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Drug Induced Adverse Effects in Radiographic Procedures

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ABSTRACT:

Radiographic procedures have revolutionized diagnostic medicine by enabling non-invasive visualization of internal structures. However, the use of drugs—particularly contrast media—in these procedures is not without risk. Adverse drug reactions (ADRs) during radiographic imaging, especially hypersensitivity and organ-specific toxicities, pose significant clinical challenges. This review examines the spectrum of drugs used in radiographic procedures, categorizes associated adverse effects, analyzes the underlying mechanisms, and discusses preventive strategies and clinical management. Emphasis is given to iodinated contrast media, barium sulfate, gadolinium-based agents, and the incidence and pathophysiology of hypersensitivity and nephrotoxicity. Strategies for patient safety, including premedication, patient history screening, and advancements in low- osmolar and iso-osmolar contrast agents, are also addressed..

Keywords: Contrast media, Radiographic procedures, Adverse reactions, Iodinated agents, Gadolinium agents, Hypersensitivity, Nephropathy, Patient safety

INTRODUCTION

Radiographic procedures play a critical role in the diagnosis and management of various medical conditions by providing detailed images of internal organs and systems. To enhance image clarity and diagnostic accuracy, pharmacological agents—particularly contrast media—are routinely administered. These include iodinated contrast media (ICM) for X-ray and CT imaging, gadolinium-based contrast agents (GBCAs) for MRI, and barium sulfate for gastrointestinal studies[1,2].

Although generally safe, these agents are associated with drug-induced adverse effects ranging from mild allergic reactions to life-threatening complications. Common adverse reactions include immediate or delayed hypersensitivity, contrast-induced nephropathy (CIN), and nephrogenic systemic fibrosis (NSF)[3,4,5]. The severity and likelihood of these events are influenced by patient-specific factors such as a history of allergies, asthma, renal impairment, and concurrent use of medications like beta-blockers or nephrotoxic drugs [6,7].

Given the increasing use of imaging techniques in clinical practice, it is essential for healthcare professionals to understand the risks associated with contrast agents. This review aims to summarize the types of drugs used in radiographic procedures, the mechanisms of their adverse effects, risk factors, diagnostic tools, and evidence-based strategies for prevention and management to promote safer imaging practices[8,9].

COMMON IMAGING-RELATED DRUGS

1. Iodinated Contrast Media (ICM)

ICM remain the most widely used contrast agents in CT and angiography, and low- osmolality non-ionic formulations are currently preferred due to significantly lower rates of adverse reactions compared with older high-osmolality ionic agents.

- Adverse reactions are classified as allergic-like (idiosyncratic) or physiologic (dose- dependent effects such as warmth, metallic taste, nausea, and vomiting).
- Recent evidence emphasizes that although the incidence of severe hypersensitivity reactions is <0.04%, they require immediate recognition and management with epinephrine as first- line therapy.
- Contrast-Induced Nephropathy (CIN/CI-AKI) is still debated, but preventive strategies such as IV isotonic saline hydration and use of minimum contrast dose remain strongly recommended.

- Recent evidence suggests that patients on metformin therapy should be monitored closely for lactic acidosis risk, especially if renal function deteriorates after contrast exposure[10,11,31].

2. Gadolinium-Based Contrast Agents (GBCAs)

GBCAs are used in MRI procedures .While generally safer, they may cause NSF in patients with impaired renal function[4,12].

GBCAs are categorized as linear and macrocyclic chelates, with macrocyclic agents showing superior stability and lower risk of NSF.

- Hypersensitivity reactions are less common than with iodinated contrast but may include urticaria, bronchospasm, hypotension, and rare anaphylaxis.
- Recent evidence notes that delayed hypersensitivity reactions (onset >1 hour, often skin- related) are increasingly recognized, though underreported.
- NSF is almost exclusively associated with older linear GBCAs in patients with severe renal impairment (GFR <30 mL/min/1.73m²), and strict screening protocols have drastically reduced its incidence.
- An emerging concern is gadolinium retention in brain, bone, and skin tissues, observed even in patients with normal renal function, though no clear clinical consequences have yet been established.
- Pediatric patients and pregnant women are considered special risk groups, where GBCAs should be avoided unless essential[4,12,31].

3. Barium Sulfate

Barium sulfate is considered pharmacologically inert because it is not absorbed from the gastrointestinal tract under normal conditions. This makes it a safe choice for contrast studies of the GI tract.

- However, complications can occur if it leaks into the peritoneal cavity (e.g., due to bowel perforation), where it can cause severe peritonitis, adhesions, or fibrosis.
- Aspiration of barium during swallowing studies is a known risk, especially in elderly patients, children, or those with swallowing disorders. This may lead to acute pneumonitis or airway obstruction ("barium pneumonia").
- In rare cases, hypersensitivity or anaphylactic reactions have been reported, usually linked to additives (stabilizers, suspending agents, preservatives) rather than barium itself.
- Repeated or high-dose use of barium may lead to severe constipation, fecal impaction, or bowel obstruction, especially in patients who are dehydrated or immobilized.
- In neonates and infants, small bowel obstruction or necrotizing enterocolitis has been reported after barium studies.
- Extravasation during rectal administration can cause local tissue inflammation or fibrosis.
- To minimize risks, careful patient preparation (fasting, hydration, and bowel cleansing), adequate swallowing instructions, and selection of appropriate suspension viscosity are important safety measures.
- When perforation of the GI tract is suspected, water-soluble contrast agents (e.g., Gastrografin/diatrizoate meglumine) are preferred instead of barium sulfate[1,31].

4. Adjunctive Medications

Corticosteroids and antihistamines are often used prophylactically in patients with a history of contrast reactions.

Corticosteroids (e.g., prednisone, methylprednisolone) and antihistamines (e.g., diphenhydramine, cetirizine) are the most widely used prophylactic medications for patients with a history of contrast hypersensitivity.

- Premedication regimens:
  - Elective/standard regimen: Prednisone 50 mg orally at 13, 7, and 1 hour before contrast, plus diphenhydramine 50 mg orally/IV 1 hour before.
  - Rapid/urgent regimen: Methylprednisolone IV every 4 hours (two doses) with antihistamines. Less effective but useful in emergencies.
- H2 receptor antagonists (ranitidine, famotidine) are sometimes added to reduce gastrointestinal and cutaneous histamine-mediated symptoms.
- Second-generation antihistamines (cetirizine, loratadine) are increasingly preferred for prophylaxis because they are effective with fewer sedative effects than diphenhydramine.
- Limitations: Premedication lowers risk and severity but does not fully prevent reactions, especially non-IgE-mediated reactions (e.g., direct mast cell activation). Breakthrough reactions occur in up to 20% of premedicated patients.
- Beta-blocker caution: Patients on beta-blockers may not respond adequately to epinephrine in case of anaphylaxis. Adjunctive use of glucagon has been recommended if epinephrine is less effective.

- Emergency preparedness remains crucial: Even with premedication, epinephrine, oxygen, IV fluids, and resuscitation equipment must be immediately available.
- Individualized approach: Not all patients require premedication. It should be reserved for those with moderate to severe prior contrast reactions; mild urticaria may not warrant full prophylaxis.
- Desensitization protocols (under allergist supervision) can be considered in patients who require contrast but have severe prior reactions.
- Recent guidelines (ACR 2023, Vega 2024) recommend documenting the exact premedication regimen and outcome for future reference in the patient's medical record[7,8,13].

TYPES OF ADVERSE DRUG REACTIONS

1. **Hypersensitivity Reactions**

- These are the most commonly reported and can be:
  - Immediate (within 1 hour): Urticaria, angioedema, bronchospasm, or anaphylaxis.
  - Non-immediate (1 hour to 7 days): Maculopapular rash, delayed urticaria, mild fever.
- These reactions may be IgE-mediated (true allergy) or non–IgE mediated (direct mast cell activation).
- More common with iodinated contrast media; can also occur with gadolinium-based agents (less frequent).
- Skin testing can help identify true allergic reactions to ICM[3,11,14].

2. **Contrast-Induced Nephropathy (CIN)**

CIN is a form of acute kidney injury that occurs 24–72 hours after ICM exposure, especially in patients with pre-existing renal dysfunction or diabetes[6,15]

- Higher risk in patients with pre-existing renal impairment, diabetes, dehydration, or concurrent nephrotoxic drugs.
- Preventable with adequate hydration, minimizing contrast dose, and avoiding repeat exposure.
- Pathogenesis involves renal vasoconstriction, medullary hypoxia, and direct tubular epithelial cell toxicity caused by iodinated agents.
- The risk is higher with intra-arterial contrast administration (e.g., during angiography) compared to intravenous use.
- Use of iso-osmolar contrast agents (iodixanol) has been associated with lower rates of CIN compared to low-osmolar agents in some studies.
- Biomarkers such as cystatin C and neutrophil gelatinase–associated lipocalin (NGAL) are being studied for early detection of CIN before serum creatinine rises.
- CIN is associated with increased hospital stay, need for dialysis, and higher short-term mortality in high-risk patients.

3. **Nephrogenic Systemic Fibrosis (NSF)**

Linked to GBCAs, NSF is a rare but serious condition that affects patients with advanced kidney disease.[4,12]

- Causes skin thickening, joint contractures, and systemic fibrosis.
- Incidence has decreased with macrocyclic GBCAs and strict renal function screening.
- Characterized by progressive skin thickening, woody induration, hyperpigmentation, and reduced joint mobility; systemic involvement may affect muscles, lungs, and heart.
- Histology shows dermal fibrosis, proliferation of fibroblasts, and mucin deposition.
- The risk is highest with linear non-ionic GBCAs (e.g., gadodiamide, gadopentetate), while macrocyclic agents are much safer.
- Hemodialysis immediately after GBCA exposure can reduce the risk of NSF in dialysis patients, though not fully protective.
- Cases have also been reported after off-label high-dose or repeated gadolinium use, such as in angiography or patients undergoing multiple MRIs.

4. **Physiological / Chemotoxic Reactions**

- Dose-related, non-allergic effects caused by the osmolality, viscosity, or ionic nature of contrast media.
- Symptoms: nausea, vomiting, warmth, metallic taste, vasovagal reactions, and hemodynamic changes (bradycardia, hypotension).
- Generally self-limiting and mild, but can be distressing to patients.

- Caused by osmolality-related shifts of fluid and electrolytes, leading to symptoms like vasodilation, hypotension, or pulmonary edema.
- High-osmolality contrast agents can cause erythrocyte crenation and endothelial cell injury, worsening microcirculatory flow.
- Neurological toxicity may present as seizures, cortical blindness, or confusion when contrast enters the CNS, especially during angiographic procedures with blood–brain barrier disruption.
- Cardiovascular effects include transient changes in heart rate, arrhythmias, or myocardial depression, particularly in patients with pre-existing cardiac disease.
- Osmotic diuresis can result in fluid–electrolyte imbalance (e.g., dehydration, hyponatremia) in vulnerable patients.

RISK FACTORS FOR ADRS IN RADIOGRAPHIC PROCEDURES

Adverse drug reactions (ADRs) in radiographic procedures are influenced by a combination of patient-related, drug-related, and procedure-related factors:

1. Patient-Related Risk Factors

- History of hypersensitivity: Prior allergic-like or anaphylactic reaction to contrast media is the strongest predictor of recurrence.
- Atopy and asthma: Patients with asthma, hay fever, or multiple drug allergies are more prone to bronchospasm and urticaria.
- Renal dysfunction: Reduced glomerular filtration rate (eGFR <60 mL/min/1.73 m²) increases the risk of contrast-induced nephropathy (CIN) and gadolinium-related nephrogenic systemic fibrosis (NSF).
- Age extremes: Elderly patients (due to comorbidities and polypharmacy) and neonates/infants (due to immature renal function) are at higher risk.
- Cardiovascular disease: Heart failure, hypotension, or dehydration enhances susceptibility to renal injury from contrast media.
- Concurrent medications:
  - Nephrotoxic drugs (NSAIDs, aminoglycosides, cisplatin) increase CIN risk.
  - Beta-blockers may mask tachycardia in anaphylaxis and reduce responsiveness to epinephrine.
  - Metformin in renal impairment may precipitate lactic acidosis after ICM exposure.
- Pregnancy: Though rare, fetal exposure to contrast media carries potential risks, and maternal renal impairment increases complications.

2. Drug-Related Risk Factors

- Osmolality and ionicity of contrast agents**:** High-osmolality ionic iodinated agents are associated with more ADRs than low-osmolar or iso-osmolar non-ionic formulations.
- Type of gadolinium agent**:** Linear chelates have higher NSF risk compared to macrocyclic agents.
- Cumulative exposure**:** Repeated doses in short intervals (<72 hours) increase nephrotoxicity.

3. Procedure-Related Risk Factors

- Route of administration**:** Intravascular administration carries higher systemic risk than oral/rectal use.
- Contrast dose and rate of injection**:** Large volumes or rapid bolus injection raise the likelihood of hypersensitivity or CIN.
- Emergency procedures**:** Limited time for risk stratification or premedication increases the chance of ADRs[4,10,15].

DIAGNOSTIC TOOLS AND TESTING

1. Skin Testing:

- Skin prick test: Detects immediate IgE-mediated hypersensitivity.
- Intradermal test: More sensitive but carries a small risk of triggering a mild reaction.
- Patch test: Useful for identifying delayed hypersensitivity reactions (e.g., maculopapular rashes).
- Sensitivity is moderate, but a positive test strongly supports IgE involvement.

2. Laboratory Testing:

- Serum tryptase levels: Elevated levels within 1–2 hours of reaction confirm mast cell activation and support the diagnosis of anaphylaxis.

- Basophil activation test (BAT): A research-based in vitro tool that identifies IgE-mediated reactions with higher sensitivity.
- Renal biomarkers: Serum creatinine, eGFR, and cystatin C are used to assess risk and monitor CIN development.

3. Imaging and Functional Assessment

- Renal ultrasound or Doppler may be used to evaluate renal perfusion post-contrast in high- risk patients.
- Cardiac monitoring is recommended for patients with suspected severe anaphylaxis or cardiovascular comorbidities.

4. Provocation Tests

- Rarely performed due to risk, but under controlled settings, re-challenge with diluted contrast can confirm causality if skin and in vitro tests are inconclusive.

5. Pharmacovigilance Tools

- Use of Naranjo ADR probability scale or WHO-UMC causality assessment helps in systematic documentation and confirmation of ADRs in radiographic settings.

According to a 6-year study, skin testing was positive in 23% of patients with prior ICM reactions, and was more useful in those with immediate hypersensitivity[14].

PREVENTION AND MANAGEMENT

Preventing and managing drug-induced adverse effects in radiographic procedures is critical for ensuring patient safety. Strategies range from thorough pre-procedure screening to the use of safer contrast agents, appropriate premedication, and emergency preparedness.

1. Patient Screening and Risk Assessment

- A detailed patient history is the cornerstone of prevention. Clinicians should inquire about:
  - Previous reactions to contrast media (especially moderate-to-severe)
  - History of asthma, atopy, or other allergies
  - Current renal function (e.g., eGFR, serum creatinine)
  - Concurrent medications (e.g., metformin, beta-blockers, NSAIDs)[2,4,6].

Patients with renal impairment are at increased risk of contrast-induced nephropathy (CIN) and nephrogenic systemic fibrosis (NSF) when exposed to iodinated or gadolinium-based agents, respectively. Renal function should be assessed in patients over 60 years old, with diabetes, hypertension, or chronic kidney disease.

Use structured questionnaires to systematically capture history of allergy, asthma, renal disease, and drug use.

- Employ electronic health record (EHR) alerts for patients with known contrast allergies to prevent accidental re-exposure.
- Assess hydration status (urine output, recent diuretic use) before procedures to minimize risk of CIN.
- Consider genetic predispositions (e.g., polymorphisms in IL-4, IL-13 pathways) which may increase susceptibility to hypersensitivity.
- Evaluate cumulative radiation/contrast exposure in oncology or chronic illness patients, as repeated exposure raises ADR risks.

2. Premedication Protocols

- For patients with a history of hypersensitivity to contrast media, premedication may reduce the severity of allergic-like reactions. Common regimens include:
  - Prednisone 50 mg orally, 13, 7, and 1 hour before contrast administration
  - Diphenhydramine 50 mg orally or IV, 1 hour before the procedure[6].

Alternative regimens are available for urgent situations, though less effective than standard 13-hour protocols[17]. However, premedication does not prevent all reactions, especially non- IgE-mediated ones, and should not replace vigilance or emergency preparedness[3,9].

Alternative antihistamines (e.g., cetirizine or loratadine) can be used in place of diphenhydramine in patients intolerant to sedating agents.

- Short-term premedication regimens (e.g., IV methylprednisolone 1–2 hours before) may be used in emergencies, although less effective than standard regimens.
- Leukotriene receptor antagonists (e.g., montelukast) are being explored as adjuncts to reduce bronchospasm risk in asthmatic patients.

- Personalized premedication strategies may be tailored depending on the type of prior reaction (immediate vs delayed).
- Desensitization protocols, though rarely needed, can be used for patients with unavoidable contrast exposure and severe prior reactions.

3. Use of Safer Contrast Agents

- Selecting the appropriate contrast media can significantly reduce adverse event risks:
  - Use non-ionic, low-osmolality or iso-osmolar iodinated contrast media instead of older ionic, high-osmolality types[10].
  - For patients with renal impairment, prefer macrocyclic gadolinium agents over linear ones to reduce NSF risk[4,12].
- Utilize the lowest effective dose of contrast agent based on body weight and imaging indication.
- Apply dual-energy CT or other dose-reduction technologies to achieve diagnostic quality with less contrast volume.
- For gadolinium agents, avoid linear chelates entirely in high-risk populations, even if renal function is borderline normal.
- Consider carbon dioxide angiography or contrast-free MR angiography in vascular imaging to avoid ICM use in renal impairment.
- Encourage multidisciplinary consultation (radiologist, nephrologist, allergist) before high- risk procedures.
- Additionally, reducing contrast volume and using alternative imaging (e.g., non-contrast CT, ultrasound, or MRI) may be appropriate in high-risk individuals[7].

4. Hydration and CIN Prevention

- To prevent CIN, adequate hydration before and after contrast administration is essential, especially in patients with chronic kidney disease. Isotonic saline or sodium bicarbonate solutions are commonly used.
  - Typical regimen: 1 mL/kg/h of normal saline for 6–12 hours before and after contrast exposure[5].

Avoiding repeat contrast exposure within 48–72 hours is also recommended[15].

- Oral hydration protocols (e.g., 500 mL water before and after procedure) may be used in outpatients who cannot receive IV fluids.
- N-acetylcysteine supplementation has been investigated for CIN prevention, though evidence is mixed; it may still be considered in very high-risk cases.
- Use of statins (e.g., atorvastatin) pre-procedure has shown renoprotective effects in some studies.
- Avoid concurrent nephrotoxic medications (NSAIDs, aminoglycosides) around the time of imaging whenever possible.
- Post-procedure renal monitoring (serum creatinine within 48–72 hours) is recommended for high-risk patients.

5. Emergency Preparedness and Monitoring

- All radiology departments must be equipped to manage acute contrast reactions. This includes:
  - Immediate availability of epinephrine, oxygen, IV fluids, antihistamines, and corticosteroids
  - Staff trained in Advanced Cardiac Life Support (ACLS)
  - Monitoring high-risk patients for 30–60 minutes post-procedure for delayed reactions[11].
- Establish institution-wide contrast reaction protocols with clear role assignments for staff.
- Keep emergency carts with epinephrine auto-injectors and airway management equipment in all imaging suites.
- Simulated drills for staff should be conducted regularly to ensure preparedness for anaphylaxis or cardiac arrest.
- Implement post-procedure telephone follow-up for outpatients at high risk of delayed hypersensitivity reactions.
- Document oxygen saturation and blood pressure continuously during contrast administration in high risk patients.

6. Documentation and Reporting

- Any adverse reaction should be documented in the patient's medical record and flagged for

future procedures. Use of contrast media allergy alert bracelets or EMR alerts can help prevent re-exposure[8].

- In cases of suspected IgE-mediated reactions, referral to an allergist for skin testing or desensitization protocols is advised[14].
- Use structured ADR reporting forms to capture reaction type, timing, severity, and intervention used.
- Flag patients in hospital systems with "contrast allergy" alerts to prevent inadvertent re- exposure.

- Encourage patient-held records (allergy cards or bracelets) to inform future healthcare providers.
- Submit reports to national pharmacovigilance databases to strengthen collective knowledge of ADR patterns.
- Conduct root-cause analysis for every severe ADR to identify modifiable system-level risk factors.

PHARMACOVIGILANCE AND ADR REPORTING

Despite the clinical importance of ADRs in radiographic procedures, underreporting is a major barrier to effective pharmacovigilance. Studies indicate that only 10–20% of contrast- related adverse events are formally reported. The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) and the Indian Pharmacopoeia Commission (IPC) under the Pharmacovigilance Programme of India (PvPI) encourage healthcare professionals to report all suspected ADRs. In radiology, structured documentation of adverse events is critical to avoid repeat exposure and to build institutional safety databases. The use of electronic medical records (EMRs) with contrast allergy alerts and integration with national pharmacovigilance systems can enhance reporting. Additionally, continuous education and sensitization of radiology staff, pharmacists, and physicians about ADR reporting are essential. Improving pharmacovigilance will help in early identification of new or rare adverse effects, refine prevention strategies, and improve patient safety outcomes in diagnostic imaging practices[22,29,30].

EPIDEMIOLOGY OF ADVERSE DRUG REACTIONS IN RADIOGRAPHIC PROCEDURES

The global incidence of adverse drug reactions (ADRs) associated with radiographic contrast agents varies depending on the type of agent used, the population studied, and reporting practices. Adverse reactions to iodinated contrast media (ICM) occur in approximately 3– 12% of patients receiving high-osmolar agents, whereas the incidence drops to 0.2–0.7% with

modern non-ionic, low-osmolar agents. Severe life-threatening reactions such as anaphylaxis occur in 0.01–0.04% of cases. Gadolinium-based contrast agents (GBCAs) are associated with overall adverse reaction rates of 0.07–2.4%, with serious reactions being rare (0.001– 0.01%). The incidence of nephrogenic systemic fibrosis (NSF), once reported in up to 4% of patients with severe renal impairment, has markedly declined due to the preferential use of macrocyclic gadolinium agents and strict screening protocols. In India, comprehensive data are limited, though regional pharmacovigilance reports indicate underreporting remains a challenge. Epidemiological studies highlight the importance of robust ADR surveillance systems, especially in developing countries where imaging utilization is increasing rapidly[10,20].

CONCLUSION

Radiographic imaging is indispensable in modern medicine, yet the use of contrast media— especially iodinated and gadolinium-based agents—carries the risk of significant adverse drug reactions (ADRs). As reviewed, these range from mild hypersensitivity responses to severe, potentially life-threatening complications such as anaphylaxis, contrast-induced nephropathy (CIN), and nephrogenic systemic fibrosis (NSF). While newer, low-osmolality and macrocyclic agents have improved safety profiles, vulnerable patients remain at risk due to factors like renal dysfunction, prior allergic reactions, and concomitant medications.

Evidence from current literature—including Kvedariene et al., Brockow et al., and Widmark—emphasizes the importance of risk stratification, the role of diagnostic tools like skin testing, and the effectiveness of structured premedication protocols in mitigating immediate and delayed reactions. Additionally, proper hydration strategies, use of safer contrast agents, and emergency preparedness are vital in preventing and managing adverse outcomes.

Ultimately, enhancing patient safety in radiographic procedures hinges on a multidisciplinary approach: thorough patient screening, individualized preventive strategies, adherence to updated guidelines, and a robust institutional response system. Continued research, clinician education, and systematic reporting will further refine protocols, reduce preventable complications, and ensure that diagnostic benefits outweigh pharmacologic risks.

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