The pathophysiology and retention of gadolinium

Brent Wagner, MD

Associate Professor of Medicine

South Texas Veterans Health Care System, Department of Medicine/Nephrology
University of Texas Health Science Center at San Antonio, San Antonio, Texas
Objectives

- **Elucidation** of the mechanisms of gadolinium-based contrast agent-induced toxicity is an **active area of investigation**

- The focus of this presentation is the work in my laboratory concerning the **mechanisms** of gadolinium-based contrast agent **toxicity** and how this is **manifested systemically**

- A **model** has been **established** in rodents

- One gadolinium-based contrast agent has been used in these experiments, Omniscan (gadodiamide/caldiamide), but the **findings** may be **applicable** for the other gadolinium-based contrast agents
Overview

- There are many different chemical formulations of gadolinium-based contrast agents used in magnetic resonance imaging.
- Gadolinium-based contrast agents have been linked to ‘nephrogenic’ systemic fibrosis cases.
- There is evidence that gadolinium is deposited in the central nervous system.
- The central nervous system toxicity warrants more study.
- Gadolinium-based contrast agents are biologically active.
- Little is known about the metabolism of gadolinium-based contrast agents, their biologic effects, and the implications of retained gadolinium.
- The toxic effects and mechanisms of gadolinium-based contrast agents is a major gap in our knowledge.
- Understanding the pathophysiology of gadolinium-induced systemic fibrosis will be critical for future discoveries.
- How gadolinium from different contrast agents distributes throughout the body is an active area of investigation.

Wagner B et al, Adv Chronic Kidney Dis, 2017
The periodic table of elements

<table>
<thead>
<tr>
<th>H</th>
<th>He</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>Be</td>
</tr>
<tr>
<td>Na</td>
<td>Mg</td>
</tr>
<tr>
<td>K</td>
<td>Ca</td>
</tr>
<tr>
<td>Rb</td>
<td>Sr</td>
</tr>
<tr>
<td>Cs</td>
<td>Ba</td>
</tr>
<tr>
<td>Fr</td>
<td>Ra</td>
</tr>
<tr>
<td>La</td>
<td>Ce</td>
</tr>
<tr>
<td>Ac</td>
<td>Th</td>
</tr>
</tbody>
</table>
‘Nephrogenic’ systemic fibrosis, a man-made disease caused by magnetic resonance imaging contrast agents

Gadolinium-based contrast agents can be acutely nephrotoxic in humans

Degeneration of tubular epithelial cells

Flattening of tubular epithelial cells

Calcium phosphate

Cellular proliferation

Glomerulosclerosis

Toluidine blue stain - Kidney

H&E stain - Kidney

Immunostain - Kidney

Electron microscopy - Kidney

Akgun H et al, Archives of Pathology & Laboratory Medicine, 2006
Widespread biodistribution of gadolinium-based contrast; remnants in the kidney cortex up to 7 days after a single, clinically-relevant injection in rat

Differential effects of gadolinium-based contrast agents in rats

**H&E staining - Skin**

**Immunohistochemical staining – Skin**
Fibronectin
GAPDH

**Immunoblot - Skin**

Gadodiamide administration in mice with normal renal function

Mice (C57BL6)

Control

Gadodiamide

Kidney

Skin

Gadodiamide (20-25 doses)

(2.5 mmol/kg body weight, i.p.)

Sacrifice

Gadolinium content, kidney

Gadolinium content, skin

Gadolinium content, cerebrum

Gadolinium content, cerebellum

***

0

2000

4000

60

20

40

0

500

1000

5000

0

20

40

60

0

500

1000

2000

4000

5000

Gadolinium (µg/g tissue)

Gadolinium (µg/g tissue)

Gadolinium (ng/g tissue)

Gadolinium (ng/g tissue)
Electron microscopy shows *electron-dense deposits* in the kidneys of gadodiamide-treated mice *with normal renal function*.

*Transmission electron microscopy* - Glomeruli

*Transmission electron microscopy* - Tubules

Wagner laboratory, unpublished
The renal deposits resemble Gd$_2$O$_3$ disordered mesh-like nanowire/nanoparticle aggregates *in vitro*

Transmission electron microscopy - Mesangium

Transmission electron microscopy - Tubule

Transmission electron microscopy - Water

Transmission electron microscopy – Phagolysosomal-simulated fluid

Wagner laboratory, unpublished

Gadodiamide induces renal fibrosis in mice

Control 
Gadodiamide

PAS staining - Kidney
Fibronectin
Collagen IV

Control 
Gadodiamide

PAS staining - Kidney

免疫印迹 - 皮肤

Wagner laboratory, unpublished

Fibronectin
GAPDH
220 kDa
Gadodiamide induces oxidative stress in the mouse kidney

**DHE fluorescence with confocal laser scanning microscopy**

**Amplex red assay**

Wagner laboratory, unpublished
Gadodiamide induces skin fibrosis in mice with normal renal function

H&E staining - Skin

Cellularity

Skin fold thickness

Control
Gadodiamide
Control
Gadodiamide

Immunofluorescent staining - Skin

Fibronectin (marker of fibrosis)

DAPI (nuclei)

Wagner laboratory, unpublished
Gadodiamide treatment leads to inflammation and bone marrow-derived cells to the dermis in mice with normal renal function.

Wagner laboratory, unpublished
Gadodiamide increases oxidative stress in the skin of mice with normal renal function.

**3-Nitrotyrosine**

Control | Gadodiamide

**DAPI (nuclei)**

Control | Gadodiamide

**Immunofluorescent staining - Skin**

**In situ DHE staining and confocal microscopy - Skin**

Wagner laboratory, unpublished
Experimental design: Tagged bone marrow transplant in mice with normal renal function

Green fluorescent protein (GFP) donor mice

1 $\times$ $10^7$ cells

Engraftment

Control

Gadodiamide

2.5 mmol/kg i.p. for 4 weeks

GFP

Collagen IV

Merge

DAPI (nuclei)

Immunofluorescent staining – Kidney

Wagner laboratory, unpublished
Gadodiamide induces the recruitment of bone marrow-derived fibroblasts to the skin in mice
Biopsies of patients with NSF demonstrate significant expression of the hematopoietic progenitor marker CD34.

*H&E staining - Skin
Dermal hyper-cellularity

*Immunostaining for CD34 - Skin

Clinical photographs of a patient showing skin lesions

Conclusions

- **Gadolinium retention** can be detected in **humans** and in **our models**; This allows the **mechanistic** study of gadolinium-induced **organ injury**

- The pathologic **effects** of gadolinium-based contrast agents are **not well-characterized**

- Our experiments show that **renal insufficiency** is **not requisite** for fibrosis

- Mechanistically, our experiments demonstrate that it is the recruitment of **bone marrow-derived cells** that mediate the **deleterious actions**

- We provide examples of important avenues to **understanding the mechanisms of disease** (lending itself to the **discovery of biomarkers**)

- **Dechelation** of gadolinium is a **hypothetical** pathologic mechanism.

- Studies concerning the biologic effects of **rare earth metals** in general and their **retention** in human organs are in the **nascent stage**

- The **science** on this topic is at **ground zero**
Working hypothesis

Patient with normal kidney function

MRI
Gadolinium-based contrast exposure

Gadolinium-induced disease

Impaired function

Gadolinium retention

Organ injury

MRI
Gadolinium-based contrast exposure

Biomarkers
Precision/Personalized Medicine
Working hypothesis

Patient with normal kidney function

Gadolinium-based contrast exposure

Gadolinium retention

Organ injury

Impaired function

Gadolinium-induced disease

Pre-existing conditions (obesity, diabetes, pregnancy, inflammation, etc.)

MRI

Gadolinium-based contrast exposure
Acknowledgments

UTHSCSA
Nephrology

Wagner’s Laboratory
- Chunyan Tan
- Catherine Do, M.D.
- Viktor Drel, Ph.D.

Yves Gorin, Ph.D.
- Denis Féliers, Ph.D.
- Jeffrey L. Barnes, Ph.D.
- Seema Ahuja, M.D.
- Doug-Yoon Lee, Ph.D.
- Hanna E. Abboud, M.D.

Rush University Medical Center
Internal Medicine Department
- Jochen Reiser, M.D., Ph.D.

Northwestern

Keith MacRenaris, Ph.D.

UTSA

Miguel Yacaman, Ph.D.
Josefina Arellano-Jimenez, Ph.D.

UNC

Michael Jay, Ph.D.
John Prybylski, Ph.D.

Supported by:

- NIDDK
  NIH RO1DK102085 (PI)

- Veterans Administration
  Merit Award I01BX001958 (PI)
  Career Development Award (PI)
  VISN 17 New Investigator Award (PI)