Gadolinium–Based Contrast Agent Recommendations

(Revised 06/07/2018)

Introduction:

Nephrogenic systemic fibrosis is the only known adverse health effect related to gadolinium-based contrast agents (GBCAs). Recent studies have documented retention of gadolinium within the body in patients with normal renal function, highlighted by retention in parts of the brain. The health-related effects of gadolinium retention in this setting are as yet unknown.

Background:

To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. NSF is a fibrosing disease that primarily involves the skin and subcutaneous tissues but can also involve the lungs, esophagus, heart, and skeletal muscles. Awareness of the association of NSF with certain gadolinium-based contrast agents and kidney failure has prompted more judicious use of contrast agents, better patient screening, and the selection of contrast agents with safer profiles. The result has been a significant reduction in the incidence of cases of NSF.

Gadolinium retention in the body, including the brain, for months to years after receiving GBCAs has been recently documented. Although incompletely elucidated, several studies indicate that gadolinium retention is more common and for a longer period in agents that rely on a linear chelate. As with NSF, the gadolinium ion is felt to precipitate into the tissue when it loses binding with the chelate. Various studies paint an incomplete picture, but macrocyclic agents appear to be more stable with less deposition in the brain and for shorter periods of time. The macrocyclic GBCAs include the Group II agents Dotarem, Gadovist, and ProHance.

Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks. However, further investigation is being undertaken to assess the safety of the contrast agents including better understanding the factors leading to retained gadolinium and the long-term health effects.

Required Action:

Based on the ongoing scrutiny of the safety of GBCAs, in their 5-16-18 update, the FDA recommends that all MRI centers provide a Medication Guide to an outpatient the first time they

receive a GBCA provided on the Medication Guides webpage, and the Medication Guide should be provided to any patient who requests the information[1].

In all instances, any contrast agent should be used if deemed necessary, and the lowest dose needed for diagnosis should be used. Attempts should be made to minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies. However, do not avoid or defer necessary GBCA MRI scans.

Gadolinium-Based Contrast Agents

The ACR Committee on Drugs and Contrast Media and the ACR Subcommittee on MR Safety categorize gadolinium based contrast media (GBCA) into 3 groups:

Group I: Agents associated with the greatest number of NSF cases:

Gadodiamide (Omniscan® – GE Healthcare)

Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)

Gadoversetamide (OptiMARK® – Covidien)

Group II: Agents associated with few, if any, unconfounded cases of NSF:

Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)

Gadoteridol (ProHance® – Bracco Diagnostics)

Gadoterate meglumine (Dotarem® – Guerbet)

Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)

Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported:

Gadoxetate disodium (Eovist® – Bayer HealthCare Pharmaceuticals)

Patient Screening

In order to minimize the risk for patients with renal failure of developing NSF, the following guidelines are recommended by the ACR and excerpted from the 2017 ACR Manual on Contrast Media[2]**:**

Group II agents
The ACR Committee on Drugs and Contrast Media considers the risk of NSF in patients receiving standard or lower than standard doses of group II GBCAs is extremely low or possibly nonexistent. The assessment of renal function with a questionnaire or laboratory testing is optional when the group II GBCAs are used.

Group I and III agents
Patients receiving group I GBCAs should be considered at risk of developing NSF for any of the following conditions:

- Dialysis
- Severe or end-stage CKD
- Acute Kidney Injury

Outpatient Screening
Patients receiving group I or group III agents should be screened for renal impairment.

This list should not be considered comprehensive and represents a blend of published data and expert opinion:

- History of renal disease
  - Dialysis
  - Kidney transplant
  - Single kidney
  - Kidney surgery
  - History of cancer involving the kidney(s)
- History of hypertension requiring medical therapy
- History of diabetes mellitus

Once an outpatient is identified as being at risk for having reduced renal function based on screening, renal function should be assessed by laboratory testing (checking results of prior laboratory tests performed within an acceptable time window and ordering new laboratory tests only if necessary) and calculation of eGFR. However, if the patient is on dialysis, laboratory testing and calculation of eGFR is not useful.

For adults, eGFR calculation should be performed using the Modification of Diet in Renal Disease (MDRD) equation. The four-variable MDRD equation takes into account age, race, gender, and serum creatinine level. This information can be used to calculate the patient's glomerular filtration rate (GFR) using the MDRD equation found at eGFR calculator.

eGFR timing prior to administration of Group I and Group III Gadolinium-containing contrast for patients with risk factors:

Prior eGFR ($ml/min/1.73m^2$)	When should new eGFR be obtained prior to MRI?
None available	Within 2 days
45-59	Within 6 weeks
< 44	Within 2 days
On dialysis	eGFR not needed

Usage Recommendations for Group I and III agents:

- Patients with eGFR < $30ml/min/1.73m^2$ (Chronic Kidney Disease 4 and 5) should not receive Group I agent contrast. If contrast required, Group II agents should be used.
- Patients with mild to moderate chronic kidney disease Chronic Kidney Disease 3 (eGFR 30 -59 $mL/min/1.73m^2$):
  - No special precautions.
- Patients with CKD 1 or 2 (eGFR 60-$119ml/min/1.73m^2$):
  - Any GBCA can be administered.
- In general, patients with acute kidney injury (regardless of eGFR values) should receive group II GBCAs.
- Patients at risk who must receive contrast should receive the lowest possible dosage for contrast effectiveness. The referring physicians and patients should be fully advised of the potential risks of developing nephrogenic systemic fibrosis and informed of the clinical manifestations of this process as detailed below, excerpted from the referenced FDA advisory[1]. Informed consent should be obtained in these patients.
- In patients on hemodialysis, immediate dialysis (within 2 hours) is recommended and an additional dialysis within 24 hours should be considered. Patients on peritoneal dialysis receive virtually no benefit from peritoneal dialysis following contrast. In these cases hemodialysis should be considered3. However, the usefulness of hemodialysis in the prevention of NSF is unknown.
- Report possible cases of NSF to the FDA through the FDA's MedWatch program: http://www.fda.gov/medwatch/report/hcp.htm.

Recommendation

This recommendation is based on weighing several factors. Macrocyclic agents carry a more favorable safety profile in regard to NSF and appear to exhibit more favorable kinetics in body and brain retention compared to the linear agents. The macrocyclic agents include the Group II agents Dotarem, Gadavist, and ProHance. Additionally, the ACR states that laboratory values are not required for patients receiving a Group II agent. Lastly, although the macrocyclic agents have a higher incidence of allergic reaction compared to the linear agents, serious reactions are exceedingly rare for all. Of the macrocyclic agents, Dotarem appears to have the lowest rate of documented adverse reactions followed by Gadavist and ProHance. Based on this best currently available information, Dotarem and Gadavist are our recommended GBCAs.

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1. Medication Guides webpage

2. James H. Ellis, MD F, Matthew S. Davenport M, Jonathan R. Dillman M, et al. *ACR Manual on Contrast Media.*; 2017. https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast-Manual/Contrast_Media.pdf?db=web. Accessed November 10, 2017.