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REVIEW ARTICLE

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Adverse reactions to intravenous iodinated contrast media: a primer for radiologists

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Abstract Adverse reactions to intravenous iodinated contrast media may be classified as general and organ-specific, such as contrast-induced nephrotoxicity. General adverse reactions may be subclassified into acute and delayed types. Acute general adverse reactions can range from transient minor reactions to life-threatening severe reactions. Non-ionic contrast media have lower risk of mild and moderate adverse reactions. However, the risk of fatal reactions is similar for ionic and non-ionic contrast media. Adequate preprocedure evaluation should be performed to identify predisposing risk factors. Prompt recognition and treatment of acute adverse reactions is crucial. Risk of contrast induced nephrotoxicity can be reduced by use of non-ionic contrast media, less volume of contrast, and adequate hydration. The radiologist can play a pivotal role by being aware of predisposing factors, clinical presentation, and management of adverse reactions to contrast media.

Keywords Iodinated contrast media · Contrast media · Complications · Radiocontrast nephropathy · Radiology and radiologists · Iatrogenic injury

Introduction

Iodinated contrast media is the most commonly used drug in diagnostic radiology. In the United States alone, more than 50 million CT studies are performed annually, and about 50% of CT studies use intravenous iodinated contrast media [1]. Increase in utilization of contrast media has also occurred in cardiac catheterization and coronary interventions. With this ever-increasing trend of contrast media usage for radiological studies, it is important for the radiologists, interventional cardiologists and referring physicians to be aware of adverse reactions to contrast media and their management. In this article, we will review the classification, incidence, pathogenesis, predisposing factors, clinical features, treatment, and prevention of adverse reactions to iodinated contrast media.

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Classification

Adverse reactions to intravenous iodinated contrast media are broadly classified into general and organ-specific adverse effects, such as contrast induced nephrotoxicity, and cardiovascular, pulmonary, and neurotoxicity. The general adverse reactions are further subclassified into acute and delayed reactions [2, 3]. Acute general adverse reactions are summarized in Table 1. Mild reactions are of short duration, self-limiting, and generally do not require specific treatment. However, moderate and severe reactions represent serious degrees of reactions that need immediate management. A delayed adverse reaction is defined as a reaction which occurs 1 h to 1 week after contrast injection, which is predominantly a skin reaction [2].

Acute general reactions

Incidence

Mild acute reactions occur in 15% of patients receiving ionic and 3% of patients receiving non-ionic contrast media [4]. Moderate reactions are seen in 1–2% of patients with ionic and 0.2–0.4% patients with non-ionic contrast media [5]. Severe reactions can occur in 0.2% of patients receiving ionic contrast media and 0.04% patients receiving non-ionic contrast media [5]. The risk of adverse reactions is lower with non-ionic than with ionic contrast media by a factor of 5 for mild reactions and a factor of 10 for severe reactions [4–6]. Fatal reactions are rare and the

Table 1 Clinical presentation of acute general adverse reactions to iodinated contrast media

Mild	Moderate	Severe
Nausea	Severe vomiting	Pulmonary edema
Vomiting	Extensive urticaria	Cardiac arrhythmias
Limited urticaria	Laryngeal edema	Cardiac arrest
Mild pallor	Dyspnea	Circulatory collapse
Pain in injected extremity	Rigors	Unconsciousness

risk is similar with non-ionic and ionic contrast media (1:170,000) [4].

Deaths due to intravenous contrast media

Although deaths from contrast media injection are rare, when deaths occur, they are more common in women, elderly ("wrinkled"), whites, and in those with concurrent debilitating ("weakened") medical conditions (four W's: "Women, Wrinkled, White, Weakened" have increased risk of mortality due to contrast media adverse reaction). Deaths due to contrast media are often associated with acute renal failure and anaphylaxis. A recent review of 48 deaths from contrast media injection reported that the causes of death due to contrast media include renal failure (58%), anaphylaxis and allergy (19%), cardiopulmonary arrest (10%), respiratory failure (8%), and stroke and cerebral hypoxia (4%) [7].

Predisposing factors

The prevalence of adverse reaction to contrast media with ionic contrast media is 17–35% in patients with previous adverse reaction [8, 9]. Use of non-ionic contrast media reduces the prevalence of recurrent adverse reactions to 5% [10, 11].

The risk of adverse reactions to contrast media increases due to several predisposing factors. Table 2 summarizes the predisposing factors for general adverse reactions to contrast media. It is crucial to know the presence of predisposing factors in a patient before administration of contrast media. Acute adverse reactions are more frequent in persons between 20 and 50 years of age and are less frequent above 50 years [6]. However, these reactions tend to be more severe in the elderly, as they are unable to withstand severe systemic events like a cardiopulmonary reaction. History of allergy increases the risk of severe reactions to contrast media three times and previous adverse reaction to contrast media increases the risk by five times [4]. Asthma increases the incidence of severe adverse reactions by ten times for high-osmolality contrast media and six times for low-osmolality contrast media [4].

Table 2 Predisposing risk factors for general acute adverse reactions to contrast media

Previous adverse reactions
History of asthma
History of allergy
Heart disease
Dehydration
Hematological conditions like sickle cell anemia, polycythemia and myeloma
Pre-existing renal disease
Infants and elderly
Anxiety
Beta-blockers, non-steroidal anti-inflammatory drugs, interleukin-2

The effect of beta-blockers on adverse reactions to contrast media is controversial. Lang et al. reported increased incidence of anaphylactoid reactions to contrast media in patients taking beta-blockers [12]. Conversely, in another study, Greenberger et al. reported that nonselective beta-blockers, cardioselective beta-blockers or calcium channel antagonists did not increase the risk of anaphylactoid reactions to contrast media [13]. Interestingly, both studies reported sluggish response to treatment for anaphylactoid reactions to contrast media in patients taking beta-blockers [12, 13].

Pathogenesis

The pathogenesis of general adverse reactions to contrast media is not well-understood and is likely to be multifactorial. Most of general adverse reactions to contrast media are considered idiosyncratic or pseudoallergic reactions. They are unpredictable, not dose-dependent, and may involve the release of histamine and other biological mediators, such as serotonin, prostaglandins, bradykinin, leukotrienes, adenosine, and endothelin. There is no conclusive evidence that adverse reactions to contrast media are allergic as antibodies to contrast media could not be consistently demonstrated [4]. Chemotoxic effects of contrast media occur due to direct molecular toxicity and their physiological properties. Chemotoxic effects are more common in debilitated and medically unstable patients.

Treatment

General guidelines

The radiologist should weigh the possible clinical benefits to the at-risk patient from a contrast-enhanced radiological study against the small, but ever-present risk of contrast media reaction before administration of contrast. The general policy of contrast media usage for radiological studies should be the lowest dose, concentration, and number of injections to get the required diagnostic clinical information. A previous uneventful contrast medium injection does not ensure the safety of current contrast medium injection. An emergency cart with facilities for airway management, oxygen and masks, intravenous fluids, and appropriate drugs must always be immediately available and must be regularly checked. An infallible alarm

system must be available to call for experienced medical assistance, electrocardiogram (ECG), and defibrillation.

Specific treatment

Though mild general reactions are self-limiting, when they occur, the intravenous access must be retained and the patient should be observed until full recovery. Persistent vomiting can be treated with prochlorperazine maleate 12.5 mg diluted to 10 ml with normal saline injected intravenously over 2 min. Chlorpheniramine maleate 4–8 mg orally or 10–20 mg intravenously slowly over 2 min can be administered to patients with severe urticaria. Moderate wheeze can be treated with 100% oxygen mask inhalation (10–15 l/min) and salbutamol nebulization (5 mg in 2 ml saline). Management of severe reactions is summarized in Table 3.

Prevention

The proposed pretreatment regimens for the prevention of adverse reactions to contrast media include administration of corticosteroids with or without antihistamines. Administration of steroid prophylaxis still remains a contentious subject. The incidence of adverse reactions in high-risk patients was reduced to 9% with ionic contrast media and 0.5% with non-ionic contrast media, when 50 mg prednisolone was administered at 13, 7, and 1 h before injection of contrast medium [14, 15]. Some studies have shown that methylprednisolone premedication (32 mg given 12 and 2 h before contrast medium injection) reduces the overall number of adverse reactions and mild adverse reactions [16, 17]. However, Dawson et al. suggested that corticosteroid pretreatment is not beneficial and should be abandoned [18]. Furthermore, the recommended corticosteroid prophylaxis regimen of oral methylprednisolone 32 mg given at 12 and 2 h before contrast administration is not possible in urgent contrast enhanced studies.

Some authors recommend combining steroids with antihistamines for pretreatment. Kelly et al. reported that a pretreatment regimen including prednisone (50 mg orally every 6 h for three doses ending 1 h before contrast injection), and diphenhydramine (50 mg intramuscularly, 1 h before contrast injection) reduced the risk of adverse reaction to ionic contrast media from 17–35% to 5% in high-risk patients [19]. Interestingly, no study has documented that antihistamine alone without corticosteroid prevents adverse reactions [20]. Prompt recognition and management of adverse reactions is invaluable in preventing life-threatening conditions. The patient should never be left alone for at least 20 min after contrast media injection, as 94–100% of severe and fatal reactions occur within 20 min of the contrast medium injection [21].

Table 3 Treatment of severe general acute adverse reactions to contrast media

Severe bronchospasm
1. Oxygen by mask (6–10 l/min)
2. Salbutamol nebulization (5 mg in 2 ml of saline)
3. Adrenaline injection if the bronchospasm is progressive
Laryngeal Edema
1. Oxygen by mask (6–10 l/min)
2. Adrenaline (1:1,000) 0.5 ml intravenous injection with ECG monitoring
Hypotension without bradycardia
1. Elevate patient's legs
2. Oxygen by mask (6–10 ml/min)
3. Intravenous fluids (normal saline or ringer lactate)
4. If unresponsive, dopamine 2–5 μg/kg/min infusion or adrenaline injection
Vagal reaction
1. Elevate patient's legs
2. Oxygen by mask (6–10 l/min)
3. Intravenous fluids (normal saline or ringer lactate)
4. Atropine 0.6 mg intravenously, repeat if necessary at 3–5 min up to 3 mg total
Anaphylactoid generalized reaction
1. Call for resuscitation team
2. Ensure patent airways
3. Elevate patient's legs
4. Oxygen by mask (6–10 l/min)
5. Intravenous fluids (normal saline or ringer lactate)
6. Hydrocortisone 500 mg intravenously
7. Adrenaline (1:1,000) 0.5 ml intravenous injection with ECG monitoring

Delayed general adverse reactions

A delayed adverse reaction is defined as a reaction which occurs 1 h to 1 week after contrast injection, which is predominantly skin reaction [2]. Delayed reactions are more common in young adults, women, and patients with allergic history. Iso-osmolar non-ionic contrast media have higher incidence of delayed adverse reactions [22, 23]. The incidence of delayed adverse reactions is 10.9% for iso-osmolar dimeric contrast media and 5.6% for low-osmolar monomeric contrast media [22]. Although, the pathogenesis of delayed reactions is not well-understood, it appears that many are T-cell-mediated reactions. Predisposing factors for delayed reactions include previous delayed reaction and interleukin-2 therapy [2]. Contrast media may not be the actual cause for the other reported delayed symptoms, such as nausea, vomiting, headache, joint pain, and fever. Skin reactions are true delayed reactions, which include maculopapular rash, erythema, urticaria, and angioedema. Most delayed skin reactions are mild to moderate and self-limiting. Prophylaxis is generally not recommended for delayed adverse reactions to contrast media.

Intravenous contrast media extravasation

Extravasation of intravenous contrast media occurs in 0.035–0.2% of patients with the use of a mechanical power injector [24]. Risk factors for extravasation include infants, elderly, and chronically ill, debilitated patients, venous thrombosis, multiple venous puncture attempts, tourniquets, and injections on dorsum of hand, foot, or ankle. Clinical presentation includes burning pain, tenderness, edema, and erythema. Severe injury results in blistering, sloughing off of skin, and compartment syndrome. Initial treatment comprises of elevation of affected extremity, ice packs, and close observation for 2–4 h. Plastic surgery consultation is recommended when the extravasated contrast media volume exceeds 30 ml of ionic contrast media or 100 ml of non-ionic contrast media [24].

Contrast-induced nephrotoxicity

Definition

Two definitions have been proposed for contrast-induced nephrotoxicity. Solomon et al. defined contrast-induced nephrotoxicity as an acute decrease in renal function manifested by an increase in baseline serum creatinine of at least 0.5 mg/dl (44 μmol/l) within 48 h of injection of contrast [3]. Porter defined contrast-induced nephrotoxicity as a serum creatinine increase of: a) greater than 25%, if baseline serum creatinine is less than 1.5 mg/dl or b) greater than 1.0 mg/dl, if baseline serum creatinine is greater than 1.5 mg/dl, when either occurs within 72 h after contrast injection [3].

Incidence

The reported incidence of contrast-induced nephrotoxicity varies widely due to lack of uniformity in the definition of contrast-induced nephrotoxicity. In patients with no history or signs/symptoms of renal disease, the risk of contrast-induced alteration in renal function is below 1% [5]. The risk increases to 12–27% in the presence of pre-existing renal impairment [4]. The reported incidence of contrast-induced nephrotoxicity in the presence of diabetic nephropathy is 50% [4].

Predisposing factors

Predisposing factors for contrast-induced nephrotoxicity include acute renal failure as pre-existing renal insufficiency (serum creatinine level ≥1.5 mg/dl), diabetes mellitus, dehydration, cardiovascular disease, and the use of diuretics, advanced age (≥70 years), myeloma, hypertension, and hyperuricemia [3]. The age threshold for a high risk of contrast-induced nephrotoxicity is not well-established and actually seems to be changing, as people are healthier at older ages. For patients with pre-existing renal insufficiency and, more clearly, for those with renal insufficiency and diabetes, non-ionic contrast media are less nephrotoxic than ionic contrast media [3]. The proposed benefit of less risk of nephrotoxicity of newer iso-osmolar, non-ionic contrast media remains to be investigated thoroughly.

Pathogenesis

The exact pathogenesis of contrast-induced nephrotoxicity is not well-understood. The suggested main factors in the pathophysiology of contrast-induced nephrotoxicity include a reduction in renal perfusion caused by a direct effect of contrast media on the kidney and toxic effects on the tubular cells. Reduction of renal perfusion is due to activation of the tubulo-glomerular feedback response and the release of endogenous vasoactive mediators, such as endothelin and adenosine. A reduction in the intra-renal production of the vasodilators nitric oxide and prostacyclin may also contribute to the pathogenesis of contrast-induced nephrotoxicity.

Prevention

Hydration by intravenous fluids and use of minimum required dose of non-ionic contrast media are proven protective measures to prevent contrast-induced nephrotoxicity [25]. Most prophylactic regimens require at least 6–12 h before hydration, which may not be feasible in an urgent contrast-enhanced study. Hydration regimen comprises of intravenous administration of 0.9 or 0.45% saline at 100 ml/h starting 6–12 h before contrast media injection and continued for 4–12 h afterwards. Although initial results were encouraging, and some centers have employed oral *N*-Acetylcysteine regimen for prophylaxis, data about the potential additional protection provided by oral *N*-Acetylcysteine are still inconclusive at this time to recommend this as a standard of care [25]. The oral *N*-Acetylcysteine prophylaxis regimen is 600 mg of *N*-Acetylcysteine given twice daily for 48 h, beginning 24 h before contrast injection. Sodium bicarbonate infusion 1 h before contrast injection followed by another 6 h of infusion after contrast injection may prove to be a useful intervention, but this regimen requires further study [25]. The evidence for regular use of pre-emptive renal replacement therapy, theophylline, or fenoldopam for prophylaxis of contrast-induced nephrotoxicity is weak and should not be the standard of care based on the current published evidence [25].

Strategies for contrast-induced nephrotoxicity risk screening

Tippins et al. reported that 97% of patients with elevated serum creatinine (≥2.0 mg/dl) had risk factors for contrast-induced nephrotoxicity [26]. Indications for baseline serum

creatinine measurement before intravenous contrast media injection are summarized in Table 4. Most centers employ a serum creatinine threshold of 1.5 mg/dl for detection of patients at high risk for contrast-induced nephrotoxicity. However, considerable derangement of renal function can be masked by a normal appearing serum creatinine report. Hence, the current recommendation is to screen high-risk patients with estimated glomerular filtration rate (GFR). Derangement of GFR can occur in a patient due to undetected chronic renal disease though the creatinine measurements are normal. The Modification of Diet in Renal Disease (MDRD) study group equation is an accurate method for GFR estimation from serum creatinine [27]:

$$GFR = 186 \times (serum\ creatinine) - 1.154 \times (age) - 0.203 \times k$$

For women, k=0.742; for men, k=1

Multiply by 1.210 if African-American

The risk of contrast-induced nephrotoxicity based on estimated GFR is summarized in Table 5. Recently, some vendors are investigating rapid strip-test-based methods for quick measurement of serum creatinine when patients arrive for contrast-enhanced radiological studies [28]. Such methods to estimate serum creatinine can enable efficient detection of patients at risk for contrast-induced nephrotoxicity.

Metformin therapy and the risk of lactic acidosis

When patients taking metformin receive iodinated contrast media, they are at risk for lactic acidosis. If renal dysfunction occurs due to iodinated contrast media, an accumulation of metformin can occur and cause lactic acidosis. According to the American College of Radiology (ACR) guidelines, metformin should be discontinued at the time of an examination or procedure using intravascular contrast media, withheld for 48 h after the procedure, and reinstated only after renal function has been re-evaluated and found to be normal [3]. However, the examination may proceed even if the patient took a dose of metformin on the morning of the examination.

Table 4 Indications for serum creatinine measurement before intravenous administration of iodinated contrast media

History of kidney disease
Family history of renal failure
Diabetes treated with insulin or other medications prescribed by a physician
Myeloma
Collagen vascular disease
Medications: metformin, non-steroidal anti-inflammatory drugs, aminoglycosides

Table 5 Risk of contrast induced nephrotoxicity based on estimated glomerular filtration rate (GFR)

GFR (ml/min/1.73 m^2)	Risk of contrast induced nephrotoxicity	Intravenous iodinated contrast media
60	Negligible	Safe
30–60	Moderate	Use only if clinically essential prophylaxis required
<30	High	Contraindicated

Administration of contrast media to pregnant patients and nursing mothers

When given in usual clinical doses, iodinated contrast media cross the human placenta and enter the fetus [3]. No adequate and well-controlled teratogenic studies of the effects of these agents in pregnant women have been performed. While it is not possible to conclude that iodinated contrast media present a definite risk to the fetus, there is insufficient evidence to conclude that they pose no risk. The ACR recommends that iodinated contrast media may be given to pregnant patients only when [3]:

- the diagnostic information requested using contrast-enhanced study cannot be obtained via other means (such as ultrasound)
- the information needed affects the care of the patient and fetus during the pregnancy
- it is not prudent to wait to obtain this information until after the patient is no longer pregnant

Less than 1% of iodinated contrast media is excreted into breast milk, out of which only 1% is absorbed by the infant's gut. According to ACR recommendations, it is safe for the mother and infant to continue breast-feeding after receiving contrast media [3]. However, if the mother remains concerned about any potential ill effects to the infant, she may abstain from breast-feeding for 24 h [3].

Conclusion

Prompt recognition and treatment are invaluable in blunting an adverse response of a patient to contrast media, and may prevent a reaction from becoming severe or even life-threatening. Proper patient evaluation and procedure selection, and adequate prophylactic measures can prevent some adverse reactions. Knowledge, training, and preparation are crucial for appropriate and effective therapy in the event of an adverse reaction. Radiologists and their staff need to review the treatment algorithms regularly so that each can accomplish his or her role efficiently.

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