Teaching Module IV
Nephrogenic Systemic Fibrosis (NSF)
Delayed adverse reactions to GBCA

Nephrogenic Systemic Fibrosis

This slide deck was prepared by:

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Learning objectives

• General considerations on GBCA
• Delayed adverse reactions to GBCA
• Update knowledge on NSF
• Physicochemical properties of GBCA
• Guidelines and recommendations
Gadolinium-based contrast agents (GBCA)

- Supposed to be very safe in general

- No deterioration of renal function in early studies with the standard dose of 0.1 mmol/kg

- CE-MRI studies preferred in patients with renal dysfunction

- Bold off-label applications in MRA and myocardial viability studies
## GBCA in clinical use

<table>
<thead>
<tr>
<th>Gd chelate (trade name)</th>
<th>Body regions approved</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate dimeglumine (Magnevist®)</td>
<td>CNS, whole body</td>
<td>EU, USA, Jap</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan®)</td>
<td>CNS, whole body</td>
<td>EU, USA, Jap</td>
</tr>
<tr>
<td>Gadoterate meglumine (Dotarem®)</td>
<td>CNS, whole body</td>
<td>EU, Jap</td>
</tr>
<tr>
<td>Gadoteridol (Prohance®)</td>
<td>CNS, whole body</td>
<td>EU, USA, Jap</td>
</tr>
<tr>
<td>Gadobutrol (Gadovist®, Gadavist®)</td>
<td>CNS, liver, kidney</td>
<td>EU, USA</td>
</tr>
<tr>
<td>Gadobenate dimeglumine (MultiHance®)</td>
<td>CNS, liver, angio</td>
<td>EU, USA</td>
</tr>
<tr>
<td>Gadoversetamide (OptiMARK®)</td>
<td>CNS, liver</td>
<td>EU, USA</td>
</tr>
<tr>
<td>Gadoxetic acid disodium (Primovist®, Eovist ®)</td>
<td>Liver</td>
<td>EU, USA, Jap</td>
</tr>
<tr>
<td>Gadofosveset (Vasovist®, Ablavar ®)</td>
<td>Vessels (abd., limbs)</td>
<td>(EU), USA</td>
</tr>
</tbody>
</table>
MR contrast agents safety considerations

• Same acute non-renal adverse reactions as Iodine based CM, but less frequent

• Nephrogenic systemic fibrosis (NSF)

• Nephrotoxicity
Nephrogenic Systemic Fibrosis (NSF)

NSF affects patients with advanced or acute renal insufficiency

- Scleroderma like skin lesions
- Flexion contractures of joints
- Fibrosis may also affect liver, lung, heart, muscles
Clinical presentation of NSF

- Skin lesions
  - Erythematous papules, brownish plaques
  - Symmetric distribution of the limbs
  - Peau d’orange
  - Thickening of cutis – “woody texture”

- Pain

- Pruritus

- Burning sensation (neuropathic pain)

- Large variations in clinical presentations varying from a single plaque to severe disability and death
NSF
Histopathologic findings in NSF

• Gold Standard = deep skin biopsy

• Cells resembling fibroblasts
  • CD 34 and procollagen I positive
  • TGF-β1 expression

• Thickened, chaotic collagen bundles

• The histological picture varies with the duration of the disease.
Prevalence

• Based on visual inspection ~18% after Omniscan
• Based on patients records ~5% after Omniscan

• Macrocyclic agents ~0%
Prognosis of NSF

• Natural history - not well understood

• Sometimes slight improvement in mobility

• Complete spontaneous healing in patients with ongoing kidney disease has not yet been reported

• 5% or less have an exceedingly rapid progressive disease course that may result in death
NSF and GBCA

• Strong evidence of GBCA triggering NSF

• Mostly affect patients with severe renal insufficiency (grade 4 and 5) i.e. eGFR < 30 mL/min per 1.73 m² or ARF

• Higher incidence of NSF with multiple administrations of GBCA

• NSF has been almost exclusively associated with the use of linear GBCA

• Proinflammatory or profibrotic conditions may act as cofactors
Stability of GBCA is an important factor in the pathogenesis of NSF

*In vitro* and *in vivo* studies

Linear GBCA are less stable compared to macrocyclic agents
• Thermodynamic stability ($K_{\text{therm}}$) – describes affinity of Gd for the ligand at pH 14

• Conditional stability ($K_{\text{con}}$) – describes equilibrium considering all protonated forms of the ligand at pH 7.4

• Variable amounts of free ligands or calcium complexes in some agents to ensure chelation of any free Gd$^{3+}$
GBCA – Stability

- Kinetic stability describes speed of dissociation
- Assessed by measuring dissociation half-life under acidic conditions
Non-ionic molecules are thermodynamically less stable in comparison to ionic chelates.

\[ [K_{\text{con}}] \]

- Gadoversetamide (Optimark) non-ionic (15.0)
- Gadodiamide (Omniscan) non-ionic (14.9)
- Gadoteridol (ProHance) non-ionic (17.1)
- Gadobutrol (Gadovist) non-ionic
- Gd-DTPA (Magnevist) ionic (18.1)
- Gadobenate (MultiHance) ionic (18.4)
- Gd-DOTA (Dotarem) ionic (18.8)
GBCA - Stability

- $K_{\text{therm}}$

- Gadoversetamide (Optimark) 16.6
- Gadodiamide (Omniscan) 16.9
- Gd-DTPA (Magnevist) 22.1
- Gadobutrol (Gadovist) 21.8
- Gadobenate (MultiHance) 22.6
- Gadoteridol (ProHance) 23.8
- Gd-DOTA (Dotarem) 25.8
• Excess chelates

• Gadoversetamide (Optimark)  28.40
• Gadodiamide (Omniscan)  12.00
• Gd-DTPA (Magnevist)  00.40
• Gadoteridol (ProHance)  00.23
• Gadobutrol (Gadovist)  00.00
• Gadobenate (MultiHance)  00.00
• Gd-DOTA (Dotarem)  00.00
**GBCA - Stability**

**Molecular structure**

- Macrocyclic agents are kinetically much more stable than linear chelates

<table>
<thead>
<tr>
<th>GBCA</th>
<th>Stability</th>
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</thead>
<tbody>
<tr>
<td>Gadoversetamide (Optimark)</td>
<td>Linear</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>Linear</td>
</tr>
<tr>
<td>Gd-DTPA (Magnevist)</td>
<td>Linear</td>
</tr>
<tr>
<td>Gadobenate (MultiHance)</td>
<td>Linear</td>
</tr>
<tr>
<td>Gadobutrol (Gadovist)</td>
<td>Cyclic</td>
</tr>
<tr>
<td>Gadoteridol (ProHance)</td>
<td>Cyclic</td>
</tr>
<tr>
<td>Gd-DOTA (Dotarem)</td>
<td>Cyclic</td>
</tr>
<tr>
<td>Extracellular Gd-CM</td>
<td>Type</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Gadoversetamide (OptiMark)</td>
<td>Non-ionic linear</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>Non-ionic linear</td>
</tr>
<tr>
<td>Gadopentetate (Magnevist)</td>
<td>Ionic linear</td>
</tr>
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<td>Non-ionic cyclic</td>
</tr>
<tr>
<td>Gadoteridol (ProHance)</td>
<td>Non-ionic cyclic</td>
</tr>
<tr>
<td>Gadoterate (Dotarem)</td>
<td>Ionic cyclic</td>
</tr>
</tbody>
</table>

* pH=1.2, 37°C Port Br J Radiol 2008; 81: 258-259
• Unstable molecules are indicated by:

  • Low $K_{\text{therm}}$ value
  • Low $K_{\text{con}}$ value
  • Low kinetic stability
  • Presence of large amount of excess chelate
  • Linear molecules are less stable compared to macrocyclic agents
  • Non-ionic linear molecules are thermodynamically less stable than ionic ones
Release of gadolinium in serum from GBCA over 15 days

Frenzel et al. Invest Radiol 2008
Release of gadolinium in Serum + phosphate from GBCA over 15 days

Frenzel et al Invest Radiol 2008
NSF and GBCA

• Low stability GBCA are prone to undergo transmellation with endogenous ions leading to the release of free gadolinium.

• Peripherally deposited Gd has fibrogenic effects in tissues.
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

No recent update has been published.
Current guidelines

- FDA
- ACR
- EMA
- ESUR

At last – after 4½ years
In general - all 4 agree
All agree in general (since September 9th 2010)

- *Gadodiamide, gadopentetate dimeglumine and gadoversetamide* are high risk agents and should not be used in patients with GFR < 30 ml/min and only with caution in patients with GFR between 30 and 60 ml/min.

- GFR must always be determined before administration of these agents.

- Lowest possible dose and at least 7 days between injections in patients with GFR between 30 and 60 ml/min.

- Pregnancy: Contraindicated, Lactation: Stop for 24 hr. in Europe
All agree in general (since September 9th 2010)

- For the other GdCA

- Only with caution in patients with GFR <30 ml/min and on dialysis; lowest possible dose; >7 days between 2 injections; Dialysis after injection for patients already on hemodialysis

- GFR determination recommended in risk groups

- Pregnancy: Only in vital indication; Lactation: OK
ESUR Guidelines

• **Patients at higher risk of NSF**
  – Patients with CKD 4 and 5 (GFR < 30ml/min)
  – Patients on dialysis
  – Patients with reduced renal function who have had or are awaiting liver transplantation
ESUR Guidelines

• **Patients at higher risk of NSF**
  – Patients with CKD 4 and 5 (GFR < 30ml/min)
  – Patients on dialysis
  – Patients with reduced renal function who have had or are awaiting liver transplantation

• **Patients at lower risk of NSF**
  – Patients with CKD 3 (GFR 30-59ml/min)
  – Children under 1 year, because of their immature renal function
ESUR Guidelines

• **Patients at higher risk of NSF**
  – Patients with CKD 4 and 5 (GFR < 30ml/min)
  – Patients on dialysis
  – Patients with reduced renal function who have had or are awaiting liver transplantation

• **Patients at lower risk of NSF**
  – Patients with CKD 3 (GFR 30-59ml/min)
  – Children under 1 year, because of their immature renal function

• **Patients not at risk of NSF**
  – Patients with normal renal function
Highest risk of NSF

- **Contrast agents**
  - Gadodiamide (Omniscan®)
  - Gadopentetate dimeglumine (Magnevist®)
  - Gadoversetamide (Optimark®)
Highest risk of NSF

- **Recommendations**
- These agents are **CONTRAINDICATED** in
  - patients with CKD 4 and 5 (GFR < 30 ml/min), including those on dialysis
  - patients with reduced renal function who have had or are awaiting liver transplantation
Highest risk of NSF

- **Recommendations**
- These agents are **CONTRAINDICATED** in
  - patients with CKD 4 and 5 (GFR < 30 ml/min), including those on dialysis
  - patients with reduced renal function who have had or are awaiting liver transplantation
- These agents should be used with **CAUTION** in
  - patients with CKD 3 (GFR 30-60 ml/min)
  - children less than 1 year old
  - Smallest amount, 7 days apart
  - Pregnancy: No
  - Lactation: stop 24 hours
- Serum creatinine (eGFR) measurement before administration: **Mandatory**
Intermediate risk of NSF

- **Contrast agents**
  - Gadobenate dimeglumine (Multihance®)
    - *Special feature:* Similar diagnostic results can be achieved with lower doses because of its 2-3% protein binding.
  - Gadofosveset trisodium (Vasovist®)
    - *Special feature:* It is a blood pool agent with affinity to albumin. Diagnostic results can be achieved with 50% lower doses than extracellular Gd-CM. Biological half-life is 12 times longer than for extracellular agents (18 hours compared to 1½ hours, respectively).
  - Gadoxetate disodium (Primovist®)
    - *Special feature:* Organ specific gadolinium contrast agent with 10% protein binding and 50% excretion by hepatocytes. Diagnostic results can be achieved with lower doses than extracellular Gd-CM.
Low risk of NSF

- **Contrast agents**
  - Gadobutrol (Gadovist®)
  - Gadoterate meglumine (Dotarem®)
  - Gadoteridol (Prohance®)
Intermediate and Low risk of NSF

• **Recommendation**
  - With caution in patients with GFR < 30 ml/min
    - Smallest amount, 7 days apart
    - Pregnancy – only vital indications
    - Lactation – discuss it with the patient
  - Serum creatinine (eGFR) measurement before administration: **Not mandatory**
Recommendations for all patients

• In all patients use the smallest amount of contrast medium necessary for a diagnostic result.
Recommendations for all patients

- In all patients use the smallest amount of contrast medium necessary for a diagnostic result.
- Never deny a patient a clinically well-indicated enhanced MRI examination.
Recommendations for all patients

• In all patients use the smallest amount of contrast medium necessary for a diagnostic result.
• Never deny a patient a clinically well-indicated enhanced MRI examination.
• Always use an agent that leaves the smallest amount gadolinium in the body.
Ethical issue

Don’t go into panic because of NSF
NSF - a complication that could be avoided
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; 48:593-596
Risk for Nephrogenic Systemic Fibrosis with Gadoteridol (ProHance) in Patients Who Are on Long-Term Hemodialysis

Robert F. Reilly

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 gadodia-mide (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 Affair’s 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 gadodia-mide 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 ≤ 30 ml/min) who received the ionic macrocyclic agent Dotarem between July 05 to July 06.

Janus et al., The FINEST study, Eur J Radiol 2009
Thank you!