Contrast Media 2016: What’s new?

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Disclosures

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- Paid consultant: FDA and NCI
Update 1

GADOLINIUM DEPOSITION
Gadolinium Deposition

- **Kanda 2014**
  - Increased SI in dentate nucleus on unenhanced T1w imaging correlates with prior GBCM exposure

- **Agents**
  - Gadopentetate (Magnevist)
  - Gadodiamide (Omniscan)

Gadolinium Deposition

• McDonald 2015
  - Increased dentate nucleus signal intensity is linearly related to:
    • Dose of gadodiamide
    • Amount of actual gadolinium deposited in the brain
  • Gd State? Unknown.
  • Dose threshold for Gd detection: ~4 doses

McDonald RJ al. Radiology 2015
Gadolinium Deposition

McDonald RJ al. Radiology 2015
Gadolinium Deposition

Kanda 2015

- Dose effect
- SI changes: ≥4 doses

Gadolinium Deposition

- Radbruch 2015
  - Increased SI in dentate nucleus is dependent on agent

- Agents
  - Yes: gadopentetate dimeglumine (Magnevist)
  - No: gadoterate meglumine (Dotarem)
Gadolinium Deposition

- Cao 2015 - Effect of agent

![Graphs showing DCP SI Ratio vs. Gadopentetate Dimeglumine Administration (No.) and Gadobutrol Administration (No.).]

**gadopentetate** (linear ionic)  **gadobutrol** (macrocyclic)
Gadolinium Deposition

- Robert 2015 - Effect of agent (rats)
  - 20 injections of 0.6 mmol Gd/kg (6x dose/inj) over 5 weeks

Gadolinium Deposition

- Weberling 2015 - Gadobenate
  - DN-Pons similar to gadopentetate
  - DN-CSF less than gadopentetate

Weberling LD et al. Invest Radiol 2015
Gadolinium Deposition

- **Flood 2016 - Gadopentetate**
  - DN-Pons SI higher in exposed children

Flood TF et al. Radiology 2016 [epub ahead of print]
<table>
<thead>
<tr>
<th>NSF</th>
<th>“High-risk”</th>
<th>“Low-risk”</th>
<th>Gd Deposits</th>
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Gadolinium Deposition

- NSF: Non-Specific Fluorescence
- Gd Deposits: Gadolinium Deposits

- OptiMARK: Low-risk
- Omniscan: High-risk
- Magnevist: High-risk
- MultiHance: High-risk
- Eovist: Low-risk
- Ablavar: Low-risk
- ProHance: Low-risk
- Gadavist: Low-risk
- Dotarem: Low-risk
National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain

Ashkan A. Malekani, MD, Kristina M. Brooks, PharmD, L. Henry Bryant, PhD, Robert Evers, BSRT, Parag Kumar, PharmD, Daniel S. Reich, MD, PhD, David A. Bluemke, MD, PhD

1. GBCAs should be used only when clinically indicated or when specified in an institutional review board—approved protocol.
2. When GBCAs are required, consider the use of a macrocyclic GBCA (eg, gadobutrol, gadoteridol, gadoterate meglumine) rather than a linear agent.

3. For patients with documented sensitivity (eg, hives) to macrocyclic agents, it is appropriate to use linear agents when clinically indicated.
4. MRI protocols should always consider FDA label indications and dosing schemes for administration of GBCAs.
Gadolinium Deposition

- **Current state, circa 2016**
  - Medical Gd is depositing in deep brain nuclei
    - Dose-dependent, irrespective of renal function
    - Despite intact blood-brain barrier
    - Greatest effect with least stable agents
  - No histologic changes or known clinical phenotype
  - Unknown state of Gd complex
GBCAs provide crucial, life-saving medical information. Each time a gadolinium-enhanced MRI study is considered, it would be prudent to consider the clinical benefit of the diagnostic information or treatment result that MRI or MRA may provide against the unknown potential risk of gadolinium deposition in the brain for each individual patient. Particular attention should be paid to pediatric and other patients who may receive many GBCA-enhanced MRI studies over the course of their lifetimes. If the decision for an individual patient is made to use a GBCA for an MRI study, multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain.

(No specific recommendation for macrocyclics or against linear agents)
Gadolinium Deposition

- Ferric iron may trigger transmetallation reactions, even for macrocyclics (gadoterate), depositing Gd in children, an effect reversible with chelation.
Update 2

CORTICOSTEROID PROPHYLAXIS
We give preps to prevent allergic-like reactions.

In doing so, we make an uncommon event rarer.

But it doesn’t always work.

How many patients need a prep to save one life?
Study of 1,051 subjects who had received a steroid prep. Reaction rates were benchmarked against the literature. In those who had had a prior iodinated contrast reaction, the NNT with a steroid prep to prevent one reaction was estimated to be:

- 69 for a reaction of any severity (95% CI: 39-304)

Allergic-like reaction

**Number Needed to Treat**

<table>
<thead>
<tr>
<th>Severity</th>
<th>NNT (95% CI)</th>
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**LOCM, Steroid Preps, NNT**  
*Mervak 2015*

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### Prep Time to Prevent One Reaction

<table>
<thead>
<tr>
<th>Severity</th>
<th>Time (95% CI)</th>
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<tr>
<td>Any reaction</td>
<td>35 days (20-152)</td>
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<tr>
<td>Severe reaction</td>
<td>285 days (195-542)</td>
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<tr>
<td>Lethal reaction</td>
<td>~80 years</td>
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</table>

Many preps are required to prevent one reaction.

Most patients receive no personal benefit.

Prepping takes a LONG time.

Is it worth it?
Premedication Risks

Inpatients

• 1424 prepped matched to 1425 non-prepped inpatients

• Premedicated inpatients:
  - Significant delay in time to CT (median: 25 hours, p<0.0001)
  - Significantly longer length of stay (median: 25 hours, p<0.0001)
  - Significantly more infections (5.1% vs. 3.1%, p=0.008)

• Does prepping inpatients hurt more than it helps?
<table>
<thead>
<tr>
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<th>Severe Reaction</th>
<th>Lethal Reaction</th>
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<tbody>
<tr>
<td>Hypothetical Cohort</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Additional Hospital Length-of-Stay</td>
<td>72 days</td>
<td>593 days</td>
<td>162 years</td>
</tr>
<tr>
<td>Additional Cost of Hospitalization</td>
<td>$159,131 USD</td>
<td>$1,312,256 USD</td>
<td>$131,211,400 USD</td>
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<tr>
<td>Additional Hospital-Acquired Infections</td>
<td>0.7 infections</td>
<td>5.5 infections</td>
<td>551 infections</td>
</tr>
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<td>Additional Hospital-Acquired Infection-Related Deaths</td>
<td>0.04 deaths</td>
<td>0.3 deaths</td>
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## Premedication Risks
### Inpatients

### Multivariate Sensitivity Analysis

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<td>32 deaths</td>
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<tr>
<td>Hypothetical Cohort, Best-Case Scenario (all variables)</td>
<td>21 days</td>
<td>211 days</td>
<td>38 years</td>
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<tr>
<td>Additional Hospital Length-of-Stay</td>
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<tr>
<td>Additional Cost of Hospitalization</td>
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<td>Additional Hospital-Acquired Infections</td>
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<td>Additional Hospital-Acquired Infection-Related Deaths</td>
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<td>0.05 deaths</td>
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Steroid Preps c.2016

- Many regimens are needed to prevent one reaction of any severity \textit{(NNT=69)}; to save a life requires \textit{\sim} 50,000.

- Premedicating inpatients is associated with substantial cost and harm that is likely greater than the benefits.

- The time has come to consider testing alternative approaches to premedication in an inpatient setting.

- The ACR Manual continues to suggest premedication for “at risk” patients, but has not been recently edited.

“Substantial inconsistencies exist between the recommendations of the five international guidelines about contrast medium administration in patients who are taking metformin. These are, in part, caused by the low level of evidence underpinning guideline recommendations.”

Goergen SK et al. Radiology 2010
“At present, there is no evidence to support guideline recommendations to stop metformin administration or to retest renal function after contrast medium administration in patients with normal baseline renal function…”

Goergen SK et al. Radiology 2010
FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function

- Metformin can now be used in patients with mild renal impairment, and sometimes in moderate renal impairment
- Also, risk stratify by eGFR instead of serum creatinine
FDA April 2016

- Do not use metformin if eGFR < 30
- Do not start metformin if eGFR 30-45
- Discontinue metformin at time of iodinated contrast if:
  - eGFR 30-60
  - Liver disease, alcohol, heart failure
  - Intra-arterial contrast
- If metformin is discontinued, re-evaluate 48h after procedure, re-start if “stable”
ACR Manual 2016

- These updated rules are still rather aggressive
- And ACR pushed back in June 2016:

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1The U.S. Food and Drug Administration (FDA) has issued guidelines and drug labeling for metformin since 1995, and the component of these FDA guidelines related to administration of iodinated contrast material in patients taking metformin has been made progressively less rigorous since the original version. The ACR Committee on Drugs and Contrast Media recognizes that the latest (as of this writing, dated 4-8-2016) FDA guidelines and drug labeling are still more restrictive than those in this chapter of the ACR Manual on Contrast Media. Nevertheless, the committee authoring this Manual has reviewed the evidence and believes that the prevailing weight of clinical evidence on this matter allows less stringent yet safe patient management which should reduce patient cost and inconvenience. This footnote is designed to alert readers that the ACR recommendations differ in case their personal philosophy or institutional policies necessitate adherence to the more restrictive FDA guidelines.

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The Committee recommends that patients taking metformin be classified into one of two categories based on the patient’s renal function (as measured by eGFR).

**Category I**

In patients with no evidence of AKI and with eGFR ≥30 mL/min/1.73m², there is no need to discontinue metformin either prior to or following the intravenous administration of iodinated contrast media, nor is there an obligatory need to reassess the patient’s renal function following the test or procedure.¹

**Category II**

In patients taking metformin who are known to have acute kidney injury or severe chronic kidney disease (stage IV or stage V; i.e., eGFR < 30), or are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.
UMHS 2016

- We use an eGFR < 45 threshold (rather than <30) for IV
- Note that the evidence base behind any of this is anecdotal, and extrapolates from what we know re: CIN

Davenport et al. Radiology 2013 and 2014
McDonald et al. Radiology 2014 and 2015
Thank you
matdaven@med.umich.edu