Invited Commentary

Risk of Gadolinium-Based Contrast Agents in Chronic Kidney Disease—Is Zero Good Enough?

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In the 1990s and early 2000s, numerous patients with chronic kidney disease (CKD) were exposed to gadolinium-based contrast agents (GBCAs) for contrast-enhanced magnetic resonance imaging (MRI). At the time, the use of GBCAs was considered a safe alternative to iodinated contrast used with computed tomographic scans because the risk of contrast-induced nephropathy could be avoided. During this period, a small number of patients with CKD developed a debilitating skin condition, initially called nephrogenic fibrosing dermopathy, because the most obvious manifestations were diffuse skin thickening and fibrosis. The condition was occasionally severe enough to involve the heart, lungs, liver, and skeletal muscle and was later renamed nephrogenic systemic fibrosis (NSF). Patients with NSF experienced significant morbidity due to irreversible systemic fibrotic changes and higher mortality than patients without NSF.[1]

Related article

Nephrogenic systemic fibrosis was initially a mystery; in 2006, 2 case-control studies[2,3] identified an association between GBCAs and NSF in patients with chronic CKD. The US Food and Drug Administration (FDA) issued an advisory about the association of GBCAs and NSF in 2006[4] and subsequently issued a black box warning in 2007,[5] instructing physicians to avoid the use of all GBCAs in patients at risk for NSF. The pathophysiologic cause of NSF was later confirmed by histopathologic evaluation, which revealed gadolinium deposition in skin biopsy specimens of affected patients. Given that kidney failure greatly increases the elimination half-life of GBCAs, it was postulated that gadolinium ions dissociate from their underlying binding ligand during the prolonged retention period, allowing tissue deposition and the eventual development of NSF.[1]

Most nephrologists, who were on the front lines and exposed to the devastating and irreversible consequences of this condition, took the approach of near-complete avoidance of contrast-enhanced MRI in at-risk patients, which largely eliminated incident cases of NSF. However, the FDA updated its gadolinium warning in 2010, specifying that 3 agents (gadopentetate dimeglumine, gadodiamide, and gadoversetamide) were responsible for most cases of NSF and therefore contraindicated in CKD . In the same update, the FDA stated that other GBCAs could be used cautiously under certain circumstances.[6] Given this guidance, a natural question arose about whether the association with NSF was a true class effect or specific to the structure of those early agents. Indeed, newer GBCAs differ in their biochemical and physical properties compared with older GBCAs, resulting in tighter chelation of the underlying gadolinium, which may reduce the risk of tissue deposition.[1] The American College of Radiology (ACR) recognizes these newer agents, termed group II agents (gadobenate dimeglumine, gadobutrol, gadoteridol, and gadoterate meglumine), for which there is little evidence of an association with NSF. Furthermore, the ACR guidelines state that group II agents can be safely used in patients with advanced CKD and those receiving dialysis, provided that they receive dialysis after exposure.[7] Many hospitals and health systems, including our own institution, have since adopted routine use of group II agents for all contrast-enhanced MRI studies. However, despite the reassuring safety profile of group II agents, some nephrologists continue to discourage the use of contrast-enhanced MRI in patients with advanced CKD for fear of NSF, which may result in less than ideal imaging or exposure to iodinated intravenous contrast, raising the risk of contrast nephropathy and loss of residual kidney function in patients undergoing dialysis.

In this issue of *JAMA Internal Medicine*, Woolen et al[8] report a systematic review and meta-analysis of the risk of NSF in patients with stage 4 and 5 CKD receiving group II GBCAs, including patients undergoing dialysis. They report a 0% pooled incidence of unconfounded NSF in 4931 patients who received these GBCAs with an upper bound of risk of 0.12% to 1.59%. The wide range in the upper bound of risk for different agents was owing to sample size, because some agents had fewer than 350 published exposures (gadobutrol and gadoteridol). This study supports the contention that the risk of NSF is exceedingly low in patients with CKD exposed to group II agents.

There are some limitations to this study. It is unclear how many of these exposures were in patients receiving dialysis, who have the highest risk of developing NSF, although at least 1 study included in the meta-analysis reported outcomes in this population. In addition, a pooled risk estimate does not reflect differences in risk according to level of kidney function. Nonetheless, one cannot ignore the fact that not a single reported case of NSF occurred in nearly 5000 patient exposures.

So how does this study change the story of GBCA use in patients with kidney disease? Overall, the strength of the evidence favors a more permissive approach to using group II GBCAs in patients with CKD, especially when contrast-enhanced MRI is the superior imaging modality. There remains a disconnect between the more conservative approach still maintained by the FDA and the more permissive guidelines from the ACR. This incongruity may be mirrored by a disconnect between nephrologists and radiologists, with the former concerned that the lack of cases may be driven by avoidance of GBCAs in high-risk patients and the latter more convinced by the biochemical case for safety of newer GBCAs.

Given the emerging data that group II agents are rarely (if ever) associated with NSF, our opinion is that group II GBCAs

can be used cautiously in at-risk patients, including those receiving dialysis, provided patients are given the lowest possible dose, repeated exposures are avoided, and patients treated with hemodialysis receive it shortly after GBCA administration. We agree with the ACR guideline that written informed consent is not necessary when using group II GBCAs in at-risk patients,[7] but we believe that ordering health care professionals should counsel patients of the potential risks of GBCAs as they would discuss risks and benefits of other medications and contrast agents.

Avoidance of contrast-enhanced computed tomographic imaging out of concern for the risks of contrast nephropathy has been routine practice in patients with advanced CKD. Avoiding MRI as well risks diagnostic delay and could lead to adverse consequences. In the population with stage 5 CKD, contrast-enhanced MRI may be superior to contrast-enhanced computed tomography because it could mitigate the risk of precipitating dialysis initiation and, among patients already receiving dialysis, could prevent the loss of residual renal function, which is associated with higher mortality. In the end, changing practice behavior could be challenging, especially among nephrologists who practiced during the emergence of NSF and the countless nephrology trainees who were taught to strictly avoid GBCAs. Nephrologists may need to come to terms with our natural tendency to avoid errors of commission more assiduously than errors of omission. Perhaps the combination of zero events and a solid biochemical rationale will help get us there.

ARTICLE INFORMATION

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REFERENCES

1. Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ. Gadolinium-based contrast agents: a comprehensive risk assessment. *J Magn Reson Imaging*. 2017;46(2):338-353. doi:10.1002/jmri.25625

2. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006;17(9):2359-2362. doi:10.1681/ASN.2006060601

3. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21(4):1104-1108. doi:10.1093/ndt/gfk062

4. US Food and Drug Administration. Public health advisory—gadolinium containing contrast agents for magnetic resonance imaging (MRI). http://wayback.archive-it.org/7993/20170112033022/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053112.htm. Published June 8, 2006. Accessed September 19, 2019.

5. US Food and Drug Administration. FDA requests boxed warning for contrast agents used to improve MRI images. http://wayback.archive-it.org/7993/20170112033008/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108919.htm. Published May 23, 2007. Accessed September 19, 2019.

6. US Food and Drug Administration. FDA drug safety communication: new warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warnings-using-gadolinium-based-contrast-agents-patients-kidney. Updated February 6, 2017. Accessed September 19, 2019.

7. American College of Radiology. ACR manual on contrast media version 10.3. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Published 2018. Accessed September 9, 2019.

8. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: a systematic review and meta-analysis [published online December 9, 2019]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.5284