Gadolinium Deposition: Making Current Patients Future Patients?

State-of-the-Art Body MR Imaging Sunrise Session

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Disclosures

- None
Objective

- Discuss potential risk of gadolinium deposition in children
Gadolinium-Based Contrast Agents (GBCAs)

- First approved for clinical use in 1986 in the EU and 1988 in the US
Gadolinium-Based Contrast Agents (GBCAs)

- First approved for clinical use in 1986 in the EU and 1988 in the US
- > 250 million administrations worldwide in the 30 years since
GBCAs

- Gadolinium bound to organic chelating agent
  - Promote elimination, minimize interaction with endogenous ligands, decrease toxicity
"We created this website as a way to alert people to a problem that was not yet recognized by the FDA and medical industry."

"…have Gadolinium Toxicity recognized as a serious medical condition that can potentially happen to any Gadolinium-exposed patient"
Gadolinium Toxicity

- Primarily attributed to dissociation of Gd$^{3+}$ from the organic chelating agent
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- Primarily attributed to dissociation of Gd$^{3+}$ from the organic chelating agent
  - Competitive antagonist of Ca$^{2+}$-binding enzymes and calcium channels
  - Transmetallation with Zn$^{2+}$, Ca$^{2+}$, Cu$^{2+}$, Fe$^{3+}$

Rogosnitzky Biometals 2016;29:365-376
Gadolinium Toxicity

- High doses of “free” Gd$^{3+}$ in rodents
  - Mineral deposits in capillary beds (lung, kidneys)
  - Hepatocellular and splenic necrosis
  - Gastric mucosal hyperplasia
  - Neurotoxicity
  - Thrombocytopenia

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- Gd-EDTA has LD$_{50}$ of 0.3 mmol/kg in mice

GBCA Kinetic Stability in vitro

- Stability: macrocyclic ionic > macrocyclic nonionic > linear ionic > linear nonionic
Dissociation promoted by low pH, metal ions, phosphate, carbonate
GBCA Pharmacokinetics

- Short plasma elimination ($t_{1/2}$ 1.6 hours) and urinary elimination ($t_{1/2}$ 2.6 hours) phases
- Very similar for linear and macrocyclic GBCAs
GBCA Pharmacokinetics

- Prolonged urinary excretion phase related to deep compartment distribution
- Rate correlated with stability and much faster for macrocyclic GBCAs ($t_{1/2}$ 6 hours) than linear GBCAs ($t_{1/2}$ 24-102 hours)

Lancelot Invest Radiol 2016;51:691-700
Pediatric GBCA Pharmacokinetics

- Plasma elimination of macrocyclic gadobutrol slightly slower in neonates compared to older children and adults

<table>
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<tr>
<th>Parameter</th>
<th>Adults* (n = 101)</th>
<th>2–17 y† (n = 130)</th>
<th>0 to &lt;2 y (n = 43)</th>
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- GFR 20-30 mL/min/1.73 m² at birth (lower in premies), increases rapidly during neonatal period, then gradually increases and comparable to adult by 1-2 years of age
Gadolinium Deposition

- May be chelated, protein-bound, insoluble salt, or intra-macrophage
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- Human deposition first reported in 1989
  - Cerebral masses in Erdheim-Chester case remained enhanced 8 days after gadopentetate injection

Precontrast T1-WI  Postcontrast T1-WI  6 days later

Tien Radiology 1989;172:791-792
Gadolinium Deposition

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  - Only 72% of administered gadodiamide eliminated after 5 days and 4 hemodialysis sessions

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  - Deposition in femoral head specimens 2.5 x greater with gadodiamide than gadoteridol

- Causative role in nephrogenic systemic fibrosis (NSF) reported in 2006

References:
Nephrogenic Systemic Fibrosis (NSF)

- Risk correlates inversely with GBCA stability and GFR
  - 18% of severe chronic renal failure patients given high doses of gadodiamide, compared to 1% for gadopentetate

Only 3 cases (all with co-morbidities) in post-marketing surveillance of 29 million uses of macrocyclic gadobutrol

Endrikat Invest Radiol 2016;51:537-543; Tweedle Applied Radiol 2014;May:S1-S118
NSF Case Distribution by GBCA Class

No cases associated solely with protein-interacting linear GBCAs, despite being labeled as medium-risk by EU

Tweedle Applied Radiol 2014;May:S1-S118
Nephrogenic Systemic Fibrosis (NSF)

- Gadolinium deposition along subcutaneous vessels and connective tissue septa persisting for several years after GBCA administration

Birka Anal Chem 2015;87:3321-3328
Nephrogenic Systemic Fibrosis (NSF)

- Gadolinium deposition along subcutaneous vessels and connective tissue septa persisting for several years after GBCA administration
- Insoluble GdPO$_4$ from gadopentetate (linear)
- Intact gadoteridol (macrocyclic)
Nephrogenic Systemic Fibrosis (NSF)

- Related to both renal excretory and biosynthetic dysfunction
  - Improvement with improved renal function or transplant but not dialysis

Nephrogenic Systemic Fibrosis (NSF)

- Related to both renal excretory and biosynthetic dysfunction
  - Improvement with improved renal function or transplant but not dialysis
- Nearly eradicated due to risk mitigation strategies
### 2010 Guidelines

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<th>Patients at risk</th>
<th>Risk stratification</th>
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| Patients with severely impaired renal function | High-risk GBCAs: Contra-indicated  
Medium- and low-risk GBCAs: use lowest possible dose, pause of 7 days between two GBCA enhanced procedures |
| Patients with moderately impaired renal function | High-risk GBCAs: Use single injection of minimum dose, pause 7 days between two GBCA enhanced procedures  
Medium- and low-risk GBCAs: Use minimum dose, pause 7 days between two GBCA enhanced procedures |

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| Neonates < 4 weeks | High-risk GBCAs: Contra-indicated  
Medium- and low-risk GBCAs: Use lowest possible minimum dose, pause 7 days between two GBCA enhanced procedures |
Pediatric NSF

- 17 cases with documented GBCA exposure identified in RADAR post-marketing surveillance program
  - 12 with gadodiamide +/- other GBCA
  - 5 with unknown GBCA
  - None < 6 years of age
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- 17 cases with documented GBCA exposure identified in RADAR post-marketing surveillance program
  - 12 with gadodiamide +/- other GBCA
  - 5 with unknown GBCA
  - None < 6 years of age

- No cases in GARDIAN study of macrocyclic gadobutrol in 1,124 children
  - Only 6 with GFR < 60 mL/min/1.73 m²
22-year-old with history of craniopharyngioma and multiple gadolinium-enhanced MRI exams

Precontrast T1-WI
Gadolinium Deposition in the Brain

- Dose-dependent SI increase in dentate nuclei and globi pallidi, even with intact BBB and normal renal function, following intravenous or intrathecal linear GBCAs

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- Dose-dependent SI increase in dentate nuclei and globi pallidi, even with intact BBB and normal renal function, following intravenous or intrathecal linear GBCAs

- Studies generally show no SI increase after multiple doses of macrocyclic GBCAs in adults or children
  - Case reports of SI increase with gadobutrol in adults

Gadolinium Deposition in the Brain

- SI increase is an underestimate of gadolinium content
  - Little effect of insoluble Gd salts on T1 relaxation

Murata Invest Radiol 2016;51:447-453; Roberts Neurology 2017;88:1206-1208
Gadolinium Deposition in the Brain

- SI increase is an underestimate of gadolinium content
  - Little effect of insoluble Gd salts on T1 relaxation
  - Inductively coupled plasma mass spectrometry shows deposition after administration of both linear GBCAs and macrocyclic gadoteridol

Murata Invest Radiol 2016;51:447-453; Roberts Neurology 2017;88:1206-1208
Gadolinium Deposition in the Brain

- Unknown clinical significance
  - Deposition mostly in endothelial wall of blood-brain barrier, but also beyond BBB in neural interstitium
  - No histopathologic damage in humans or rat model
  - No unconfounded neurologic symptoms yet identified

McDonald Radiology 2015;275:772-782
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Absence of evidence is not evidence of absence.

(Martin Rees)
National Center for Toxicological Research (NCTR) will study this possible safety risk further.

Consider limiting use to clinical settings in which the additional information provided by the GBCA is necessary.
Pharmacovigilance and Risk Assessment Committee (PRAC) recommends suspension of marketing authorization for four intravenous linear GBCAs:

- Gadodiamide
- Gadoversetamide
- Gadopentetic acid
- Gadobenic acid
Pediatric GBCA Usage

- Around 80% have switched or switching to macrocyclics within next year
- Concern for brain deposition most common rationale
Gadolinium Deposition in Bone

- Reservoir for long-term deposition and slow release into the bloodstream
  - Occurs with both linear and macrocyclic GBCAs in adults with normal renal function
  - Correlated with brain levels, but > 20x brain levels

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- ? Increased in children due to more active osteogenesis
Gadolinium Deposition in Bone

- Retention much longer with linear GBCAs, and longer with gadobutrol than other macrocyclics

- > 8 years retention and predominantly unchelated form for linear GBCAs

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<td>Macrocyclic $^{153}$Gd-GBCA</td>
<td>Gd-DO3A</td>
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Gadolinium Deposition in Bone

- Retention much longer with linear GBCAs, and longer with gadobutrol than other macrocyclics

- > 8 years retention and predominantly unchelated form for linear GBCAs

- May explain cases of delayed NSF in patients developing renal failure years after being exposed to linear GBCAs when healthy

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Proposed novel disease developing within one year after exposure to GBCAs in setting of normal renal function
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Associated with both linear and macrocyclic GBCAs
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- Diagnostic criteria: Glove-and-sock distribution of pain, skin thickening and discoloredation, central torso pain, bone pain, headache and clouded mentation, laboratory evidence of gadolinium persisting in blood or other tissues beyond 30 days following MRI
Gadolinium deposition disease: Initial description of a disease that has been around for a while

Richard C. Semelka a, Joana Ramalho a, b, Ami Vakharia a, Mamdoh AlObaidy a, c, Lauren M. Burke a, Michael Jay d, Miguel Ramalho a, e

a Department of Radiology, University of North Carolina, Chapel Hill, NC, USA
b Department of Radiology, Centro Hospitalar Lisboa Central, Lisbon, Portugal
c Department of Radiology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
d Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA
e Department of Radiology, Hospital Garcia de Orta, Almada, Portugal

- Resembles mild form of NSF with some distinct features
- Not reported in children
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- Not validated
  - Based on survey of two online gadolinium toxicity support groups
  - No control group
  - No evaluation of skin histology
  - No evaluation of clinical indications for MRI
Knowledge Gaps

- What are the biodistribution and speciation of gadolinium retention?
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- Are there clinically significant disorders other than NSF?

- How should the risk influence clinical practice?
You Are Part of the Experiment

- Anthropogenic gadolinium present in lakes, estuaries, coastal waters, groundwater and tap water

You Are Part of the Experiment

- 7-fold increase in gadolinium levels over the past 20 years in the San Francisco Bay
First, Do No Harm

- Up to 1% rate of preventable adverse event per pediatric hospitalization, often related to misdiagnosis

- Preventable medical errors far more likely to cause severe harm than gadolinium deposition
“Patients should not be unnecessarily deprived of crucial, sometimes life-saving medical data from gadolinium contrast-enhanced MRI.”
Summary

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- Other than NSF, clinical disorders attributable to gadolinium deposition remain to be defined.
- Deposition less with macrocyclic GBCAs, but intra-class differences exist.
- Children will be exposed longer to gadolinium deposits.
- Need GBCAs with higher stability and relaxivity.