Safety of Extracellular Water-soluble Gadolinium Based Contrast Agents (GBCA)

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Safety of GBCA

• Chemical nature and types of GBCA
• Adverse reactions to GBCA
  • Classification
  • Incidence
  • Risk factors
  • Prevention and management
GDBCs are chelated Gd ions. Gd+++ is responsible for enhancing the MRI signals but it is very toxic, to avoid its toxic effect it has to be strongly bound in a chelate while it is inside the body.
GBCA

Chelate

Linear

Macrocyclic

Gd

GBCA
GBCA

**Ionic**

- **Linear**
  - Gd-DTPA
  - Ionisk lineært Gd kompleks

- **Cyclic**
  - Gd-DOTA
  - Ionisk makrocyklisk Gd kompleks

**Non-ionic**

- **Linear**
  - Gd-DTPA-BMA
  - Non-ionisk lineært Gd kompleks

- **Cyclic**
  - GdHP-DO3A
  - Non-ionisk makrocyklisk Gd kompleks
GBCA, Linear Ionic

- Gadopentetate dimeglumine, Magnevist
- Gadobenate dimeglumine, MultiHance
- Gadoxetic acid disodium, Eovist/Primovist (for liver imaging)
- Gadofosveset trisodium, Ablavar (blood pool agent)
GBCA, Linear Nonionic

- Gadodiamide, Omniscan
- Gadoversetamide, OptiMARK
GBCA, Macrocyclic

- Gadoterate meglumine, Dotarem, macrocyclic, ionic
- Gadoteridol, ProHance, macrocyclic, nonionic
- Gadobutrol, Gadovist, macrocyclic, nonionic
Important physicochemical features that influence the safety of GBCA

• **Stability** of the GBCA complex and propensity to release free Gd
  
  » The most important safety aspect of Gd-CM particularly in patients with reduced renal function

• **Osmolality and Viscosity**
  
  » Not crucial as the volume of GBCM injected is small (<40ml) in most applications
Stability of GBCA

– Macroyclic chelate offers a better protection and binding to Gd+++ in comparison to the linear structure

Morcos SK, Br J Radiol, 2007; 80: 73-76
Macro cyclic Chelate

- Macro cyclic
  - Pre-organised
  - Rigid ring
  - Near optimal size to cage Gd^{+++}
For the Gd+++ to break free from a macrocyclic chelate simultaneously must break 5 to 6 coordination sites.
Linear Chelate

- Linear
  - Open chains
  - Flexible
  - Fold and unfold easily over the Gd ion
Gd can break free easily from the linear chelate as the separation occurs sequentially.

Stability of GDBC

Ionicity

- Non-ionic linear chelates are less stable than ionic ones
  - Replacement the negatively charged carboxyl groups by neutral non ionic groups weaken the grip of the chelate to Gd+++  

Morcos SK, Br J Radiol, 2007; 80: 73-76
In the non-ionic linear chelate the carboxyl groups are reduced to 3 as the other two carboxyl groups have been replaced by non ionic methyl amide

The amide has a weaker binding to Gd+++ in comparison to the negatively charged carboxyl groups

Decrease the grip of the chelate on the Gd atom
Stability of GBCA

- Macroyclic
- Ionic linear
- Non-ionic linear
Classification of Adverse Reactions to GBCA

1. Acute non-renal adverse reactions
   - Urticaria
   - Vomiting
   - Hypotension
   - Vagal reaction
   - Anaphylcatoid-like reaction
   - Larynx edema
   - Bronchospastic reaction

2. Acute renal adverse reactions
   - Contrast induced nephropathy

3. Site reactions

4. Delayed or late adverse reaction (NSF)
- Acute adverse reactions
  - Incidence
  - Risk factors
  - Prevention and management
Incidence of Acute Reactions to Gd-CA

• A survey of 78,353 injections (from 2001 to 2006) in Ann Arbor, Michigan, USA
  – Incidence of all reactions was (54 injections) **0.07%**
    • Mild  74% (40 injections)  (0.05%)
    • Moderate  19% (10 injections)  (0.01%)
    • Severe  7% (4 injections)  (0.005%)

Incidence of Acute Adverse Reactions to GBCAs

- A survey of 825,535 injections in the USA
  - Incidence of reactions was very low

<table>
<thead>
<tr>
<th>GBCA</th>
<th>Magnevist</th>
<th>Omniscan</th>
<th>ProHance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of injections</td>
<td>687,255</td>
<td>74,275</td>
<td>64,005</td>
</tr>
<tr>
<td>Mild</td>
<td>0.016%</td>
<td>0.016%</td>
<td>0.077%</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.004%</td>
<td></td>
<td>0.047%</td>
</tr>
<tr>
<td>Severe</td>
<td>0.001%</td>
<td></td>
<td>0.017%</td>
</tr>
</tbody>
</table>

Murphy KP et al, Acad Radiol 1999, 6:656-664
Efficacy and safety of macrocyclic agents: Dotarem

• A review of efficacy and safety of Dotarem in 24,308 patients in Germany from January 2004 to October 2005

• Adverse events were reported in only 0.04% of cases

• The vast majority were mild events

• Only one severe reaction (anaphylactic shock) but the patient recovered

Efficacy and safety of macrocyclic agents: Dotarem

- A recent large study of 84,621 patients

- Adverse events (e.g., nausea, vomiting, and urticaria) were observed in 0.34% of the examinations and were mostly rated as minor.

- There were 8 patients (0.009%) with serious adverse events

Maurer M et al, Eur J Radiol 2012;81:885-90
Efficacy and safety of macrocyclic agents: Gadovist
review of 14,299 patients

Seventy-eight of the 14,299 patients (0.55%) reported at least one ADR. The most frequently reported ADR was nausea, which occurred in 36 patients (0.25%).

Two (0.01%) serious ADRs were reported.

Safety of macrocyclic agents: ProHance

Assessment of Adverse Reaction Rates during Gadoteridol-enhanced MR Imaging in 28,078 Patients

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Mark E. Lockhart, MD, MPH
Beth Winningham, RT
David N. Bolus, MD

| Purpose: | To determine adverse reaction rates in a tertiary care clinical setting after adoption of gadoteridol as the institutional routine magnetic resonance (MR) imaging contrast agent. |
| Materials and Methods: | With institutional review board approval, informed consent waiver, and HIPAA compliance, a prospective observational study of 28,078 patients who underwent intravenous administration of gadoteridol was conducted. |
Overall reaction rate was 0.666% (187 patients), including 177 mild, six moderate, and four severe reactions.

**Conclusion:**

The observed adverse reaction rate to gadoteridol was lower than previously reported. Specifically, the rate of nausea (0.530%) was less than half the rate (1.4%) in clinical trials of 1251 patients, leading to FDA approval in 1992. Rates of adverse reactions for this macrocyclic contrast agent are comparable to those published for linear gadolinium-based contrast agents.
A retrospective study evaluated 158,796 GBCA injections.
Conclusion

- GBCA are safe with low incidence of acute adverse reactions (0.06%)

- Incidence of serious reaction was rare, around 1 in 40,000

- Possibility that non-ionic linear GBCA and gadopentate dimeglumine may have fewer adverse events compared with gadobenate dimeglumine
Immediate Hypersensitivity Reaction to Gadolinium-based MR Contrast Media

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Min-Hye Kim, MD
Whal Lee, MD, PhD
Kyung-Up Min, MD, PhD
Moon-Hee Han, MD, PhD
Sang-Heon Cho, MD, PhD

**Purpose:**
To determine the incidence and risk factors of immediate hypersensitivity reactions to gadolinium-based magnetic resonance (MR) contrast agents.

**Materials and Methods:**
Institutional review board approval and a waiver of informed consent were obtained. A retrospective study of patients who had been given gadolinium-based MR contrast media between August 2004 and July 2010 was performed by reviewing their electronic medical records. In

Jung JW et al, Radiology 2012; 264: 414-422
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of incidences</td>
<td>112/141 623 (0.079)</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>93 (83.0)</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (7.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>11 (9.8)</td>
</tr>
</tbody>
</table>

Jung JW et al, Radiology 2012; 264: 414-422
Jung JW et al, Radiology 2012; 264: 414-422
Limitations

- **Retrospective**, not suitable for comparing incidence of reactions amongst different GBCAs

- **No difference** in the incidence of acute reactions was established amongst different types of GBCAs through prospective studies
Incidence of Acute reactions with MultiHance and Magnevist

Adult, parallel group studies
- MultiHance 10.9%
- Magnevist 7.9% (p = 0.21)

Adult, crossover studies
- MultiHance 8.0%
- Magnevist 8.5% (p = 0.84)

Pediatric study
- MultiHance 12.9%
- Magnevist 14.6% (p = 0.75)

Most adverse reactions were minor, transient, and self-limiting

Similar incidence of adverse reactions between MultiHance and Magnevist

Adverse reactions to ICM and Gd-CA

From 2002 to 2006, a total of 456,930 contrast doses (298,491 low-osmolar iodinated, 158,439 gadolinium) in a single centre

A total of 522 cases of adverse effects (0.11% of total) were identified (458 (0.15%) low-osmolar iodinated, 64 (0.04%) gadolinium)

Hunt CH et al, AJR 2009; 193:1124–1127
STUDY CONCLUSION

• Both ICM and GBCA are associated with a very low rate of adverse effects.

• Most adverse effects were mild

• A higher incidence was observed with ICM

Hunt CH et al, AJR 2009; 193:1124–1127
## Incidence of Acute Reactions to ICM (LOCM & HOCM) and GBCA

<table>
<thead>
<tr>
<th>Contrast Agent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOCM</td>
<td>5-15%</td>
<td>2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>LOCM</td>
<td>1-3%</td>
<td>0.2%</td>
<td>0.04%</td>
</tr>
<tr>
<td>GBCA</td>
<td>0.05%</td>
<td>0.01%</td>
<td>0.005%</td>
</tr>
</tbody>
</table>

Katayama et al, Radiology 1990; 175: 621-628
Dilman J et al, AJR 2007; 189: 1533-1538
Summary

Acute Adverse Reactions to
GBCA

• General safety is excellent with overall incidence of acute reaction $< 1\%$
• Lower incidence in comparison to ICM
• Majority are mild and usually self-limiting
• A small number of patients require medical management
• No important difference in the incidence of acute reactions amongst GBCAs
Risk Factors

- Previous moderate or severe reaction to CM (ICM or GBCA)
- Asthma
- Allergy requiring medical treatment

ADRs increase by at least a factor of 3-4

Dilman J et al, AJR 2007; 189: 1533-1538
ACR Manual on Contrast Media, version 6, 2008
Prevention and Management

• Identify patients at risk
  − Avoid CM administration unless it is deemed crucial for the patient’s management
  − Patients with a history of serious previous CM reaction, use a different contrast agent
  − Careful observation for at least 30 minutes
  − Be prepared to treat any reaction
Management of Acute Reactions

www.esur.org
GBCA
Acute renal adverse reactions
"Contrast induced nephropathy"
Several reports erroneously recommended the use of GBCA for X-ray examinations in patients with significant renal impairment to avoid nephrotoxicity.
• GBCAs are more nephrotoxic than iodinated contrast media at
  • Equi-molar concentration
  • Equivalent X-ray attenuating doses

Nyman et al, Radiology 2002; 223: 162-166
GBCA are nephrotoxic

Incidence of CIN with GBCA

- Digital Subtraction angiography with 0.27 to 0.42 mmol/kg Gd-DTPA: 9.5%
- MR-angiography with 0.31 to 0.41 mmol/kg Gd-DTPA: 1.9%
- Dialysis in 40%

Sam II AD et al J Vasc Surg 2003
The use of GBCA for radiographic examinations is not recommended to avoid nephrotoxicity in patients with renal impairment since they are more nephrotoxic than iodinated contrast media in equivalent X-ray attenuating doses.
Delayed or late adverse reaction to GBCA

Nephrogenic Systemic Fibrosis (NSF)
Clinical Picture

- Scleroderma like skin lesions which are painful
- Flexion contractures of joints
- Fibrosis may also affect liver, lung, heart, muscles
Patients at risk of NSF

- Patients with CKD (GFR \( \leq 30\text{ml/min} \))
- Patients on dialysis
- Patients suffering from acute renal failure
NSF and GBCA
Clinical Data

- **Onset**: in the majority a few days to 3 months after receiving certain types of GBCA
- **Dose**: range 18ml-50ml
- **Incidence** amongst patients with ESRD who exposed to low stability GBCA ~ 5%

Markmann P et al, JASN 2006
Thomsen, Dawson, Morcos, Clin Radiol 2006; 61: 905-906
Thomsen H, Eur Radiol 2006; 16: 2619-2621
Epidemiology of NSF
Published Case Reports

- Up to October 2009 in peer-reviewed literature
  - Omniscan: 347 patients
  - Magnevist: 89 patients
  - OptiMark: 5 patients
  - Unspecified Gd-CM: 151 patients
  - Gadovist: one patient
The high prevalence of NSF with low stability agents suggests that the stability is an important factor in the pathogenesis of NSF
Pathophysiology

Importance of the stability of GBCAs

– The kidney is the main route of elimination of Gd-CM and **biological half life** in presence of normal renal function is around **90 minutes**.

– In patients with renal impairment **biological half life** is prolonged (**30 hr or more**) increasing the possibility of **transmetallation** of low stability Gd-CM with endogenous ions and release of free Gd ions

– Released Gd ions may deposit in tissues and cause fibrosis
TRANSMETALLATION
Linear chelates
TRANSMETALLATION
MACROCYCLIC CHELATES
Courtesy Prof RN Muller (Mons, Belgium)
In December 2007, the Scientific Advisory Group (SAG) for Diagnostics of the CHMP was convened to discuss the approach of the PhVWP. The SAG agreed with the PhVWP that the risk of developing NSF depends on the type of gadolinium-containing contrast agent used, and advised that these agents should be categorised into three groups:

- **high risk:** gadoversetamide (OptiMARK), gadodiamide (Omniscan) and gadopentetic acid (Magnevist, Magnegita, and Gado-MRT-ratiopharm);
- **medium risk:** gadofosveset (Vasovist), gadoxetic acid (Primovist) and gadobenic acid (MultiHance);
- **low risk:** gadoteric acid (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist).
Prevention of NSF

Identify the high-risk patients BEFORE CM administration
Identifying patients with CKD

– Serum Cr measured routinely before contrast injection [mandatory before the use of high risk GBCA]

or

– Selective measuring of Sr Cr using a questionnaire (history of renal disease, proteinuria, prior kidney surgery, hypertension, gout or diabetes mellitus)

Morcos SK, Clin Radiol 2004; 59: 381-389
Evaluate Renal Function Before CM Administration

Estimated GFR (eGFR)

» Cockcroft-Gault equation

\[
GFR = \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{72} \times \text{sr Cr (mg/dL)} \times (0.85 \text{ for females})
\]

Or

» Modification of Diet in Renal Disease study “MDRD” equation

\[
GFR = 170 \times [\text{sr Cr}]^{-0.999} \times [\text{age}]^{-0.176} \times [0.762 \text{ for females}] \times [1.180 \text{ if patient is black}] \times [\text{sr urea nitrogen}]^{-0.170} \times [\text{albumin}]^{+0.318}
\]

eGFR < 30ml/min is a risk factor for NSF
Identifying patients with renal impairment

*Remember!*

- Patients with **acute renal failure** may have initially **normal serum Cr**. These patients should be judged on clinical ground [ITU patients, multiple trauma and hypotension, severe infection, acute heart failure]

- Patients with **low body mass** may have **normal serum Cr** in spite of marked reduction in GFR
Prevention of NSF

- Patients with GFR \( \leq 30 \text{ml/min} \) including those on dialysis should not receive non-ionic linear chelates or Magnevist

- The most stable GBCA should be used in these patients (macrocyclic GBCA)

- The lowest possible dose
- Allow at least one week before giving more GBCA

- Patients on haemodialysis can be scheduled to have the dialysis session shortly after the MRI examination

- Patients on peritoneal dialysis should be asked to do several rapid exchanges after the examination
ESUR Guidelines on NSF

Patients at risk of NSF

- Patients with CKD (GFR ≤ 30ml/min)
- Patients on dialysis
- Patients suffering from acute renal failure
ESUR Guidelines on NSF

• Do not use in patients at risk of NSF
  • Omniscan
  • Magnevist
  • OptiMark
In High Risk Patients

- Use a GBCA with high stability
- Give the lowest dose possible to achieve a diagnostic examination
- Allow at least one week before giving more GBCA

Note:
Do not deny at risk patients clinically important MR examinations
NSF; a complication that could be avoided
Animal Data

• Injection of Gd-CAs in rats with reduced renal function (5/6 subtotal nephrectomy)

• Omniscan induced skin lesions but no dermatological changes were observed with Dotarem

Haylor J et al, Radiology 2012
263: 107-116
Histological changes after Omniscan. No histological response following exposure to Dotarem.

4 weeks post exposure to GBCA
Tissue Gadolinium Retention
Dotarem vs Omniscan

Gd concentration in serum
Omniscan (8.8 nmol/g), Dotarem (2.02 nmol/g)
GD Deposition in rat skin (Omniscan)

Extracellular Gadolinium Hotspots
Intracellular Gd (fibroblast)

Intracellular Gd hotspots
Skin Gadolinium Following Use of MR Contrast Agents in a Rat Model of Nephrogenic Systemic Fibrosis

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Josef Schroeder, PhD
Bart Wagner, BSc
Faith Nutter, BSc
Gaëlle Jestein, BSc
Jean-Marc Idée, PhD
Sameh Morcos, FRCP

Purpose:
To detect the ultrastructural site of gadolinium retention in skin by using an animal model of nephrogenic systemic fibrosis and compare a linear, low-stability gadolinium chelate (formulated gadodiamide) with a macrocyclic, high-stability gadolinium chelate (gadoterate meglumine).

Materials and Methods:
Experimental procedures were performed according to rules and regulations laid down by the UK Home Office (Animal Procedures Act of 1986). Male Wistar rats were subjected to 5/6 subtotal nephrectomy (creatinine clearance, 25% normal). Gadolinium-based contrast agents, formulated gadodiamide (n = 9) and gadoterate meglumine (n = 11), were administered intravenously (2.5 mmol/kg
CLINICAL DATA
At the centre which reported the largest series of cases with NSF:

Since they have stopped gadodiamide in March 06 and switched to a macrocyclic MRI-CM they have not seen a single new case of NSF

Thomsen et al, ACTA Radiologica 2007
Risk for Nephrogenic Systemic Fibrosis with Gadoteridol (ProHance) in Patients Who Are on Long-Term Hemodialysis

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Division of Nephrology, Veterans Affairs North Texas Health Care System and University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

Background and objectives: Recent studies strongly link nephrogenic systemic fibrosis to gadolinium administration for magnetic resonance imaging. In a recent advisory, the Food and Drug Administration stated that all gadolinium-containing chelates are potentially associated with nephrogenic systemic fibrosis; however, most reported cases are linked to gadodiamide (Omniscan) and gadopentetate dimeglumine (Magnevist). Given the severe consequences of nephrogenic systemic fibrosis, it is critical to define the risks associated with each gadolinium-containing chelate. The purpose of this study was to examine nephrogenic systemic fibrosis risk in a hemodialysis population exposed to gadoteridol (ProHance).

Design, setting, participants, & objectives: Appointment logs were used to generate a database of all long-term hemodialysis patients at the Dallas Veterans Affairs since August 2001. These patients were then examined in the Veterans Affairs electronic medical record system for gadolinium exposure during magnetic resonance imaging from 2000 through 2007, a period during which gadoteridol was the sole contrast agent used.

Results: A total of 141 patients were identified with 198 gadoteridol exposures. No cases of nephrogenic systemic fibrosis were identified. The observed frequency of nephrogenic systemic fibrosis was compared with the expected frequency (2.4%) using one-way $\chi^2$ and binomial analysis, yielding a $P < 0.05$, indicating that the result was not explained by chance alone.

Conclusions: It is concluded that the risk for nephrogenic systemic fibrosis with gadoteridol in patients who are on long-term hemodialysis may be lower than with gadodiamide and gadopentetate dimeglumine.


No cases of NSF were identified in dialysis patients who received ProHance
A recent study documented that no cases of NSF were seen in 135 patients with advanced renal impairment (GFR $\leq 30$ ml/min) who received the ionic macrocyclic agent Dotarem between July 05 to July 06.

Janus N et al., (The FINEST study)
Eur J Radiol 2010;73:357-359
THANK YOU FOR YOUR ATTENTION
لا تيأس النصر قادم