Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting: What the Pharmacist Needs to Know

Presented as a Live Webinar
Thursday, February 4, 2016
1:00 p.m. – 2:00 p.m. ET

On-demand Activity
Live webinar recorded and archived to be watched at your convenience
Available after March 28, 2016

www.ashpadvantage.com/contrastmedia

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Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting: 
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Activity Overview

This educational activity will review currently available iodine-based contrast agents in terms of use, dosing, route of administration, and safety profile. Specific clinical situations for which use of a particular agent would be advantageous will also be explained. Effective approaches to screening and managing patients at risk of developing adverse effects will be discussed. The activity will conclude with a description of safe handling and storage processes for contrast media that should be employed by the pharmacy department.

Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- Review currently available iodinated contrast agents with respect to use, dosing, and safety profile in adults and children.
- Review the routes of administration of available iodinated contrast media.
- Explain how to screen and manage patients at risk of adverse effects with iodinated contrast agents.
- Describe safe handling and storage processes that should be employed when handling contrast agents.

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Webinar Information

Visit www.ashpadvantage.com/contrastmedia to find

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Additional Educational Activities

- On-demand activity based on the live webinar (1 hour CPE, available after March 28, 2016) – Please note that individuals who claim CPE credit for the live webinar are ineligible to claim credit for the on-demand activity.

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Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting:  
What the Pharmacist Needs to Know

Activity Faculty

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Ed Kent is Director, VHA Mountain States (VHAMS) Pharmacy RxNetwork, which represents 51 hospitals across a ten-state region. Pharmacy directors and clinical coordinators from 35 affiliated member organizations formed the Integrated Delivery Network (IDN), which resulted in the regional formulary standardization and clinical process improvement in all pharmacy service areas. Ed’s primary responsibilities include identifying formulary standardization and clinical process improvement opportunities; analyzing and assessing the potential for savings; contacting vendor’s national account managers; developing and requesting proposals; negotiating contract enhancements; developing strategies for successful implementation; auditing all partner’s performance; identifying any/all remaining opportunities for conversion; and reporting the financial impact to all key stakeholders. Overall Member satisfaction exceeds 92%.

Ed received his B.S. Pharmacy degree from the University of Iowa. Ed is a member of the American Society of Health-System Pharmacists and is a past member of the Novation Pharmacy Executive Strategic Planning Council (2007).

Prior to joining VHA, Ed worked 10 years as the Pharmacy Manager/Director of Billings Clinic (formerly Deaconess Billings Clinic), in Billings, Montana. In 2004, Billings Clinic and Ed accepted a VHA Mountain States and National Leadership Award for Clinical Effectiveness: Cardiac Care (CHF/MI). In 2005, Ed was recognized by VHA Mountain States with an Excellence Award for Supply Chain Management: Pharmacy ADA Consolidation Initiative. Since 2002, seven of his pharmacy staff members were nominated and received Billings Clinic Excellence Awards for Personal Service Excellence.

At VHA, Ed’s performance has been recognized with several awards and recognition, including a 2009 Member Engagement Satisfaction Award, 1Q 2010 WOW Award, 2010 Business Unit Plan Achievement and Financial Stewardship Awards.
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Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting: WHAT THE PHARMACIST NEEDS TO KNOW

Ed Kent, B.S.Pharm.
Director, Mountain States Pharmacy Network
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Billings, Montana

1.0 hr. CPE

Disclosures
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• Review currently available iodinated contrast agents with respect to use, dosing, and safety profile in adults and children.
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• Describe safe handling and storage processes that should be employed when handling contrast agents.

Radiocontrast Media

• Purpose: improve the visibility of x-ray images of internal body structures
  • Computed tomography (CT or CAT scan)
  • Radiography
  • Fluoroscopy

• Types:
  • Barium, which is administered orally or rectally
  • Iodine, which is administered orally, rectally, body cavity, and intravascularly

• How It Works
  • Iodine “dye” absorbs X-ray radiation preventing it from passing through which changes the appearance of surrounding tissue – “contrast-enhanced”

Pharmacy Oversight – Collaboration with Radiology

• 2004: The Joint Commission (TJC) defined diagnostic agents and radiopharmaceuticals as a “drug” – MUST comply with Medication Management standards
  • Director of Pharmacy is responsible for oversight of all medication-related areas

• Centers for Medicare and Medicaid Services (CMS) Condition of Participation (COP)
  • Preparation of radiopharmaceuticals included in Pharmaceutical Services standards in the Code of Federal Regulations (42 CFR 482.25) and Nursing Services standards (42 CFR 482.23(c))

• All CMS “deemed” Accrediting Organizations base their standards on CMS’ COP:
  • The Joint Commission (TJC), The American Osteopathic Association’s Healthcare Facilities Accreditation Program (HAP), Det Norske Veritas (DNV)’s National Integrated Accreditation for Healthcare Organizations (NIAHO)

• State Department of Health, State Board of Pharmacy, FDA

Iodinated Contrast Media - Classification

• Categorized by chemical structure [monomer and dimer], Ionization, and osmolality

• Structure based on modifications of the 2, 4, 6-tri-iodinated benzene ring structure

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Iodinated Contrast Media: Classification and Use

**High-osmolality Iodinated Contrast Media**
- Greater than 1000 mOsm/kg (5–8X Normal Plasma Osmolality)
- 100% Ionic (two generic names: anion and cation)
- NOT routinely given intravascularly due to adverse physiological effects
- Restricted to GI tract (oral/rectal), bladder, gallbladder, uterus, and fallopian tubes
- Store HOCM (oral/other) separate from i.v. formulations

**Low-osmolality Iodinated Contrast Media**
- Broad use: intravascularly, intra-arterially, oral, rectal, gastrointestinal, bladder, intra-articularly, intrauterine
- General Properties:
  - Osmolality ranges 290 to 844 mOsm/kg
  - Normally used concentration: 200 to 370 mgI/mL (300 mgI/mL most often used)
  - Cost is approximately 10x higher than HOCM
  - Associated with lower incidence of adverse drug reactions compared to HOCM
- LOMC sub-categories:
  - Non-ionic Monomer: Osmolality = 290 to 370 mOsm/kg
  - Non-ionic Monomer: osmolality = 290 to 844 mOsm/kg (marketed as “iso-Osmolar Contrast”)
  - ~ 50% the osmolality of non-ionic monomers at the same iodine concentration
  - Only “iso-osmolar contrast” is iodoxin
  - Due to higher expense = Do to cost; use is limited

Iodinated Contrast Media – Concentration
- Iodine is iodine to all X-ray scanners; equivalent milligrams concentrations of iodine are viewed the same, regardless of the carrier molecule
- X-ray radiopacity is directly proportional to the organically bound iodine per mL or organically bound iodine infused per milliliter per second
  - “mgI/mL” in a body cavity or space or
  - “mgI/mL/sec” when infused intravascularly
- Iohexol 300 mgI/mL = ioprofin 300 mgI/mL = 320 mgI/mL iodoxin
  - 85 mL of iopamidol 370 mgI/mL delivers the same amount of iodine as 100 mL of iodoxin 320 mgI/mL, and iopamidol, at this concentration, is more radiopaque if administered at an equivalent infusion rate
- Deeper, visceral internal body structures require a greater concentration of iodine to obtain clear X-ray images

Iodinated Contrast Media – Osmolality
- Osmolality is a measure of the number of dissolved particles per Kilogram (Osmolality is per Liter) of water
- Normal human plasma: 270–300 mOsm/kg
- Normal cerebrospinal fluid: 280–300 mOsm/kg
- Osmolality depends on concentration and ionicity
- Higher osmolality relates to some of the adverse events of ICM
- Magnitude (and duration) of osmolality deviation from “normal” are important along with size and blood flow of the vasculature
- Osmolality has a threshold phenomenon for causing pain and ultimately tissue damage
  - Peripheral vein: < 600 mOsm/kg - no injection site pain
  - > 900 mOsm/kg - injection site burning and pain
- D5NS, D5UR, and D10W all have an osmolality of ~ 600 mOsm/L
- Adult patients: Osmolality of an IV solution administered via peripheral vein should be below 900 mOsm/L

mg/mL = milligrams iodine per milliliter

See page 14 for enlarged view
Warming Iodinated Contrast Media

- Warming from room (25°C) to body temperature (37°C) reduces viscosity by 50%
- Warming reduces injection pressures needed for higher injection rates needed to improve vascular opacification
  - Warming (to 37°C) has NO EFFECT on adverse event rates with LDCM at 300mgI/mL, or lower concentrations at injection speeds less than 6 mL/sec
  - Warming of concentrations above 300 mgI/mL - 3X reduction of extravasation and incidence of adverse events
    - Viscosity of ioxitalm at 23°C = 26.6P~15x normal; viscosity of ioxitalm at 37°C = 11.8P~7x normal - so warming to body temperature reduces viscosity by 50%
    - At equivalent iodine concentrations, the viscosity of the non-ionic dimer, remains two times greater than non-ionic monomers
- Warming of ICM is recommended as follows:
  - High rate i.v. (DCRM power injectors) 15 mL/sec
  - Injections of viscous LCM iodinated contrast media with concentrations above 300 mgI/mL
  - Direct arterial injections through small-caliber catheters (5 French or smaller)
  - Intravenously injected arterial studies in which timing and peak enhancement are critical

Polling Question

Which of the following statements is FALSE?

a. HOCM is associated with a higher incidence of adverse drug events
b. ICM with an osmolality >900 mOsm/Kg causes injection site burning, pain and potentially cellular and tissue damage
c. HOCM should be stored separate from intravascular LOCM
d. Products with equivalent concentrations of iodine produce the same X-ray results regardless of the ICM carrier molecule
e. Warming to body temperature (37°C) is needed to reduce injection pressures and the inherent risk of extravasation and other adverse reactions for all LOCM ICM

Viscosity of Low-osmolality Iodinated Contrast Media

- Normal Plasma viscosity = 1.4 - 1.8 cP at 37°C

Dosing: Concentration and Volume

- GI Tract Imaging: HOCM or LOCM?
  - If previous allergic reaction to barium (rare: 1/750,000 exams) use HOCM or LOCM
  - If barium is unavailable, generally use HOCM, unless LDCM is clinically preferred or less expensive
  - "Injectable" LOCM is clinically preferred over barium and HOCM if:
    - Potential perforation of GI tract (e.g., abdominal trauma)
    - Neonates and patients at risk for aspiration

Recent HOCM drug shortages (e.g., Gastrografin®/Gastroview®) and price changes have led to more oral and rectal administration of "injectable LOCM"

- All LOCM can be administered orally/rectally - diluted or full strength
  - Iohexol (Omnipaque®) is only FDA approved LDCM for oral use
    - Better taste than HOCM
    - Less risk for aspiration ADE
    - Generally, a diluted solution containing 13 to 15 mgI/mL is recommended
  - Omnepaque ORAL Preparation protocol: See FDA package insert

Iodinated Contrast Media: Barium or HOCM or LOCM

- FDA-approved range for adult low-osmolar contrast media enhanced CT head and body exams: 30 to 60 grams iodine
  - Infants and young children: dosing is weight-based (i.e., mg iodine per Kg)
  - General guidelines: “Use minimum dose necessary to achieve adequate visualization”
    - Factors that determine how much iodinated contrast media a patient receives:
      - Scanner technology (strength and speed) and radiologist’s preference
      - Patient’s clinical condition and procedure(s) being performed
      - Concentration influences image quality - depends on location and depth of the area of interest and equipment employed
    - Surface features (e.g., weins) lower concentrations used (e.g., 200-250 mgI/mL)
    - Deep features (e.g., arteries/coronary angiogram) higher concentrations necessary
      - 300 mgI/mL (2700) to 300 to 370mgI/mL (adult)
    - Myelography: adults 180 to 300 mgI/mL; child 180mgI/mL
  - Volume
    - Depends on the number and size of the vessels or size of the cavity imaged
    - Myelography: adults/children NOT TO EXCEED 20 mL in intraocular space
    - Dual injector technology – saline “chaser” following ICM infusion can reduce wasted ICM left in infusion lines

Iodinated Contrast Media: Concentration and Dosing

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Intra-arterial Doses for Adult Patients

<table>
<thead>
<tr>
<th>Procedure (ICM Concentration)</th>
<th>Injection Site</th>
<th>Adult Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-arterial Amipaque (300 mg/mL)</td>
<td>Right Common Femoral</td>
<td>10-20 mL</td>
<td>20 mL</td>
</tr>
<tr>
<td>Intra-arterial Amipaque (300 mg/mL)</td>
<td>Left Common Femoral</td>
<td>10-20 mL</td>
<td>20 mL</td>
</tr>
<tr>
<td>Intra-arterial Nipam (150 mg/mL)</td>
<td>Right Common Femoral</td>
<td>10-20 mL</td>
<td>20 mL</td>
</tr>
</tbody>
</table>

mg/mL = milligrams iodine per milliliter

Intravenous Doses for Adult Patients

<table>
<thead>
<tr>
<th>Procedure (ICM Concentration)</th>
<th>Injection Site</th>
<th>Adult Dose</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-venous Amipaque (400-2000 mg/mL)</td>
<td>Pericardial tamponade</td>
<td>0.3-1 mL/kg</td>
<td>1 mL/kg</td>
</tr>
<tr>
<td>Intra-venous Amipaque (400-2000 mg/mL)</td>
<td>Right atrial injection (25-50 cm)</td>
<td>0.2-0.4 mL/kg</td>
<td>0.4 mL/kg</td>
</tr>
<tr>
<td>Intra-venous Amipaque (400-2000 mg/mL)</td>
<td>Right atrial injection (100 cm)</td>
<td>0.1-0.2 mL/kg</td>
<td>0.2 mL/kg</td>
</tr>
<tr>
<td>Intra-venous Amipaque (400-2000 mg/mL)</td>
<td>Right atrial injection (10 cm)</td>
<td>0.01-0.02 mL/kg</td>
<td>0.02 mL/kg</td>
</tr>
</tbody>
</table>

mg/mL = milligrams iodine per milliliter

Pharmacokinetics of Commonly Used Injectable ICM

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
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<th>Pharmacokinetic Parameter</th>
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</thead>
<tbody>
<tr>
<td>Eliminated by Biliary excretion</td>
<td>Eliminated by Biliary excretion</td>
<td>Eliminated by Biliary excretion</td>
<td>Eliminated by Biliary excretion</td>
</tr>
<tr>
<td>Primary mode of elimination: Kidney, via glomerular filtration</td>
<td>Primary mode of elimination: Kidney, via glomerular filtration</td>
<td>Primary mode of elimination: Kidney, via glomerular filtration</td>
<td>Primary mode of elimination: Kidney, via glomerular filtration</td>
</tr>
<tr>
<td>Severe renal impairment: Elimination half-life: 16 to 84 hours</td>
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<td>Severe renal impairment: Elimination half-life: 16 to 84 hours</td>
</tr>
<tr>
<td>Secondary mode: Liver metabolism with biliary excretion - slow and limited</td>
<td>Secondary mode: Liver metabolism with biliary excretion - slow and limited</td>
<td>Secondary mode: Liver metabolism with biliary excretion - slow and limited</td>
<td>Secondary mode: Liver metabolism with biliary excretion - slow and limited</td>
</tr>
<tr>
<td>Low plasma protein binding</td>
<td>Low plasma protein binding</td>
<td>Low plasma protein binding</td>
<td>Low plasma protein binding</td>
</tr>
<tr>
<td>Low volume of distribution due to low lipid solubility</td>
<td>Low volume of distribution due to low lipid solubility</td>
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<td>Low volume of distribution due to low lipid solubility</td>
</tr>
</tbody>
</table>

Polling Question

Which of the following statements is FALSE?

a. FDA-approved ADULT dose for LOCM enhanced CT head and body exams is 30 to 60 grams iodine

b. Myelography imaging (i.e., intrathecal injections) dosage volumes should not exceed 20 mL

c. Injectable ICM is primarily eliminated via liver metabolism and biliary excretion. It half-life is 24 hours in patients with normal renal function

d. For GI tract imaging; oral LOCM is the preferred if there is a risk of GI tract perforation

Safety Considerations

Incidence, Risk Factor Assessment, Prevention & Treatment

- Acute adverse reactions
- Delayed adverse reactions
- Allergic reactions
- Post-contrast acute kidney injury (AKI) and contrast-induced nephropathy (CIN)
- Special populations
- Extravasation

Adverse Reactions Overview

- Adverse drug reactions (ADR) categorized based as: Acute or Delayed, based on time of onset
- Acute adverse reactions occur within 1 hour of the injection
- Delayed adverse reactions occur after 1 hour to 1 week after the injection
- Severity of ADRs range from minor physiological disturbances to rare, severe events
- Incidence varies with class of contrast used

Acute Adverse Reactions Classification

- Mild Symptoms (self-limiting)
  - Treatment: Observation and reassurance (minimize patient anxiety)
  - Symptoms: Nausea, mild vomiting, urticaria, itching

- Moderate Symptoms (potential to be severe)
  - Treatment: Responds to symptomatic treatment. Continue to treat and monitor to ensure symptoms abate.
  - Symptoms: Severe vomiting, marked urticaria, bronchospasm, facial/laryngeal edema, and vasovagal symptoms

- Severe Symptoms (potential morbidity/death)
  - Treatment: CPR/code cart, usually hospitalization
  - Symptoms: Hypotensive shock, respiratory arrest, cardiac arrest or severe arrhythmia, convulsion


Iodinated Contrast Media – Allergic-like Reactions

- Allergy Myth: “True allergy to iodine is not possible”1,2
- Iodine is an essential trace element (thyroid hormone); NOT an allergen
- No cross-reactivity between ICM and iodine-rich substances
- Allergy to “iodine-rich” seafood (e.g., shellfish) are due to proteins, not iodine
- Relative risk of cross-reactivity to ICM in patients with various food allergies5: 3.0 – seafood; 2.9 – eggs, milk, or chocolate; 2.6 – fruit and strawberries; 2.2 – asthmatics
- Reactions to iodinated solutions or ointments (e.g., povidone iodine) are unrelated to iodine (due to irritant or allergic dermatitis reaction to the formulation)
- “Allergic-Like” reactions to ICM are due to an inflammatory cytokine response to irritating hyperosmolar, ionic agents
- Replace “iodine allergy” with more accurate, specific, and descriptive terms
  - “Iodinated contrast media sensitivity”
  - “Seafood intolerance”
  - “Povidone-iodine dermatitis”


Iodinated Contrast Media: Physiologic Reactions

- Anxiety1,2,3
  - Screening and prophylaxis is recommended. Anxiety can evolve and potentiate the severity of contrast reactions.
  - May be necessary to pre-medicate some patients with oral or IV benadrylazepine

- Vasovagal
  - Hypotension with bradycardia and/or nausea/vomiting, generally mild and self-limited
  - Cause unknown; increased vagal tone from CNS; most likely fueled by anxiety
  - Treatment: observation, calm and reassurance

- Cardiovascular toxicity
  - More common during angiography than intravenous administration
  - No difference between IOCM and ICM
  - Heart failure patients – increased risk of pulmonary edema due to osmotic load and vasovagal effects of ICM

- Neurotoxicity – direct chemotoxic effects; primarily seen with HODM


Acute Adverse Reactions: Risk Factor Screening

- Product Specific
  - High-osmolality ionic contrast media: avoid or minimize intravenous use for all patients (e.g., iohexol/magne-mipaque 60% w/v (Conray®) 60%) = 1,400 mOsm/L)

- Patient-Related
  - Previous history of ICM reaction: 7.17% increased rate of mild reactions; mild reactions not shown to increase the rate of severe reactions
  - Previous moderate or severe acute ICM reaction: 9X increased rate of subsequent acute reactions. But, previous severe reaction not shown to increase the rate of subsequent severe reactions
  - Any severe allergic response to medications or food that required medical treatment
  - Hereditary predisposition (atopic syndrome): asthma, hay fever, allergic rhinitis, or dermatitis (eczema/poigeriasis)
  - Note seasonal phenomenon of increased acute reactions during high pollen counts


Acute Adverse Reactions: Prevention

- Consider an alternative test not requiring ICM
- Use a different ICM agent (than before)
- Test dose “offers no value”
- Premedication1,2
  - Elective procedure
    - Oral prednisone preferred over i.v. administration – must begin oral doses at least 6 hours prior
    - H-1 antihistamine oral or i.v. 1 hr prior (e.g., diphenhydramine 50 mg)
  - Emergency procedure
    - Methylprednisolone 40 mg i.v or hydrocortisone 200 mg i.v every 4hrs prior to ICM (or omit entirely and give only H-1 antihistamine i.v.)
    - Diphenhydramine 50 mg i.v. 1 hr prior to ICM


Delayed Adverse Reactions

- Definition: An event occurring more than 1 hour to 1 week after ICM injection; majority occur between 3 hrs and 2 days1
- Incidence: 0.5%–1%
- More common with iso-osmolar dimer (IOCM): ioxaglate (Visipaque®). 10 – 14%,2,3,4
- Even more common in patients treated with Interleukin-2 (up to 2 yrs)2
- Clinical features:
  - Seldom reported to Radiologist
  - Majority cutaneous adverse events (persistent skin rash with or without itching)
  - Usually mild to moderate severity, rarely requires hospitalization or is life-threatening
  - May require symptomatic treatment (antihistamines and/or corticosteroids; antipyretics; anti-emetics; fluids)

Contrast

ACR

Post-function

b. ICM

a. Anxiety

Which of the following statements is FALSE?

a. Anxiety is a risk factor for contrast media reactions and should be assessed and pretreated, if appropriate
b. ICM should not be used in patients reporting an allergy to povidone-iodine
c. Delayed adverse reactions are more common with the iso-osmolar dimer, ioxilanol, than with LOCM monomers

Delayed Adverse Reaction: Incidence of Symptoms

Delayed Adverse Reactions: Recurrence and Prophylaxis

- Recurrence rates are 25% or higher
- T-Cell mediated hypersensitivity — efficacy of corticosteroid and/or H1-antihistamine prophylaxis is unknown
- Premedication prophylaxis is not currently recommended with only a history of mild delayed cutaneous reactions - recommend alternative LOCM be used

Polling Question

Post-Contrast Acute Kidney Injury (PC-AKI) and Contrast-Induced Nephropathy (CIN)

Post-contrast Acute Kidney Injury and Contrast-induced Nephropathy: Definition

- Post-contrast acute kidney injury (PC-AKI): A general term for sudden deterioration in renal function that occurs within 48 hours following intravascular administration of iodinated contrast medium
  - PC-AKI may occur regardless of whether the contrast media was the cause
  - PC-AKI is a correlative diagnosis
- Contrast-induced nephropathy (CIN): A specific term for sudden deterioration in renal function that is caused by the intravascular administration of iodinated contrast media
  - CIN is a subgroup of PC-AKI
  - CIN is a causative diagnosis
- ACR (2015) “Unfortunately, very few published studies have a suitable control group to permit the separation of CIN from PC-AKI”
  - At present, the position of ACR is that CIN is a real, albeit rare entity — true incidence of CIN requires further study
  - Prior to 2007, CIN studies failed to include a control group of patients not receiving contrast and failed to adjust for normal fluctuations in serum creatinine

Post-contrast Acute Kidney Injury and Contrast-induced Nephropathy: Pathogenesis

- PC-AKI may be caused by ANY nephrotoxic event (including CIN) that is coincident to intravascular administration of ICM
  - Note there is a normal physiologic fluctuation in serum creatinine (SCr)
  - Patients with an elevated SCr at baseline have a greater variance in daily measurements than normal patients
- CIN Pathophysiology is not well understood but is believed to be caused by
  - Renal vasconstriction causing renal medullary ischemia
  - Osmotic and direct chemotoxic mechanisms
  - Direct tubular toxicity
  - Direct cytotoxic effect of ICM on tubular epithelial cells

References:
Contrast-induced Nephropathy: Incidence and Patient Harm

- 3rd leading cause of hospital-acquired acute kidney injury
- Overall incidence of CIN (~6.5%) among patients with risk factors
  - Primary Risk Factor: Stage III and IV chronic kidney disease (CKD)
  - eGFR between 15 to 45 mL/min/1.73m²
  - ~6 million US adults (3.5% of population) are at 5-10X increased risk for CIN
- Diabetics with CKD have the greatest risk
- Patient harm:
  - Increased length of stay (LOS): 2 days (average)
  - 0.4 to 1% of patients require dialysis – increases LOS by 17 days
  - Increased in-hospital mortality
  - 22% mortality during index hospitalization vs. 1.4% w/o CIN
  - Increased post-discharge mortality and morbidity
  - 1 year mortality: 12.1% w/CIN vs. 3.7% w/o CIN
  - 5 year mortality: 44.6% w/CIN vs. 14.5% w/o CIN
  - All have a much higher incidence of renal, cardiac, and neurological events

1. Solomon, R. Kidney Int. 2003;63:2256-2263

Contrast-induced Nephropathy: Relative LOCM Risk

- 42 trial, meta-analysis (n = 10,048) of controlled trials of LOCM and iso-osmolar iodinated contrast media (IOCM)
- Aim: Determine if there is a difference in nephrotoxic potential between commonly used LOCM and IOCM products
- Purpose: perform a systematic review and network (mixed treatment comparison) meta-analysis of randomized trials focusing on renal safety of LOCM or IOCM-ICM
- Conclusions:
  - Iodixanol, iomeprol (not US approved), iopamidol and ioversol – similar renal safety profile
  - Iohexol and ioxaglate have a poorer renal safety profile
  - Iopromide - further data is required


See page 15 for enlarged view

Contrast-induced Nephropathy: Cardiac Arterial Angiography

- Preferentially use lower risk IV LOCM for larger volume and/or cardiac angiography studies
  - Iohexol (Omnipaque™)
  - eGFR 15 to 30 mL/min/1.73m² with no additional risk factors – avoid use of iohexol
  - eGFR 15 to 30 mL/min/1.73m² with multiple risk factors – avoid use of iohexol


CIN High Risk Patient: Risk Reduction Strategies

- Determine eGFR prior to procedure; if not possible, follow eGFR ≤ 45 mL/min/1.73m² protocols
- Diabetic (higher risk) than non-diabetic
- Consider alternative imaging strategies (ultrasound, non-contrast MR)²
- Use the least nephrotoxic LOCM at the lowest effective dose (concentration and volume)²
  - Iodixanol (Visipaque™), iopamidol (Isovue™), ioversol (Optiray™)
  - Iopromide (Ultravist) – need more clinical data
- Routine/emergency hydration protocols³
  - Scheduled exam: encourage oral fluids (1-2 L 8 hr before and after) and i.v. normal saline or i.v. sodium bicarbonate (154 mEq/L in Dextrose 5% Water)
  - Emergency exam: i.v. sodium bicarbonate
  - Mannitol has no benefit
  - Furosemide, routine use, may be harmful
- Antioxidants
  - Acetylcysteine oral (scheduled) - insufficient evidence of efficacy³


CIN High Risk Patient: Risk Reduction Strategies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Creatinine</th>
<th>eGFR</th>
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<tr>
<td>Iohexol</td>
<td>&lt; 1.4</td>
<td>≥ 45</td>
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<td>Iodixanol</td>
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<td>45 – 30</td>
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<tr>
<td>No i.v contrast</td>
<td>&gt; 2</td>
<td>&lt; 30</td>
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DIABETIC

<table>
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<th>eGFR</th>
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</tr>
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<td>Iodixanol</td>
<td>1.8 – 3</td>
<td>30 – 15</td>
</tr>
<tr>
<td>No i.v contrast</td>
<td>&gt; 3</td>
<td>&lt; 15</td>
</tr>
</tbody>
</table>

NON-DIABETIC

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Contrast-induced Nephropathy: Screening Guidelines When is a Baseline Serum Creatinine Needed

- Baseline serum creatinine (Scr) required prior to ICM injection for patients with CIN risk factors
- Patients without the following risk factors DO NOT REQUIRE a baseline Scr:<ref>1,2</ref>
- Age > 60
- History of renal disease (i.e., eGFR ≤ 60 mL/min/1.73m²)
- History of hypertension requiring medical therapy
- History of diabetes mellitus
- Intra-arterial ICM injection<ref>3</ref> or CT angiography exam<ref>4</ref>
- No agreed-upon maximum interval between baseline renal function assessment and ICM administration in at-risk patients<ref>5</ref>
- Outpatients: typically 30 to 60 day interval (some 6 months)
- Inpatients: typically 1 to 2 weeks
- Shorter interval recommended for patients with a new risk factor or heightened risk of renal dysfunction (e.g., abdominal trauma)


Patient Screening for Other Medication Risk Factors

- Other medication risk factors NOT related to CIN:
  - Myelography: Anticoagulants and antiplatelets
  - Warfarin – stop within 4 days
  - Novel oral anticoagulants and dual antiplatelet should be held and resumed per protocol
  - Interleukin-2 (within 2 years): increased risk of delayed skin reactions
  - Beta-Blockers: May impair the management of bronchospasm and response to epinephrine (use should be documented and assessed)


Metformin

- Metformin does not increase risk of CIN
- Patients who develop PC-AKI while taking metformin are susceptible to lactic acidosis
  - Normally, 90% of metformin is excreted unchanged by the kidneys in 24 hrs.
  - Incidence of lactic acidosis (Radiology): 0 to 0.084 cases per 1,000 patient years<ref>1,2</ref>
- Patient mortality / Metabolic acidosis ~ 50%
- Patient Management is risk-based<ref>3</ref>
  - Category I: Patients with no evidence of AKI and eGFR ≥ 60 mL/min/1.73m², there is no need to discontinue metformin either prior to or following ICM administration, nor is there an obligatory requirement to reassess the patient’s renal function following the procedure
  - Category II: Patients with acute kidney injury or moderate to severe chronic kidney disease (defined as eGFR < 30), or are undergoing arterial catheter studies that might result in emboli to the renal arteries, metformin should be temporarily discontinued at the time of the procedure, withheld for 48 hours, and reinstated ONLY after renal function has found to be normal


Patient Screening: Special Populations

- Pregnancy category B – Routine pregnancy screening is not recommended
  - Use if clinically necessary (in-vivo tests (rat/rabbits ~100x human doses) report no mutagenic or teratogenic effects)
- Breast feeding<ref>4</ref> – Low risk. Use supplemental breast milk for 24 hrs – if desired
  - < 0.01% of the intravascular maternal ICM dose is absorbed systemically infant
- Neutropenia
  - Use caution if less than 12 months of age: Scr ≥ 1.5 mg/dl, CHF, or asthma
- Myasthenia gravis
  - Historically considered a relative contraindication only for HOCM, but 2013 study reported significant disease-related symptom exacerbations (weakness, dyspnea) within 24 hours after LCM vs. no contrast
- Tachyarrhythmias
  - Untreated Graves’ Disease
  - Multinodular goiter and thyroid autonomy and/or live in area of dietary iodine deficiency
  - Refer to Endocrinologist


Patient Screening: Unique Considerations for Children

- Unique Considerations (["strange"] sensations coupled with anxiety or fear)
- Injection-related physiological effects or side-effects more significant in young children
  - Sensation of warmth, burning, and nausea – “unusual feeling” for an infant or young child
  - Recommended sedation to avoid:
    - Crying/Moving – Necessitating repeated exposure to ICM and radiation
    - Use lowest effective LOCM/IOCM iodine concentration to reduce osmolarity and viscosity (i.e. risk of extravasation)
    - Osmolarity - small children particularly susceptible to osmotic loads and fluid shifts
    - Viscosity - small vessels influence catheter size and increase injection pressures
  - Assessing Renal Function: estimated GFR better than serum creatinine
    - Bedside Schwartz Equation:
      - eGFR (mL/min/1.73 m²) = (0.41 × height) / serum creatinine
      - Height in cm; Serum creatinine in mg/dl


Patient Screening: Unique Considerations for Children

- Iodine Agent | Concentration (mg/dL) | Increase Iodine Concentration (%) | Osmolarity (mOsm/kg) | Increase Osmolarity (%) | Viscosity (cp @ 37°C) | Increase Viscosity (%) |
- Iohexol 240 | 240 | Baseline | 520 | Baseline | 3.4 | Baseline |
- Iohexol 300 | 300 | 25% | 672 | 29% | 6.3 | 85%
- Iohexol 350 | 350 | 40% | 844 | 62% | 10.4 | 208%
- Iopamidol 250 | 250 | Baseline | 524 | Baseline | 3 | Baseline |
- Iopamidol 300 | 300 | 20% | 616 | 18% | 4.7 | 57%
- Iopamidol 370 | 370 | 48% | 796 | 52% | 9.4 | 213%

- Recommend IOCM - ioxaglate (not shown in table) or LOCM at lowest effective iodine concentration
- Reducing iodine concentration disproportionally reduces osmolarity and to a greater extent viscosity

Extravasation

- Incidence: LOCW
  - Intraosseous ICM extravasation: 0.1 to 0.9% (2/1,000 to 1/1,006 patients)
  - Sequelae
    - Usually non-eventful
    - Acute local inflammatory response peaks in 24 to 48 hrs - rarely a severe event, no permanent injury
  - Best prevented by proper technique, vascular access device, and patient communication
  - Intra-arterial contrast injections into peripheral vessels of the arm, legs, or head can be quite painful - IOCM/LOCM are preferred
  - Avoid small vessels (hand, wrist, foot, ankle): IOCM/LOCM (lowest viscosity) are preferred

- Treatment
  - Observation – several hours prior to discharge
    - Elevation of affected extremity above the heart
    - Hot or cold compresses – no evidence favoring one over other
    - No evidence of benefit or harm: aspiration of fluid and/or local injection of corticosteroids or hyaluronidase
  - Surgical consultation if prolonged pain or tissue injury


Safe Handling - CDC Safe Injection Practices

- ICM are super-saturated solutions: Do not mix ICM with other drugs or solutions
- Aseptic and USP 797 Sterile Compounding guidelines must be followed. Applies to all areas
  - BUD assigned: Inside ISO Class 5: Can be stored up to 3 days at room temperature
  - Outside ISO Class 5: Use immediately (≤ 1 hour)
- CDC Safe Injection Practices guidelines*: - incorporate into policies and procedure
  - Do not administer medications from single-dose vials or ampules to multiple patients
  - Proprietary, contrast media
  - Do not use bags or bottles of v/solution as a common source for multiple patients
  - Do not “pre-spike IV bags”
  - Multi-dose vial (MDV) used for multiple patients
    - Medication from MDV must be drawn up outside of immediate treatment area or MDV must be discarded after treatment (i.e., used for only one patient)
    - Use a re-used 28 day BUD from the date of opening or puncture except when:
      - Original BUD is shorter
      - Manufacturer specifies in package insert

BUD = Beyond Use Date;  MDV = Multi-Dose Val
*Direct Impact EP (Non-compliance is likely to create an immediate risk to patient safety or quality of care)

Polling Question

For an adult patient with an eGFR between 15 to 30 mL/min/1.73m² who is undergoing a cardiac angiography exam with contrast, which iodinate contrast media should be used to minimize the risk of contrast-induced nephropathy?

a. Iodixanol (Visipaque®) 320
b. Iodixanol (Visipaque®) 320, lopamidol (Isovue®) 370, or Ioversol (Optiray®) 350
c. Iodixanol (Visipaque®) 320, Iohexol (Omnipaque®) 350, lopamidol (Isovue®) 370, loversol (Optiray®) 350
d. Iodixanol (Visipaque®) 320, Iohexol (Omnipaque®) 350, Iopamidol (Isovue®) 370, Iothalamate meglumine (Conray®) 60% 300 mgI/mL, loversol (Optiray®) 350

Summary

- Director of Pharmacy is responsible for compliance with medication management standards, including the Radiology Department – with few, notable, exceptions
- Non-ionic, low-osmolality iodinated contrast media (LOCM) are the safest agents for intravascular and intrathecal administration
- “Injectable” LOCM should be substituted for barium and HOCM for patients at risk for aspiration or GI tract perforation
- Iodine allergy is a “medical myth.” However, patients should be screened for sensitivities that put them at risk for adverse reactions
- Chronic kidney disease is the most important risk factor for developing CIN
- CIN prevention is essential to reduce in-hospital length of stay, morbidity and mortality
- Estimated Glomerular Filtration Rate (eGFR) is a more accurate predictor for assessing CIN risk than serum creatinine
- There is no agreed-upon eGFR threshold below which the risk of CIN is considered so great that intravascular ICM should never be administered
- LOCM used for contrast-enhanced imaging of non-communicative patients (neonates/young children) should be carefully selected – using minimum concentrations and balancing the physical properties of osmolality and viscosity
Iodinated Contrast Media - Classification

- Categorized by chemical structure (monomer and dimer), ionization, and osmolality
- Structure based on modifications of the 2, 4, 6-tri-iodinated benzene ring structure

Iodinated Contrast Media: Classification and Use

IONIC HIGH-OSMOLALITY CONTRAST MEDIA (HOCM) >1,000 mOsm/Kg
Use: Oral or Gastrointestinal1, Intrauterine, Bladder

Ionic Monomers
- Oral/GI: diatrizoate sodium/diatrizoate meglumine (Gastrografin®, Gastrowiew®), diatrizoate sodium (Hexabrix®, Hypaque®)
- Intrauterine: iopamidol meglumine/diatrizoate meglumine (Sinogran®)
- Bladder: iohexol meglumine (Conray®, CystoConray®), diatrizoate meglumine (Cystografin®)

Use: Arteriography Only
- Ionic Dimer
  - loxaglate (Hexabrix®) - withdrawn from U.S. Sept. 2015

NON-IONIC LOW-OSMOLALITY CONTRAST MEDIA (LOCM) <900 mOsm/Kg
Use: Intravascular, Intrahecal2, Intrauterine, Bladder, Oral/Rectal

Nonionic Monomers
- iohexol (Omnipaque®), iopamidol (Iosovue®), iopromide (Ultravist®, Iopamiron®)

Nonionic Dimers (Iso-osmolar contrast)
- iodixanol (Visipaque®)

1Oral/Rectal: iohexol only FDA approved; others off-label use
2Intrahecal: lohexol, iopamidol only FDA approved; 180-300 mgI/mL; concentrations only, 10-20 mL max

Higher Osmolality
Goal is to lower osmolality

Lower Osmolality
Pharmacokinetics of Commonly Used Injectable ICM

### Pharmacokinetics

<table>
<thead>
<tr>
<th>Chemical Name (Trade Name)</th>
<th>Protein Binding (%)</th>
<th>Volume Distribution</th>
<th>Metabolism</th>
<th>Elimination Half-life</th>
<th>Route Elimination</th>
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</thead>
<tbody>
<tr>
<td>Iohexol (Visipaque®)</td>
<td>0%</td>
<td>0.28 L/kg</td>
<td>None</td>
<td>1.2–1.88 min (2.3 hrs renal insufficiency)</td>
<td>98% renal</td>
</tr>
<tr>
<td>Iopromide (Ultravist®)</td>
<td>1%</td>
<td>0.2 L/kg</td>
<td>None</td>
<td>6.2–40 hours</td>
<td>94% renal</td>
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<tr>
<td>Iopamidol (Isovue®)</td>
<td>1%</td>
<td>0.35 L/kg</td>
<td>Minimal</td>
<td>2 hours</td>
<td>92–98% renal, 10% feces</td>
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<tr>
<td>Iohexol (Omnipaque®)</td>
<td>Low</td>
<td>0.108–0.219 L/kg</td>
<td>Minimal</td>
<td>2 hours</td>
<td>100% renal</td>
</tr>
<tr>
<td>Ioversol (Optiray®)</td>
<td>0%</td>
<td>Not Reported</td>
<td>None</td>
<td>1.6–2 hours</td>
<td>95% or greater</td>
</tr>
<tr>
<td>Ixoglat (Hexabrix®)</td>
<td>Negligible</td>
<td>10 L</td>
<td>None</td>
<td>1.37 minutes</td>
<td>94% renal</td>
</tr>
</tbody>
</table>

- **Primary mode of elimination: Kidney, via glomerular filtration**
  - Normal renal elimination half-life: 2 hours; 100% cleared in 24 hours
  - Severe renal impairment: Elimination half-life: 16 to 84 hours
    - Secondary mode: Liver metabolism with biliary excretion – slow and limited
    - Dialysis effectively removes ICM
  - Low plasma protein binding
  - Low volume of distribution due to low lipid solubility

### Contrast-induced Nephropathy: Cardiac Arterial Angiography

- Preferentially use lower risk IV LOCIM for larger volume and/or cardiac angiography studies
  - Iohexol (Omnipaque®)
    - eGFR 15 to 30 mL/min/1.73m² with no additional risk factors – avoid use of iohexol
    - eGFR 30 to 45 mL/min/1.73m² with multiple risk factors – avoid use of iohexol

**Patient Screening: Unique Considerations for Children**

<table>
<thead>
<tr>
<th>LOCM Agent</th>
<th>Concentration mg/mL</th>
<th>Increase Iodine Concentration (%)</th>
<th>Osmolality (mOsm/Kg)</th>
<th>Increase Osmolality (%)</th>
<th>Viscosity (cp @ 37 C)</th>
<th>Increase Viscosity (%)</th>
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<td>Baseline</td>
<td>520</td>
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<tr>
<td>Iohexol 300</td>
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<td>25%</td>
<td>672</td>
<td>29%</td>
<td>6.3</td>
<td>85%</td>
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<td>Iohexol 350</td>
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<td>46%</td>
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<td>Baseline</td>
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<tr>
<td>Iopamidol 300</td>
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<td>616</td>
<td>18%</td>
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<tr>
<td>Iopamidol 370</td>
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<td>48%</td>
<td>796</td>
<td>52%</td>
<td>9.4</td>
<td>213%</td>
</tr>
</tbody>
</table>

- Recommend IOCM - iodixanol (not shown in table) or LOCM at lowest effective iodine concentration
- Reducing iodine concentration disproportionally reduces osmolality and to a greater extent viscosity

Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting: What the Pharmacist Needs to Know

Resources

American College of Radiology
- www.acr.org

ACR Manual on Contrast Media, version 10.1, 2015

Association for Professionals in Infection Control and Epidemiology
- www.apic.org

APIC 2010: Safe Injection, Infusion, and Medication Vial Practices in Health Care

Centers for Disease Control
- www.cdc.gov

CDC Guidelines: Safe Injection Practices to Prevent Transmission of Infections to Patients

CDC Infection Prevention Checklist for Outpatient Settings

Centers for Medicare and Medicaid (CMS)
- www.cms.gov

Conditions of Participation: Hospitals (Survey, Certification, and Compliance)
- https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/CertificationandCompliance/Hospitals.html

CMS Memorandum: Safe Use of Single Dose/Single Use Medications to Prevent Healthcare-associated Infections

European Society of Urogenital Radiology
- www.esur.org

- ESUR Guidelines – 8.1 Contrast Media
  www.esur.org/esur-guidelines/

- ESUR Guidelines – 9.0 Contrast Media Guidelines (order direct via email to: raymond.oyen@uzleuven.be)

ISMP Medication Safety Alert!
- www.ismp.org

- ISMP Medication Safety Alert!® Acute Care edition (biweekly email subscription)
Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting:
What the Pharmacist Needs to Know

http://ismp.org/newsletters/acutecare/default.aspx

- The Joint Commission
  - www.jointcommission.org
    - FAQ for current standards
    - FAQ for current NPSG
    - Current and Past Copies of:
      - Sentinel Event Alert
      - Sentinel Event Alert Issue 52: Preventing Infection from the Misuse of Vials
      - http://www.jointcommission.org/sea_issue_52/
      - Pre-publication standards

- University of Wisconsin, Contrast Media Tutorial, Jessica B. Robbins, MD and Myron A. Pozniak, MD (Dec 2015)
  - ESUR Guidelines – 8.1 Contrast Media

  o Myron A. Pozniak, MD
    mpozniak@uwhealth.org
<table>
<thead>
<tr>
<th>Product</th>
<th>Generic name (concentration in mg contrast/ml)</th>
<th>Ionicity</th>
<th>Iodine+ (mg/ml)</th>
<th>Viscosity+ 25°C (cp or mPa.s)</th>
<th>Viscosity+ 37°C (cp or mPa.s)</th>
<th>Osmolality (mOsm/kg H2O)</th>
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<td>370</td>
<td>22.0*</td>
<td>10</td>
<td>774</td>
</tr>
<tr>
<td>Cholografin® (Bracco)</td>
<td>iopamidol (520)</td>
<td>Ionic</td>
<td>257</td>
<td>6.6</td>
<td>5</td>
<td>664</td>
</tr>
</tbody>
</table>


* Measured at 200°C.
Self-assessment Questions

1. Which of the following is a risk factor for contrast-induced nephropathy?
   a. Diabetes mellitus.
   b. Hypervolemia.
   c. Gout.
   d. Chronic kidney disease.

2. Which of the following is not a risk factor for adverse reactions to iodinated contrast media?
   a. Psoriasis.
   b. Allergic response to medications or food that requires medical treatment.
   c. Use of low-osmolality iodinated contrast media.
   d. Previous moderate or severe acute reaction to iodinated contrast media.

3. Which of the following statements is FALSE?
   a. X-ray radiopacity is directly proportional to the organically bound iodine.
   b. X-ray response to iodine concentration varies among iodinated contrast media products with equal concentrations of iodine.
   c. Low-osmolality contrast media is associated with lower incidence of adverse drug reactions compared to high-osmolality contrast media.
   d. Low-osmolality contrast media are non-ionic dimers or monomers.

4. Which of the following statements is FALSE?
   a. Iodinated contrast media with an osmolality above 900 mOsm/L is not approved for peripheral vascular administration.
   b. Low-osmolarity contrast media is approved by the FDA for peripheral vascular administration.
   c. High-osmolality contrast media is restricted for use in the GI tract and body cavities.
   d. Patients at risk for GI perforation should receive barium or high-osmolality contrast media.

5. Which of the following is NOT a possible acute adverse reactions to iodinated contrast media?
   a. Urticaria.
   b. Bronchospasm.
   c. Nausea.
   d. Allergic reaction to iodine.

6. Which of the following regarding contrast-induced Nephropathy (CIN) is FALSE?
Best Practices in the Use of Iodinated Contrast Media in the Clinical Setting:
What the Pharmacist Needs to Know

a. Is caused by the intravascular administration of iodinated contrast media.
b. Has an incidence of approximately 6.5% in patients with risk factors.
c. Patients on beta blockers have an increased risk for CIN.
d. Determining an eGFR prior to a procedure is a recommended risk reduction strategy.

Answers
1. b
2. c
3. b
4. d
5. d
6. c