Diagnostic Imaging Pathways - Contrast Agents: Gadolinium Contrast for MRI Scans

Gadolinium and Nephrogenic Systemic Fibrosis (NSF)

Gadolinium is a rare earth metal which has special paramagnetic properties, making it useful as a contrast agent for MRI scans. The agents can be administered intravenously or orally, and are often used for the enhancement of blood vessels or pathology (e.g. brain tumours).

Nephrogenic Systemic Fibrosis (NSF)

Gadolinium (Gd) containing contrast agents have recently been associated with the development of Nephrogenic Systemic Fibrosis (NSF) and should be used with caution in patients with renal failure pending further study. 6,7,9,10

NSF, formerly known as Nephrogenic Fibrosing Dermopathy (NFD), is a rare scleroderma-like disease characterised by thickening, induration and hardening of the skin with predilection for the distal extremities and occurs only in patients with renal failure (receiving dialysis, particularly peritoneal dialysis or creatinine clearance <20mL/min). Over 400 cases have been recorded since it was originally described in 1997. 12 Proximal involvement of the trunk and abdomen, including internal organs may occur. 1,2 Sparing of the head and face in NSF is a distinguishing feature of NSF along with the absence of typical serological markers associated with scleroderma.

It is postulated that Gd dissociation following contrast administration leads to insoluble Gd salt deposition in the interstitium, which provides a nidus for fibrosis. 16 The different classes of commercially available Gd chelate contrast agents are ionic or non-ionic ligand-binding groups within linear, non-linear or macrocyclic molecules. Since it is postulated that free Gd stimulates NSF, increased dissociation from chelates is thought to increase the risk of NSF. The various classes of clinically available Gd–containing agents have different stabilities, with the macrocyclic agents having the greatest stability and therefore the least likely to cause NSF. (see Table)

Diagnosis is confirmed by deep skin biopsy which demonstrates thickened collagen bundles with surrounding clefts, mucin deposition and proliferation of fibroblasts and elastic fibres. Signs of inflammation are absent histologically. 3 Disability due to limited mobility may occur in up to 58% of patients 4 and NSF has been associated with at least one patient death. 1

The US Food and Drug Administration (FDA) issued a Public Health Advisory warning in June 2006 following a notification by the Danish Health Authority of 25 cases of NSF following gadodiamide exposure. 5 Approximately 1600 cases of NSF have been reported to the US Food and Drug Administration (FDA). 6 Approximately 85% of NSF has been associated with gadodiamide, 13% with gadopentate dimeglumine and few cases with gadoversetamide. 6 In addition, gadolinium has been found to be present in affected tissue specimens of patients with NSF. 7,8

Risk factors and clinical course of NSF

The factor common to all patients developing NSF is renal impairment, especially end-stage kidney
disease. Sensitizing events such as a pro-inflammatory condition (major surgery or vascular events) and unidentified triggers may play a part. Acidosis was implicated in one study of 9 dialysis patients exposed to gadodiamide but was not confirmed in another study of 13 patients with NSF. Cessation of gadolinium administration to patients with renal failure by this group resulted in no new cases of NSF.

Gadolinium exposure has preceded the onset of NSF symptoms by few days to three years with a median interval of 62 days. In 5 percent of cases the course of the disease is rapidly progressive.

Several reports suggest a dose-response relationship.

**Classification of Gd-based contrast agents (GBCAs) and risk of NSF**

The European Medicines Agency has classified GBCAs into high, intermediate and low risk for NSF. The American College of Radiology classifies them according to the number of cases of NSF reported for each agent. This is shown in the Table below (modified from 11).

<table>
<thead>
<tr>
<th>Group</th>
<th>Name</th>
<th>Brand Name</th>
<th>Chelate/Charge</th>
<th>Stability</th>
<th>NSF Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gadodiamide</td>
<td>Omniscan</td>
<td>Linear/non-ionic</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>1</td>
<td>Gadoversetamide</td>
<td>OptiMARK</td>
<td>Linear/non-ionic</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>1</td>
<td>Gadopentate dimeglumine</td>
<td>Magnevist</td>
<td>Linear/non-ionic</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>Gadobenate dimeglumine</td>
<td>MultiHance</td>
<td>Linear/non-ionic</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2</td>
<td>Gadoxetate disodium</td>
<td>Primovist, Eovist</td>
<td>Linear/non-ionic</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>2</td>
<td>Gadofosvset trisodium</td>
<td>Vasovist, Ablavar</td>
<td>Linear/non-ionic</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>3</td>
<td>Gadobutrol</td>
<td>Gadovist, Gadavist</td>
<td>Macrocyclic/non-ionic</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>
### Gadoteridol
- ProHance
- Macrocyclic/non-ionic
- High
- Low

### Gadoterate meglumine
- Magnescope
- Macrocyclic/ionic
- High
- Low

## Recommendations for the use of GBCAs

The following is an amalgamation of the European Society of Uroradiology (ESUR) and the ACR recommendations.

- **For patients with end-stage or chronic or severe or moderate renal impairment or acute kidney injury**
  - Group 1 / high risk GBCAs are contraindicated
  - Choose alternative modality to MRI if possible
  - If GBCAs are essential use a low-risk macrocyclic GBCA (see Table), use the lowest possible dose to achieve a diagnostic quality scan
  - If a GBCA is administered to patients who are on haemodialysis, it is prudent (although of unproven efficacy) that they should undergo haemodialysis within 2 hours with prolonged dialysis time and increased flow rates and volume. In patients who are not already receiving dialysis, this should not be initiated just to extract the Gadolinium agent
  - In patients with chronic renal impairment who are anuric, consider iodinated contrast-enhanced CT which does not have the risk of NSF, nor of furthering renal impairment

- **For patients not known to have renal impairment**
  - For use of high-risk GBCAs, assess the patients clinically and perform eGFR
  - Outpatients should be screened with questions regarding
    - Age (>60 regarded as risk factor)
    - Hypertension
    - Diabetes mellitus
    - History of dialysis or renal transplant
    - Single kidney
    - Past renal surgery or renal cancer
  - A positive response should lead to eGFR estimation
  - All inpatients should have eGFR performed

- **All patients**
  - Use lowest possible dose of GBCAs to achieve a diagnostic quality scan
  - Record the name and dose of GBCA administered
  - Avoid re-administration of a GBCA within 7 days
  - Monitor for signs and symptoms of NSF after a GBCA is administered to a patient suspected or known to have impaired elimination of the drug

- **Children and infants**
  - less than 4 weeks of age: high-risk GBCAs are contraindicated under ESUR guidelines
  - 1 month to 1 year of age: caution advised with regard to high-risk GBCAs (ESUR guidelines)
  - ACR guidelines differ from ESUR in that the adult guidelines should be applied
Lactating and pregnant women
- ESUR guidelines state
  - High-risk GBCAs contraindicated in pregnancy
  - Lactating women cease breastfeeding for 24 hours following administration of high-risk GBCA
- No specific ACR recommendation

RANZCR guidelines on the use of gadolinium-containing MRI contrast agents

These guidelines can be accessed via the following link: [17]

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Date of next review: July 2016

References - Gadolinium and Nephrogenic Systemic Fibrosis (NSF)


