VIEWPOINT

Gadolinium Retention After Contrast-Enhanced MRI

Deborah Levine, MD
Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Robert J. McDonald, MD, PhD
Division of Neuroradiology, Department of Radiology, Mayo Clinic, Rochester, Minnesota.

Herbert Y. Kressel, MD
Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Corresponding Author: Deborah Levine, MD, Department of Radiology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (dlevine@bidmc.harvard.edu).

Gadolinium-based contrast agents (GBCAs) revolutionized magnetic resonance imaging (MRI) examinations by depiction of pathology otherwise undetectable on unenhanced MRI or other imaging modalities. Since initial regulatory approval in 1988, it is estimated that more than 450 million GBCA doses have been administered worldwide. In the United States, it is estimated that approximately 8.8 million MRI procedures involving gadolinium administration were performed in 2016.[1] GBCAs have excellent safety profiles with rates of acute adverse reactions (0.07%-2.4%) substantially lower than adverse events observed with iodinated contrast material used during computed tomography or angiography. Most reactions are mild, including injection site pain, headache, nausea, paresthesias, and dizziness. Anaphylactic reactions are rare (0.001%-0.01%).

GBCAs contain the rare earth metal gadolinium chelated to linear or macrocyclic organic ligands that provide a means of safely administering and excreting an otherwise toxic element. GBCA chelates were initially thought to remain largely intact, with most agents being excreted renally and some excreted hepatically. These assumptions were challenged in the late 1990s with the discovery of nephrogenic systemic fibrosis (NSF), a rare condition among patients exposed to GBCAs with severely compromised kidney function, in which patients demonstrate progressive accumulation of gadolinium in skin tissues over time, even in the absence of additional GBCA exposure, suggesting mobilization from tissue reservoirs such as bone.[2] Although the mechanism is incompletely understood, GBCA dechelation (dissociation of the gadolinium from the organic ligand) is thought to play a central role in this disease.

In 2006 the US Food and Drug Administration (FDA) alerted the public about cases of NSF and in 2007 a boxed warning about GBCA was added to product labeling. In 2010 additional details were added regarding screening for acute and chronic kidney disease prior to contrast-enhanced MRI, with particular mention of avoidance of agents associated with greater risk of development of NSF, including Magnevist, Omniscan, and Optimark.[3] Since these changes in practice were implemented new instances of NSF have almost completely been eliminated.

In 2014 a positive correlation was observed among 381 patients undergoing MRI between cumulative GBCA exposure and T1 signal intensity in the dentate nucleus and globus pallidus.[4] Subsequent postmortem studies using inductively coupled plasma mass spectrometry in13 patients exposed to 4 or more GBCA examinations confirmed the presence of retained gadolinium in all patients, compared with no gadolinium in 10 patients without such exposure.[5] It is now recognized that gadolinium is retained in minute amounts throughout the brain parenchyma after contrast-enhanced MR examinations, even in areas without T1 signal intensity changes. In addition, gadolinium has been detected following single-dose intravenous administration of linear and macrocyclic agents.[6] The extent of gadolinium retention correlates with cumulative GBCA dose and GBCA chelate stability/lability, although the chemical forms being retained may differ between the GBCA subclasses.

It is unclear if the tiny amounts of retained gadolinium cause adverse clinical sequelae. In a population-based study of 246 557 patients, of whom 99 739 (40.5%) received at least 1 dose of gadolinium, rates of parkinsonism were 1.16% among those with noncontrast MRI and 1.17% among those with at least 1 dose of gadolinium, with no significant difference in the rates after adjusting for confounders.[7] However, in 2017 the Medical Imaging Drugs Advisory Committee (MIDAC) of the FDA reported on 132 patients with a variety of clinical manifestations after GBCA exposure, including joint and cognitive symptoms, some of which overlap with symptoms previously reported by patients with NSF.[1] Because these symptoms are relatively acute in onset,[1] often beginning shortly after a single GBCA exposure, the causal association has been questioned because these joint and cognitive symptoms manifested before gadolinium retention would be expected to occur.

In December 2017 the FDA issued a safety communication about GBCA as part of its postmarket monitoring of drug safety, requiring a class-wide warning about gadolinium retention in the labeling of these agents, and additional studies by manufacturers to assess the safety of these agents.[1] At the request of the FDA, the 4 GBCA manufacturers in the United States coauthored a "Dear Health Care Provider" letter in May 2018 to alert prescribers that gadolinium from GBCA may remain in the body for months to years after injection.[8] This letter summarized research findings that retention is highest with linear agents and lowest and similar among the macrocyclic GBCAs. The letter also clarified that neither pathologic nor clinical consequences of GBCA retention in the brain have been proven.[8]

To educate patients, the FDA and the GBCA manufacturers developed a medication guide specific to each GBCA that would be distributed to patients prior to an MRI with GBCA. These guides inform patients that minute amounts of gadolinium are retained, greater retention occurs more with gadolinium chelated to linear ligands, and despite some rare reports, so far no harmful effect has been identified.

Limitations of Prior Research on GBCA Retention

Although GBCAs have been in clinical use for more than 30 years, knowledge of their effects on humans is limited. First, animal studies oversimplify the understanding of GBCA pharmacokinetics and biodistribution. In mice, more than 99% of GBCA is excreted primarily

through the urinary tract within 24 hours. In humans, however, 73% to 99% of GBCA is excreted within 24 hours, varying with the specific GBCA; this small unexcreted fraction in humans can be retained in multiple tissues including bone, skin, and brain. Second, the in vivo tissue distribution, trafficking between tissues, and chemical identity of these retained gadolinium species remain poorly understood. Third and most important, data on the biological activity and toxicologic potential of these retained gadolinium forms also are limited.

Of particular concern is the need to understand the effects of gadolinium retention in potentially vulnerable populations including (1) patients who undergo frequent MRI examinations with GBCA; (2) fetuses and children exposed to GBCA; and (3) patients with high bone turnover such as those with osteoporosis or renal osteodystrophy who may be at risk due to the storage of gadolinium within bone parenchyma.

Current evidence does not suggest a strong association between GBCA exposure and adverse clinical sequelae. However, existing data largely originate from retrospective sources that were not intended nor sufficiently powered to study subtle or rare clinical effects of gadolinium exposure. Informatics techniques utilizing preexisting clinical databases may identify currently unknown risk factors for gadolinium retention and allow creation of targeted registries incorporating prospective standardized assessment of neurocognition and symptoms. Ongoing studies that assess the normal aging process or even cancer screening protocols such as those for prostate cancer or breast cancer might provide useful data.

Research Roadmap Workshop

In February 2018 a meeting cosponsored by the American College of Radiology, Radiological Society of North America, and National Institutes of Health (NIH) convened at the NIH campus to discuss knowledge gaps surrounding gadolinium retention and to promote collaborations and support future funding opportunities for such research.[9] Attendees included researchers, experts from industry, and representatives of the FDA. Based on the expert consensus of this group, a prioritized roadmap for future research efforts was generated to better understand the clinical importance of gadolinium retention for patients receiving these contrast agents.[9]

Conclusions

Contrast-enhanced MR examinations are a crucial part of the imaging armamentarium for diagnosis and follow-up of many disease processes. As with all imaging examinations, the risks of the test must be weighed against the need for diagnosis and appropriate management. The benefits of contrast-enhanced MR are widely recognized; thus, it is essential to better understand the potential risks.

Collaborative research efforts are needed to address the gaps in knowledge related to the potential adverse effects of gadolinium. Such efforts will help quantify the risk-benefit ratio for GBCAs and determine what clinical risks, if any, are associated with chronic gadolinium exposure in human tissues. As it is likely that the low frequency of adverse effects will challenge the ability to appropriately power prospective studies, the research roadmap developed at the workshop is intended to encourage relevant funding agencies around the world to support and facilitate meaningful large-scale collaborative research efforts that can provide answers to the many questions regarding the clinical importance of gadolinium retention.

ARTICLE INFORMATION

Published Online: September 12, 2018. doi:10.1001/jama.2018.13362

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Levine reported serving as expert witness in a trial regarding the Essure device (Bayer Healthcare). Dr McDonald reported receiving an investigator-initiated grant and serving as a consultant to GE Healthcare regarding contrast agent development and safety, with all funds going to Mayo Clinic; serving as a consultant to Bracco Diagnostics regarding contrast agent safety, with all funds going to Mayo Clinic; and receiving indirect financial support from Bayer AG in the form of a scholar grant, with all funds going to RSNA. Dr Kressel reported receiving compensation for serving as director of science and communication from the International Society for Strategic Studies in Radiology; and receiving compensation from RSNA for serving as the editor of *Radiology*, 2008-2017.

Additional Contributions: We thank the sponsors and participants in the workshop, and in particular the authors of the main manuscript published in *Radiology*.[9] These coauthors include J. Weinreb, E. Kanal, M.S. Davenport, J.H. Ellis, P.M. Jacobs, R.E. Lenkinski, K.R. Maravilla, M.R. Prince, H.A. Rowley, and M.F. Tweedle.

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