Background on Gadolinium

What is Gadolinium?

Gadolinium is a Rare Earth Element (REE) with paramagnetic properties. On the Periodic Table its symbol is Gd and its atomic number is 64. Gadolinium is one of 15 metallic chemical elements known as the Lanthanide Series. Lanthanides have been referred to as “bone seekers” because they tend to deposit in bone.

Tests have confirmed that Gadolinium deposits in bone where it can remain for many years. Gadolinium (Gd³⁺) has an ionic radius very similar to that of Calcium (Ca²⁺) which is why Gd³⁺ is so toxic in biological systems – Gd³⁺ can compete with Ca²⁺ in all biological systems that require Ca²⁺ for proper function and, in doing so, the trivalent Gd³⁺ ion binds with much higher affinity.

Gadolinium is toxic to mammals and it has no known biological use in the human body.

Gadolinium-Based Contrast Agents are used for MRI and MRA.

Gadolinium has several specialized uses, but we will focus on its paramagnetic properties. In the early 1980s contrast agent developers determined that Gadolinium’s paramagnetic properties could be used to enhance images of abnormal tissue on Magnetic Resonance Imaging (MRI) scans.

Since free Gadolinium is toxic, the Gadolinium ion must be chelated or bound to a ligand (molecule) before it can be used as a contrast agent. The resulting complex is a Gadolinium-Based Contrast Agent or GBCA which is injected intravenously during a contrast-enhanced MRI. GBCAs are also used for contrast-enhanced Magnetic Resonance Angiography (MRA). (Note that MRI and MRA are also performed without contrast.)

The intravenously administered GBCA should move rapidly through the body and then be excreted primarily via the kidneys before the toxic Gadolinium ion and ligand can separate. With normally functioning kidneys, most of the GBCA should be excreted in less than two hours after injection with the remainder being excreted over the next few days. However, impaired kidney function causes the GBCA to remain in the body for much longer periods of time which can result in the separation of the contrast agent and retention of the toxic Gadolinium ion.

In their 1984 report “Gadolinium-DTPA as a Contrast Agent in MRI: Initial Clinical Experience in 20 Patients”, Carr et al warned that “care should obviously be taken in patients with impaired renal and/or hepatic function where high in vivo concentrations of Gd-DTPA may occur for prolonged periods”. Gd-DTPA, also known as Magnevist, was the first Gadolinium-Based Contrast Agent and it was approved by the FDA in 1988. (See Background on GBCAs for details.)
When severe skin problems first appeared in 1997 in a group of dialysis patients, the connection was not made to that initial warning about the use of Gadolinium-Based Contrast Agents in renally-impaired patients. It wasn’t until 2006 that retained Gadolinium from GBCAs was confirmed as the probable cause.

When Gadolinium is retained in the body, it can have serious consequences – the most serious being an incurable and potentially life-threatening disease known as Nephrogenic Systemic Fibrosis or NSF which is thought to primarily affect patients with severely impaired kidney (renal) function. It is widely recognized by the medical community and government agencies that the toxicity of retained Gadolinium is the primary contributor to the development of NSF.

NSF was first thought to be a skin disease, but it was later learned that retained Gadolinium adversely affects all body systems by causing extensive fibrosis and calcification of connective tissue and internal organs. (See Background on NSF for details.)

**Patients exposed to GBCAs are at risk of retaining Gadolinium.**

The risks associated with the administration of Gadolinium-Based Contrast Agents to patients with severely impaired kidney function (eGFR <30) are well-documented and recognized by the medical community and FDA. Patients with normal kidney function are not thought to be at risk of retaining Gadolinium from GBCAs; however, published literature indicates that some Gadolinium from each dose of contrast may remain in the body of all patients exposed to GBCAs.

A 1991 article by Rocklage et al titled “Metal Ion Release from Paramagnetic Chelates: What is Tolerable?” reported that “minute amounts of chelated or unchelated metals are likely to remain in the body for an extended period and could possibly result in a toxic effect.” They also said it was “unlikely that MRI contrast agents would be administered repeatedly in patients”. Unfortunately, many patients do have multiple MRI scans with contrast which can result in more Gadolinium remaining in the patient’s body.

Researchers have estimated that approximately 1% (15 mg) of the 1.5 grams of injected Gadolinium from each dose of contrast (0.1 mmol/kg body weight) may be released from the contrast agent and deposited in the bones of GBCA exposed patients including those with normal kidney function.

The long-term and cumulative effects of retained Gadolinium are unknown as are the additive effects of the double or triple doses often used for contrast MRAs.

Besides severely impaired kidney function, there are other factors that can increase the risk of retaining Gadolinium. Those risk factors include acidosis, transient acute kidney injury (AKI), recent surgery, inflammatory events, abnormal vascularity, compromised blood-brain barrier, cumulative dosage, and transmetallation. Other than kidney impairment, researchers have found that transmetallation presents the greatest potential risk for the release of the toxic metal ion from the chelate. Transmetallation is a potential risk for every GBCA exposed patient. (See Risk Factors for more details.)

**Gadolinium can deposit in brain tissue.**

MRIs with contrast are frequently performed when the brain is being imaged. The brain is protected from potentially harmful compounds in the blood by the semi-permeable Blood-Brain Barrier (BBB). The intact BBB protects the brain from damage, whereas the dysfunctioning BBB allows influx of normally excluded hydrophilic molecules into the brain tissue. A brain tumor or lesion causes a
disruption or break in the BBB. That “break” gives the Gadolinium-Based Contrast Agent access to the brain – regardless of the patient’s level of renal function at the time of his or her contrast procedure.

GBCA product labeling indicates that Gadolinium-Based Contrast Agents “do not cross an intact blood-brain barrier”; however, “disruption of the blood-brain barrier” or “abnormal vascularity” allows accumulation in lesions such as neoplasms (tumors), abscesses, and subacute infarcts. That is why Gadolinium is deposited in brain tumors and brain lesions, such as those seen in Multiple Sclerosis. The abnormal brain tissue then becomes more clearly defined or enhanced on magnetic resonance (MR) images. Gadolinium should not remain in the body; however, the literature indicates that Gadolinium retention has occurred.

A 1995 case report by Martinez noted persistent Gadolinium retention in an extra-axial brain stem lesion of a patient with Erdheim-Chester Disease. Gadolinium retention was confirmed by comparing precontrast and postcontrast images from two MRIs performed 23 days apart. A 1989 case report of Erdheim-Chester disease reported persistent enhancement of intracerebral lesions 8 days after injection with Gd-DTPA. Chemical analysis of the biopsy specimen revealed a high concentration of Gadolinium.

A 2009 study by Fulciniti et al found that a Gadolinium-containing contrast agent promoted Multiple Myeloma (MM) cell growth. Autopsies of 8 MM patients with repeated exposure to the agent found “massive amounts of Gadolinium accumulation in tissues regardless of their renal function”.

A 2010 study by Xia et al found insoluble deposits containing Gadolinium in 7 brain tumor biopsies from 5 patients whose eGFRs were above 53 ml/min, confirming that brain tumors alter the Blood-Brain Barrier which allows the injected GBCA to deposit in brain tissue, even in patients without severe kidney problems.

A 2013 study by Kanda et al found that abnormally high signal intensity detected in two regions of the brain on unenhanced T1-weighted images was related to the number of previous Gadolinium-based contrast enhanced MRIs that had been undergone by the population of patients with normal renal function.

Patients with Multiple Sclerosis (MS) routinely have MRIs with contrast to monitor disease activity and response to treatment. Gadolinium will enhance “active” MS lesions due to a breakdown in the Blood-Brain Barrier. Serial contrast MRIs have shown that active lesions generally enhance for a period of 1 to 2 months on average. The enhancing lesion evolves to a chronic T2 hyperintense lesion, which is the non-specific ‘footprint’ of the prior inflammatory event. It has been speculated “that the initial enhancing-inflammatory lesion events in the brain, place into motion, at an early stage, the processes that ultimately lead to cerebral atrophy, and these processes may include early axonal injury”.

While the role of enhancing-inflammatory lesions in the development of cerebral atrophy in MS is unclear, studies have demonstrated that cerebral atrophy paralleled that of contrast enhancing lesion accumulation. As noted by Simon, atrophy, particularly that resulting from volume loss around the third ventricle, appears to be predicted by the presence of enhancing lesions at baseline. Patients without enhancing lesions at baseline showed no increment (increase) in third ventricle width, while the enhancing group showed significant increments in atrophy. The enhancement is the result of deposited Gadolinium; however, the literature does not indicate whether or not Gadolinium deposition or retention leads to brain atrophy.

Retention of Gadolinium from contrast MRIs has been confirmed in a patient with MS. Results of provoked urine testing for toxic metals after administration of the chelating agent EDTA showed high
levels of Gadolinium. The chelating agent can extract elements from tissue in much higher quantity than would normally be excreted in urine. Removal of Gadolinium and other metals by chelation therapy was reported to definitively improve the patient’s MS symptoms.

While the presence of a brain tumor or lesion alters the Blood-Brain Barrier, there are other ways that the BBB might be crossed or temporarily altered, such as the following:

- Lack of a BBB on the Optic Nerve Head, circumventricular organs (CVOs) and Chorid Plexuses
- Having Type II Diabetes or white matter hypersensitivity like hypertension
- Diffusion into the vitreous and aqueous humors of the ocular globes, perivascular spaces, and ventricles of the brain
- Diffusion into the subarachnoid and subdural spaces
- Effects of Electromagnetic Pulse (EMP) and Electromagnetic Fields (EMF)

Note that findings of delayed and hyperintense enhancement of Cerebrospinal Fluid (CSF) have been reported in patients with normal renal function.

Here are other important facts about Gadolinium and GBCAs.

- Gadolinium is neurotoxic. It inhibits mitochondrial function and induces oxidative stress.
- Gadolinium-Based Contrast Agents can be nephrotoxic.
- Residual Gadolinium from GBCAs has been found in bone and other tissue of study animals that did not have NSF-like skin lesions.
- A 2004 study by Gibby confirmed deposition of Gadolinium in bone tissue from patients with normal renal function 4 days after exposure to a GBCA.
- A 2008 study by Abraham et al presented findings that indicate deposited Gadolinium (Gd) may be mobilized over time from bone stores. “regardless of renal function at present”.
- A 2009 study by Darrah et al found Gadolinium in hip bone removed from a patient 8 years after her last contrast MRI, confirming Gadolinium deposits in bone where it can remain for many years.
- A 2011 Mayo Clinic Study by Christensen et al found detectable concentrations of Gadolinium in fresh tissue specimens taken from two control subjects with normal renal function. Both patients had previous GBCA exposure, one 8 months and the other 16 months before their biopsy.
- The release of Gadolinium from all linear Gd complexes in human serum from healthy volunteers was several orders of magnitude greater than predicted by conditional stability constants.
- Studies have shown that GBCAs affect blood and tissue of subjects with normal kidney function.
• All GBCAs and Gadolinium Chloride (GdCl\textsuperscript{3+}) have been found to stimulate fibroblast proliferation in tissue taken from healthy subjects. (Fibroblasts play a role in the production of connective tissue and fibrosis.)\textsuperscript{99,103,104}

• Macrocyclic agents are thought to be more stable and thereby safer to use; however, even they have been found to deposit in tissue.\textsuperscript{88,105,106} There are now confirmed cases of NSF caused by macrocyclic agents as well.\textsuperscript{107,108}

• Retained Gadolinium affects more than the skin. Autopsies of deceased NSF patients have found extensive multiorgan fibrosis and calcification, as well as vascular and extracellular deposits of Gadolinium.\textsuperscript{109}

Areas affected include: liver, lungs, intestinal wall (ileum), kidney, lymph node, skeletal muscle, diaphragm, mitral valve, aortic arch, great vessels of the heart, cardiac conduction system, left ventricle and septum, blood vessels, atrial myocardium, lesser pelvis, testes, adrenal glands, pancreas, colon, thyroid, gastrointestinal tract including esophagus and stomach, eye, brain parenchyma, subarachnoid space, dura mater including that surrounding the spinal cord.\textsuperscript{110,111,112,113,114,115,116,117,118,119,120,121}

• Patients with normal kidney function are excreting levels of Gadolinium that are well above Mayo Laboratories Reference Range (>0.4 mcg/specimen) as long as several years after their last contrast-enhanced MRI or MRA. (See Self-Study of Retained Gadolinium and Appendix 1 of Symptom Survey Report.)

• Results of our Symptom Survey Report show high levels of commonality in participants’ chronic symptoms of Gadolinium Toxicity. The symptoms are similar to those of NSF patients (See Appendix 2 of Symptom Survey Report.)

The FDA and medical industry directly involved with NSF and GBCAs are aware of these facts. However, clinicians have been told that patients with normal kidney function do not retain Gadolinium and are therefore not at risk from a contrast-enhanced MRI or MRA. Because of that, Gadolinium-related health problems may be greatly underreported.

Editorial comment:

Note the various findings in patients with normal kidney function mentioned throughout this Background on Gadolinium. It would seem that these findings might explain why patients with normal kidney function (meaning eGFR >60) are presenting clinically with various symptoms of Gadolinium Toxicity after a contrast MRI or MRA. The severity of each patient’s symptoms likely depends on the total amount of Gadolinium that he or she retained from the intravenously administered Gadolinium-based Contrast Agent.

NSF may be the most severe manifestation of Gadolinium Toxicity, but there is no logical reason to think it is the only one. We believe that Gadolinium Toxicity is a “disease of degrees”, all of which are potentially serious and life-changing.

Have you been affected by retained Gadolinium from a contrast MRI?

Anyone who has unexplained symptoms that you believe were caused by retained Gadolinium from a contrast MRI or MRA should report it to the FDA by filing a MedWatch Adverse Event Report. Call 1-
800-FDA-1088 or report via the FDA website at
http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm

When filing a report online, remember that Gadolinium-Based Contrast Agents are considered
prescription medications or drugs.

It is important that Adverse Event Reports related to Gadolinium-Based Contrast Agents are filed with
the FDA or the full scope of Gadolinium-related health problems may never be brought to light.
Patients outside the U.S. report to their country’s equivalent governing agency.

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