Toxicity of contrast agents

N. Grenier, Bordeaux
Iodine contrast agents

Iodine atom:
- atomic n° 53
- 3 atoms per benzene structure

Radicals:
- dissociable (ionic): COO-H, COO-Na ou COO-Meglumine
- non dissociable (non-ionic)
Low osmolarity contrast agents (LOCM)

Increase the number of iodine / mol

- 2 molecules for 6 iodine atoms

Decrease the number of particles

- 1 molecule for 3 iodine atoms

\[ = \frac{6}{2} \quad \text{and} \quad = \frac{3}{1} \]
Isosmolar contrast agents (IOCM)

Increase the number of iodine / mol

Nonionic dimer

1 molecule for 6 iodine atoms

= 6/1
## Iodine contrast agents

<table>
<thead>
<tr>
<th></th>
<th>Iodine atoms</th>
<th>Particles</th>
<th>I/P</th>
<th>Osmolality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ionic monomers</strong></td>
<td>3</td>
<td>2</td>
<td>1.5</td>
<td>High osmolality</td>
</tr>
<tr>
<td><strong>Non-ionic monomers</strong></td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>Low osmolality</td>
</tr>
<tr>
<td><strong>Ionic dimers</strong></td>
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<td>2</td>
<td>3</td>
<td>Low osmolality</td>
</tr>
<tr>
<td><strong>Nonionic dimers</strong></td>
<td>6</td>
<td>1</td>
<td>6</td>
<td>Iso- osmolality</td>
</tr>
</tbody>
</table>
Nephrotoxicity of iodine CA

• **Mechanisms**
  
  – direct toxicity
    • cellular toxicity
    • tubular obstruction
    • « osmotic nephrosis »
  
  – ischemia
    • vasoconstriction, in medulla +++
    • mechanisms:
      – alteration of intracellular [Ca],
      – globular aggregation,
      – Release of vaso-active substances (adenosine, endotheline...)

Liss P et al. Acad Radiol 1998
Nephrotoxicity of iodine CA

• **Definition**: «increase of SCr within 3 days following injection of CA without any other cause»:
  - either absolute: > 44µmol/l
  - or relative: > 25%
Nephrotoxicity of iodine CA

- **Incidence:**
  - Low incidence in patients with normal renal function (0-10%)
  - More frequent if renal risk factors (12-27%)
  - 3rd most frequent cause of renal failure in hospitals after hypotension and surgery
  - Increases morbidity and mortality *

* Lévy, JAMA 96

Dangas G et al. Am J Cardiol 2005
Morbidity and Nephrotoxicity of iodine CA

- One year survival without any event

Gruberg et al. JACC 2000; 36: 1542-1548
Nephrotoxicity of iodine CA

- **Risk factors:**
  - pre-existing RF (130 µmol/l)
  - diabetes
  - Nephrotoxic drugs (Ab, NSAI +++)
  - dehydration
  - Cardiopathy with diuretics
  - myeloma
  - age > 70 years

Maximal risk: diabetes and RF +++
Renal risk with preexisting RF and diabetes

McCullough (2003)
Incidence of CIN

- Factors of variation:
  - Definition de la NCI
  - Type of population
    - Out-patients vs in-patients
    - Risk factors
  - Type and duration of follow-up
  - Hydration state
  - Type of CA
  - Doses of CA
  - Route of administration
  - ...

Which incidence after IV injection?

- **Analysis of literature (2006):**
  - 40 about IV injections in humans:
    - 9 showed no effect on renal function
    - 31 showed CIN
  - Only 2 had a control group
  - In-patients +++
  - No preparation

*Rao QA & Newhouse JH, Radiology 2006*
Which incidence after IV injection?

- **Studies after IV injection of LOCM-IOCM**

<table>
<thead>
<tr>
<th>Study and Year of Publication</th>
<th>No. of Subjects*</th>
<th>Agent(s) Used</th>
<th>Criteria for CIN</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalta Paima et al (1982)</td>
<td>8 (all with RI)</td>
<td>Iopamidol</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>Levorstad et al (1982)</td>
<td>34</td>
<td>Iohexol</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>Rankin and Eng (1985)</td>
<td>220</td>
<td>Iohexol</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>McClenman et al (1986)</td>
<td>30</td>
<td>Ioxaglate</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>Spattaro et al (1987)</td>
<td>30</td>
<td>Ioxaglate</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>Cochran et al (1988)</td>
<td>85</td>
<td>Iopamidol</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>Campbell et al (1990)</td>
<td>478 (80 with RI)</td>
<td>Ioxaglate, Iopamidol</td>
<td>0.5 mg/dL Increase in Scr</td>
<td>No difference in Scr increase between three CM</td>
</tr>
<tr>
<td>Harris et al (1991)</td>
<td>51 (all with RI)</td>
<td>Iohexol</td>
<td>&gt; 50% Increase in Scr</td>
<td>CIN in one (2%) subjects</td>
</tr>
<tr>
<td>Moore et al (1992)</td>
<td>250 (&lt;3% with RI)</td>
<td>Iohexol</td>
<td>&gt;33% or 1.4 mg/dL Increase in Scr</td>
<td>CIN in three (1.2%) subjects</td>
</tr>
<tr>
<td>Newhouse et al (1994)</td>
<td>200</td>
<td>Iopromide, Iopamidol</td>
<td>Increase in Scr</td>
<td>No significant change in Scr</td>
</tr>
<tr>
<td>Lundqvist et al (1996)</td>
<td>63 (all with RI)</td>
<td>Iohexol</td>
<td>&gt;25% Decrease in GFR</td>
<td>Nine (14%) subjects with decreased renal function, 12 (19%) subjects with improved renal function</td>
</tr>
<tr>
<td>Carraro et al (1998)</td>
<td>64 (all with RI)</td>
<td>Iopromide, Iodixanol</td>
<td>≥50% Increase in Scr</td>
<td>CIN in no subjects (7 = 32) who received LOCM and in two (3%) of 32 who received IOCM²</td>
</tr>
<tr>
<td>Tepel et al (2000)</td>
<td>83 (41 also received NAC, all had RI)</td>
<td>Iopromide</td>
<td>≥0.5 mg/dL Increase in Scr</td>
<td>CIN in nine (21%) of 42 subjects without NAC</td>
</tr>
<tr>
<td>Luft et al (2002)</td>
<td>33 (all with RI)</td>
<td>Iopentol</td>
<td>&gt;0.5 mg/dL or &gt;25% Increase in Scr</td>
<td>CIN in three (9%) subjects</td>
</tr>
<tr>
<td>Garcia-Ruiz et al (2004)</td>
<td>50 (all with RI)</td>
<td>Iopromide</td>
<td>≥20% Increase in Scr</td>
<td>CIN in two (4%) subjects</td>
</tr>
<tr>
<td>Becker and Reiser (2005)</td>
<td>100 (all with RI)</td>
<td>Iodixanol</td>
<td>&gt;0.5 mg/dL Increase in Scr</td>
<td>CIN in nine (9%) subjects</td>
</tr>
<tr>
<td>Barrett et al (2006)</td>
<td>153 (all with RI)</td>
<td>Iopamidol, Iodixanol</td>
<td>≥0.5 mg/dL Increase in Scr</td>
<td>CIN in no subjects (7 = 77) who received LOCM and in two (3%) of 76 who received IOCM³</td>
</tr>
</tbody>
</table>

*Katzberg & Barrett, Radiology 2007*
Which incidence after IV injection?

- Analysis of literature (2006):
  - Controlled studies
    - Cramer BC et al, Arc Int Med 1985:
      - 193 with contrast (HOCM) and 233 wo contrast
      - $\uparrow$ SCr in 4/193 (2.1%) and 3/233 (1.3%) – NS
      - High risk roup: RF in 0/19 (with CA) and 2/46 (4.3%) (wo CA)

    - Heller CA et al, Med J Aust 1991:
      - 292 with HOCM, 187 with LOCM, 405 wo contrast
      - $\uparrow$ SCr in 12/292 (4%), 23/187(12%) and 16/405 (4%)
Spontaneous changes of SCr in patients with CKD

32,161 patients without administration of CA.
Dosage of SCr during 5 consecutive days

More than 50% of pts showed a spontaneous modification of SCr ≥ 25%

In patients with SCr > 177 µmol/L, increase ≥ 25% → in 16%

Necessity of control groups!

Newhouse JH et al. AJR 2008

Fig. 1—Fraction of patients with threshold creatinine change. Figure shows fraction of patients having relative change in creatinine level at indicated percentages on a specific day versus day 0. Lower thresholds are more likely to be reached, and decreases are more common than increases. Totals sum to more than 100% because higher percentage of change (e.g., 50%) is included in results for lower thresholds (e.g., 15%).
## LOCM vs IOCM with IV injection

<table>
<thead>
<tr>
<th>Study</th>
<th>Competitor</th>
<th>Population</th>
<th>Design</th>
<th>CIN (%)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraro 1998</td>
<td>Ultravist 300</td>
<td>64, SCr ≥ 1.5</td>
<td>Prosp, randomized, open-label, single center</td>
<td>V = 3.1 LOCM = 0</td>
<td>No difference</td>
</tr>
<tr>
<td>Kolehmainen &amp; Soiva 2003</td>
<td>Xenetix 350</td>
<td>50, SCr ≥ 1.5</td>
<td>Prosp, randomized, open-label, multi-center</td>
<td>V = 16 LOCM = 16</td>
<td>No difference</td>
</tr>
<tr>
<td>Barrett 2006 IMPACT</td>
<td>Iopamiro/Isovue 370</td>
<td>153, SCr ≥ 1.5 or CrCl ≤ 60</td>
<td>Prosp, randomized, open-label, multi-center</td>
<td>V = 2.6 LOCM = 0</td>
<td>No difference</td>
</tr>
<tr>
<td>Thomsen 2008 ACTIVE</td>
<td>Iomeron 400</td>
<td>148, SCr ≥ 1.5</td>
<td>Prosp, randomized, open-label, multi-center</td>
<td>V = 6.9 LOCM = 0 (p = 0.02)</td>
<td>LOCM better</td>
</tr>
<tr>
<td>Kuhn 2008 PREDICT</td>
<td>Iopamiro/Isovue 370</td>
<td>248, SCr ≥ 25%</td>
<td>Prosp, randomized, open-label, multi-center</td>
<td>V = 4.9 LOCM = 5.6</td>
<td>No difference</td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>Ultravist 370</td>
<td>117, SCr ≥ 1.5 or eGFR ≤ 60</td>
<td>Prosp, randomized, open-label, single-center</td>
<td>V = 5.1 LOCM = 18.5</td>
<td>IOCM better</td>
</tr>
</tbody>
</table>
Viscosity and physiopathology of CIN

↑ plasmatic viscosity
  ↑ Resistance in vasa recta
  ↓ Perfusion of vasa recta
  ↓ Medullary hypoxia

↑ Viscosity in renal tubules
  ↓ GFR
  ↓ Tubular reabsorption
  ↓ Tubular obstruction
  ↑ renal interstitial pressure
  ↑ tubular lesions
Viscosity and physiopathology of CIN

Seeliger E et al. JASN 2007

Jost G, Invest Radiol 2009
Does that mean....

.... A lot of noise for nothing ?
Nephrotoxicity of iodine CA

• **Incidence:**
  – Probably much lower than expected after IV injection

• **Prevention in risk patients:**
  – Identification of risk patients
  – Search for alternative technique
  – Hydration +++
    • 1-2 ml/kg/h of saline 0.9% or bicarbonate
    • 4-6h before => 12h-24h after
  – Stop all nephrotoxic drugs (24h)
  – Medications:
    • theophylline ?
    • acetylcysteine (Mucomyst) ?
Toxicity of Gd-chelates

• Nephrotoxicity:
  – No nephrotoxicity demonstrated at recommended doses
  – More nephrotoxic than iodine CA at equimolar dose

• Nephrogenic systemic fibrosis
  – In patients with severely impaired renal function
• The world's first NSF case was identified in 1997 in California, USA
• The condition was first reported in the literature in 2000 by Cowper et al
• Initially, the disease was thought to affect only the skin and was given the name Nephrogenic Fibrosing Dermopathy
• The original name was replaced by “Nephrogenic Systemic Fibrosis” when it became clear that the disease affects multiple organs and several tissues

Julluru, Radiographics 2009
History

NDT Advance Access published January 23, 2006

Interesting Case

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

Thomas Grobner
Department of Nephrology, General Hospital of Wiener Neustadt, A-2700 Wiener Neustadt, Austria

Keywords: end stage renal disease; gadolinium-DTPA; metabolic acidosis; nephrogenic fibrosing dermopathy

Fast Track

Nephrogenic Systemic Fibrosis: Suspected Causative Role of Gadodiamide Used for Contrast-Enhanced Magnetic Resonance Imaging

Peter Markmann, Lone Skov, Kristian Rossen, Anders Dupont, Mette Brinnes Damholt, James Goya Heaf, and Henrik S. Thomsen
Department of *Nephrology and ‡Diagnostic Radiology, Copenhagen University Hospital at Herlev, Herlev, Departments of †Dermatology and ‡Pathology, Copenhagen University Hospital at Gentofte, Hellerup, and §Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark

Nephrogenic systemic fibrosis is a rare disease of unknown cause that affects patients with renal failure. Single cases led to the suspicion of a causative role of gadodiamide that is used for magnetic resonance imaging. This study therefore reviewed all of the authors’ confirmed cases of nephrogenic systemic fibrosis (n = 13) with respect to clinical characteristics, gadodiamide exposure, and subsequent clinical course. It was found that all had been exposed to gadodiamide before the development of nephrogenic systemic fibrosis. The delay from exposure to first sign of the disease was 2 to 75 days (median 25 days). Odds ratio for acquiring the disease when gadodiamide exposure was 32.3 (95% confidence interval 1.9 to 549.2; P < 0.001). Seven (54%) patients became severely disabled, and one died 21 months after exposure. No other exposure/event than gadodiamide that was common to more than a minority of the patients could be identified. These findings indicate that gadodiamide plays a causative role in nephrogenic systemic fibrosis.


January 2006
5 patients

July 2006
13 patients
NSF - Clinical findings

NSF cutaneous lesion morphology

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papules</td>
<td>32%</td>
</tr>
<tr>
<td>Plaques</td>
<td>58%</td>
</tr>
<tr>
<td>Nodules</td>
<td>17%</td>
</tr>
<tr>
<td>Erythema</td>
<td>39%</td>
</tr>
<tr>
<td>Induration</td>
<td>78%</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>41%</td>
</tr>
<tr>
<td>Contracture</td>
<td>50%</td>
</tr>
<tr>
<td>Edema</td>
<td>32%</td>
</tr>
<tr>
<td>Blisters/ulcers</td>
<td>2%</td>
</tr>
<tr>
<td>Hair loss</td>
<td>2%</td>
</tr>
</tbody>
</table>

Cowper, Eur J Radiol 08
NSF - Clinical findings

Superficial pink plaques: early sign

Indurated brown plaques: deeper lesions

In progressive NSF, the skin becomes fibrotic with a shiny appearance and subcutaneous tissue is diminished.

Cowper, Eur J Radiol 08
NSF - Clinical findings

Contractures in lower distal extremity

Contractures in upper distal extremity

Prominent yellow scleral plaque

Cowper, Eur J Radiol 08
Clinical findings: outcome

- Severely affected patients are unable to walk
- NSF may cause severe morbidity and even mortality in some patients
- Improvement in a small percentage of patients following recovery of renal function

Mendoza FA. Semin Arthritis Rheum 2003
Jimenez S. Arthritis Rheum 2004
Swartz RD. Am J Med 2003
NSF - Clinical findings

- Differential Diagnosis:

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleromyxedema</td>
</tr>
<tr>
<td>Eosinophilic faciitis</td>
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<tr>
<td>Esinophilia-myalagia syndrome</td>
</tr>
<tr>
<td>Toxic oil syndrome</td>
</tr>
<tr>
<td>Sclerodermoid graft-versus-host disease</td>
</tr>
<tr>
<td>Fibroblastic rheumatism</td>
</tr>
<tr>
<td>B2-microglobulin amyloidosis</td>
</tr>
<tr>
<td>Systemic sclerosis/morphea</td>
</tr>
<tr>
<td>Sclerodermia of Buschke</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Carcinoid syndrome</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Calciphylaxis</td>
</tr>
<tr>
<td>Lipodermatosclerosis</td>
</tr>
<tr>
<td>Dermatofibrosarcoma protuberans</td>
</tr>
<tr>
<td>Melanoma (spindle-cell variant)</td>
</tr>
<tr>
<td>Granuloma annulare</td>
</tr>
</tbody>
</table>

*Thomsen, Eur J Radiol 08*
Histology

Cowper, Eur J Radiol 08
Histology

Thickening of subcutaneous septas

increased spindle cells, thick, pink collagen bundles, and intervening myxoid material (light pink)

Fibrocytes

Immature collagen matrix

Cowper, Eur J Radiol 08
Histology

- **Differential Diagnosis:**

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<td>Melanoma (spindle-cell variant)</td>
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<td>Granuloma annulare</td>
</tr>
</tbody>
</table>

*Thomsen, Eur J Radiol 08*
NSF and renal function

• Facts:
  – Patients with normal or moderate renal failure never develop NSF
  – The risk of developing NSF increases with severity of renal failure
  – Majority of risk patients do NOT develop NSF
  – No age, ethnic or gender preference

• Risk factors:
  – Patients with CKD (GFR < 30ml/min)
  – Patients on dialysis
  – Patients suffering from acute renal failure
  – Patients with hepato-renal syndrome
  – Patients requiring liver transplantation
Gd-chelates

- **Biodistribution of approved agents**
  - These agents are eliminated mainly by the kidney with an exclusive glomerular filtration (same than iodine CA)

---

*Aime S et al, JMRI 2009*
Gd-chelates

- **Pharmacokinetics of approved agents:**
  - Their blood half-life is around 2h when function is normal
  - This half-life can reach 30h to 120h in case of severe renal failure
  - Renal failure increases the exposition of tissues to Gd-chelates
  - Dialysis after injection increase the clearance of these agents

\[
C_p = Ae^{-at} + Be^{-bt}
\]

Aime S et al, JMRI 2009
Physiopathology

• **Possible co-factors of development of NSF:**
  - Repeated and increasing exposition to the CA
  - High blood concentration of phosphate and ionized calcium
  - Hypoalbuminemia
  - Liver insufficiency, particularly before liver transplantation
  - Concomitant pro-inflammatory state
  - Metabolic acidosis
  - Treatment with high doses of erythropoietin

*Hypotheses*
Prevalence

Difficult to know:
- around 3% and 7% in risk patients
- depends on the series
- depends on the type of CA

![Bar chart showing number of cases from 2002 to 2008]
Prevalence

Reported cases:

- Around 500 reported cases but all are not proved
- In publications: 186 « non confounded » cases in 2008
  - 134 with Omniscan
  - 18 with Magnevist
  - 2 with Optimark
  - 1 with Prohance

- Other cases are « confounded »
## Confounded cases

- **Ex: Dotarem**

<table>
<thead>
<tr>
<th>#</th>
<th>Date du rapport</th>
<th>Survenue De la FSN</th>
<th>Produits associés</th>
<th>Pays</th>
</tr>
</thead>
</table>
Gd-chelates

**Macrocyclique**
- **Gd**<sup>3+</sup>
  - DOTA-Gd (Dotarem<sup>R</sup>)
  - HP-DOA3Gd (Prohance<sup>R</sup>)

**Linéaire**
- **Gd**<sup>3+</sup>
  - DTPA-Gd (Magnevist<sup>R</sup>)
  - DTPA-BMA-Gd (Omniscan<sup>R</sup>)

**"Pseudo cyclique"**
- **Gd**<sup>3+</sup>
  - Multihance<sup>R</sup>

Gadovist<sup>R</sup>
Optimark<sup>R</sup>
# Stability of Gd-chelates

## Table 1. Physico-chemical characteristics of clinically available extracellular gadolinium based contrast agents [9, 11]

<table>
<thead>
<tr>
<th>Extracellular Gd-CM</th>
<th>Type</th>
<th>Thermodynamic stability constant</th>
<th>Conditional Stability</th>
<th>Amount of excess chelate (mg/ml)</th>
<th>Kinetic stability (dissociation half life at pH 1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadoversetamide, Gd-DTPA-BMEA (OptiMark, Tyco, USA)</td>
<td>Non-ionic linear</td>
<td>16.6</td>
<td>15</td>
<td>28.4</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadodiamide, Gd-DTPA-BMA (Omniscan, GE, USA)</td>
<td>Non-ionic linear</td>
<td>16.9</td>
<td>14.9</td>
<td>12</td>
<td>35 s</td>
</tr>
<tr>
<td>Gadobutrol, Gd-BT-DO3A (Gadovist, Schering, Berlin)</td>
<td>Non-ionic cyclic</td>
<td>21.8</td>
<td>Not available</td>
<td>Not available</td>
<td>5 min</td>
</tr>
<tr>
<td>Gadoteridol, Gd-HP-DO3A (Prohance, Bracco, Italy)</td>
<td>Non-ionic cyclic</td>
<td>23.8</td>
<td>17.1</td>
<td>0.23</td>
<td>3 h</td>
</tr>
<tr>
<td>Gadopentetate Gd-DTPA (Magnavist, Schering, Berlin)</td>
<td>Ionic linear</td>
<td>22.1</td>
<td>18.1</td>
<td>0.4</td>
<td>10 min</td>
</tr>
<tr>
<td>Gadobenate, Gd-BOPTA, (Multihance, Bracco, Italy)</td>
<td>Ionic linear</td>
<td>22.6</td>
<td>18.4</td>
<td>None</td>
<td>Not available</td>
</tr>
<tr>
<td>Gadoterate, Gd-DOTA (Dotarem, Guerbet, France)</td>
<td>Ionic cyclic</td>
<td>25.8</td>
<td>18.8</td>
<td>None</td>
<td>&gt; 1 month</td>
</tr>
</tbody>
</table>
Physiopathology

• Transmetallation

\[ \text{Gd}^{3+} - L + M \quad \leftrightarrow \quad M - L \]

% of exchange with Zinc in vitro (solv 25 nM)

% Retention in bones at 14 days (Mice, 0.4 mmol/kg)

\[ \begin{array}{c|c|c|c}
\text{Dota-Gd} & \text{Gd} & \text{Gd DTPA} & \text{Gd DTPA - BMA} \\
\text{HP - DO3A} & \text{HP DO3A} & \text{Linear} & \\
\text{Macrocyclic} & & & \\
\end{array} \]

\[ \begin{array}{c|c|c|c}
\text{Dota-Gd} & \text{Gd} & \text{Gd DTPA} & \text{Gd GTPA - BMA} \\
\text{HP - DOA3} & \text{Linear} & & \\
\text{Macrocyclic} & & & \\
\end{array} \]

Tweedle MF Invest. Radiol. 1992; 27:S2-S6
Gd concentration in skin biopsies 5 days after the last injection of Gd-CM
(2.5 mmol/kg IV, 5 times/week X 4 weeks)

Sieber M et al, Invest Radiol 2008; 43: 65-75
and Eur Radiol 2008; 18: 2164-2173
Physiopathology

Skin biopsy showing free gadolinium

Abraham, Eur J Radiol 08
Open Questions

• It is unknown whether Gd deposition results in non-NSF subjects as well, and if so, whether such deposition correlates with impaired renal function.

• In the cases of Gd deposition in NSF patients, it is likely that the Gd is no longer associated with its chelator, but this has still not been definitively shown.

• Is the form of Gd the same in skin deposits compared to internal organs?

• If dechelation occurs, then where does it occur and how is the Gd transported to other organs?
How to reduce the Risk of NSF?

- Patients with GFR<30ml/min including those on dialysis should not receive non-ionic linear chelates or Magnevist.
- The most stable Gd-CM should be used in these patients (macrocyclic Gd-CA).
- The lowest possible dose.
- Allow at least one week before giving more Gd-CM.
- Patients on haemodialysis can be scheduled to have a dialysis session shortly after the MRI examination.
- Patients on peritoneal dialysis should be asked to do several rapid exchanges after the examination.
Recommendations

« black blood »

« white blood » (TOF)
CIN vs NSF

Nephrogenic Systemic Fibrosis Versus Contrast-Induced Nephropathy: Risks and Benefits of Contrast-Enhanced MR and CT in Renally Impaired Patients


Diego R. Martin, MD, PhD,1* Richard C. Semelka, MD,2 Arlene Chapman, MD,3 Harm Peters, MD,4 Paul J. Finn, MD, PhD,5 Bobby Kalb, MD,1 and Henrik Thomsen, MD6,7

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<table>
<thead>
<tr>
<th>Relative Incidence of CIN Versus NSF-Omniscan Versus NSF-Other; Relative Incidence of Mortality Related to CIN Versus NSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN</td>
</tr>
<tr>
<td>Patients at risk                                                   Incidence</td>
</tr>
<tr>
<td>Moderate to severe renal failure (Scr &gt; 1.8 mg/dl)</td>
</tr>
<tr>
<td>(GFR &lt; 60ml/min)</td>
</tr>
<tr>
<td>NSF-Lower Stability Agent (Gadodiamide)</td>
</tr>
<tr>
<td>Severe renal failure (GFR &lt; 15 ml/min)</td>
</tr>
<tr>
<td>NSF-Higher Stability and/or Low Dose Agents</td>
</tr>
<tr>
<td>Severe renal failure (GFR &lt; 15 ml/min)c</td>
</tr>
</tbody>
</table>

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*aLow end of range associated with venous and high end of range arterial administrations.

*bMost studies have shown a 2%–5% risk, but with a more recent report showing that this risk, including milder presentations, may be as high as 18% after gadodiamide administration (51).

*cPresumed as the number of NSF cases remain too small to assess with no peer-reviewed cases yet reported.

« We suggest that in patients with poor renal function, especially those on dialysis, the choice of contrast-enhanced CT or MRI should be based on the expected diagnostic benefits. However, the current evidence shows that stable GBCAs are safer than ICA with this patient population. »
Conclusions

• **Iodine CA:**
  – Nephrotoxicity of CA is probably overestimated with IV injections
  – However, detection of risk patients and prevention must stay the rule

• **NSF:**
  – It is a complication linked to unstable agents which have to be waved in risk patients
  – However, use of Gd injections should be rationalized in these risk patients
ESUR Guidelines on Contrast Media

Contrast Media Safety Committee

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