

Received Date : 17-Feb-2015

Revised Date : 22-May-2015

Accepted Date : 08-Jun-2015

Article type : Comment

Article Category: Comment

Iodinated contrast reactions – ending the myth of contrast allergic reactions to iodinated contrast agents in Urological Practice.

Veeru Kasivisvanathan¹², Bhamini Vadhvana³, Ben Challacombe⁴, Asif Raza^{13*}

¹Department of Urology, Northwick Park Hospital, London North West Healthcare NHS Trust, Watford Road, Harrow, HA1 3UJ

²Division of Surgery and Interventional Sciences, University College London

³Department of Urology, Ealing Hospital, London North West Healthcare NHS Trust, Uxbridge Road, Southall, UB1 3HW

⁴Department of Urology, Guy's Hospital, Guy's and St Thomas NHS Foundation Trust

*Corresponding Author:

Mr Asif Raza MBBS FRCS (Urol) FEBU

Consultant Urological Surgeon

Honorary Senior Lecturer Imperial College Medical School, London

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bju.13204

This article is protected by copyright. All rights reserved.

Department of Urology,
Ealing Hospital,
London North West Healthcare NHS Trust,
Uxbridge Road,
Southall,
UB1 3HW
Email: asifraza@nhs.net

Article type: Comment

Conflicts of Interest: None of the authors have conflicts of interest to declare

Introduction

Iodinated contrast agents (ICA) are an essential part of the urologist's everyday practice, allowing enhanced imaging of the urinary tract. Contrast is administered directly into the urinary tract during retrograde pyelograms, JJ stent insertion, ureterorenoscopy, urethrography and cystography. Contrast can also be administered intravenously, for example during CT urogram studies in the investigation of haematuria. Increasingly, patients are labelled as having a contrast "allergy" when in fact this is a misnomer as it is not a true allergy. As a result of this misconception, these patients are often managed inappropriately with suboptimal imaging. This article aims to dispel uncertainty in this area and will summarise the evidence for the pathophysiology of contrast reactions, risk factors for them and practical advice on how to prevent and manage them.

Types of reactions

Iodinated contrast reactions are classified into several groups: idiosyncratic (also termed anaphylactoid), and non-idiosyncratic (also termed non-anaphylactoid). Idiosyncratic reactions are further divided into mild, moderate and severe (Table 1). Mild reactions are normally self-limiting

and manifest within minutes of contrast injection with nausea and urticaria. Severe reactions causing hypotension and bradycardia will require immediate medical treatment. Non-idiosyncratic reactions include altered oral metallic taste and contrast-induced nephropathy. A systematic review looking at over 500,000 patients in six studies who were given intravenous ICA identified that the risk of any contrast reaction was 0.2-17% and a severe reaction was 0.02-0.5% [1].

Pathophysiology

Contrast reactions are not true allergic reactions as there is no activation of the IgE-mediated pathway. The pathophysiology of idiosyncratic reactions to ICA is not fully understood, though it is proposed that enzyme induction leads to the release of vasoactive substances including serotonin and histamine, the activation of a physiologic cascade and the complement system [2]. Non-idiosyncratic reactions are hypothesized to result from the contrast media disrupting the homeostasis of the blood circulation. The degree of this disruption is dependent on contrast media properties such as osmolality, which causes shifts in fluid volumes and ionicity, which causes free ions in the circulation that may disrupt electrical charges associated with nervous or cardiac activity [2].

With allergic reactions, prior exposure to an allergen is required, which leads to sensitisation and the production of IgE, which forms an IgE-allergen complex. On re-exposure to the allergen this leads to potentially catastrophic consequences thus re-exposure to the allergen should be avoided at all costs. However, as reactions to ICA do not induce an immunological memory response, it is possible for patients with previous contrast reactions to receive contrast again without a catastrophic reaction.

ICA administered directly into the urinary tract are believed to have their systemic effect after being reabsorbed through the uroepithelium [3]. In the largest Urological-specific study published to date, following 783 retrograde pyelograms and cystourethrograms, an incidence of idiosyncratic reactions of 0.26% was demonstrated [4]. However, ionic high-osmolar contrast, which is no longer commonly used in current practice, was used in this study and there may be a lower incidence in contemporary practice. Severe reactions, though rare, have been reported in contemporary Urological case

reports, even with the use of non-ionic contrast media, thus prevention and treatment of reactions to ICA should be given due care [3].

Risk factors

Low-osmolar non-ionic contrast agents, such as iohexol and ioversol, are the main types of contrast agent used in clinical practice today. This is because compared to ionic contrast agents formerly used, a fourfold decreased risk of adverse reactions has been demonstrated [1]. Injecting ICA in high volumes under pressure can increase reabsorption of contrast [1]. A systematic review demonstrated that the subset of patients with prior contrast reactions, food allergies (including seafood allergies) or atopy have a 2-5 times greater incidence of any contrast reaction [1]. The reasons for these associations are poorly understood.

Minimising risk of contrast reactions for the practising Urologist

Given the reports of severe consequences of anaphylactoid reactions, existing European Association of Urology and European Society of Urogenital Radiology Guidelines have adopted a cautious approach to minimising the risk of contrast reactions in patients who are to undergo procedures involving iodinated contrast reaction (See Table 2). Patients identified as having had moderate to severe previous contrast reactions, allergies requiring medical management or severe atopy may be considered for further pre-procedural preventative treatment.

A randomised controlled trial by Lasser et al showed that administration of two doses of oral corticosteroids at 6-24 hours before and 2 hours before intravenous contrast administration reduced the incidence of contrast reactions when compared to placebo [5]. A meta-analysis of four randomised controlled trials showed that the use of H1-receptor antihistamines pre-procedurally significantly reduced the overall rate of contrast reactions (pooled RR, 0.4) [6]. These results are reflected in the guidelines seen in Table 2.

Another option is to consider alternative contrast agents. Non-ionic gadolinium-based agents such as gadodiamide have been used for percutaneous nephrostolithotomy, antegrade pyelography and nephrostograms [7]. Urologists may wish to ensure that theatres keep gadolinium contrast. Alternatively on the day of the procedure, these agents can be obtained from the MRI department.

Some simple precautions should be taken for all patients with previous contrast reactions and severe atopy. The smallest volume necessary of a non-ionic ICA should be used, and injecting at high pressure, particularly in obstructed systems should be minimised. Urologists should ensure that the drugs and equipment required for resuscitation are available in theatre prior to starting a case.

Conclusion

Contrast reactions are not allergies as they are not IgE-mediated and therefore patients with prior reactions can receive contrast again. Whilst rare, the consequences of contrast reactions can still be serious. In high-risk patients who have had moderate to severe prior contrast reactions or who have severe atopy, precautions can therefore be taken to minimise the risk of subsequent contrast reactions. These precautions include pre-medication with oral corticosteroid and antihistamine and the use of alternative contrast agents such as gadolinium-based agents. Urologists should ensure they use the smallest volume of contrast required and that they inject at low pressure.

References

- [1] Schabelman E, Witting M. The relationship of radiocontrast, iodine, and seafood allergies: a medical myth exposed. *The Journal of emergency medicine*. 2010 Nov; **39**:701-7
- [2] Singh J, Daftary A. Iodinated contrast media and their adverse reactions. *Journal of nuclear medicine technology*. 2008 Jun; **36**:69-74; quiz 6-7
- [3] Armstrong PA, Pazona JF, Schaeffer AJ. Anaphylactoid reaction after retrograde pyelography despite preoperative steroid preparation. *Urology*. 2005 Oct; **66**:880
- [4] Weese DL, Greenberg HM, Zimmern PE. Contrast media reactions during voiding cystourethrography or retrograde pyelography. *Urology*. 1993 Jan; **41**:81-4

- Accepted Article
- [5] Lasser EC, Berry CC, Mishkin MM, Williamson B, Zheutlin N, Silverman JM. Pretreatment with corticosteroids to prevent adverse reactions to nonionic contrast media. *AJR American journal of roentgenology*. 1994 Mar; **162**:523-6
- [6] Delaney A, Carter A, Fisher M. The prevention of anaphylactoid reactions to iodinated radiological contrast media: a systematic review. *BMC medical imaging*. 2006; **6**:2
- [7] Spinosa DJ, Angle JF, Hagspiel KD, et al. Feasibility of gadodiamide compared with dilute iodinated contrast material for imaging of the abdominal aorta and renal arteries. *Journal of vascular and interventional radiology : JVIR*. 2000 Jun; **11**:733-7

Table 1: Pertinent features in initial assessment and immediate treatment for patients reacting to Iodinated Contrast Agents. Adapted from the European Society of Urogenital Radiology contrast media guidelines.

History	Patient-related: previous iodinated contrast reaction, severe atopy, cardiac disease, renal disease and dehydration, haematological (high baseline eosinophilia or histamine levels) and metabolic conditions	
	Contrast-related: high osmolality, ionic contrast agent	
Initial assessment and recommended treatment	Mild: nausea, vomiting, urticaria, pruritis	Treatment: observation, antiemetic
	Moderate: Marked urticarial Bronchospasm, Laryngeal oedema, Vagal reaction (hypotension, bradycardia)	Treatment: H1-antihistamine Oxygen, beta-2-agonist Intramuscular adrenaline (e.g. 0.5mg) Elevate legs, intravenous fluids, atropine 0.6-1mg intravenously every 3-5min, up to 3mg
	Severe: Hypotensive shock, respiratory arrest, cardiac arrest, convulsion	Treatment: Call for resuscitation team. Oxygen, fluids, elevate legs, intramuscular adrenaline (e.g. 0.5mg) and intravenous H1 antihistamine (e.g. 50mg diphenhydramine).

Table 2: Current guidelines for pharmacological prevention of contrast reactions in patients with previous moderate to severe contrast reactions or allergies requiring medical treatment

Guidelines	Recommendation
European Society of Urogenital Radiology	Two doses of oral prednisolone 30mg (or methylprednisolone 32mg) at 12 and 2 hours before contrast administration
European Association of Urology Urolithaisis Guidelines	A single dose of corticosteroid (e.g. prednisolone 30 mg) between 12 and 2 hours before the contrast medium is Injected Corticosteroid can be combined with an intramuscular injection of an antihistamine agent (e.g. clemastine 2 mg), given 1 hour before administration of contrast medium