Disclosures

Industry or Professional Relations

• GE Healthcare – Scientific Advisor & Investigator-Initiated Research Support
• ACR Committee Member – Drugs and Contrast Media

Off Label Use

• None
Talk Outline

1. GBCA and Gadolinium Retention Background
2. Macrocyclic vs. Linear GBCAs
3. Are Gadolinium Deposits Toxic?
4. Are Gadolinium Deposits Clinically Relevant?
5. Why Not Just Use Macrocyclic GBCAs?
GBCA Safety

- Over 450 million GBCA doses administered worldwide!
- Adverse effects can be severe, and even life altering/ending.
- We have an obligation to mold our practice patterns to the safety profile of these agents and to take steps to minimize harm to patients.

### GBCA Enhanced Scans/Year: 40 million
Cumulative doses: 450 million

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
<th>Cases / year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Rxn</td>
<td>0.1%</td>
<td>40,000</td>
</tr>
<tr>
<td>Mod. Rxn</td>
<td>0.01%</td>
<td>4,000</td>
</tr>
<tr>
<td>Severe Rxn</td>
<td>0.001%</td>
<td>400</td>
</tr>
<tr>
<td>NSF</td>
<td>0.00001%*</td>
<td>4-40</td>
</tr>
</tbody>
</table>
**Gadolinium-Based Contrast Agents (GBCAs)**

*Available as of 2020*

**Linear GBCAs**
- **Omniscan** (gadodiamide)
  - GE Healthcare
  - 1993
- **Multihance** (gadobenate dimeglumine)
  - Bracco
  - 2004

**Specialty GBCAs**
- **Eovist** (gadoxetate disodium)
  - Bayer Healthcare
  - 2008

**Macrocyclic GBCAs**
- **Prohance** (gadoteridol)
  - Bracco
  - 1992
- **Gadavist** (gadobutrol)
  - Bayer Healthcare
  - 2011
- **Dotarem** (gadoterate meglumine)
  - Guerbet
  - 2013
- **Clariscan** (gadoterate meglumine)
  - GE Healthcare
  - 2019
High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material

**Purpose:** To explore any correlation between the number of previous gadolinium-based contrast material administrations and high signal intensity (SI) in the dentate nucleus and globus pallidus on unenhanced T1-weighted magnetic resonance (MR) images.

**Materials and Methods:** The institutional review board approved this study, waiving the requirement to obtain written informed consent. A group of 381 consecutive patients who had undergone brain MR imaging was identified for...
Intracranial Gadolinium Retention
PRELIMINARY MR EVIDENCE

3/8/2004 1st scan
3/17/2006 7th scan
4/16/2008 13th scan
8/11/2011 19th scan
3/4/2014 26th scan
Intracranial GBCA Retention

STUDY DESIGN / METHODS

STUDY INCLUSION/EXCLUSION CRITERIA

1) Underwent 4+ Gd-enhanced or 1+ unenhanced brain MRIs
2) Had appropriate pre-contrast T1W sequences
3) Underwent autopsy with antemortem consent

Contrast Exposed Group: N = 13
Non-contrast Group: N = 10

EMR SEARCH

1) Demographics
2) Comorbidities
3) Labs at time of MRI
eGFR, Alk Phos, AST, Bilirubin

TISSUE ANALYSIS

- ICP-Mass Spectrometry
- Transmission Electron Microscopy
- Light Microscopy
# Intracranial Gadolinium Retention

**CONFIRMATORY ICP-MS EVIDENCE**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Pearson Correlation Coefficient</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Globus Pallidus</td>
<td>$\rho_{\text{ICP-MS}} = 0.49$</td>
<td>$p = 0.08$</td>
</tr>
<tr>
<td>Thalamus</td>
<td>$\rho_{\text{ICP-MS}} = 0.57$</td>
<td>$p = 0.03$</td>
</tr>
<tr>
<td>Dentate</td>
<td>$\rho_{\text{ICP-MS}} = 0.93$</td>
<td>$p &lt; 0.0001$</td>
</tr>
<tr>
<td>Pons</td>
<td>$\rho_{\text{ICP-MS}} = 0.62$</td>
<td>$p = 0.02$</td>
</tr>
</tbody>
</table>

---

**McDonald et al., Radiology 2015**

---

**Images:**
- **Basal Ganglia:**
  - First MRI exam (E)
  - Last MRI exam (G)
- **Posterior Fossa:**
  - First MRI exam (F)
  - Last MRI exam (H)
Intracranial Gadolinium Retention
CONFIRMATORY TEM EVIDENCE

Control Patient

Gadolinium Exposed Patient

McDonald et al, Radiology 2015

Light Microscopy

Capillary Lumen

Capillary Wall

Nucleus
Intracranial Gadolinium Retention
HOW WIDESPREAD IS THIS PHENOMENON?

- Gd retention was observed in patients exposed to linear and macrocyclic GBCAs.

- Gd appears to be retained in nearly every tissue!

McDonald et al, Unpublished data
**CHEMICAL JUSTIFICATION**

**Linear GBCA**

Weaker Gd: Chelate Binding

More Likely to Spend Time in Dissociated State

**Macrocyclic GBCA**

Stronger Gd: Chelate Binding

Less Likely to Spend Time in Dissociated State
• Gadolinium tissue concentration is not entirely class-dependent
• Gadavist levels are much higher than ProHance, and within 2-4 –fold of linear agents.
• Similar pattern of differentiation is seen in other organs, at higher [Gd].

McDonald et al, in press, Radiology 2017
ICP-MS RESULTS – BRAIN

Macrocyclic vs. Linear GBCAs

Wks after inj.

Group

Control
HP-DO3A
ProHance
BT-DO3A
Gadavist
DOTA
Dotarem
EOB-DTPA
Eovist
BOPTA
MultiHance
DTPA
Magnevist
DTPA-BMA
Omniscan

Basal Ganglia

Gd concentration (mg Gd/g tissue)

0
5
10
15
20

Dentate

Gd concentration (mg Gd/g tissue)

0.0
0.2
0.4
0.6

0
5
10
15
20

Gd concentration (mg Gd/g tissue)

0.0
0.2
0.4
0.6
## Gadolinium Retention

### EMA AND FDA RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Findings</th>
<th>EMA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard for drug suspension</td>
<td>Precautionary principle</td>
<td>Evidence of harm</td>
</tr>
<tr>
<td>Current standing</td>
<td>Linear GBCAs banned*</td>
<td>No current ban</td>
</tr>
<tr>
<td>Request for ongoing research</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Involved in ongoing research</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
QUESTION: Is Gadolinium Toxic?

YES
QUESTION: Are Gadolinium Deposits Toxic?
Are Gd Deposits Toxic?

Mechanisms

| Nephrotoxicity (reduced glomerular filtration rate) | In vitro | Renal tubular cells | Heinrich et al. 2007 |
| Nephrotoxicity (acute tubular necrosis)           | In vivo  | Pigs                | Elmstahl et al. 2006 |
| Hematoxicity (reduced WBC count)                  | Case report | Human | Akgun et al. 2006 |
| Hepatotoxicity (vacuolar degeneration, disorganized hepatic cords) | In vivo | Mice | Chen et al. 2015 |
| Pancreatitis                                      | Case report | Human | Blasco-Perrin et al. 2013 |
| Neurotoxicity (myoclonus, ataxia, tremor, neuronal death, and hemorrhage) | In vivo | Rats | Ray et al. 1996 |
| Neurotoxicity (encephalopathy)                    | Case report | Human | Hui and Mullins 2009 |

NSF & OTHER MECHANISMS

[Diagram of mechanisms involving Gd deposits and NSF]
Multiple studies have found no histologic changes in brain tissues of patients exposed to GBCAs (McDonald et al, 2015, McDonald et al, 2017, Fingerhut et al, 2018).

Numerous preclinical studies have also not found histologic changes due to GBCA administration.
Are Gd Deposits Clinically Significant?

- The Single Most Important Question

- **Real World Data:** Over 450 million doses of IV GBCAs have been administered over the past 30 years (Linear > Macrocyclic) **WITHOUT** widespread reports of neurotoxicity. However, scientific proof is needed!

- **How Do We Go About Testing This?**
  1. Preclinical Models
  2. Retrospective Human Data
  3. Prospective Human Data
Are Gd Deposits Clinically Significant?

WHAT SYMPTOMS TO EXAMINE?

### Dentate Nucleus
- Coordination (planning and initiation) of limb movement

### Basal Ganglia
- Learning and memory
- Coordination of movement; filtering out undesired movements; posture and balance
- Implicated in anxiety and mood disorders

Are Gd Deposits Clinically Significant?

Using a preclinical rat model to study the effect of Gd on locomotor, cognitive/memory, mood & balance/coordination function.

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Agent</th>
<th>Dose (mmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Gadopentetate</td>
<td>2.5</td>
</tr>
<tr>
<td>3</td>
<td>Gadodiamide</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>Gadoversetamide</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>Gadobenate</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>Gadoteridol</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>Gadobutrol</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>Gadoterate</td>
<td>2.5</td>
</tr>
<tr>
<td>9</td>
<td>Gadoxetate</td>
<td>2.5</td>
</tr>
<tr>
<td>10</td>
<td>Gadodiamide</td>
<td>0.6</td>
</tr>
<tr>
<td>11</td>
<td>Gadoterate</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Tissue Analysis:
- ICP
- Mass Spectrometry
- Transmission Electron Microscopy
- Light Microscopy

 mayo clinic rodent behavioral core facility

open field arena

Y-maze

novel object recognition

ladder rung task

social anxiety test

are Gd deposits clinically significant?
Are Gd Deposits Clinically Significant?

Using a preclinical rat model to study the effect of Gd on locomotor, cognitive/memory, mood & balance/coordination function.

- No differences between GBCA-exposed and control rats were observed for any behavioral test.
### NEGATIVE FINDINGS

<table>
<thead>
<tr>
<th>Findings</th>
<th>GBCA</th>
<th>Species</th>
<th>Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No increased risk of Parkinsonism diagnosis</td>
<td>Multiple</td>
<td>Human</td>
<td>No specific</td>
<td>Welk et al. 2016</td>
</tr>
<tr>
<td>No change in neurologic test results, no increased risk of developing mild cognitive impairment</td>
<td>Gadodiamide</td>
<td>Human</td>
<td>No specific</td>
<td>McDonald et al. 2016</td>
</tr>
<tr>
<td>No signs of cerebellar toxicity</td>
<td>Gadoterate</td>
<td>Human</td>
<td>No specific</td>
<td>Perrotta et al. 2017</td>
</tr>
<tr>
<td>No correlation between T1 hyperintensity and worse clinical outcomes</td>
<td>Multiple</td>
<td>Human</td>
<td>MS</td>
<td>Cocozza et al. 2019</td>
</tr>
<tr>
<td>No neurological and neurocognitive/psychological abnormalities</td>
<td>Gadodiamide</td>
<td>Human</td>
<td>Crohn’s</td>
<td>Mallio et al. 2019</td>
</tr>
<tr>
<td>No association with MS severity</td>
<td>Gadodiamide</td>
<td>Human</td>
<td>MS</td>
<td>Zivadinov et al. 2019</td>
</tr>
<tr>
<td>No neurological/neuropsychological impairment in the DN and GP</td>
<td>Multiple</td>
<td>Human</td>
<td>GBM</td>
<td>Vymazal et al. 2019</td>
</tr>
</tbody>
</table>
### POTENTIALLY POSITIVE FINDINGS

<table>
<thead>
<tr>
<th>Findings</th>
<th>GBCA</th>
<th>Species</th>
<th>Condition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased T1 signal in dentate nucleus in exposed patients correlated</td>
<td>Multiple</td>
<td>Human</td>
<td>MS</td>
<td>Forslin et al. 2017</td>
</tr>
<tr>
<td>with lower verbal fluency scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In utero GBCA exposure was associated with increased risk of various</td>
<td>Multiple</td>
<td>Human</td>
<td>Pregnancy</td>
<td>Ray et al. 2016</td>
</tr>
<tr>
<td>skin conditions, stillbirth, and neonatal death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Are Gd Deposits Clinically Significant?

GADOLINIUM DEPOSITION DISEASE

Studies encompassing 139 patients.
Constellation of symptoms, including neuropathic pain, fatigue, joint stiffness, headache, cognition changes.
Are Gd Deposits Clinically Significant?

GADOLINIUM DEPOSITION DISEASE

- No control group, no way to confirm causality.
- No correlation between reported symptoms and Gd levels.
- Lots of missing data.
Are Gd Deposits Clinically Significant?

GADOLINIUM DEPOSITION DISEASE

Gadolinium in Humans: A Family of Disorders

OBJECTIVE. The literature informs us that gadolinium can cause health issues. At least four major gadolinium disorders, including the two well-recognized nephrogenic systemic fibrosis and severe acute adverse event, have been identified.

CONCLUSION. We propose naming the histopathologically proven presence of gadolinium in brain tissue “gadolinium storage condition,” and we describe a new entity that represents symptomatic deposition of gadolinium in individuals with normal renal function, for which we propose the designation “gadolinium deposition disease.”

THE FDA DOES NOT FIND SUFFICIENT CAUSAL EVIDENCE FOR GDD

Semelka RC, et al AJR 2016;207:229-233
Are Gd Deposits Clinically Significant?

GD RETENTION LAWSUITS

Clean Sweep of Plaintiffs’ Causation Experts in Gadolinium Litigation

By Michelle Yeary on August 13, 2019
POSTED IN EXPERTS

Voluntary Dismissal of Chuck Norris Gadolinium Case Involving Bracco

The lawsuit alleging injury from the company's MR contrast agent has been closed
Should we change clinical practice?

- GBCAs provide crucial, life-saving medical information.

- Weight the clinical benefit GBCAs may provide against the unknown risks of Gd retention.

- Consider multiple factors when choosing a GBCA: diagnostic efficacy, relaxivity, rate of adverse reactions, and amount of Gd deposited.
Why Not Just Use Macroyclic GBCAs?

- No direct evidence yet that Gd retention causes harm in patients.

- However, higher amounts of Gd are retained following linear vs. macrocylic GBCAs.

- Gd has documented toxicity.

- Why not just switch to macrocylics to be safe?
Why Not Just Use Macro cyclic GBCAs?

**Adult Patients**

- **Linear GBCAs**
- **Macro cyclic GBCAs**
- NSF "scare"
- Dotarem approved
- Gadavist approved

**Pediatric Patients**

- **Linear GBCAs**
- **Macro cyclic GBCAs**
- Gd Deposition

Source: QuintilesIMS Health, IMS National Sales Perspectives. Data extracted July 2017

Source: Symphony Health Solutions' PHAST Non-Retail Monthly, Data extracted July 2017
OTHER GBCA SAFETY CONSIDERATIONS

Why Not Just Use Macrocylic GBCAs?

Meta-analysis of 716,978 GBCA administrations.
GBCA with highest Gd retention had lowest rate of acute reactions.

Behzadi et al, Radiology 2018
Why Not Just Use Macro cyclic GBCAs?

Other GBCA Safety Considerations

<table>
<thead>
<tr>
<th>GBCA Used</th>
<th>Total Injections</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All reactions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>140,645</td>
<td>196</td>
<td>70</td>
<td>0</td>
<td>266</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>94,109</td>
<td>245</td>
<td>92</td>
<td>3</td>
<td>340</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>39,138</td>
<td>141</td>
<td>56</td>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>8053</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Allergic-like reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>140,645</td>
<td>76</td>
<td>46</td>
<td>0</td>
<td>122</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>94,109</td>
<td>107</td>
<td>75</td>
<td>3</td>
<td>185</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>39,138</td>
<td>77</td>
<td>51</td>
<td>3</td>
<td>131</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>8053</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Physiologic reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadodiamide</td>
<td>140,645</td>
<td>120</td>
<td>24</td>
<td>0</td>
<td>144</td>
</tr>
<tr>
<td>Gadobutrol</td>
<td>94,109</td>
<td>138</td>
<td>17</td>
<td>0</td>
<td>155</td>
</tr>
<tr>
<td>Gadobenate dimeglumine</td>
<td>39,138</td>
<td>64</td>
<td>5</td>
<td>0</td>
<td>69</td>
</tr>
<tr>
<td>Gadoterate meglumine</td>
<td>8053</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

- Mayo Clinic data shows a similar pattern of acute reaction rates.
- Are we replacing an unknown risk with a known one?
Gadolinium Retention

SUMMARY

1. All GBCAs cause Gd deposition in the brain and other organs.
   - Macrocyclic agents deposit less.
   - Deposition is not entirely class dependent.

2. There is no strong evidence of neurotoxicity or clinical effects associated with Gd retention.

3. A risk-benefit assessment should be performed when deciding to use GBCAs and choosing a particular GBCA.
Project Collaborators
MULTI-DISCIPLINARY TEAM

Radiology
Larry Eckel MD  Dave Kallmes MD  Jennifer McDonald PhD  Bob McDonald MD, PhD  Kent Thielen MD  Eric Williamson MD  Cliff Jack MD

Neurology
Eoin Flanagan MBBCh  Sean Pittock MBBCh  Ron Petersen MD PhD

Applied Neuroradiology Laboratory
J. Ayers-Ringler PhD  Daying Dai MD PhD  Ram Kadirvel PhD  Avinash Nehra MD  Susie Han  Gabe Tudor

Mayo Clinic Rodent Behavior Core
Doo-Sup Choi PhD  Katie Wininger  J. Ayers-Ringler PhD

Laboratory Medicine & Pathology
Mark Jentoft MD  Dave Murray MD, PhD  Paul Jannetto PhD

Biochemistry
Jon Charlesworth  Trace Christenson  Jeff Salisbury PhD

Statistics
Rickey Carter PhD  Terry Therevaux PhD
Thank you
mcdonald.jennifer@mayo.edu