated benzoic acid derivative into a non-ionic molecule. An ionic dimeric contrast agent soon followed, ultimately giving way to the non-ionic dimers of the 1980s – the most popular agents used today. This last class of CM has an osmolality similar to that of blood (290 mOsm/kg).[6] Table I lists the classes and names of agents available in clinical practice to date. The development of new products has focused mainly on reducing the osmolality of the injected solution and in the process has significantly reduced the occurrence of adverse reactions to CM exposure.[7]

Table I. Commercially available monomeric and dimeric X-ray contrast media (reproduced from Christiansen,[8] with permission from Lippincott Williams & Wilkins)

Generic name	Trade name[a]
Monomeric contrast media	
Ionic monomers	
Meglumine iothalamate	Conray®
Meglumine ioxithalamate	Telebrix®
Sodium amidotrizoate	Urografin®, Hypaque®
Non-ionic monomers	
Iohexol	Omnipaque™
Iopentol	Imagopaque™
Ioxitol	Oxilan®
Iomeprol	Iomeron®
Ioversol	Optiray®
Iopromide	Ultravist®
Iobitridol	Xenetix®
Iopamidol	Iopamiro®
Dimeric contrast media	
Ionic dimer	
Ioxaglate	Hexabrix®
Non-ionic dimers	
Iotrolan	Isovist®
Iodixanol	Visipaque®

a The use of trade names is for product identification purposes only and does not imply endorsement.

Just as CM has evolved over the past 50 years, so too has our understanding of the pathophysiology behind the 'allergy-like' adverse reactions to CM. This review will characterise those reactions (both immediate and delayed type) and examine the current evidence elucidating their mechanisms. In most cases, specific immunological pathways still need to be well characterised. Pathway involvement may also differ between individuals and further research is required to elucidate their exact details. This review concludes by analysing the most important consequence of where this leaves us today and what it all means (in terms of treatment and prophylaxis) for the countless physicians who must administer the millions of yearly doses of CM.

1. Types of Adverse Reactions

Adverse reactions to CM are typically divided into two classes: the immediate reactions that occur within 1 hour of contrast administration and the delayed reactions usually occurring between 1 hour and 1 week later.

Immediate reactions to CM produce a spectrum of symptoms that resemble anaphylactic reactions. These responses can range anywhere from nausea, itching, urticaria and angioedema to bronchoconstriction, laryngeal oedema, hypotension and even death[9-11] (see table II). They account for 20–30% of all reactions to CM.[12] Minor to moderate immediate CM reactions are encountered in as many as 12% of patients receiving high-osmolality ionic contrast agents and up to 3% of patients receiving low-osmolar, non-ionic CM.[4] In a large-scale prospective study, Katayama et al.[4] reported that severe reactions occur much less frequently, with incidences of 0.22% in patients receiving high-osmolality agents and 0.04% in patients receiving low-osmolality CM. However, the increased frequency of non-ionic CM use has made these agents responsible for the greatest absolute number of severe reactions.[13] Fatal reactions are exceedingly rare (1 : 100 000) with both types of contrast media.[5] Given these statistics, it is no surprise that most physicians currently prefer to use non-ionic CM agents.

Delayed reactions to CM are mainly mild to moderate skin reactions of the maculopapular exanthematous and urticarial/angioedematous types. Headache, nausea, vomiting, dizziness[15] and even thyrotoxicosis[16] (in rare individuals) have also been reported. Most of the late-onset skin reactions become apparent after a latency of 3 hours to 3 days and disappear within 1 week.[17] Spontaneous resolution with little or no therapy is usual. Despite figures of the incidence of late-onset CM reactions quoted as high as 8%,[17] Yasuda and Munechika[15] have showed that the truer frequency is approximately 2.1%. Their study was the first scientific placebo-controlled analysis of this issue that minimised false positive results and subjective patient responses. For unknown reasons, non-ionic dimeric contrast agents seem to cause more delayed cutaneous reactions than both ionic and non-ionic monomers.[18,19]

Several factors predispose patients to CM reactions (see table III).[6] These include, most significantly, previous adverse reactions to CM and a history of atopy, allergy or asthma.[20] Katayama et al.[4] found a 6-fold increase in reactions to both ionic and non-ionic CM following a previous adverse event. After carefully skin-testing reactors versus controls, Enright et al.[21] found that atopic individuals (those with allergic profiles by both history and skin/serum assays) were twice as likely to adversely react to CM than non-atopic individuals. This conclusion was confirmed by a large-scale prospective study conducted by Katayama et al.[4]

Table II. Clinical manifestations of allergy-like reactions to contrast media, divided by organ system (reproduced from Christiansen et al.,[14] with kind permission of Springer Science and Business Media)

Organ system	Clinical symptoms
Cutaneous (skin)	Erythema, urticaria, pruritus, angioedema, maculopapular eruptions, erythema multiforme, fixed drug eruptions, vasculitis
Cardiovascular	Hypotension, light-headedness, dizziness, fevers, chills, vasodilation, tachycardia, cardiac arrest, shock
Gastrointestinal	Nausea, vomiting
Respiratory	Dyspnoea, laryngeal oedema, bronchospasm, coughing, sneezing

Although most of the original studies grouped immediate and delayed contrast reactions, much of the new research has focused on defining risk factors for delayed reactions.[20,22] However, to date, there have still not been good studies separating out and comparing risk factors with each type of reaction. Of note, there have been no reports indicating that individuals with a previous delayed allergy-like reaction are at increased risk for developing an immediate reaction and vice versa.[17,20] Other general risk factors to adverse reactions to CM include age (higher in younger patients [aged 10–39 years][4]), gender (females more than males[17]) and seasonality (periods of pollinosis[22]).

2. Pathophysiology of Contrast Medium Reactions

Despite intense debate and research over the past 30 years, perhaps no aspect of CM reactions has been as poorly understood as the mechanisms underlying their respective pathogenesis. As the symptoms have always appeared allergy-like, scientists

Table III. Risk factors predisposing to general allergy-like reactions to contrast media (reproduced from Morcos and Thomsen,[6] with kind permission of Springer Science and Business Media)

Previous reactions to contrast media
History of allergy/atopy
History of asthma/bronchospasm
Cardiac disease
Dehydration
Renal disease
Age: very young/old patients
Haematological/metabolic diseases (e.g. sickle cell, polycythemia)
Anxiety/depression
Medications (β-adrenoceptor antagonists [β-blockers], interleukin-2, aspirin [acetylsalicylic acid], NSAIDs)
Seasonality: periods of pollinosis

have repeatedly tried to find sound immunological data to support their hypotheses. Although distinct holes still remain, their efforts have, nevertheless, yielded a better understanding of both immediate and delayed CM reactions.

2.1 Immediate

The most contentious dispute is the nature of the immediate reactions. The common cutaneous (erythema, urticaria, angioedema), cardiovascular (hypotension associated with tachycardia), respiratory (dyspnoea, bronchoconstriction) and digestive (nausea, vomiting, abdominal pain and diarrhoea) symptoms clearly resemble an anaphylactic response. Characteristic of anaphylaxis, there is conclusive evidence that that these reactions involve the granular release of histamine by mast cells and basophils. *In vivo* studies performed by Laroche et al.[23] reported increased plasma levels of histamine and tryptase (a specific marker of mast cell degranulation) in >70% of patients with immediate severe reactions to contrast media. Furthermore, the levels of both these markers correlated well with the severity of the reaction, which indicated that mast cell degranulation was responsible for the clinical symptoms of these immediate reactions.[23]

However, *in vivo* histamine release could be due to an IgE-mediated mechanism, a non-specific effect related to the hyperosmolality of the injected CM solution or the chemical toxicity of the administered molecule. Attempting to prove the allergic hypothesis, Brasch[24] has demonstrated that rabbits and guinea-pigs can produce specific IgG antibodies against analogues of CM and CM themselves. Other human studies have also favoured an IgE-mediated reaction. In a multicentre study comparing 20 patients with mild to severe reactions to CM versus controls, Laroche et al.[23] demonstrated significantly higher levels of specific IgE to Sepharose-bound ionic CM in affected subjects. Mita et al.[25] similarly showed specific IgE antibodies to protein-bound CM in the sera of some patients who were immediate reactors to ionic CM. Along with two patients in the Laroche study, there have been various other case reports describing evidence for an IgE-mediated immediate reaction to CM that is based on positive intradermal and skin prick tests.[11,26-29] Most recently, Laroche and his colleagues were able to show positive skin tests among those with the most severe, systemic responses in a series of CM reactors.[30]

Minor immediate reactions, which occur in the majority of affected patients, may be related to a dose-dependent, non-specific histamine release. A large body of evidence indicates that CM can activate human mast cells and basophils by IgE-independent mechanisms. Although certainly not the only factor, there has long been a direct *in vitro* correlation between the osmolality of CM and histamine release.[31-33] This could, in part, explain the higher incidence of immediate reactions with the first generation, high-osmolar ionic CM. However, many authors suggest that there are likely to be other direct, chemotoxic mechanisms that may be responsible for immediate CM reactions. These may include complement activation[20] or some yet to be defined pathways.

Recently, Lasser[1,34] has put forward a new theory to explain immediate CM reactions. Based on a series of red blood cell hemagglutination studies where CM had the ability to inhibit antigen-antibody binding, he contends that CM may act as 'pseudoantigens' (implying the ability to act like antigen, yet remaining unable to stimulate the formation of specific antibodies). He believes that in high concentrations, CM aggregation occurs, allowing non-specific

immunoglobulin-mediated (Fc portion of IgE) histamine release. However, this theory must remain conjecture until Lasser has direct *in vitro* and *in vivo* evidence to substantiate his claims. Additionally, Sontum et al.[35] have provided evidence against the ability of CM to aggregate in concentrated solutions. Although available data are in favour of an IgE-mediated mechanism for the severe or very severe immediate reactions, the pathophysiology of the milder acute reactions still remains poorly defined and is likely to be multifactorial. Further elucidation will require multicentre prospective studies and significant research.

2.2 Delayed

Unlike the immediate reactions, there is much more scientific unanimity when trying to explain the pathophysiology behind delayed CM reactions. These mostly cutaneous reactions, while usually taking the form of a maculopapular rash, urticaria and angioedema, can even present as iododerma,[36,37] fixed drug eruptions[14,38,39] or erythema multiforme.[40] There is strong circumstantial evidence to date that most of the CM-induced delayed skin reactions are caused by type IV hypersensitivity mechanisms. These mechanisms involve a pool of antigen-specific memory T cells in the skin that through cytokine secretion, produce the clinical symptoms instigated by eosinophils, monocytes and activated cytotoxic T cells. This assumption is based on the described clinical histories, risk factors, skin test results, results from provocation testing and descriptions of histological findings appearing after skin and provocation testing.[14]

First, the aforementioned clinical symptoms are similar to those of other drug-induced adverse reactions that are clearly T cell mediated. The reported onset (4–7 days after first exposure to a contrast medium and 1–2 days after re-exposure) and fading (within 1 week) of skin eruptions is also compatible with a T cell stimulation model.[8] Patch and delayed intradermal testing has additionally been routinely successful, with approximately 50% of patients reacting not only to the culprit CM but also to other, structurally similar contrast media.[20,41,42] The histopathology of skin eruptions, and positive skin and provocation test sites, also provide good evidence for a T cell-mediated mechanism. A dermal lymphocyte rich infiltrate accompanied by intradermal spongiosis and sometimes hydropic degeneration of the basal cell are among the typical findings.[8,40,41] Although the exact mode through which CM interact with T cells remains unclear, further investigations into this subject will likely only add to the evidence pointing to type IV hypersensitivity in delayed CM reactions.

3. Treatment and Prophylaxis

Just as there has been progress in characterising the aetiology of CM reactions, so too has there been development in learning how to prevent and treat them. Although far from complete, these data have definite clinical management implications for the physicians who repeatedly administer these agents.

3.1 Immediate

Clinicians trying to prevent immediate anaphylactic reactions to CM must first understand their risk factors. Most importantly, these include history of allergy or atopy and history of previous immediate reaction to CM.[6] Few patients have histories of *both* an immediate and delayed response.[17,20] Given that most previous immediate responders were likely to have been given an ionic CM, studies have showed that the switch to non-ionic CM alone resulted in a significant improvement in all categories of symptomatic reoccurrence.[4,43]

Significant controversy surrounds the issue of prophylactic corticosteroid treatment for patients at high risk of an adverse reaction. While Lasser et al.[44] demonstrated that corticosteroid prophylaxis (usually given >6 hours prior to treatment) reduced the incidence of reactions to ionic CM, Wolf et al.[43] contested that using non-ionic CM alone was the only proven beneficial measure. Supporting evidence for those who advocate prophylactic corticosteroid and antihistamine treatment for high risk patients given non-ionic CM comes from the work by Greenberger and Patterson,[45] and Lasser et al.[46] No studies have so far been conducted to evaluate

the effect of pre-treatment in patients with a previous reaction to a non-ionic CM. The recent guidelines issued by the European Society of Urogenital Radiology (ESUR) state that while all high-risk patients should receive non-ionic agents, there is only *conclusive* agreement on corticosteroid/antihistamine treatment in those who receive ionic CM.[47] It should be noted that corticosteroid use exposes the patient to well known adverse effects such as gastrointestinal ulcers, mood disturbances, a relative immunodeficient state and hyperglycaemia. Lastly, practitioners must be aware that serious, life-threatening reactions have been reported despite the use of premedication.[23,48-51]

Skin testing is another prophylactic measure of much dispute. Although positive skin tests have been found in certain immediate reactors to CM,[3,7,11,23,26-28,52] their predictive value is far from

Table IV. European Society of Urogenital Radiology 2004 guidelines for treating acute adverse reactions to contrast media (reproduced from Thomsen et al.,[55] with kind permission of Springer Science and Business Media)

Generalised anaphylactoid reaction
1. Call resuscitation team
2. Suction airway as needed
3. Elevate patient's legs if hypotensive
4. Oxygen by mask (6–10 L/min)
5. Intramuscular adrenaline (epinephrine) [1 : 1000], 0.5mL (0.5mg) in adults; repeat as needed. In paediatric patients: 0.01 mg/kg to 0.3mg maximum dose
6. IV fluids (e.g. normal saline, lactated Ringer's solution)
7. Histamine H_1 receptor antagonist (e.g. IV diphenhydramine 25–50mg)
Urticaria
Scattered, transient: supportive treatment including observation
Scattered, protracted: appropriate H_1-antihistamine intramuscularly or intravenously should be considered. Drowsiness and/or hypotension may occur
Profound: consider adrenaline 1 : 1000, 0.1–0.3mL (0.1–0.3mg) intramuscularly in adults, 0.01 mg/kg intramuscularly up to 0.3mg maximum in children; repeat as needed
Bronchospasm
1. Oxygen by mask (6–10 L/min.)
2. β_2-adrenergic receptor agonist metered dose inhaler (2–3 deep inhalations)
3. Adrenaline
a. normal blood pressure – intramuscular 1 : 1000, 0.1–0.3mL (0.1–0.3 mg), smaller dose in patient with coronary artery disease or elderly. In paediatric patients: 0.01 mg/kg up to 0.3mg maximum
b. hypotensive – intramuscular 1 : 1000, 0.5mL (0.5mg). In paediatric patients: 0.01 mg/kg up to 0.3mg maximum
Laryngeal oedema
1. Oxygen by mask (6–10 L/min.)
2. Intramuscular adrenaline (1 : 1000), 0.5mL (0.5mg) for adults; repeat as needed
Hypotension
Isolated
1. Elevate patient's legs
2. Oxygen by mask (6–10 L/min.)
3. IV fluids; rapidly, normal saline or lactated Ringer's solution
4. If unresponsive: adrenaline 1 : 1000, 0.5mL (0.5mg) intramuscular; repeat as needed
Vagal (hypotension and bradycardia)
1. Elevate patient's legs
2. Oxygen by mask (6–10 L/min.)
3. Atropine 0.6–1.0mg IV; may repeat if necessary after 3–5min, to 3mg total (0.04 mg/kg in adults). In paediatric patients: 0.02 mg/kg IV (0.6 mg/dose maximum) to 2mg total
4. IV fluids: rapidly, normal saline or lactated Ringer's solution

IV = intravenous.

proven as they may result in false negatives.[23] Given that the most severe immediate reactions may be IgE mediated, it is probably only wise to skin test in these unique subjects. Experience has shown that reactors with a positive skin test to a responsible CM have safely received another CM that provided negative results.

Although others have suggested provocative rechallenges for the most serious responders or 'test doses' for all patients,[53] no data support such strategies and they may just bring about false security. In fact, such rechallenges or trial doses[53] may cause death and must be avoided. The ultimate decision of whether to administer CM in high-risk patients comes down to cost/benefit analysis. In very high-risk patients, most physicians avoid giving the agents altogether. But when the examination is considered essential, non-ionic CM and potentially corticosteroid/antihistamine prophylaxis are to be administered only after careful explanation of the risks to the patient.

As important as prophylaxis, physicians must be fully aware of how to treat immediate anaphylactic reactions. Although most immediate reactions to CM resolve spontaneously,[6] even non-ionic agents can cause severe, life-threatening reactions.[3,9,28,29,48,50] Unfortunately, a recent study showed very poor emergency management skills by the physicians who administer most CM agents. Only 43% knew the correct adrenaline dose, notable inadequacies were discovered with corticosteroid, antihistamine, atropine and intravenous fluid use, and only 26% had completed a resuscitation course in the past 2 years.[54] Routine cardiopulmonary resuscitation and clinical management skills should be required of *all* physicians who administer CM. Just recently, ESUR has published new guidelines regarding management of acute CM reactions (see table IV).[55] Resuscitation equipment must also be checked regularly and kept readily available. Any patients who experience systemic reactions should have their procedures stopped immediately.

3.2 Delayed

Preventing delayed CM reactions requires first that radiologists and patients understand the risk factors (atopy, previous similar reactions) that may bring on skin reactions up to 7 days after agent exposure. In patients who experience eruptions, several investigators, with notable exceptions,[15] have shown that patch and delayed intradermal tests are useful for confirming a late-onset allergic reaction to CM and for studying cross-reactivity patterns in order to recommend alternative products for future studies.[8,14,20,40-42] Recently, the sensitivity of these tests have been questioned. In a case series, 5 of 12 patients had a non-serious relapse of the reaction upon receiving a CM to which they were skin-test negative.[56] Provocation testing with a stepwise increase in CM dose may, therefore, be attempted to verify negative skin test results.[56] While repeat reactions may occur despite its use,[14] intravenous injection of corticosteroid treatment has also been recommended in order to avoid repeat reactions if the causative agent is readministered.[41] For undiagnosed patients, a contrast medium that is structurally different from the product that precipitated the first reaction should be used if re-exposure is required.[8] Lastly, while most late-onset cutaneous reactions are self-limiting, moderate to severe maculopapular exanthema, fixed drug eruptions, urticaria or erythema multiforme may require treatment, including corticosteroids and antihistamines.[8] Patients should be advised to seek medical care if they experience skin reactions up to 1 week after CM injection.

4. Conclusion

Diagnostic exams requiring the use of CM will only increase as the population ages and technology advances. Although non-ionic agents may reduce the incidence of severe immediate reactions, we will likely continue to see 'allergy-like' responses to all CM agents until newer formulations can be developed that do not elicit the reaction. In order to deal with this reality over the long-term, scientists must add to recently acquired data and engage in additional research and multicentre prospective studies to better delineate the mechanisms behind both im-

mediate and delayed CM reactions, find new risk factors for reaction and develop effective pretreatment protocols. In the short term, radiologists, cardiologists and prescribing physicians need to better understand the risk factors and prophylactic measures involved with CM procedures and be ready to treat responders (especially those with severe reactions) at a moment's notice.

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