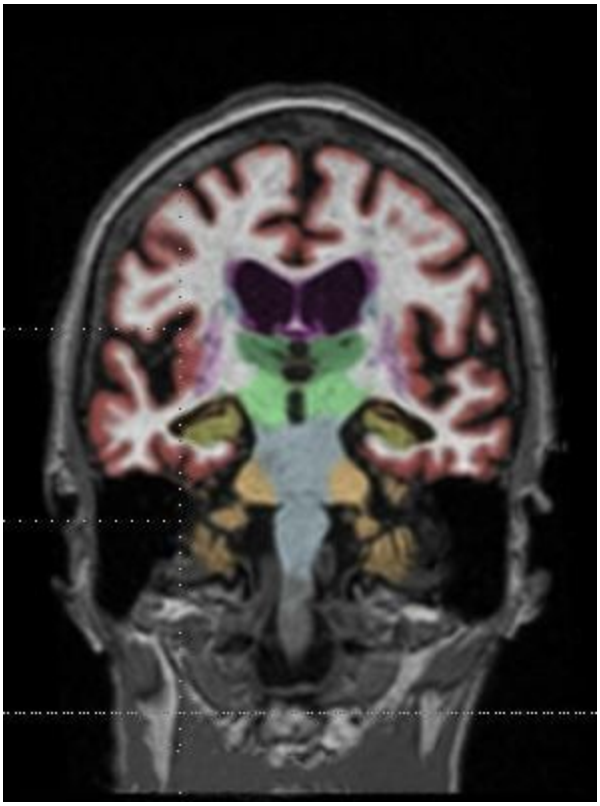
The Debate Over Gadolinium MRI Contrast Toxicity

itnonline.com/article/debate-over-gadolinium-mri-contrast-toxicity

February 16, 2018



> *Gadolinium contrast agents (GBCAs) are partly retained in the brain, raising safety concerns, as seen in this MRI.*

One of the biggest concerns in radiology in recent years is the safety of gadolinium-based contrast agents (GBCAs) used in magnetic resonance imaging (MRI). Radiologists and patients began to question the safety of gadolinium a few years ago when a study came out in late 2014 showing the agent is deposited and retained in the brain.[1] This, combined with a small percentage of patients who claim their health was harmed following gadolinium exams, has sparked a big debate in radiology over the safety of these agents.

This issue was raised in several sessions and with experts ITN spoke with at the 2017 Radiological Society of North America (RSNA) meeting last November. It was clear at RSNA that many radiologists have concern about gadolinium deposition and and possible effects of gadolinium toxicity.

“There have been reports from patients with side effects that they attribute to the gadolinium contrast agents, and that is something that has our attention as radiologists,” said Max Wintermark, M.D., professor of radiology and chief of neuroradiology, Stanford Hospital and

Clinics. “I get a number of phone calls from patients each week who are concerned, so we have the discussion about risk versus benefits.”

It is known that patients with renal insufficiency cannot filter the gadolinium from their body, so it is included as a U.S. Food and Drug Administration (FDA) warning label on the contrast packaging. But, there has been little evidence showing patient safety issues in those with normal renal function. Boxed warnings are also included for known hypersensitivity relations that can occur, especially in patients with allergic disorders.

There are numerous patient-created groups on social media that discuss MRI gadolinium toxicity issues, which have raise public awareness on the topic of possible connections with previously unknown gadolinium side effects. The biggest public relations boost for these patients came in November 2017 when action movie actor Chuck Norris filed a lawsuit against a contrast vendor and the contrast distributor for allegedly poisoning his wife Gena. She had several contrast MRI exams and the suit alleges numerous adverse health effects began after these exams. Norris is seeking $10 million in damage.[2]

The suit alleges she contracted what is being called “gadolinium deposition disease.” It is a term often used by patients who claim they now have chronic health problems from their contrast MRI exams. However, the term is not accepted by many in the medical community because of the lack of scientific evidence showing a direct connection with the contrast agents. The lawsuit described Gena’s symptoms as burning pain throughout her body, violent shaking, numbness, tingling, weakness, cognitive deficits, kidney damage and trouble breathing. These symptoms are similar to others often reported in patient social media groups.

“The lawsuit will increase public awareness, along with all the positive and negative outcomes that brings along,” said Emanuel Kanal, M.D., director of MRI services and professor of radiology and neuroradiology at the University of Pittsburgh Medical Center, one of the key speakers on this topic at RSNA. “The negative outcomes are the potential for hysteria with patients opting out of contrast exams, when they really, strongly need it, and the potential patient benefit is so massive that not getting the contrast could truly cause harm to them.” He said the positives of public awareness is that it will prompt more questions to be answered through clinical study to ensure medicine has a better understanding of these agents. “We need to be able to respond to our patients when they ask us questions about the agents we are using,” he said.

Lack of Evidence Showing Harm From Gadolinium

Physicians have largely been reluctant to directly link gadolinium agents to these maladies, because there is little clinical evidence showing a direct correlation. Symptoms can also vary greatly between patients reporting problems. Gadolinium contrast agents have been used in

hundreds of thousands of patients over the past couple decades and the clinical evidence shows it is safe in most patients, Wintermark said. Until the past few years, it was not widely known that the gadolinium accumulated and was retained in tissues, especially the brain. Wintermark said it was previously thought the agent was entirely excreted from the body. He said a couple large scale studies are underway, but it will take time to gather data to determine the long-term effects of gadolinium retention.

“I am not completely convinced gadolinium is not toxic,” Kanal said. “I don’t know which way to turn yet. The issue is a lack of data showing toxicity, but lots of data showing it is safe.”

This lack of evidence showing patient harm was echoed by other speakers in RSNA sessions.

“We don’t know what the clinical significance is, which is why we continue to do clinical research on this,” said Sheela Agarwal, M.D., U.S. medical affairs, Bayer Healthcare, who spoke during a Bayer-sponsored lunch at RSNA on the topic of gadolinium safety. She said there have been about 50 studies that have come out on this subject in the past few years, but none of them offer a smoking gun showing gadolinium retention leads to chronic disease. “It’s very difficult for us as clinicians to call something a disease if we cannot definitely connect causality,” she explained.

What is the FDA Doing About Gadolinium Toxicity Concerns?

The FDA agrees that more research is needed and there is not enough evidence to impose a regulatory clampdown on GBCAs. In September 2017, the FDA’s Medical Imaging Drugs Advisory Committee (MIDAC) voted overwhelmingly to recommend new labels on gadolinium-based contrast agents (GBCAs) warning of the possibility of gadolinium retention in the body.[3] The labels will further explain that linear GBCAs carry a greater risk than macrocyclic agents, and that there is a greater risk for certain patient populations. In December 2017, the FDA announced in a drug safety communication it is requiring these new warnings to be included on all GBCAs.[4] The FDA also called for increased patient education and requiring gadolinium contrast vendors to conduct additional animal and clinical studies to assess the safety of these agents.

The FDA stated there is no clinical evidence that directly links gadolinium retention 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.

“The health consequences, if any, are as of yet entirely unknown, and so far there are no known consequences of retained gadolinium,” Kanal said. “It does not mean that there are none, it just means that we don’t know of any at this stage and more studies are needed.

That appears to be the conclusions of the FDA and the MIDAC committee so far." He said the American College of Radiology (ACR) and International Society for Magnetic Resonance in Medicine reached a similar conclusion.

However, in July 2017, the European Medicines Agency (EMA) issued a final opinion that recommended restricting the use of some linear gadolinium-based contrast agents (GBCAs) and suspending the marketing authorizations of others, citing concerns about gadolinium deposition.[5] But, the EMA said it supports the continued use of macrocyclic GBCAs. The EMA stated "there is currently no evidence that gadolinium deposition in the brain has caused any harm to patients. However, the EMA has recommended restrictions for some intravenous linear agents in order to prevent any risk that could potentially be associated with gadolinium brain deposition."

The EMA recommended suspending the marketing authorizations of GBCAs Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide) and OptiMark (gadoversetamide). The group cited the benefit-risk balance is no longer favorable for certain linear GBCAs. But, the EMA recognized certain linear GBCAs are still needed for liver imaging, so retained Primovist (Eovist in the U.S., gadoxetate disodium) and MultiHance (gadobenate dimeglumine).

Kanal pointed out ACR came out with a statement last fall disagreeing with the EMA recommendations. "From a fixed amount of data, there are very divergent conclusions being reached on both sides of the Atlantic," Kanal explained. "Multiple, further studies are clearly warranted."

What is Known About Gadolinium Deposition

There are two classes of GBCAs based on their chemical shape — linear and macrocyclic agents. Agarwal said there are four studies[6,7,8,9] that have shown linear agents have more retention in the brain than macrocyclic agents. However, recent studies have also shown all agents, including macrocyclic, leave gadolinium behind in the brain to some level. While deposition in the brain has been the main reason for concern in recent years, she said in animal studies, there was 100 times more gadolinium retained in skin and bones than there was in the brain.

"We have known for decades that there is residual amounts of these agents left behind in the human body, and the level varies from agent to agent," Kanal said. "But, for whatever reason, when Dr. Kanda in December 2013 showed there was a change in the magnetization behavior in parts of the brain,[1] and then the literature went on to find it was related to the presence of gadolinium, that caused a substantial amount of reaction and concern."

To decrease the toxicity of gadolinium, Kanal said it is put together with another chaperone or ligand molecule. He explained this chelation of the gadolinium molecule massively increases the safety index and allows it to be used as a contrast agent to humans. However, for the gadolinium that is retained in the body, Kanal said there is a theory that as long as the agent remains in a chelated, imprisoned format, it is safe.

“But, if the gadolinium were to pop off that ligand molecule, it might lead on to diseases such as nephrogenic systemic fibrosis (NSF),” he explained. “Now some people are wondering if the same thing applies for the brain. But, the brain is different and it does not heal damage through fibrosis, the brain heals by gliosis. So, we are not even sure in having gadolinium in what form is it going to be dangerous, if at all. We don’t really understand that right now. There is a tremendous amount of pressure to say when it separates it becomes a problem and leads to NSF.” He said this fact might be true, but you cannot automatically assume that when the gadolinium separates from the chelated molecule that it leads to other problems.

“Today, there is still a massive amount that we still don’t know. But, just because we don’t see any harm does not mean that there isn’t any, and just because it disassociates, does not mean it does any harm in that organ,” Kanal explained. When gadolinium separates, he said it might go to phosphate or carbonate, and gadolinium phosphate may precipitate out to the basal ganglia in the brain. “But, calcium, another metal that we know, precipitates out in the brain and it is a normal finding,” he said. Even if there is precipitation of gadolinium in some form in the brain, the question is it inert or is it actually harmful. “We have no way of knowing, at this stage it is just too early to tell. But, there is such concern that we are finding the industry, in my opinion, has substantial difficulty separating knowledge from opinion and from hype,” Kanal said. “But, I think everyone would agree that it would be better if we did not have any residual gadolinium left in the body.”

He said there is a tendency to group all macrocyclic agents and linear agents together and say these agents all act the same. But, recent studies have shown agents, even in the same class, do not all behave the same, so they should not be lumped together.

What Radiologists Can Do Right Now About Gadolinium

Kanal said the new public awareness will force radiologists to begin personally approving all contrast doses before exams to ensure they are justified, weighing the risk benefit for each patient. He said radiologists should not be relying on referring physicians who order exams and do not know the differences between these agents and who really do not understand the potential safety issues.

“These are pharmaceutical agents, and these are our patients,” Kanal said. “We are not just a ‘doctor’s doctor,’ these are literally and legally our patients and as a radiologist I will be held legally responsible for every decision I make about my patient. Every decision I make,

whether through commission or omission, it is my decision. If I allow a drug to be given because a referring physician ordered it, that too is my legal responsibility, and if there is harm, liability."

The University of Pittsburgh has a process where radiologists need to review all orders requesting contrast exams for final approval before a patient is scanned. Kanal does emergency radiology and about a fifth of the orders requesting contrast are cancelled because the contrast, or the MRI, are not needed.

"[At Stanford] we review every single MRI exam, we review the indication for the exam, past medical history, we review the previous imaging," Wintermark said. "After that, we protocol each study and try to decide what is best for the patient. Whenever we use these contrast agents, we want to make sure there is a clear benefit for the patient. Like anything we use in medicine, there is always a benefit, but there is also potential for risks and as radiologists we need to decide with the patients what is best for them."

Need for a Gadolinium Dose Tracking, Patient Registry

One way to track the safety of gadolinium agents in a scientific format would be through the creation of a patient registry. Patient data, the contrast dose, type of agent used, MRI system, protocols used and patient history could be included in registry data so as patients say they are experiencing health concerns or potential adverse reactions, this can be tracked in a large population to identify similarities.

This is already done with many types of implantable devices, in some cases where the FDA mandated such a post-market surveillance and medical societies host and administer the registry data collection as a third party.

"I think it will be likely that a patient registry will be created in the near future," Kanal said.

However, a big issue facing radiology is that most departments currently do not record contrast dosages or even what specific agent was used. "It is very difficult to find out from the EMR how many administrations of gadolinium contrast there were or the doses used," Agarwal said.

"In the past, radiology as a speciality has been an abysmal failure in recording accurately how much we gave or even what agent we gave," Kanal said. However, he expects with the current concern over gadolinium, there will be a rapid and massive movement toward treating contrast agents much more like the prescription drugs they are. This includes recording the doses, what agent did the patient have last time, agent being used for the current exam, what rate was it administered and what route.

Wintermark also said there is a need for contrast dose tracking, but it can be difficult to track when imaging is performed at different locations over the course of several years. “It is important that we gather this information and put it together and hopefully in the end, we can get to the bottom of it and understand exactly what is going on and we can hopefully prevent it in the future,” he explained. “We need to collect that information, but for that information to be helpful, it needs to be collected in a rigorous fashion, because we don’t know if the symptoms being reported are from one entity or multiple entities. That is where the quality of the data collection is very important to help sort things out.”

Radiology information systems (RIS) and picture archiving and communication systems (PACS) often have no interface with contrast injectors to automatically transfer information into the patient record, so the contrast data needs to be manually transferred into the system, according to Joanne Hoener, RT(R)(MR)(CT)(CIIP), who now works as a clinical marketing specialist at Bayer and presented at an RSNA lunch session on gadolinium safety. “When you do a manual process, you will get discordance,” she said. For MRI contrast, Hoener said what needs to be recorded is dose rate, strength, time/date, agent delivered and device to deliver contrast. She said this information should be recorded in patient records anyways for a variety of reasons including future datamining.

“None of us could have predicted gadolinium deposition would become an issue, and it was not even on our radar in 2010,” Hoener said. “We need to document the contrast we use and the doses, because today it is gadolinium, but tomorrow it may be another type of agent. Technologies are available to improve contrast documentation accurately and improve workflow by removing manual documentation steps. It does not matter what vendor you use, it is all about documentation.”

Bayer Healthcare’s Radimetrics Platform for radiation and contrast dose tracking was the first and and one of the most comprehensive tracking systems. Sectra recently released a contrast tracking system for CT and MRI agents. Guerbet at RSNA 2017 also unveiled a new contrast tracking software solution for CT and said it will expand to MRI gadolinium tracking in 2018.

Should Radiology Departments Require Informed Consent Forms for Gadolinium Exams?

Patients that say they were harmed by gadolinium agents often argue they were never given any sort of informed consent documents to sign warning them of gadolinium’s potential hazards. Experts speaking at RSNA 2017 said this might be easier said than done. The main reason is that the majority of clinical data on these agents show they are safe.

“I don’t think it is necessary or warranted,” Kanal said. “I have been told from two medical malpractice attorneys that we cannot acquire informed consent if all I am telling a patient is that there are no known risks, but who knows what might happen in the future — that is not

informed consent. The new trials will help decide if informed consent will be indicated in the future."

Some practices are looking into informed consent documentation, but others do not want to do this because of fears it may open the door to litigation, Agarwal said.

Replacing Gadolinium Agents

Some MRI vendors have touted new technologies like black blood imaging, or new protocols that can reduce or eliminate the need for MRI contrast. However, Wintermark said some types of exams still require the use of gadolinium in order to answer the clinical questions the MRI is supposed to answer.

"Currently there are a number of things you can only do with gadolinium contrast agents. When exploiting the fact that the contrast is filling up the vessels to highlight them, there are other techniques that can be used. But when looking at the blush of contrast in tumors, that is something you cannot do using other techniques with the same level of sensitivity and specificity. There is ongoing research to find alternatives, but currently there is no good alternative for all the things that the gadolinium can help with."

Related Content of MRI Gadolinium Safety Concerns

VIDEO: How Serious is MRI Gadolinium Retention in the Brain and Body? An interview with Max Wintermark, M.D.

VIDEO "Big Concerns Remain for MRI Gadolinium Contrast Safety at RSNA 2017," An interview with Emanuel Kanal, M.D.

Radiology Has Failed to Properly Assess or Track MRI Gadolinium Contrast Safety

Recent Developments in Contrast Media

FDA Committee Votes to Expand Warning Labels on Gadolinium-Based Contrast Agents

European Medicines Agency Issues Update on Gadolinium Contrast Agents

ISMRM Issues Guidelines for MRI Gadolinium Contrast Agents

FDA: No Harm in MRI Gadolinium Retention in the Brain

VIDEO: MRI Gadolinium Contrast Retention in the Brain

Gadolinium May Remain in Brain After Contrast MRI

Linear GBCAs:

• Ablavar (gadofosveset trisodium)
• Eovist (gadoxetate disodium)
• Magnevist (gadopentetate dimeglumine)
• MultiHance (gadobenate dimeglumine)
• Omniscan (gadodiamide)
• OptiMark (gadoversetamide)

Macrocyclic GBCAs:

• Dotarem (gadoterate meglumine)
• Gadavist (gadobutrol)
• ProHance (gadoteridol)

References:

1. Tomonori Kanda, Kazunari Ishii, Hiroki Kawaguchi, et al. High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material. Radiology. March 2014, Volume 270, Issue 3. http://pubs.rsna.org/doi/abs/10.1148/radiol.13131669

2. Lindsey Bever. Chuck Norris claims his wife was poisoned during MRI scans, sues for $10 million. The Washington Post. Nov. 8, 2017. https://www.washingtonpost.com/news/to-your-health/wp/2017/11/08/chuck-norris-claims-his-wife-was-poisoned-during-mri-scans-sues-for-10-million/?utm_term=.2d8e7091b65a. Accessed Dec. 19, 2017.

3. Food and Drug Administration Center for Drug Evaluation and Research Summary Minutes of the Medical Imaging Drugs Advisory Committee. Sept. 8, 2017 meeting. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM579464.pdf. Accessed Feb. 16, 2018. Transcript of meeting: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/MedicalImagingDrugsAdvisoryCommittee/UCM584442.pdf

4. Gadolinium-based Contrast Agents (GBCAs): Drug Safety Communication - Retained in Body; New Class Warnings. FDA safety alert. Dec. 19, 2017. https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm589580.htm. Accessed Dec. 19, 2017.

5. EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. European Medicines Agency (EMA), July 20, 2017. http://www.ema.europa.eu/ema/index.jsp?

curl=pages/medicines/human/referrals/Gadolinium-containing_contrast_agents/human_referral_prac_000056.jsp&mid=WC0b01ac05805c516f. Accessed Jan 28, 2018.

6. Stojanov DA, Aracki-Trenkic A, Vojinovic S, et al. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. Eur Radiol. 2016 Mar;26(3):807-15. doi: 10.1007/s00330-015-3879-9. Epub 2015 Jun 25.

7. Rossi Espagnet MC, Bernardi B, Pasquini L, et al. Signal intensity at unenhanced T1-weighted magnetic resonance in the globus pallidus and dentate nucleus after serial administrations of a macrocyclic gadolinium-based contrast agent in children. Pediatr Radiol. 2017 Sep;47(10):1345-1352. doi: 10.1007/s00247-017-3874-1. Epub 2017 May 19.

8. Bjørnerud A, Vatnehol SAS, Larsson C, et al. Signal Enhancement of the Dentate Nucleus at Unenhanced MR Imaging after Very High Cumulative Doses of the Macrocyclic Gadolinium-based Contrast Agent Gadobutrol: An Observational Study. Radiology. 2017 Nov;285(2):434-444. doi: 10.1148/radiol.2017170391. Epub 2017 Sep 8.

9. Splendiani A, Perri M, Marsecano C, et al. Effects of serial macrocyclic-based contrast materials gadoterate meglumine and gadobutrol administrations on gadolinium-related dentate nuclei signal increases in unenhanced T1-weighted brain: a retrospective study in 158 multiple sclerosis (MS) patients. Radiol Med. 2018 Feb;123(2):125-134. doi: 10.1007/s11547-017-0816-9. Epub 2017 Sep 27.

10. Pasquini L, Rossi Espagnet MC, Napolitano A, et al. Dentate nucleus T1 hyperintensity: is it always gadolinium all that glitters?. Radiol Med. 2018 Jan 27. doi: 10.1007/s11547-017-0846-3.

11. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. May 22, 2017. https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm. Accessed Feb. 16, 2018.

12. FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI). July 27, 2015. https://www.fda.gov/Drugs/DrugSafety/ucm455386.htm. Accessed Feb. 16, 2018.
