Contrast Media Safety in MRI

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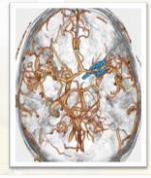
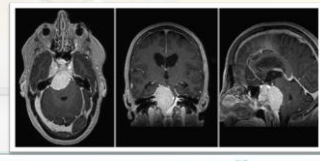
Outline

- What contrast agents are used in MRI
- Properties of CM
- Patient Interaction with CM
- Managing Adverse Events
- NSF / NFD
- GFR Calculations
- Contrast Stability

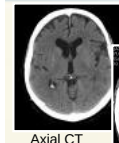
Purpose of Contrast Media

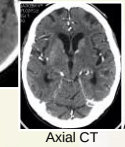
To alter an inherent contrast property of tissue

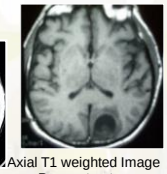


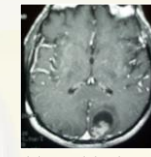


Can We Use Contrast Media in MRI, in CT?


Axial CT Pre


Axial CT Post contrast iodinated


Axial T1 weighted Image Pre contrast


Axial T1 weighted Image Post contrast (gadolinium)


White structure on white back ground


White structure on gray back ground


White structure on Dark gray back ground


White structure on black back ground


Black structure on black back ground

Contrast Media

- **Periodic Table**

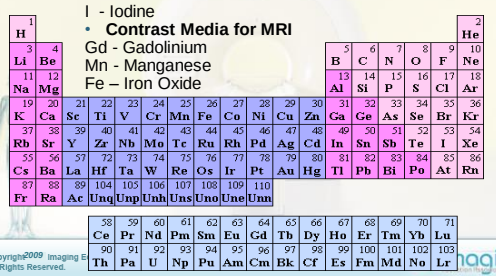
Elements
Unique Atomic Structure

- **Contrast Media for X-ray, CT, Cardiovascular**

Ba - Barium
I - Iodine

- **Contrast Media for MRI**

Gd - Gadolinium
Mn - Manganese
Fe – Iron Oxide



Gadolinium-Based Contrast Media

Paramagnetic Gd^{3+}

7 un-paired electrons

- Alters relaxation rates of water-based hydrogen in tissues
  - T1-Relaxation
  - T2-Relaxation
- Gd shortens T1-Relaxation Time
- Gd shortens T2-Relaxation Time

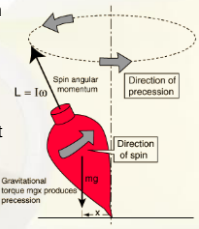
How does it work?

Relaxation times are mostly dependent on molecular tumbling rates

The bigger the molecule, the slow it tumbles and the faster it relaxes

Gadolinium is a big, slow-tumbling magnet

When gadolinium get close to a water molecule it slows it molecular tumbling rate which results in faster relaxation rates



The amount of change is given by the relaxivity (r1, r2) of the agent

Mechanisms of Action - Summary

Gadolinium-based

Alter relaxation rates (T1 and T2)

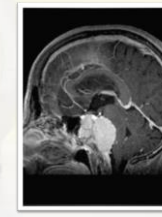
Improve effect

Increase volume

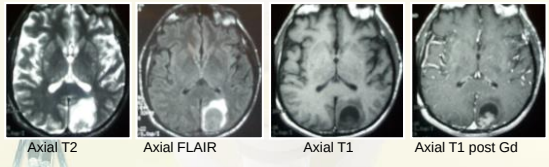
Increase concentration

Increase relaxivity (r_1 and r_2)

$$\Delta\frac{1}{T_1} = r_1[Gd]$$



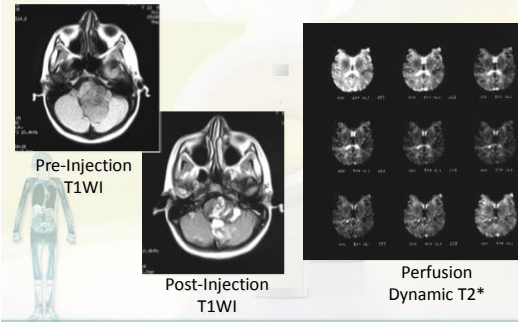
Let's Compare MR images



Axial T2 | Axial FLAIR | Axial T1 | Axial T1 post Gd

Without | With | Better?

Gadolinium Seemingly "Opposing" Affects



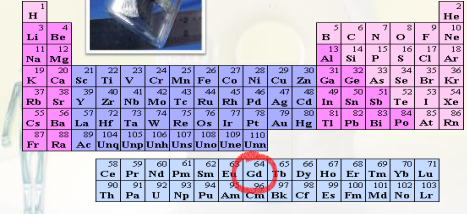
Pre-Injection T1WI

Post-Injection T1WI

Perfusion Dynamic T2*

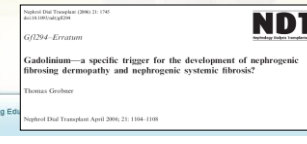
What is Gadolinium (Gd)?

Lanthanide / "rare earth" Element
Also known as a "Rare Earth Metal Ion"



Gd Nephrotoxicity… yes or no?

- Standard IV use/doses
  - Not nephrotoxic (usually)
- Iodinated contrast equivalent doses or IA use for DSA
  - Nephrotoxicity has been reported
  - Debatable if gadolinium performs better than low osmolar iodinated agents
- Patients in Renal failure .. 1998
  - Nephrogenic fibrosing dermopathy
  - Nephrogenic systemic fibrosis

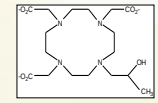

NDT
GJ1294–Erratum
Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?
Thomas Grobner

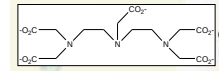
Gadolinium Toxicity

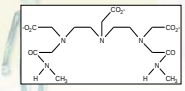
Rare Earth Metal Ion (as a contrast agent)
Heavy Metal (toxic) – as an element
To remove toxicity – Chelate "Claw"

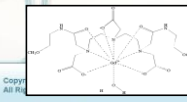

Non Toxic!
Ligand
Ionic vs Non-ionic
Can be excreted

Gadolinium Chelates


Gadoteridol
(Gd HP-DO3A or ProHance Bracco)

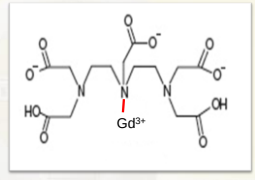


Gadopentetate dimeglumine
(Gd DTPA
Magnevist by Berlex)



Gadodiamide
(Gd DTPA-BMA
Omniscan by Nycomed)



Gadoversetamide
Optimark by Malinkrodt)


Linear Chelate

Gadopentetate Dimeglumine



chela: "crab's claw"

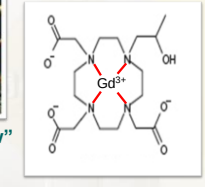
diethylenetriaminepentaacetic acid (DTPA)

Gd-DTPA (Magnevist®)

Linear Chelate / Ionic

Macrocyclic Chelate

Gadoteridol

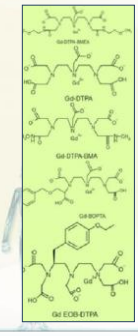


chela: "crab's claw"

Gd-HP-DO3A (ProHance®)

Macrocylic Chelate / Non-Ionic

Differences in Chelates



Optimark
Non-Ionic
Magnevist
Ionic
Omniscan
Non-Ionic
MultiHance
Ionic
Primovist
Ionic

Linear

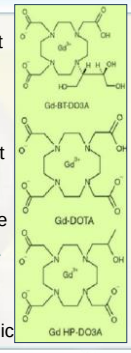
Gadovist

Primovist

ProHance

Non-Ionic

Macrocyclic



Gadolinium-Based Agents

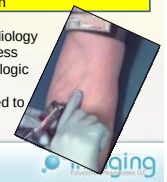
Ionic	**Non-Ionic**
Higher Stability	Lower Stability
Macrocyclic Chelate	Linear Chelate

No difference in ADE's

Runge VM: Top Magn Reson Imaging 2001 Aug:12(4):309-13
Dillman, et. al.: AJR:189 Dec 2007
Murphy, et. al.: AJR:196 Oct 1996
Runge VM: Invest Rad 2001 Vol 36, Num 2, 65-71
Shellock FG, et. al.: Invest Rad 2006 Vol 41, Num 6, 65-71
Bleicher, A, Kanal, E AJR: 191, December 2008

Contrast Administration

No patient is to be administered prescription MR contrast agents without orders from a duly licensed physician. Intravenous injection–qualified MR technologists may start and attend to peripheral IV access lines if they have undergone the requisite site-specified training in peripheral IV access and have demonstrated and documented appropriate proficiency in this area. IV-qualified MR technologists may administer FDA-approved gadolinium-based MR contrast agents via peripheral IV routes as a bolus or as a slow or continuous injection as directed by the orders of a duly licensed site physician. Administration of these agents is to be performed according to the ACR policy. The ACR approves of the injection of contrast material and diagnostic levels of radiopharmaceuticals by certified and/or licensed radiologic technologists and radiologic nurses under the direction of a radiologist or his or her physician designee who is personally and immediately available, if the practice is in compliance with institutional and state regulations. There must also be prior written approval by the medical director of the radiology department or service of such individuals. Such approval process must follow established policies and procedures, and the radiologic technologists and nurses who have been so approved must maintain documentation of continuing medical education related to materials injected and to the procedures being performed [30].



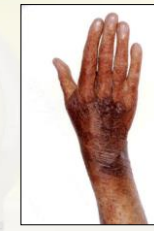
Avoid Extravasation

Animal studies do show moderate necrosis

Osmolality a consideration

Not as big of a issue as with ionic iodinated contrast

Investigative Radiology 2002 July;37(7):393-8



Risk Reduction after Gd

- View optimal metabolic profile
  - Avoid acidosis
  - Adequate dialysis
  - Control phosphorous and calcium
- Regarding transmetalation
  - Avoid –IV Iron infusion
- ***Dose***
  - ***Lowest dose possible***
  - ***Avoid repeat dose (2-3 months)***
- After Gd
  - Hemodialysis within 2 hours – repeat within 24, maybe 3rd round…
    - studies show 3-4 rounds reduce serum GDCA by 97-99%
    - = 11 – 14 hours of dialysis
  - Peritoneal dialysis not efficient – if on PD consider temp Hemodialysis (challenge – no access)

Standard Dose of Gadolinium

0.1 m mol / kg or...

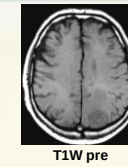
0.2 cc / kg or...

Approx. 0.1 cc/lb

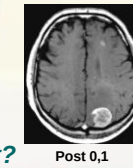
IV injection followed by 5cc saline flush

More is Better...

or is it?



T1W pre

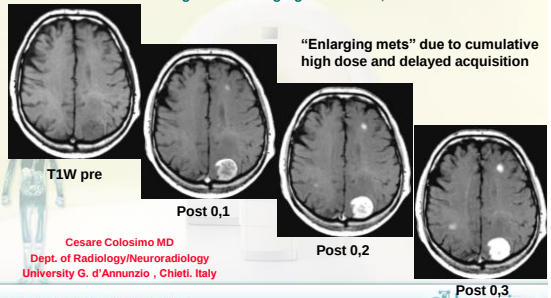


Post 0,1

More is better?

Schneider G et al: Gadobenate dimeglumine-enhanced MRI of intracranial metastases: effect of dose on lesion detection and delineation. **J Magn Reson Imaging 14: 525-539, 2001**

"Enlarging mets" due to cumulative high dose and delayed acquisition



T1W pre

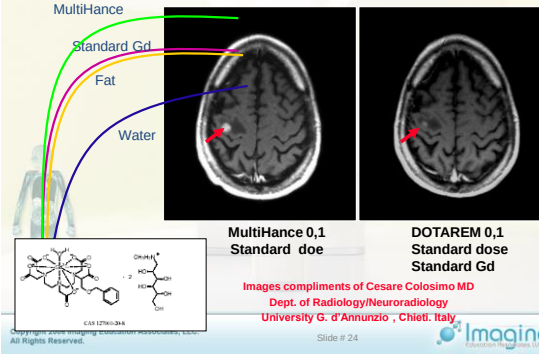
Post 0,1

Post 0,2

Post 0,3

Cesare Colosimo MD
Dept. of Radiology/Neuroradiology
University G. d'Annunzio , Chieti. Italy

Standard Gad vs New Gad… @ same dose



MultiHance 0,1
Standard doe

DOTAREM 0,1
Standard dose
Standard Gd

Images compliments of Cesare Colosimo MD
Dept. of Radiology/Neuroradiology
University G. d'Annunzio , Chieti. Italy

What can go wrong with Contrast Media (CM)?

- Side Effects
  - Taste
  - Warmth
  - Nausea
- Reactions
  - Mild
  - Moderate
  - Severe

How can we interpret "what went wrong" if we did not know the patient status in the beginning of the exam?

Before we begin…

Unfortunately, we get 'caught up' in the day-to-day challenges, and tend to become complacent.

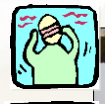
- We forget that we are caring for 'sick' people.
- We forget that we are injecting 'drugs'.
- We do not remember what we learned about the anatomy & physiology of the human body.
- We do not understand the interactions of 'medications' with the human body.
- We forget that …

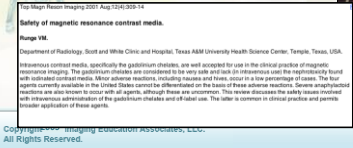
There usually is more to the story than meets the eye!

Gadolinium Side Effects

- Mild transitory HA's
- Slight increase bilirubin & blood iron
- Nausea / vomiting
- Urticaria / rash

- Less than 1% anaphylaxis or death





Top Magn Reson Imaging 2001 Aug;12(4):309-14

Safety of magnetic resonance contrast media.

Runge VM.

Department of Radiology, Scott and White Clinic and Hospital, Texas A&M University Health Science Center, Temple, Texas, USA.

Intravenous contrast media, specifically the gadolinium chelates, are well accepted for use in the clinical practice of magnetic resonance imaging. The gadolinium chelates are considered to be very safe and lack (in intravenous use) the nephrotoxicity found with iodinated contrast media. Minor adverse reactions, including nausea and hives, occur in a low percentage of cases. The four agents currently available in the United States cannot be differentiated on the basis of these adverse reactions. Severe anaphylactoid reactions are also known to occur with all agents, although these are uncommon. This review discusses the safety issues involved with intravenous administration of the gadolinium chelates and off-label use. The latter is common in clinical practice and permits broader application of these agents.

Be Prepared!

Adverse Reactions

Minor reactions occur with all agents in a low percentage of cases

The current 5 agents have *similar safety profiles*

Anaphylactic reactions are rare

Have occurred with all agents

Sites should be prepared to treat a reaction

V. Runge, *Topics in Magnetic Resonance Imaging*, 2001, Aug; 12(4):309 - 14

Contrast-Related Adverse Events

- Early reactions
  - Most reactions occur within 5 minutes of administration
- Delayed adverse events can occur

Adverse Events Then & Now

Then in CT	Then in MRI	Now in MRI
• Happened every day	• Rarely Happens	• Still Rarely Happens
• Every patient	• Select patients	• Seems like MORE…
– In and Out Patient	– Out patients (more)	• Select patients
– Same…	– In-Patients (less)	– Out patients (more)
• Severity varied	• Severity varies	– In-Patients (less)
– We were prepared	- We are not prepared	• Severity varies
– Benadryl (antihistamine)	- Drugs are locked up	- We are not prepared
– Tagamet HB	- Key is ???	- Drugs are locked up
– Epinephrine		- Key is ???

Adverse Drug Reactions

- Side effect – "In medicine, an adverse effect is a harmful and undesired effect resulting from a medication or other intervention such as surgery." Wikipedia
- Adverse reaction –
- Drugs are used on a need vs. risk basis
- Patient must be properly educated regarding potential adverse effects prior to administration
- Idiosyncratic reaction
- Bizarre effects (or idiosyncratic) - dose independent and unpredictable Wikipedia

Reaction

Sensitivity Reactions

- Ex: Bee Sting
- Antibodies mediate distribution of histamines into blood stream
- Body response
  - Reacts or
  - Does not
- Invited Guest

Fluid Shift

- Ex: Contrast Administration
- Large Molecules need water
- Water
- Leaks out of the extracellular space
- Into the blood stream
- Dragging Histamine with
- Body response
  - Reacts or
  - Does not
- Party crasher

"Allergic-Like" Reactions

- Reactions to IV Contrast Media (CM) have the same manifestations as anaphylactic reactions, and they are not true hypersensitivity reactions. …instead fluid shift…
- Immunoglobulin E (IgE) antibodies are not involved.
- Prior sensitization is not required, nor do they consistently recur in a given patient.
- For these reasons, idiosyncratic reactions to CM are called **anaphylactic reactions**.

Nasir H Siddiqi, MBBS, MD, emedicine.com

"Allergic-Like" vs "Sensitivity" Reactions

Histamine Release

The release of histamine (hist = because it's made up of histidine residues, amine = because it's a vasoactive amine) causes several allergic symptoms.

1) It contributes to an inflammatory response.
2) It causes constriction of smooth muscle.

Histamine reaction is precursor to anaphylaxis

Side Effects & Reactions

- "The most common side effect of iodine includes a warm or hot "flushed" sensation during the actual injection of the iodine and a "metallic" taste in the mouth, which usually lasts less than a minute or so. This can vary depending on the type of iodine used, the rate at which it is administered, and individual patient sensitivity. There is no treatment necessary for this sensation
- Another mild reaction that can take place following the administration of iodine is itching over various parts of the body with hives (bumps on the skin). This reaction can last from several minutes to several hours after the injection. This type of reaction is usually treated with medication administered by the radiologist, nurse, technologist or other physician.
- More serious reactions, although much less likely, may include breathing difficulty, swelling of the throat, or swelling of other parts of the body. These reactions can be more serious if not treated immediately."

http://www.imaginis.com/ct-scan/contrast.asp

Classifications of Reactions

- Mild – DOES NOT require treatment
  - Skin reaction
  - Single episode of nausea
- Moderate – OFTEN requires treatment
  - Not considered life threatening
  - Can progress to a more severe reaction if not treated
  - DOES require treatment
- Severe – DOES require treatment
  - May be life threatening
  - May threaten permanent injury such as brain anoxia
- Fatal -

Mild Adverse Reactions

- Nausea and vomiting
- Warmth
- Headache
- Dizziness
- Tremors
- Hives/Urticaria
- Pallor
- Hypertension
- Sweats
- Altered taste (metallic)
- Nasal stuffiness
- Swelling of eyes
- Anxiety
- Rash
- Fever/Chills
- Hypertension

 Slide # 21

Moderate Adverse Reactions

- Moderate degree of mild signs and symptoms or
- Systemic symptoms including:
- Symptomatic urticaria
- Tachycardia
- Hypotension (vasovagal)
- Hypertension
- Dyspnea – wheezing
- Bronchospasm
- Laryngeal edema (mild)
- Close observation

 Slide # 22

Severe Adverse Reactions

- **Life threatening**
- Moderate to severe laryngeal edema
- Moderate to severe bronchospasm
- Unresponsiveness
- Convulsions
- Contrast-induced nephropathy (CIN)
- Major adverse cardiac events (MACE)
- Arrhythmias
- Cardiopulmonary arrest
- Respiratory arrest
- **Requires prompt recognition and treatment**
- **Almost always requires hospitalization**

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Vasovagal Response

- Result of stimulation of vagus nerve
- **Bradycardia** and hypotension
- Caused by difficult IV insertion and patient anxiety.
- Abdominal compression
- Not a contrast reaction.
- Elevate legs above heart
- Possibly IV fluids or atropine
- Observation

 Slide # 24

Reported Incidents of Most Frequent AEs

Contrast Agent	No. of Patients	Headache (%)	Nausea (%)	Taste Perversion (%)	Urticaria (%)
Magnevist	1,068	3.6	1.5	0.3	0.3
ProHance	1,709	0.4	1.1	1.2	0.4
Omniscan	439/700	1.8/4.4	0.9/3.6	0.9/2.1	0.70.1
OptiMARK	1,663	7.5	2.6	5.7	N/A
MultiHance	2,367	1.9	1.3	1.1	0.3

Kirchin MA et al. *Top Magn Reson Imaging.* 2003;14:426-435.

MultiHance/Magnevist Study

287 patients enrolled in intra-individual crossover trials

Received MultiHance and Magnevist in 2 separate studies within 14 days

Adverse events rate in these patients was comparable

8% for MultiHance

9% for Magnevist

Saline (control): 17% AE

Post Marketing survey: 0.05%

Shellock FG et al. *Invest Radiol.* 2006;41:500-509.

ACR: Safe MR Practices 2007

According to the ACR *Manual on Contrast Media*, adverse events after the intravenous injection of gadolinium seem to be more common in patients who had previous reactions to an MR contrast agent.

In one study, 16 (21%) of 75 patients who had previous adverse reactions to MR contrast agents reacted to subsequent injections of gadolinium.

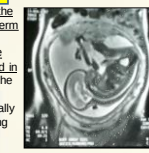
Patients with asthma seem to be more likely to have an adverse reaction to the administration of a gadolinium-based MR contrast agent

Patients with allergies also seemed to be at increased risk (approx 2 - 3.7 times compared with patients without allergies)

Patients who have had adverse reactions to iodinated contrast media are more than twice as likely to have an adverse reaction to gadolinium (6.3% of 857 patients)

MRI & Pregnancy – Gadolinium

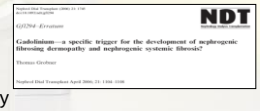
The decision to administer a gadolinium-based MR contrast agent to pregnant patients should be accompanied by a well-documented and thoughtful risk–benefit analysis. This analysis should be able to defend a decision to administer the contrast agent based on overwhelming potential benefit to the patient or fetus outweighing the theoretic but potentially real risks of long term exposure of the developing fetus to free gadolinium ions. Studies have demonstrated that gadolinium-based MR contrast agents pass through the placental barrier and enter the fetal circulation. From there, they are filtered in the fetal kidneys and then excreted into the amniotic fluid. In this location the gadolinium-chelae molecules are in a relatively protected space and may remain in this amniotic fluid for an indeterminate amount of time before finally being reabsorbed and eliminated. As with any equilibrium situation involving any dissociation constant, the longer the chelate molecule remains in this space, the greater the potential for dissociation of the potentially toxic gadolinium ion from its chelate molecule. It is unclear what impact such free gadolinium ions might have if they were to be released in any quantity in the amniotic fluid. Certainly, deposition into the developing fetus would raise concerns of possible secondary adverse effects. The risk to the fetus with administration of gadolinium-based MR contrast agents remains unknown and may be harmful.



It is recommended that pregnant patients undergoing an MR examination provide written informed consent documenting that they understand the potential risks and benefits of the MR procedure to be performed, are aware of the alternative diagnostic options available to them (if any), and wish to proceed.

Gd Nephrotoxicity… yes or no?

- Standard IV use/doses
- Not nephrotoxic (usually)
- Iodinated contrast equivalent doses or IA use for DSA
- Nephrotoxicity has been reported
- Debatable if gadolinium performs better than low osmolar iodinated agents
- Patients in Renal failure .. 1998
- Nephrogenic fibrosing dermopathy
- Nephrogenic systemic fibrosis

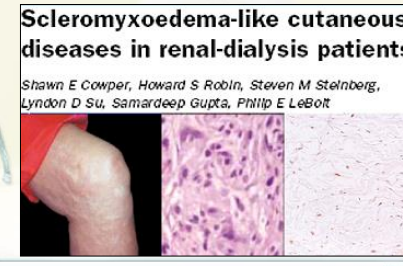

NDT

Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?

Thomas Grobner

Does the Chelate Really Matter?

- A New disease – What is it?
- Findings from …1998


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

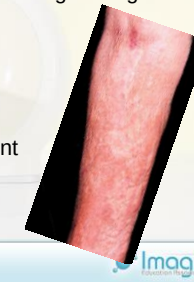
What's in a name?

This disease was…

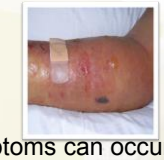
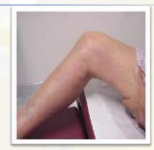
- First described in 1997, in 15 dialyzed patients
- Resembled scleromyxoedema
- So… Miss-labeled at first
- First named …
  - NFD - nephrogenic fibrosing dermopathy (skin)
  - Then … NSF - nephrogenic systemic fibrosis (organ system)
    - Circulating fibrocytes
    - Systemic nature
- Should be diagnosed by skin biopsy…
  - Generally is not…

What are the symptoms?

- After MRI…
  - Skin burning, itching, reddened/darkened patches and/or
  - Inflammation, hardening and/or tightening
- Sclerosing lesions
  - Yellow raised spot of sclera
- Orange peel skin
- Systemic component
  - Joint stiffness
  - Limited peripheral movement
  - Deep hip/rib pain
  - Muscle weakness
  - Sclerosed organs



Nephrogenic Fibrosing Dermapathy (NSF)

Symptoms can occur…
Anywhere from several weeks to 75 days

Sadowski, E. A. et al. Radiology 2007;0:2431062144

Broome DR et al. AJR:188, Feb 2007 586-92

How long until symptoms appear…

- No 'reported' cases before 1997
- No actual link
- 5 of 9 ESRD patients –
  - MRA
  - NSF 2-4 weeks later

NEW LINK?

How long until symptoms appear…

- 2 – 10 weeks after Gd (Omniscan)
- Median onset 11.5 days
- Exposure in 4 cases occurred 16-68 months prior to diagnosis
- 3 cases reported in 2 months

There is no known cure…

- No actual cure
- Treatment helps
- Treat early
- PT
- Photopheresis

How many will likely suffer from NSF…

- 13 Danish patients
- Odds 32.5 of 370 enhanced ESRD patients
- Zero out of non-exposed ESRD

There is no known cure…

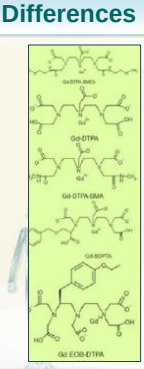
- No actual cure
- Treatment helps
- Treat early
- PT
- Photopheresis

Whose at risk?

- ESRD – highest
  - Peritoneal dialysis higher than
  - Hemo dialysis
- CKD (Chronic Kidney disease) stage 4-5
  - (no dialysis)
- GFR less than 30 ml/min/1.73 m^2
- Other risks
  - acute renal injury
  - Hepato-renal syndrome
  - Perioperative transplant period
  - Neonates and infants under 1 year

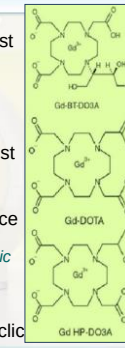
To date…
NO cases have been reported in patients with normal renal function

Differences in Chelates



Optimark
Non-Ionic
Magnevist
Ionic
Omniscan
Non-Ionic
MultiHance
Ionic
Primovist
Ionic
Linear

Gadovist
Primovist
ProHance
Non-Ionic
Macrocyclic



Stability and Transmetalation

Concerns regarding stability of chelates are not new

Desreux JF, Barthélemy PP Int J Rad Appl Instrum B. 1988;15(1):9-15

Corot C, et al. J Magn Reson Imaging. 1998 May-Jun;8(3):695-702

Puttagunta NR, Gibby WA, Puttagunta VL Invest Radiol. 1996 Oct;31(10):619-24

Gibby WA Invest Radiol. 2004 Mar;39(3):138-42

Laurent S, Elst LV, Muller RN Contrast Media Mol Imaging. 2006 May;1(3):128-37

Idée JM, et al. Fundam Clin Pharmacol. 2006 Dec;20(6):563-76

Gd Stability

There are two categories of gadolinium chelates: the macrocyclic molecules where Gd^{3+} is caged in the pre-organized cavity of the ligand and linear molecules. Gadolinium chelates differ in their thermodynamic stability constants and in their kinetic stability. In general, macrocyclic chelates are more stable than linear molecules. Even among linear agents, differences can be found. The lowest stability is reached with Gd-DTPA-BMA and Gd-DTPA-BMEA. Fundam Clin Pharmacol. 2006 Dec;20(6):563-76

REVIEW ARTICLE

Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review

Jean-Marc Idée*, Marc Port, Isabelle Raynal, Michel Schaefer, Sotiri Le Greneur, Claire Corot

ABSTRACT

INTRODUCTION

Stability Measurements

Contrast Agent	Thermodynamic Stability Constant (log K_{eq})	Conditional Stability Constant at pH 7.4
ProHance	**23.8**	**17.1**
Magnevist	**22.1**	**18.1**
MultiHance	**22.6**	**18.4**
Optimark	**16.6**	**15**
Omniscan	**16.9**	**14.9**

Kirchin MA et al. Top Magn Reson Imaging. 2003;14:426-435.

Stability Measurements

Kinetic Stability
(rate of disassociation)

Linear
no molecular charge

Gadolinium chelates	k_{obs} (s^{-1})	$T_{1/2}$
Gd-DTPA-BMA	2.0×10^{-2}	35 s
Gd-DO3A	2.3×10^{-3}	5 min
Gd-DTPA	1.2×10^{-3}	10 min
Gd-HP-DO3A	6.3×10^{-5}	3 h
Gd-DOTA	2.1×10^{-5}	>1 month

Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review

Jean-Marc Idée*, Marc Port, Isabelle Raynal, Michel Schaefer, Sotiri Le Greneur, Claire Corot

Gd in patients with Renal Disease

Radiology. 2003 Jun;227(3):639-46.

Gadodiamide administration causes spurious hypocalcemia.

CONCLUSION: Gadodiamide administration causes spurious hypocalcemia, particularly at doses of 0.2 mmol/kg or higher and in patients with renal insufficiency.

Prince MR, et. al.

Various Gd Agents

Invest Radiol. 2004 Mar;39(3):138-42

Comparison of Gd DTPA-BMA (Omniscan) versus Gd HP-DO3A (ProHance) retention in human bone tissue by inductively coupled plasma atomic emission spectroscopy.

RATIONALE AND OBJECTIVES: Human bone tissue was collected following administration of a clinical dose of gadolinium chelate (0.1 mmol per kg) to patients undergoing hip joint replacement surgery to determine if measurable differences in Gd deposition occur between 2 widely available magnetic resonance contrast agents.

CONCLUSION: Omniscan (Gd DTPA-BMA) left 2.5 times more Gd behind in bone than did ProHance (Gd HP-DO3A).

Gibby WA, Gibby KA, Gibby WA

NSF – Are Agents Equal?

- Published data: frequency of NSF not equal among all agents (Radiology 2008, 10.1148/radiol.2483072093)
- ACR: differences "may reflect a combination of differences in toxicity and market share"
- ACR: Additional risk factors postulated (high dose, repeat dose, severe liver disease, metabolic acidosis, acute pro-inflammatory event) however none are demonstrated consistently
- Repeating theme
  - Highest risk: patients with poor renal function, high dose, repeat doses, linear non-ionic agents
- Currently no NSF cases with MultiHance, ProHance, Eovist, Doterem* or Gadovist* when they were the only agent used

*not available in US

Excess Chelate

- MultiHance (gadobenate dimeglumine) 0.0 mg/mL
- ProHance (gadoteridol) 0.23 mg/mL
- Magnevist (gadopentetate dimeglumine) 0.4 mg/mL
- Omniscan (gadodiamide) 12 mg/mL
- OptiMARK (gadoversetamide) 28.4 mg/mL

Linear no molecular charge

Broome DR et al. *Am J Roentgenol.* 2007;188:586-592.

Differences in Gd Stability

Stability

Agents in the US*

Linear Non-Ionic

Lowest

Gd-DTPA-BEMA

Gd-DTPA-BMA

Macrocyclic Non-Ionic

Highest

Gd-HP-DO3A

Linear Ionic

Gd-DTPA

Gd-BOPTA

Desreux JF, Barthélemy PP: Int J Rad Appl Instrum B. 1988;15(1):9-15

Corot C, et al: J Magn Reson Imaging. 1998 May-Jun;8(3):695-702

Idée JM, et al: Fundam Clin Pharmacol. 2006 Dec;20(6):563-76

* Does not include Eovist - Liver agent w/approx 50% biliary excretion

Gd Stability – What Agents?

Stability is related to the …Affinity…

- Between chelate and Gd
- Of chelate and competing electrolytes
- Dissociation kinetics

Gadolinium Agent	Thermodynamic Stability Constant pH 11.0 (log KF')	Conditional Stability Constant pH 7.4 (log KF')
Magnevist Gadopentatate dimeglumine	22.5	18.4
Prohance Gadoteridol	23.8	17.1
Omniscan Gadodiamide	16.9	14.9
Optimark Gadoversetamide	16.6	15.0
MultiHance Gadobendate dimeglumine	22.6	18.4

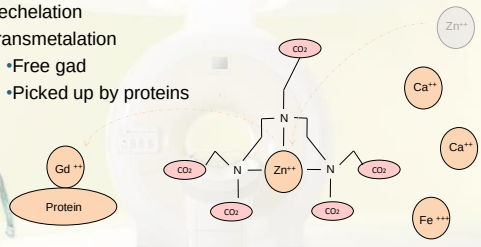
Increasing consensus

- More free Gd
- Longer in system
- Higher risk of NSF

Slide # 66

Safety & Stability… How does it happen?

- Dechelation
- Transmetalation
  - Free gad
  - Picked up by proteins



No ***known*** connection to NSF or NFD by … Transmetalation ***Theories*** that dechelation and/or transmetalation ***may relate*** to NSF

Slide # 67

Minimizing Risk

- Screen patients
  - GFR
  - Scr not good enough
- Reduce Dose / Repeat doses
- Understand the stability of agent used
- Council patients at risk
- Consider alternative imaging

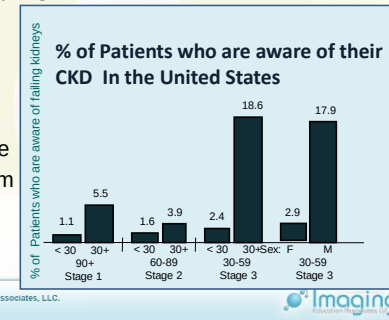
Stages

ESRD - End Stage Kidney Disease = stage 5

Stage	Description	GFR ml/min/1.73 m²	N 1000s	% of US Population
1	Kidney damage with nl or ↑ GFR	≥ 90	5900	3.3
2	Kidney damage with mild or ↓ GFR	60 – 89	5300	3.0
3	Moderate ↓ GFR	30 - 59	7600	4.3
4	Severe ↓ GFR	15 - 29	400	0.2
5	Kidney Failure	< 15 or dialysis	300	0.1

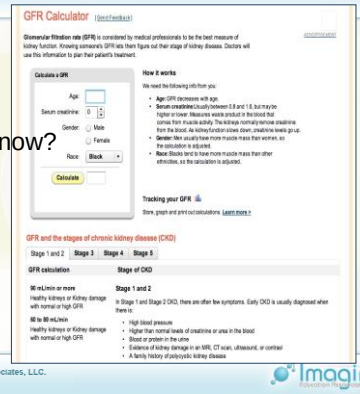
Who Knows about their kidneys?

- National Health and Nutrition Examination Survey Graph by N-HaNES
- Similar unpublished – found same… CCIS Christiana Care Imaging System



eGFR

How do we know?
divita.com



eGFR: iPhone / iPod Touch

MedScape – January 2007

Medscape Today

Medscape Alerts

Use of Gadolinium in MRI and MRA Linked to NSF/NFD in Patients With Renal Failure

Yael Waknine

January 2, 2007 — The US Food and Drug Administration (FDA) warned healthcare professionals last week about additional reports of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD) in patients with renal failure exposed to gadolinium-based contrast agents.

INFORMATION FROM INDUSTRY

EXFORGE ® (amlodipine and valsartan) tablets–
Explore the first and only therapy combining amlodipine and valsartan – the #1 prescribed drugs in their classes.
Important Safety Information. Prescribing Information.

As of December 21, 2006, the agency had received 90 reports of patients with moderate to end-stage renal failure who developed NSF/NFD within 2 days to 18 months after receiving Omniscan (made by Amersham Health, a subsidiary of GE Healthcare), OptiMARK (made by Mallinckrodt, Inc), or Magnevist (made by Berlex Laboratories, Inc) for magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). Some patients had received a high dose of the product, while others had received only 1 dose.

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NFD or NSF – ACR Recommendations

Recommendations:
At this stage, the following guidelines are recommended when considering administering a GBMCA to patients with renal failure/disease:

The development of NSF in patients with renal disease has followed the administration of some, but not all, of the FDA-approved GBMCAs. To date, the development of NSF has been associated with the isolated prior administration of—especially, and clearly predominantly— Omniscan (at rates that exceed those associated with simple market share), but also Magnevist and OptiMARK.

Nevertheless, it is thought to be appropriate to assume for now that a potential association might exist for all five FDA-approved gadolinium-based MR contrast agents until there are more definitive data to suspect otherwise.

At this time, no special treatment or handling is recommended for kidney disease patients with stage 1 or 2 chronic kidney disease (defined as presence of kidney damage with GFR > 90 mL/min/1.73 m2 or GFR between 60 and 89 mL/min/1.73 m2, respectively).

The only exception to this is that patients with any level of renal disease should not receive Omniscan for their contrast-enhanced MR examinations. This is an opinion shared by others [57] and seems prudent for all renal disease patients. Prospectively checking patient renal function, serum creatinine level, or glomerular filtration rate prior to accepting a patient for an MR imaging or angiographic examination is specifically not required.

NFD or NSF – ACR Recommendations

Recommendations:
Prospectively checking patient renal function, serum creatinine level, or glomerular filtration rate prior to accepting a patient for an MR imaging or angiographic examination is specifically not required.

Among the reasons for this is that roughly 90% of NSF patients seem to already be on dialysis and the majority of the remainder seem to be stage 5 or stage 4. Add to this the fact that one could avoid administering any of the agents with which NSF has been most strongly associated, and the fact that even in patients with severe or end-stage renal disease the incidence of developing NSF seems to be around 3–5%. Therefore, specific prospective hematologic screening is not felt to be warranted.

Instead, it is recommended that all requests for MR be prescreened, with an additional question inquiring about the presence of a history of "kidney disease or dialysis." If the disease is present but quite mild (stages 1 or 2), modification of how the study should be performed (relative to a patient with no renal disease) does not appear to be indicated except for the avoidance of Omniscan.

Conversely, if the disease is present and severe or end-stage in nature, the patient will often be aware of this level of kidney disease and will likely be under physician care for this condition.

NFD or NSF – AJKD Recommendations

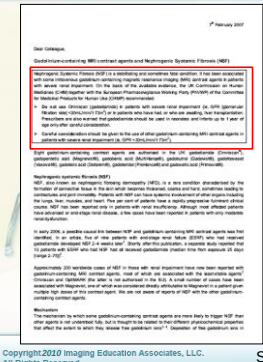
The American Journal of Kidney Diseases states [54]:

"In general, patients with GFR <30 mL/min/1.73 m2 should be referred to a nephrologist."

Thus, selecting patients with a GFR threshold of roughly 30 mL/min/1.73 m2 or already on dialysis (i.e., stages 4 and/or 5) as the level for which special consideration (including possibly hemodialysis) should be given, might represent a medically reasonable approach to, and compromise on, this issue. For patients with stage 3 CKD, the potential risks associated with withholding an MR imaging or angiographic examination could outweigh the potential risk of developing NSF, given the very few number of patients with putative GFR < 60 mL/min/1.73 m2 who have been reported to have developed NSF. Further data are clearly needed to clarify the potential risk for stage 3 CKD patients given the few cases reported and the large number of patients with stage 3 CKD and who are predominantly older than age 70 who would be affected.

Should a new diagnosis of NSF be made, it is recommended that the FDA be notified through their MedWatch program (http://www.fda.gov/medwatch/) [11] or by phone (1-800-FDA-1088), and that the international NSF registry at Yale University be notified as well (http://www.icnfdr.org) [39] to ensure that each database is kept as current as possible on this rapidly changing environment.

ISMRM Recommendations



Slide # 77

Public Health

Public Health Link

Print | Home | Back | Download Attachment

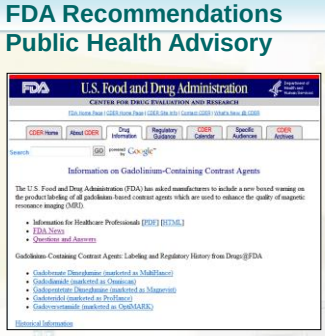
To: MHRA Drug Alerts
NHS Trusts - Medical Directors (England)
NHST/FT/007 - NHS FOUNDATION TRUSTS (ENGLAND) - MEDICAL DIRECTOR
Primary Care Trusts - Directors of Public Health
Primary Care Trusts - Medical Directors
Public Health Link
Cc (Groups): Chairman - Professional Executive Committee of PCT
Regional Directors of Public Health
Strategic Health Authorities (England) - Directors of Public Health
Territorial CMOs
Fax To:
From: Professor Gordon Duff - Chairman of the Commission on Human Medicines
Date: 26 June 2007

Reference: CEM/CMO/2007/14
Category: NON URGENT (cascade within 48 hours)

Title: GADOLINIUM-CONTAINING MRI CONTRAST AGENTS AND NEPHROGENIC SYSTEMIC FIBROSIS (NSF) - UPDATE

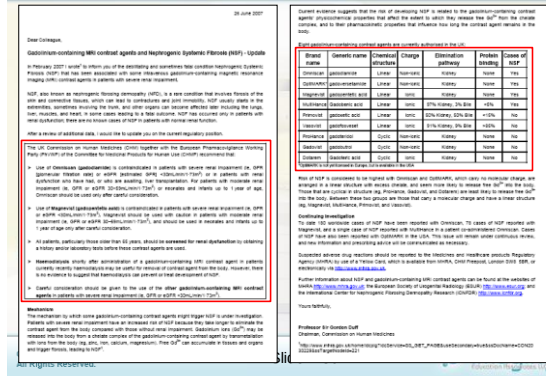
Slide # 78

FDA Recommendations Public Health Advisory



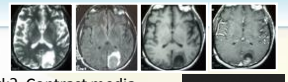
Slide # 79

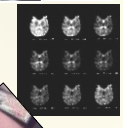
Outside of the US

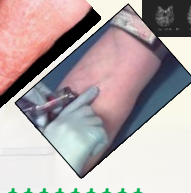


Outline

- MR Image Contrast
  - What's bright on MR?
  - What makes it Bright? Or Dark? Contrast media
- Safety Considerations
  - What do the guidelines say?
  - What about reactions?
  - What about NSF?
- Dose and Administration
  - How much?
  - Is it safe to do that?
- Indications
  - When do we want it bright?
  - How bright do we want it?
- The bottom line
  - What does it cost?







$$$$$$$$$

Slide # 81

Imaging

Contrast Media Safety in MRI

Thank you for your attention!

Carolyn Kaut Roth, RT (R)(MR)(CT)(M)(CV) FSMRT, MRSO
CEO, Imaging Education Associates LLC
www.imaginged.com candi@imaginged.com