Update on FDA approach to safety issue of gadolinium retention after administration of gadolinium-based contrast agents

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Introduction

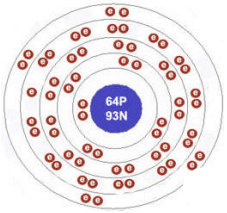
- Gadolinium-based contrast agents (GBCAs) only approved class of drugs for use with magnetic resonance imaging (MRI) available in the United States.
- Most intravenously administered drug class after saline and iodinated contrast agents.
- Mainly indicated “to detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system,” based on efficacy evidence that blinded readers report improved visualization ratings when comparing pre- plus post-GBCA images to pre-GBCA images alone
- Off-label use common

Currently marketed GBCAs

Tradename	Active ingredient (abbreviation)	Indication	Approval year	Pediatric approval (age in years)
Magnevist	gadopentetate dimeglumine (Gd-DTPA)	Neuro, Body	1988	2+
Prohance	gadoteridol (Gd-HP-DO3A)	Neuro	1992	2+
Omniscan	gadodiamide (Gd-DPTA-BMA)	Neuro, Body	1993	2+
Multihance	gadobenate dimeglumine (Gd-BOPTA)	Neuro, Vascular	2004	0+ (half-to-full dose)
Eovist	gadoxetate disodium (Gd-EOB-DTPA)	Liver	2008	0+ (one-fourth dose)
Gadavist	Gadobutrol (Gd-BT-DO3A)	Neuro, Vascular, Breast CA	2011	0+
Dotarem	gadoterate meglumine (Gd-DOTA)	Neuro	2013	0+

Retention story 1984: first GBCA

Gadolinium ion



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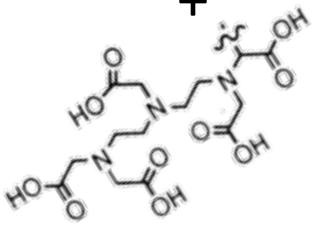
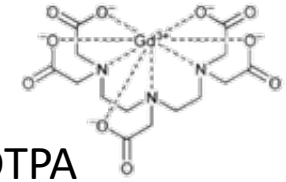


DTPA chelate

Hanns-Joachim Weinmann
Robert C. Brasch
Wolf-R. Press
George E. Wesbey

Characteristics of Gadolinium-DTPA Complex: A Potential NMR Contrast Agent

Ninth coordination site interacts with body



Gd-DTPA 8-coordination complex

Agent	Dose (mmol/kg)	Acute rat deaths (#/total)	LD_{50} (mmol/kg)
Meglumine diatrizoate	12	0/4	18
	20	1/4	
	28	4/4	
$GdCl_3$	0.3	0/5	0.5
	0.45	2/5	
	0.6	5/5	
Meglumine–Gd-EDTA	0.3	2/3	0.3
	1.2	5/5	
Dimeglumine–Gd-DTPA	2.5	0/4	10
	7.5	0/4	
	12.5	4/4	
Na_3Ca-DTPA	1	0/6	5
	2	2/6	
	4	0/6	
	6	6/6	

~20x

$GdCl_3$	Time after dose (days)	% IV Dose
Excreted:		
Urine	0–3 hr	0.05
	0–1	0.07
	0–7	0.1 ± 0.0
Feces	0–1	0.6 ± 0.4
	0–7	2.1 ± 0.5

Gd-DTPA	Time after dose (days)	% IV Dose
Excreted:		
Urine	0–3 hr	87.6 ± 1.9
	0–1	89.2 ± 2.6
	0–7	89.7 ± 2.7
Feces	0–1	5 ± 3.5
	0–7	7.4 ± 4.5

Retention story 1999: pre-NSF

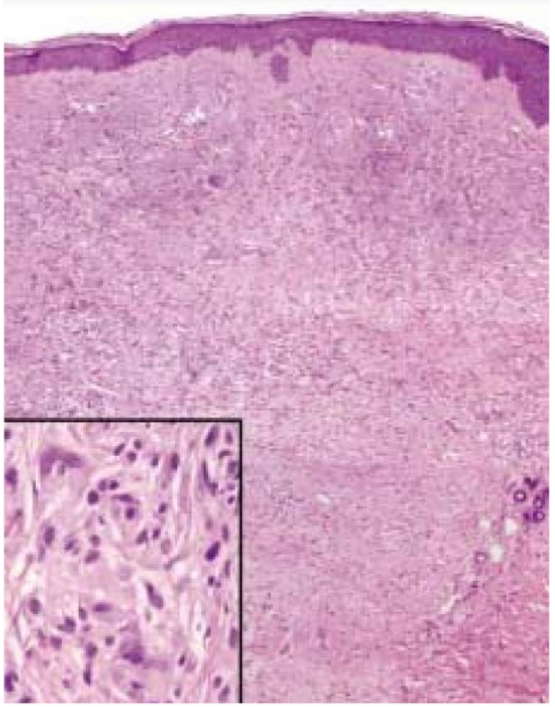
Gadolinium(III) Chelates as MRI Contrast Agents: Structure, Dynamics, and Applications

Peter Caravan,* Jeffrey J. Ellison, Thomas J. McMurry, and Randall B. Lauffer

"The successful penetration of gadolinium-chelates can be measured in many ways…The inert complex actually does not look like much at all: a little hydrophilic ball, as innocuous as a sugar molecule. And, oddly enough, it appears to be as safe."

Scleromyxoedema-like cutaneous diseases in renal-dialysis patients

Shawn E Cowper, Howard S Robin, Steven M Steinberg, Lyndon D Su, Samardeep Gupta, Philip E LeBoit



Hard, thick skin; ↑fibroblasts, thickened collagen, occasional multinucleated phagocytes

Retention story 2006-2010: NSF

Omniscan, Optimark, and Magnevist

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

See full prescribing information for complete boxed warning.

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs (5.1).

- **Do not** administer **GBCA name** to patients with:
  - chronic, severe kidney disease
  - acute kidney injury (4).
- Screen patients for acute kidney i
  that may reduce renal function.
  chronically reduced renal functi
  hypertension or diabetes), estima
  rate (GFR) through laboratory testin

All other GBCAs

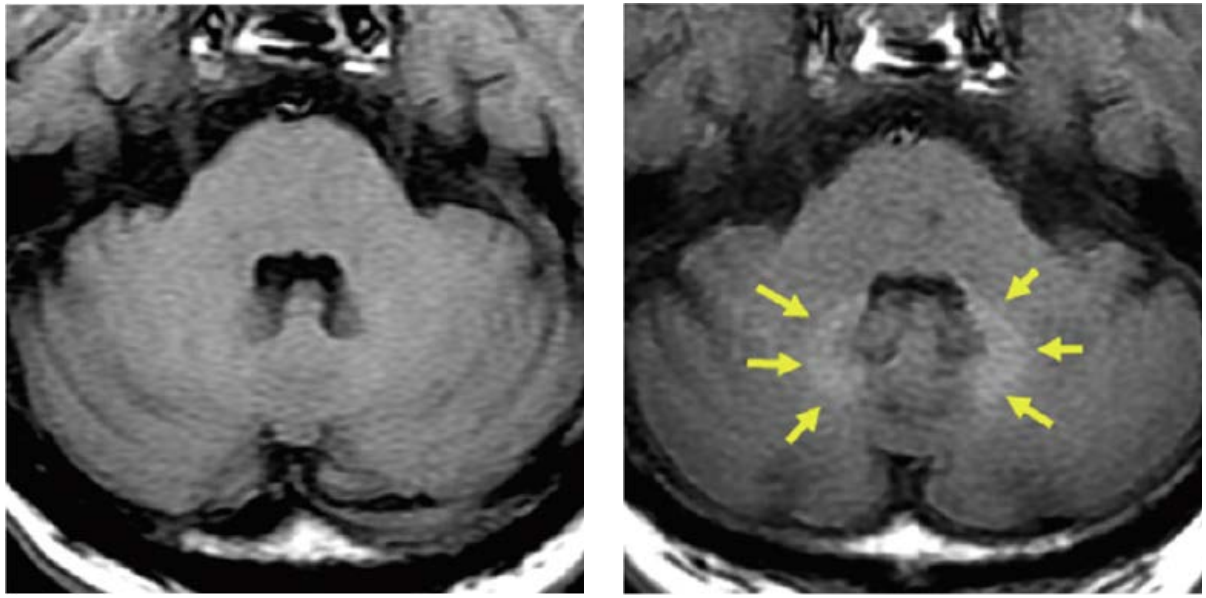
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing (5.1).**

Retention story 2014: beyond renal failure

Tomonori Kanda, MD, PhD
Kazunari Ishii, MD, PhD
Hiroki Kawaguchi, MD
Kazuhiro Kitajima, MD, PhD
Daisuke Takenaka, MD, PhD

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



FDA regulatory actions

7/27/2015: Drug Safety Communication

https://www.fda.gov/Drugs/DrugSafety/ucm455386.htm

Recent publications reported deposits of GBCAs remain in the brains of some patients who undergo four or more contrast MRI scans...Unknown whether harmful.

5/22/2017: Drug Safety Communication

https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm

All GBCAs associated with retention in brain and other body tissues...No evidence harmful…Restricting GBCA use not warranted at this time.

9/8/2017: Meeting of the Medical Imaging Drugs Advisory Committee

12/19/2017: Drug Safety Communication

5/16/2018: Medication Guide Update

https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/ucm553470.htm

https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm

Sensitive safety studies have potential to build on mostly reassuring evidence reviewed to date…FDA requiring new class warning/medication guide, human and animal studies, and enhanced pharmacovigilance.

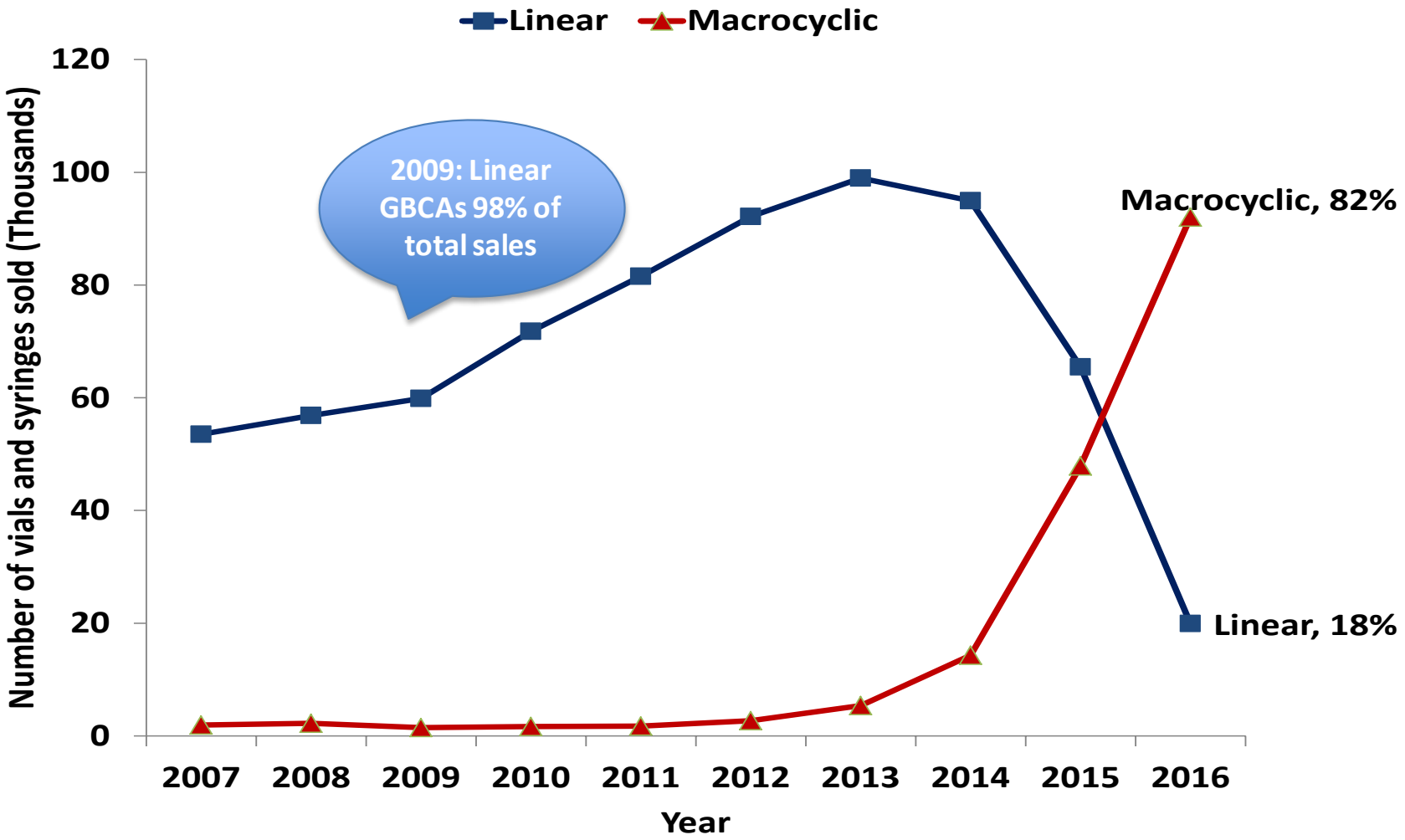
Key elements of new warning/medication guide

- MRI with a GBCA helps your doctor to see problems better than MRI without a GBCA.
- GBCAs contain a metal called gadolinium. Small amounts can stay in your body including the brain, bones, skin and other parts of your body for a long time (several months to years).
- It is not known how gadolinium may affect you, but so far, studies have not found harmful effects in patients with normal kidneys.
- Rarely, patients have reported pains, tiredness, and skin, muscle or bone ailments for a long time, but these symptoms have not been directly linked to gadolinium.
- Gadolinium stays in the body more after Omniscan or Optimark than after Eovist, Magnevist, or MultiHance. Gadolinium stays in the body the least after Dotarem, Gadavist, or ProHance.
- People who get many doses, women who are pregnant, and young children may be at increased risk. Consider retention characteristics when choosing GBCAs for these patients. Minimize repetitive and closely spaced administrations.

Approach to safety evidence generation

Classification	Type of data source	Example	Status
Descriptive	Spontaneous adverse event reporting	FAERS, manufacturer databases	Ongoing
	Publications	Scientific literature: case reports, cases series	Ongoing
		Non-peer-reviewed sources	Ongoing
	Enhanced pharmacovigilance	Standardized data collection, development of case definition	Protocol development
Analytical	Administrative databases	Mother-baby linkages	Ongoing
	Epidemiologic / observational	Cohort prospective and retrospective	Ongoing
	Immunological	Harnessing preclinical advances for biomarkers / identification of vulnerable patients	Early development
	Prospective controlled (primarily to exclude clinically meaningful magnitude of neurobehavioral harm)	Developmental and juvenile animal studies (mice and non-human primates)	Protocol finalization
		Matched control cohort trial in neurologically normal adults	Protocol finalization

GBCA sales from manufacturers to a sample* of pediatric hospitals and clinics



Source: Symphony Health Solutions' PHAST NonRetail Monthly . Data Extracted July 2017.

*Sample = 50 pediatric hospitals and 5 pediatric clinics