Literature Review

Radiocontrast Media Allergic Reactions and Interventional Pain Practice—A Review

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Background: Millions of interventional pain procedures are performed each year in the United States. Interventional pain physicians commonly administer radiocontrast media (RCM) under fluoroscopy for these procedures. However, RCM can cause various types of hypersensitivity or allergic type reactions, in an acute or delayed fashion. Furthermore, some patients report a prior history of hypersensitivity reactions to RCM when presenting to the interventional pain clinic. Both scenarios present challenges to the interventional pain physician.

Objective: To describe the various types of hypersensitivity reactions to RCM, as well as strategies to prevent and manage these reactions, within the context of interventional pain practice.

Method: A review of the literature from 1975 through 2011 regarding allergic type reactions to RCM, as well as iodine, and shellfish allergy, was undertaken in an effort to review and develop recommendations on managing these patients presenting to the interventional pain clinic. Keywords used in the literature search were: radiocontrast media, contrast allergy, contrast reaction, iodine allergy, shellfish allergy, and fluoroscopy. The included articles were concerned with the basic or clinical science of contrast allergy, including the physiology, epidemiology, diagnosis, and management of such reactions. Meta-analysis, review articles, and case reports addressing contrast media reactions were also included. Articles which discussed contrast media reactions in a peripheral fashion were excluded.

Results: In reviewing the literature, it is apparent that the mechanisms and pathophysiology of RCM hypersensitivity reactions are still being characterized, which should soon lead to improved screenings, as well as prevention and treatment strategies. Many common themes are described throughout the literature regarding patient risk factors, testing, prevention, diagnosis, and treatment of RCM allergic-type reactions.

Limitations: The current review did not perform a meta-analysis of the available data, as most of the available articles were trials that were randomly controlled. Therefore, the conclusions of the present article are general, and qualitative in nature.

Conclusion: Although the mechanisms of various RCM allergic-type reactions are not entirely understood, the interventional pain physician should have a basic understanding of patient risk factors, prevention, diagnosis, and treatment of these reactions. The current review allowed for prevention and treatment strategies for managing patients with RCM hypersensitivity reactions.

Key words: Radiocontrast media, contrast allergy, contrast reaction, iodine allergy, shellfish, allergy, fluoroscopy, interventional spine practice

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Over 75 million doses of radiocontrast media (RCM) are administered annually to patients worldwide (1). Despite the seemingly low risk, one can extrapolate that a fair number of hypersensitivity reactions to RCM will be observed. In addition, the field of interventional pain management has grown rapidly. For example, in 2005, 4 million interventional pain procedures were performed on Medicare patients; the vast majority of these procedures utilized fluoroscopy for guiding injections (2-7). Frequently, RCM is employed to facilitate visualization of the spread of medications during pain procedures. Contrast media is helpful for the identification of spread within neural structures and the epidural space, and are helpful for thedetection of inadvertent intravascular injection.

The incidence of severe hypersensitivity reactions to intravascular administration of contrast media is rare (8,9), with a rate of about 0.03%-0.16%. However, when applied to the millions of patients each year who undergo interventional pain procedures, this leaves a significant number of patients at risk.

The vast majority of these reactions are described as "anaphylactoid" in nature. However, most reactions are non-immunoglobulin E (IgE) mediated (8-20). In addition, true anaphylaxis does not necessarily have to involve IgE antibodies. The interventional pain specialist should have an understanding of the types of contrast media available and general guidelines regarding prophylaxis and treatment of RCM reactions. The purpose of this review article is to give the interventional pain physician a review of the epidemiology, pathophysiology, prevention, and treatment of allergic reactions to RCM.

Methodology

A comprehensive literature search covering 1975 through 2011 was performed. Included in the search were PubMed and OVID databases, as well as Cochrane reviews. Bibliographies from key primary and review papers were also cross-referenced for additional sources. Lastly, peer-reviewed, unindexed journals were searched. The keywords used for our search included: radiocontrast media, contrast allergy, contrast reaction, iodine allergy, shellfish allergy, and fluoroscopy.

The included articles' primary aim was to study the basic or clinical science of contrast media allergy, including the physiology, epidemiology, diagnosis, and management of such reactions. Meta-analysis, review articles, and case reports addressing contrast media reactions were also included. Articles which discussed contrast media reactions in a peripheral or tangential fashion, rather than as its primary concern or focus, were excluded.

Background

Since the introduction of RCM in the 1920s, the chemical structure, ionicity, osmolality, and total iodine content have been considered key variables in their clinical use and development. Currently, RCM can be divided into ionic monomers, ionic dimers, nonionic monomers and nonionic dimers (21). These properties affect the imaging quality and side effects associated with each agent. Table 1 describes these properties. Sodium iodide, used during the 1920s, was one of the first iodinated contrast media used for radiological imaging. One common RCM for studying neural structures at that time was called Lipiodol—a solution of 40% so-

Table 1. *Characteristics and properties of commonly used contrast agents*

Name	Ionicity/Form	Type	Iodine Concentration (mg/mL)	Osmolality (mOsm/kg H_2O)
Iodixanol	Non-Ionic Dimer	IOCM	320	290
Iomeprol*	Non-Ionic Monomer	LOCM	350	620
Ioxaglate	Ionic Dimer	LOCM	350	680
Ioxilan	Non-Ionic Monomer	LOCM	350	695
Iopamidol	Non-Ionic Monomer	LOCM	350	730
Iopromide	Non-Ionic Monomer	LOCM	350	730
Iohexol	Non-Ionic Monomer	LOCM	350	780
Ioversol	Non-Ionic Monomer	LOCM	350	790

Abbreviations: IOCM, iso-osmolar contrast medium; LOCM, low osmolar contrast medium
* Not approved in the United States

dium iodide suspended in the oil of poppy seeds (22). The benefit to toxicity profile of 40% sodium iodide is low, as this material does not yield high quality images. It is very insoluble, and side effects include severe local irritation; nausea and vomiting; arthralgias; lymph node swelling and tenderness; and hives. In 1927, a case report described the use of a more soluble 20% sodium iodide solution for diagnosing a brain abscess, which was well tolerated by the patient (22).

In the 1950s, diatrizoic acid salts with sodium, calcium, or methylglucamine were being used as contrast agents. The osmolality of these salts were > 1700 mOsm, 5-8 times that of blood. These are referred to as high osmolar contrast media (HOCM), and are also ionic in nature. The ratio of iodine to particle was 3:2 and dissociation of iodine from particle readily occurred (23). Hypotension, cardiac arrhythmias, and fluid overload are common with their use (23). Low osmolar contrast media (LOCM) were developed in the 1970s to avoid the above listed toxic affects. These newer agents had an osmolality of < 850 mOsm. The iodine to particle ratio was 3:1 and the rate of iodine dissociation was decreased. These RCM were made from benzoic acid side chains and amides, imparting them with nonionic properties (3). Despite these improvements over the older agents, adverse reactions still occurred, including nausea, angina, and anaphylaxis (23).

The 1980s brought about newer, safer agents. Monoacid dimers with 2 benzoic rings containing iodine atoms at positions 2, 4, and 6 were bound to form nonionic compounds. This allowed for 6 iodine atoms per molecule, of which only 2 particles dissociated, allowing for the favorable 3:1 iodine to particle ratio as described above, thus maintaining low osmolar properties (23), less lipophilicity, and less toxicity (21).

In 1996, the first and only currently FDA-approved iso-osmolar radiocontrast media was introduced—iodixanol. The iodine content of this agent is 300 mg/mL, and, as the name implies, its osmolarity nearly matches blood osmolarity (23).

Today, the iodine content of most agents is 250-350 mg of iodine per mL. Modern RCM are nonionic, they contain hydroxyl and amide functional groups, allowing for fewer arrhythmias and cell membrane electrical disturbances (21). However, with the development of improved imaging and digital technology, reductions in contrast media iodine content have still allowed for high quality radiographs, with less RCM required per image (23).

Epidemiology

A number of studies have tried to estimate the incidence of hypersensitivity reactions to both ionic and nonionic contrast materials. HOCM are associated with a 15% risk of any toxic reaction, while LOCM are associated with a risk of 3% for any reaction (21). The incidence of any reaction to ionic radiocontrast media is estimated to be between 0.6%-12.66% (24,25). For nonionic materials, the risk for any reaction ranges from 0.3%-3% (24). The risk for a severe hypersensitivity reaction is 0.16% with ionic contrast materials and 0.03% with nonionic contrast materials (8). The mortality rate is one to 3 per 100,000 contrast media administrations and does not differ for either ionic or nonionic agents (8). Other estimates of fatal reactions range from 1:170,000 (21) to 0.05%-0.1% (23). A recent study found that children were at lower risk, with only one severe reaction among 819 children given ioversol for computerized tomography (CT) scans (26).

In a recent retrospective study of 84,928 patients given RCM for CT imaging, 0.6% suffered an allergic-type reaction (24). Of these 545 allergic reactions, 77% were mild, 21% moderate, and 2% were severe (24).

Nonimmediate or delayed allergic type reactions may occur days after contrast medium has been administered. The estimated prevalence is about 2%-8% (21), and may happen more commonly in patients receiving interleukin-2 therapy and with the use of nonionic dimer RCM (21). These reactions are generally mild, and mainly involve the skin, although these too may rarely be severe to life threatening (27).

In recent years, the incidence of hypersensitivity reactions has decreased, as RCM have evolved from ionic, high-osmolality to nonionic, low-osmolality media. However, the expense of the LOCM agents may limit their universal use (28).

In our review of the literature, the available data constitute the best estimates of RCM reactions rates by subtype. To our knowledge, there have been no studies further describing the reaction rates by reaction type. This information would be useful to practitioners and we hope future studies will be conducted in this area.

Risk Factors for Hypersensitivity Reactions to RCM

Risk factors for contrast media reactions include, but are not limited to, previous reactions to either ionic or nonionic contrast media (6-fold increase), asthma (5-10 fold increase), history of multiple allergies (1.5-3

fold increase female gender (29), drug allergy (30) and patients taking interleukin-2 (9,10,29,31-33). Aspirin, and other nonsteroidal anti-inflammatory drugs may also increase the risk (21). Beta blockers do not impart a direct risk, but they may hinder treating hypersensitivity reactions with epinephrine, as epinephrine's effect will be antagonized. In addition, the presence of cardiovascular disease and concurrent treatment with a beta blocker is associated with a more serious reaction (34).

The Cardarelli Hospital Radiocontrast Media and Anesthetic-Induced Anaphylaxis Prevention (CHRAIAP) Working Group proposes a scale for triaging the risk factors for severe allergic reactions to RCM (Table 2) (35). Its scale may be useful to the interventional pain physician who is presented with a patient possessing risk factors for developing hypersensitivity reactions to RCM. This scale, although useful, is qualitative in nature. Future scales based upon this, perhaps utilizing a point system to produce a score for each patient, would be a useful tool for interventional pain physicians.

Shellfish allergy is related to an IgE antibody specific for a particular tropomyosin-like protein in shellfish. This has been shown by skin-prick testing studies in patients with seafood allergy (36). Any patient who claims a shellfish allergy should be questioned further to delineate a true allergy from mere food intolerance, as many patients do not distinguish between them. Food intolerances may not be of concern to the pain physician in terms of reactions to RCM, however a true shellfish allergy may be of concern. This is because patients with shellfish allergies have a 1.5-fold to 3-fold increased chance for experiencing a hypersensitivity reaction to RCM, the same risk as those with multiple Iodine is an element and trace mineral, which when absorbed by the gut, is converted to iodide and utilized for thyroid hormone production. It is a simple atom, and is not complex enough at the molecular level to serve as an antigen (36). It is feasible that iodide could act as a hapten by binding to other proteins, and thus induce a delayed-type hypersensitivity reaction (31). A recent study found that during protein iodination, iodinated tyrosine groups acted as an antigen in a guinea pig model of iodine allergy (37). However, iodine, in and of itself, is thought to be too small, molecularly, to elicit an antigen-antibody response.

It is a common misconception that "iodine allergy" is associated with shellfish allergy. However, how should patients be managed when they report a history of an iodine and/or shellfish allergy? Based on previous studies on food allergy and reactions to RCM, patients should be advised that their risk is no different from any other patient who reports a history of multiple allergies, imparting a 1.5-fold to 3-fold increased risk Interestingly, in a recent study of 601 patients undergoing an endoscopic retrograde cholangiopancreatogram utilizing oral ionic HOCM, 80 of whom had prior documented reactions to RCM and 49 who claimed shellfish allergy, none experienced a hypersensitivity reaction. In addition, these patients had not received any pretreatments to prevent an allergic reaction (38).

Table 2. **CHRAIAP Risk stratification of the major factors for anaphylaxis to RCM*

History of a previous reaction to a contrast medium
History of allergy/atopy
Mastocytosis (especially if systemic)
Contrast medium dose required
History of cardiac or metabolic disease
Injection route
-intravenous versus intra-arterial
-rate of infusion of the medium
Female gender
Age
Anxiety

*These CHRAIAP risk factors are listed in descending order of risk for anaphylactic reaction.

Pathophysiology

A number of similar hypersensitivity reactions to RCM may be experienced by the patient. The exact mechanisms of most adverse reactions to RCM are unknown and are under active investigation. Most seem to employ direct mast cell and basophil activation, and involve the release of a number of vasoactive mediators (35). IgE is not thought to play a role in the majority of RCM reactions, and therefore the reactions cannot be classified as IgE mediated anaphylaxis. It is more likely for a patient to experience a non-IgE mediated anaphylactic reaction, albeit this is also not common.

Chemotoxic reactions to RCM have been described. As RCM increase in hydrophobicity, toxicity increases. These substances are more likely to precipitate a cascade of events which are detrimental to the patient, such as "releasing vasoactive substances, complement activation, fibrinolysis, inhibition of platelet aggregation, direct neurotoxicity, decreased myocardial contractility and conduction" (21). These reactions are often dose-related.

As the osmolarity of the RCM rises, so does the risk of injection pain, increased vagal tone, nausea

and vomiting, and decreased systemic vascular resistance (21). These are known as osmotoxic reactions. Hypotension, bradycardia, loss of consciousness, and ventricular arrhythmias may result from the increased vagal tone and/or from a chemotoxicity overlaying the osmotoxicity.

Idiosyncratic reactions occur within close temporal proximity of the injection, and are not anaphylaxis, despite clinical similarity. Often these are independent of prior exposure. Symptoms are the result of release and activation of complement, cytokines, serotonin, prostaglandins, kinins, etc. (21). These reactions are often mistaken for allergic reactions, but are much more common. Coakley and Panieck (36) suggested renaming this type of reaction an "anaphylactoid, allergy-like, or pseudoallergy," to help avoid confusion to the patient and care provider. These reactions can be severe and life-threatening.

IgE-mediated anaphylaxis is another life-threatening allergic-type reaction in which RCM binds to IgE antibodies, thereby activating mast cells and basophils to release massive amounts of histamine and other vasoactive substances, leading to bronchospasm and shock. These are more likely to be predictable, and involve prior exposure. Iodide exposure, in the form of RCM, iodinates proteins, which in turn may cause an antibody-mediated reaction, as was seen in an experimental guinea pig model for studying iodine allergy (37). More recent research has described positive skin tests with cross reactivity to similar RCM in patients who report an RCM allergy (39). T-cell cross-reactivity between various RCM has also been described in 2 patients with delayed hypersensitity reactions (1). In these studies, cross-reactivity between RCM were observed in varying degrees. Skin testing is sometimes used to help in the identification of IgE-mediated reactions, however, it cannot reliably predict the severity of reactions, nor identify patients who may have non-IgE reactions.

Acute versus Delayed Reactions

Most adverse reactions to RCM present acutely, within one hour of administration. More specifically, the estimated prevalence of delayed type reactions is 2%-8% of all RCM reaction types. However, some patients will develop delayed type reactions, which may occur up to one week later. Delayed type reactions usually involve fever, pruritus, urticaria, angioedema, flushing, nausea, arthralgias, or mild maculopapular exanthemas. More severe delayed type reactions have been described, including bullous rashes, erythema multiforme, cutaneous vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and systemic eosinophilia (1,22). However, these severe delayed reactions are very rare. A T-cell mediated mechanism, involving CD4+ and CD8+ lymphocytes, is thought to be the pathophysiological basis of delayed adverse reactions (1). These T-cells also demonstrate cross-reactivity to similar RCM (1).

Symptoms/Clinical Manifestations

The symptoms and clinical manifestations vary depending on the type of reaction. Table 3 and Table 4 contain a summary of signs and symptoms of various RCM allergic type reactions.

Differential Diagnosis

During fluoroscopic interventional pain procedures, the patient may be exposed to other agents which could induce an allergic reaction. Latex, local anesthetics, adhesive tape, topical skin antiseptic agents, methylcarboxycellulose (a preservative in some steroid preparations) and antibiotics are a few examples. Identifying which agent was responsible for a reaction is difficult to determine and often requires the patient to undergo subsequent allergy testing.

Prevention

For patients that are at high risk of hypersensitivity reactions, effective pretreatment guidelines have been developed (28). Numerous pretreatment prophylactic regimens have been studied with slight variation. Almost all include a corticosteroid to target the inflammatory response, and a histamine-1 (H1)-antagonist to blunt the effects of histamine. In some clinical trials, ephedrine was added for bronchodilation, and cimetidine for its antagonism at the histamine-2-receptor (40).

Clinical trials have shown the combination of prednisone and diphenhydramine to be the most beneficial in preventing anaphylactoid reactions to RCM (30). Adverse reactions decreased from a range of 17%-35% to a range of 5%-10% when corticosteroids were combined with an H1 blocker (41,42).

There are many review articles, meta-analyses, and small studies that discuss the topic of pretreatment and prophylaxis. However, few were highly powered, prospective studies. Two such high quality studies were conducted in the 1980s. In the first study (41), 857 doses of RCM were administered to 743 patients with known prior RCM anaphylactoid reactions. Patients received either 1) prednisone and diphenhydramine, 2)

Table 3. *Common Symptoms and Clinical Manifestations of Various Reactions to RCM*

Chemotoxicity [18]
Nausea and Vomiting
Flushing
Injection Site Pain
Nephrotoxicity
Osmotoxicity
Injection Site Pain
Hypotension
Bradycardia
Loss of Consciousness
Pulmonary edema [16]
Ventricular Arrythmias
Other signs of increased Vagal Tone
Iodism
Swelling: Parotid, Sublingual, Submandibular, Lacrimal glands (aka-iodide mumps)
Skin Rashes
Coryza
Thyrotoxicosis [16]
Delayed type Reaction- *Occur within 1 hour to 1 week from RCM exposure*
Fever
Pruritis
Uticaria
Angio-edema
Flushing
Nausea
Arthralgia
Mild Maculopapular Exanthemas
Other non-specific Cutaneous Findings

Idiosyncratic Reaction -*Can be lethal, clinically similar to allergy / anaphylaxis; -Often categorized into mild, moderate, or severe reaction*
Tacchycardia
Hypotension
Tongue Swelling
Rhinitis
Wheezing
Laryngeal Edema
Bronchospasm
Shortness of Breath
Dyspnea
Palpitations
Hives
Angina
Anaphylaxis- *May be independent of prior exposure or presence of IgE antibodies. Usually occurs within minutes.*
Tacchycardia
Hypotension
Oxygen De-saturation on Pulse Oximetry
Tongue Swelling
Rhinitis
Wheezing
Laryngeal Edema
Bronchospasm
Shortness of Breath
Dyspnea
Palpitations
Hives
Angina
Shock
Cardiopulmonary Arrest
Death

prednisone, diphenhydramine, and ephedrine, or 3) prednisone, diphenhydramine, ephedrine, and cimetidine. They observed the fewest reactions when patients were treated with the prednisone, diphenhydramine, and ephedrine regimen. They also speculated if the use of cimetidine somehow negatively contributed to the patients' experience with RCM during their trial. The second study (43) was a prospective, randomized trial including 6,763 patients exposed to RCM. These patients received either 32 mg of oral methylprednisolone at 12 and 2 hours prior to exposure, 32 mg of oral methylprednisolone at least 2 hours prior to exposure, or placebo. The authors observed a significant decrease in contrast medium-induced hypersensitivity reactions, with the exception being the formation of hives, when the 2-dose regimen was provided.

Therefore, the following premedication protocols have been recommended for use in patients with a history of idiosyncratic reactions: methylprednisolone, one 32 mg tablet at 12 hours, and 2 hours before exposure

Table 4. *RCM Properties and Reaction Profiles*

Contrast Properties
-Osmolality (mOsm/kg H_2O): High >1700, Low < 850, Iso = 290. High osmolality causes fluid overload, arrhythmias, angina, hypotension, decreased vascular tone, increased vagal tone
-Particle Ratio: 3:2 leads to higher osmolality and more dissociation, where 3:1 allows for lower osmolality and less dissociation
-Iodine Content (mg/mL): Low < 250, High > 350
-Ionicity: Non ionic agents contain amides, hydroxyl and/or benzoic acid chains. Ionic agents contain diatrizoic acid salts with sodium, calcium or methylglucamine. Ionic agents cause more arrhythmias, angina, hypotension
-H_2O Solubility: Insoluble agents cause local irritation, nausea, hives, arthralgias, arrhythmias, angina. Agents with a 3:1 ratio are more H_2O soluble and less toxic
Reaction Types
-Anaphylactic: +/- IgE presence, +/- prior exposure, +/- antigen cross reactivity. RCM may also directly stimulates immune cells. Theoretically possible that high iodine content can lead to anaphylaxis via systemic protein iodination and antibody formation [31,32]
-Idiosyncratic: No prior exposure, involves cellular release of inflammatory mediators. Theoretically possible that high iodine content can lead idiosyncratic reactions via systemic protein iodination and antibody formation [31,32], +/- antigen cross reactivity
-Delayed: Often superficial/cutaneous, usually with non-ionic agents. Theoretically possible that high iodine content can lead to delayed reaction via systemic protein iodination and antibody formation [31,32], +/- antigen cross reactivity, entails cellular release of inflammatory substances
-Hypersensitivity: Typically with ionic, high osmolar agents
-Chemotoxicity: Low H2O solubility, highly osmolar, high iodine content
-Osmotoxicity : Similar to chemotoxicity
-Iodism: High iodine content, 3:2 particle ratio
-Arrhythmias: Linked with cellular membrane disturbances from ionicity and low solubility

Table 5. *Premedication Protocol*

Methylprednisolone 32mg orally, 12 and 2 hours prior to procedure
Prednisone 50mg orally 13, 7, 1 hour(s) prior to procedure
Benadryl 50mg orally 1 hour prior to procedure
Zantac 150mg orally 1 hour prior to procedure
If there is less then 13 hours (i.e. emergency procedure in high risk patient) then use 100mg IV hydrocortisone and 50mg Benadryl IV prior to procedure. If more than 2 hours elapses then repeat both medications. Zantac 50mg IV can be added.

(38)], or prednisone, one 50 mg tablet at 13 hours, 7 hours, and one hour before exposure (45). If the previous reaction was moderate or severe, or included a respiratory component, the physician may add the following: an H1 blocker, such as diphenhydramine, one 50 mg tablet one hour before the study, and an optional H2 blocker, such as cimetidine, one 300 mg tablet one hour prior to the study, or ranitidine, one 150 mg tablet one hour before the exposure (46). Using an H2 blocker without also using an H1 blocker is not recommended. Table 5 contains more information on prevention.

Recommendations for high-risk patients who must receive RCM also includes the use of iso-osmolar agents, pretreatment with a corticosteroid and an H1-antagonist, discontinuation of any beta blockers, and bedside availability of appropriate medications and equipment to treat potentially serious hypersensitivity reactions (30). Periodic reviews and updates of specific treatment plans for various reactions with the physicians and staff who use contrast media are very important to ensure optimal preparedness (3). For example, 2 recent large literature reviews regarding pretreatment strategies for patients who claim RCM allergy yielded some interesting findings. They suggested that pretreatment has not undergone rigorous scientific study (27,47). They also noted in their investigation that the evidence in this area is of a relatively low grade.

Treatment of Anaphylactoid Reaction

All interventional pain physicians should be up-to-

date with Advanced Cardiovascular Life Support (ACLS) guidelines should a serious adverse reaction occur. They should have easy access to emergency equipment, including a defibrillator, means to secure intravenous access, supplemental oxygen, emergency airway equipment, and cardiovascular drugs. In patients who develop bronchospasm, syncope, hypotension, laryngeal edema, or severe angioedema, oxygen and epinephrine should be administered immediately (0.3 mg subcutaneously every 15 to 20 minutes). Patients with bronchospasm should be given 50 mg of hydrocortisone or 10-20 mg of methylprednisolone as soon as possible. Even higher doses of steroid may be required if a life threatening anaphylactoid reaction is observed.

Gadolinium

Gadolinium, a noniodinated contrast medium, has been used successfully as an alternative for lumbar discography under fluoroscopy in patients with iodine contrast allergy (48). However, the high cost and limited availability of gadolinium has prohibited its widespread use. The use of gadolinium as an alternate contrast medium in many other imaging procedures has been reported in the literature (48-58). A recent study showed an adverse reaction rate of 0.06% with intravenous gadolinium (48,59). Severe, life-threatening allergic reactions to intravenous gadolinium have a reported frequency of 0.0003%-0.01% in the literature (48,54,60,61). Unfortunately, gadolinium has been noted to be less radiopaque during fluoroscopy when compared with iodinated contrast media (48).

Education and Simulation

Pain medicine fellows, as well as residents in anesthesiology, physical medicine and rehabilitation , radiology, neurology, and other fields which utilize RCM, need training on not only the technique of fluoroscopy, but also how to effectively recognize and manage adverse reactions to RCM. Recent advances in high fidelity simulation have allowed trainees to learn to manage rare, critical events in a controlled setting. Gaca et al (26) recently studied the use of high fidelity simulation to assess radiology resident preparedness for managing adverse reactions to RCM, and found simulation to be a valuable teaching tool. Recognizing that RCM has the potential for adverse reactions, and as medical simulation continues to expand, we anticipate simulation becoming an important tool to prepare interventional pain trainees to diagnose and treat adverse events.

Discussion

The incidence of severe hypersensitivity reactions to RCM is rare. However, millions of patients each year are exposed to doses of RCM. Therefore, a significant number of patients may experience an allergic-like reaction to contrast medium. A number of different types of hypersensitivity reactions have been described in association with RCM, including acute and delayed reactions, as well as chemotoxic, osmotoxic, iodism, idiosyncratic, and anaphylactic reactions. Each has its own underlying mechanism, as well as prevention and treatment modalities. Fortunately, the recent incidence of hypersensitivity reactions has decreased, as safer RCM have been developed. Still, the interventional pain physician may encounter patients who claim allergies to RCM, as well as iodine or shellfish. The pain physician should advise patients with shellfish or iodine allergy that they are at a similar risk of allergic reaction when compared with patients who claim a history of multiple food or drug allergies, imparting a 1.5-fold to 3-fold increased risk (44). Other populations of patients who are at higher risk of hypersensitivity to RCM include those with a documented previous reaction to RCM, resulting in a 6-fold increase, or a history of asthma, leaving them with a 5-fold to 10-fold increase.

For spinal procedures, contrast media are used to ensure adequate medication delivery to areas of pathology, as well as rule out intravascular spread, with the failure to do so resulting in rare, but devastating outcomes. Even without intravascular needle placement as seen by fluoroscopy, systemic uptake will occur. Therefore, adverse reactions to contrast media may be seen clinically. The various types of reactions, including their mechanism, recognition, prevention, and treatment, have been discussed in this review.

Recent basic science research has expanded our understanding of the underlying mechanisms of allergic type reactions to RCM, which will soon allow for the development of novel screenings, preventive, and treatment modalities. In current practice, however, for patients that are deemed high-risk, there are alternatives to conventionally used RCM. First, the avoidance of contrast medium is recommended, if possible. For example, in the performance of lumbar sympathetic blockade (LSB), a technique using loss-of-resistance to air to find the retroperitoneal space and generate an "aerogram," visible under fluoroscopy, has been described (60-65). However, in a recent study, needle placement during LSB was frequently noted to be with the psoas muscle or intravascular, thereby justifying the use of RCM (66) during

this procedure. Again, the risks-benefit ratio of proper needle placement to RCM reactions must be weighed and discussed in detail with the patient.

In patients where the administration of contrast medium is necessary, consider using noniodinated contrast medium, such as gadolinium, or a pretreatment protocol with corticosteroids. If radiocontrast media must be used in high risk patients, then iso-osmolar non-ionic dye should preferably be used. Lastly, make sure emergency resuscitation equipment is available, as well as personnel trained in ACLS.

The present review has several limitations. First, research into RCM reactions is a young and growing science, and there remain more questions than answers. The articles reviewed were not all prospective or randomized in nature. Therefore, the conclusions of this piece do not allow for a true statistical or meta-analysis. However, some general, qualitative, recommendations and conclusions can be made to help the interventional pain physician manage patients with RCM allergic-type reactions.

Conclusion

A number of allergic-like reactions to RCM may be seen by the interventional pain physician during fluoroscopic procedures, including chemotoxic, osmotoxic, iodism, idiosyncratic, and anaphylactic reactions, in an acute or delayed fashion. Patients with a history of allergy to RCM, as well as a history of asthma, or multiple drug allergies are at highest risk. A reported history of iodine or shellfish allergy presents an equal risk as that for patients with a history of multiple food or drug allergies. The interventional pain physician should not only appreciate the risk factors, but also know how to manage screening tests, and recognize, prevent, and treat these hypersensitivity reactions.

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