CDI QUALITY INSTITUTE

# CLINICAL GUIDELINES

## Gadolinium Contrast Administration Guideline

Thomas J. Gilbert M.D., M.P.P.

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- The FDA is requiring professionals to provide patients educational information that they will be asked to read prior to receiving GBCAs;
- Gadolinium-based contrast agents should only be administered if clinically indicated and if deemed medically necessary by the supervising radiologist (ACR, FDA, ISMRM);
- The need for multiple contrast injections should also be assessed by the radiologist (ACR, FDA);
- When GBCAs are required, consider the use of a macrocyclic GBCA rather than a linear agent (NIH);
- For patients with documented sensitivity to a macrocyclic agent, the use of a linear agent is appropriate (NIH);
- The assessment of renal function is optional in patients undergoing MRI using standard or below standard doses of a class II GBCA;
- Renal function should be assessed in patients considered at risk of NSF if they are to receive a class I or class III contrast agent, or if they are to receive more than the standard dose of a class II agent; and
- The lowest dose needed for diagnosis should be used in at-risk patients and generally should not exceed the recommended single dose (ACR, NIH).

**The assessment of renal function with a questionnaire or laboratory testing is optional prior to the intravenous injection of a group II Gadolinium-based contrast agent (GBCA).**

*Based on the most recent scientific and clinical evidence, the ACR Committee on Drugs and Contrast Media considers that the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration* (ACR Manual on Contrast Media Version 10.3, 2017).

Most CDI-affiliated centers currently use Dotarem (gadoterate) which is an ionic macrocyclic type II GBCA. The stability of the Gd-contrast agent appears to be an important factor in the pathogenesis of NSF. Dissociation of gadolinium chelates occurs by a process of transmetallation which is facilitated by a number of endogenous metals such as zinc, copper, calcium and iron. Macrocyclic ligands are more stable than linear ligands, and ionic agents are more stable than nonionic agents. According to stability constants and kinetic measurements, the most stable Gd-contrast agent is the ionic macrocyclic agent gadoterate (Dotarem). The other group II agents are Gadoteridol (ProHance), gadobutrol (Gadavist) and gadobenate dimeglumine (MultiHance). Gadoteridol and gadobutrol are nonionic macrocyclic agents. Gadobenate dimeglumine is a linear agent, however, it acts differently due to its protein binding characteristics.

Please note that Dotarem still posts an FDA black box warning concerning NSF and renal screening, which is at odds with the more recent ACR recommendations.

## Patients receiving group I and group III GBCAs and patients receiving more than 30 cc of Dotarem are considered high risk and renal screening is still recommended in these patients.

Patients receiving group I agents (gadodiamide/Omniscan, gadopentetate dimeglumine/Magnevist and gadoversetamide/OptiMARK) are at risk for developing NSF if they are on dialysis, have acute renal insufficiency, or if they have severe or end-stage renal insufficiency (*e*GFR < 30mL/min/1.73 $m^2$). The ACR notes that there is insufficient real-life data to determine the risk of NSF from administration of group III agents (gadoxetate disodium/Eovist), despite an alternative excretion pathway for hepatobiliary agents. Patients receiving more than 30 ccs of a Group II agent are also considered to be at risk for developing NSF.

The following risk factors have been recommended by the ACR:

- History of renal disease with
    - Dialysis
    - Kidney transplant
    - Kidney surgery
    - History of known cancer involving the kidney
- History of hypertension requiring medical therapy
- History of diabetes mellitus

In general, outpatients with risk factors should have an eGFR within an appropriate time period before the contrast examination. No eGFR is required in patients on dialysis or in patient with acute renal insufficiency. For patients with an *e*GFR < 30, the indication for contrast should be confirmed prior to the exam, a group II agent should be used if possible, and the standard recommended dose should not be exceeded.

## Outpatients on dialysis and patients with AKI do not need additional renal testing.

If a patient is on dialysis or has acute kidney insufficiency, laboratory testing and calculation of eGFR is not useful or necessary. These patients are at risk for NSF and the following precautions have been recommended by the ACR:

- Consideration should be given to performing a CT scan with iodinated contrast assuming the diagnostic yield is similar;
- Group II agents should be used if possible;
- The risk and rewards of using Eovist or high doses of Gd need to be carefully considered with the referring provider and patients in these instances;
- The patient and referring provider should be informed of the risks and benefits of using a GBCA; and
  The contrast-enhanced MRI examination should be performed as close as possible to post-procedural hemodialysis if scheduled.

## The FDA on 12-19-2017 issued a new warning concerning the retention of GBCAs in the body, and every patient is to read a new patient Medication Guide prior to receiving a GBCA. (The medication guide has not been released as of 1/23/2018.)

The FDA states that professionals should consider the retention characteristics of each agent when choosing a GBCA for patients, particularly when these patients are at higher risk for gadolinium retention. Linear agents result in more retention and retention for longer periods of time than do macrocyclic agents. Gadolinium levels in the body are lowest after administration of Dotarem, Gadavist and ProHance, and are similar across these agents. The FDA goes on to state that, to date, no adverse health event has been linked to gadolinium (except for NSF in patients with renal insufficiency). They are continuing to assess the health effects of gadolinium retention.

Brain deposition may be minimal or nonexistent in patients receiving Dotarem. Lee et al., in a 2017 publication, showed no increased T1 signal intensity in the deep brain nuclei following the administration of single or repeat doses of Dotarem in patients with normal renal function. Only patients with abnormal renal function showed an increase in T1 signal intensity. Radbruch et al. reported no signal changes in the dentate nucleus and globus pallidus following at least six consecutive MRI examinations with the use of Gadoterate meglumine. Perrotta et al., in 2017, reported the absence of cerebellar syndrome after serial injections of more than 20 doses of Gadoterate in 10 patients with primary or metastatic brain tumors.

## Anecdotal reports of gadolinium toxicity syndrome continue to surface in the lay press.

While the existence of gadolinium toxicity syndrome has not been acknowledged in scientific journals, the FDA has received reports of adverse events involving multiple organ systems in patients with normal renal function. A causal relationship between these events and gadolinium retention has not been established. Reports of this syndrome underscore the basic need to determine the appropriateness of GBCA for the MRI examination being ordered, determining the appropriateness of multiple studies, using the lowest possible dose necessary, and using agents with the lowest risk of deposition.

References:

ACR Manual on Contrast Media – Version 10.3/May 31, 2017.
https://www.acr.org/~/media/37D84428BF1D4E1B9A3A2918DA9E27A3.pdf

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**https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm**

FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue, 5-22-2017.
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