

Residual or Retained Gadolinium: Practical Implications for Radiologists and Our Patients¹

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Gadolinium-based contrast agents (GBCAs) have been used internationally for more than a quarter century in more than 100 million patients. They are indispensable adjuncts to magnetic resonance (MR) imaging in a broad spectrum of diseases for detection and therapeutic guidance. Their accumulated safety record is extraordinarily positive, with serious adverse reactions in the range of 0.03% of all administrations (1). Until 2006, it had been generally assumed that whatever GBCA had been administered to patients was excreted shortly thereafter or that whatever amount might be retained by the body long term was so small as to be clinically inconsequential. In 2006, two European groups (2,3) recognized and suggested a relationship between nephrogenic systemic fibrosis (NSF) and GBCA in patients with significant renal disease. These reports stimulated inquiries that resulted in permanent changes and restrictions in the product labeling and prescribing information for all GBCAs, created new standards of care that incorporated patient renal function before screening, modified dosing to patients with significant renal disease, and redefined our understanding of, and approach to, the safety of GBCAs as a class. The re-examination also resulted in clear distinctions in the relative safety of individual GBCAs within the clinically approved class. We have still not yet fully or conclusively identified the cause(s) of NSF or determined precisely how the use of some GBCAs resulted in the clinical manifestation of this disease while other GBCAs did not. What is now known, however, is that by limiting the use of the observed high-risk agents to patients without severe renal disease and substituting agents with an apparently lower NSF association, the incidence of NSF has

dropped dramatically. NSF taught us that, for patients with significantly impaired renal function, we had reason to be concerned about abnormally prolonged elevated gadolinium levels.

In 2014, we were first exposed to another consideration—that of residual gadolinium in patients with normal renal function. First publicized by Kanda et al in 2014 (4), the connection was made between abnormal T1 shortening in the globus pallidus and the dentate nuclei in patients who had undergone repeated prior administration of gadopentetate dimeglumine and/or gadodiamide. Strengthening their observation was the apparent dose-response relationship wherein the greater the number of previous GBCA administrations the greater the degree of observed intracranial T1 shortening. Shortly thereafter, Errante et al (5) confirmed the presence of abnormal T1 shortening in the dentate nuclei in patients with normal renal function who had received multiple doses of (only) gadodiamide. Once again, a dose-response relationship was evident in that study. A subsequent report by Kanda et al in 2015 (6) documented that the T1 shortening observed in the dentate nuclei was observed to be associated with the previous repeated administration of the ionic linear GBCA gadopentetate dimeglumine, but not the previous repeated administration of the nonionic macrocyclic GBCA gadoteridol. By observing this same effect on patients with meningiomas who had undergone repeated imaging with gadodiamide but had not undergone any sort of interim treatment, Quattrocchi et al (7) were able to confirm that the effect was due to the repeated gadodiamide administration and not to any iatrogenic therapeutic intervention(s). Detection of GBCA with MR imaging has been limited to the order of approximately 30 $\mu\text{mol/L}$ for chelated GBCA

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Conflicts of interest are listed at the end of this article.

See also the articles by McDonald et al and Radbruch et al in this issue.

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(8). Hence, the amounts deposited or detected appear to be of roughly that order.

In this issue of *Radiology*, Radbruch et al (9) add to our rapidly increasing fund of knowledge on this subject by confirming that, in a total of 100 patients studied, the dose-dependent T1 shortening effect on the global pallidus and dentate nuclei was observed with repeated previous administrations of gadopentetate dimeglumine but not with repeated previous administrations of the macrocyclic agent gadoterate. Thus, the data appear to be separating according to GBCA class, as they had in NSF. This lends support to the hypothesis that the observed T1 shortening may represent a consequence of the dissociation of the gadolinium ion from its chelating ligand molecule.

Although it had been conjectured that the observed T1 shortening was a result of gadolinium accumulation in the tissues of these patients, that hypothesis had not previously been verified. For example, calcium is known to normally accumulate in the global pallidus in some patients, and increased manganese deposition is theorized to cause the abnormal T1 shortening seen in the global pallidus in patients with severe hepatic disease or chronic hyperalimentation (10). Thus, it was possible that the accumulation or deposition of other moieties or metals might underlie the observed T1 shortening.

With the publication of the article by McDonald et al in this issue of *Radiology* (11) and Kanda et al's confirmatory findings (12), we can now confirm gadolinium deposition in these areas of T1 shortening. The McDonald group evaluated 13 autopsy specimens from patients (all with an estimated glomerular filtration rate [eGFR] of 49 mL/min/1.73 m² or higher) who had undergone at least four MR examinations with gadodiamide and 10 from subjects in whom a GBCA had never been administered. The Kanda group evaluated autopsy specimens from five patients with eGFRs greater than 45 mL/min/1.73 m² who had received at least two total doses of gadopentetate dimeglumine and either gadodiamide or gadoteridol

and compared them to the findings in five autopsy specimens from patients in whom GBCA had not been previously administered. Using inductively coupled plasma mass spectrometry, transmission electron microscopy, and light microscopy, McDonald et al (11) confirmed the presence of gadolinium in the neuronal tissues of the global pallidus, dentate nuclei, pons, and thalamus. Furthermore, a direct relationship was observed between the amount of gadolinium detected in their brains and the total cumulative lifetime gadodiamide doses for each of the 13 gadodiamide-exposed patients, which also correlated well with the degree of T1 shortening observed in these tissues. Although the detected gadolinium was predominantly clustered in the endothelial walls, roughly a third of all detected gadolinium appeared to have crossed an intact blood-brain barrier and deposited into the otherwise normal neuronal interstitium. It is not certain in what form the gadolinium (free gadolinium ion or intact gadolinium chelate) crossed the blood-brain barrier, but the facts suggest that our understanding of the biodistribution of gadolinium is yet incomplete. Also using inductively coupled plasma mass spectrometry, the Kanda group found the presence of gadolinium, not only in the global pallidus and dentate nuclei but also in frontal lobe cortex, frontal lobe white matter, and cerebellar white matter, at concentrations that far exceeded those seen in the control group. These provocative findings cause us to reconsider what we know and what we need to learn to better care for our patients.

It is widely recognized that rare earth heavy metals, such as gadolinium and other members of the lanthanide elements, can be toxic to mammals. The specifics underlying the potential toxicity of free Gd³⁺ ion (ie, gadolinium not bound in a strong gadolinium chelate) are numerous and, considering the extent to which GBCAs are being routinely used in humans, surprisingly not as well defined as we might like to think (8). Most of the known toxicity of free Gd³⁺ ion can be connected with two properties: (a) insolubility at physiologic pH resulting in very slow systemic excretion

and (b) a crystal size close to that of Ca²⁺ that allows small amounts of the tripositive Gd³⁺ to compete biologically with dipositive Ca²⁺. Long-term retention of implanted insoluble gadolinium leads to benign neoplasms (13) and fatty degeneration of liver (14). Calcium interference effects are well documented and include potential involvement in angiotensin-converting enzyme, macrophage inhibition, neurotoxicity (some of which appears to be partially blocked by the anti-oxidant *N*-acetylcysteine) (15), blocking neuromuscular transmission (16), cardiovascular, and other effects (17), but little is known about the toxicology of Gd³⁺ ion in humans, especially about the levels required to achieve clinical significance in humans.

Certainly, the acute toxicity associated with free Gd³⁺ precludes its use as a human contrast agent and is the reason it must be bound to a powerful chelating molecule. This structure permits the gadolinium chelate to remain paramagnetically active while markedly elevating the dose at which 50% of test animals acutely die (LD₅₀). For example, in rats, the LD₅₀ for GdCl₃ (0.5 mmol/kg) increases 16- to 21-fold when the gadolinium is instead bound as a Gd-DTPA (LD₅₀, 8 mmol/kg) or Gd-DOTA (LD₅₀, 10.6) (18). Thus, it is the chelation of the Gd³⁺ ion to the various chelating molecules used in the commercial gadolinium chelate preparations that renders them sufficiently acutely safe for intravenous human administration. Companies typically also determine subacute tolerance of GBCAs by applying daily or multiple weekly doses for several weeks at the highest dose that produces no acute symptoms, (ie, >10 times the clinical dose) and follow up these studies with full organ microscopic pathologic examination. Such studies are designed to, and do generally, produce some signs of toxicity at extreme doses (19).

Integral to the safety of GBCAs is the persistence of the gadolinium chelate bond for as long as the GBCA remains within the patient. With normal renal function, the typical 90-120-minute biologic half lives of these central nervous system GBCAs are sufficiently

short that the amount of dissociation of the gadolinium chelate bond that could potentially occur while the agent is still in the patient has been considered clinically trivial. However, a significant decrease in renal function increases the duration that the GBCA remains in the patient, thus increasing the potential for in vivo gadolinium chelate dissociation (20). The forces that can accomplish gadolinium chelate dissociation are well known to be available in vivo, and gadolinium chelate dissociation has been conclusively documented in human serum over days to weeks (21). This dissociated free Gd^{3+} would, if detected, be present as insoluble phosphates, bicarbonates, or hydroxides and/or possibly protein bound. The presence of elevated phosphate levels, as for example are often present in dialysis patients, increases the likelihood of gadolinium chelate dissociation for high NSF risk subclasses of the GBCA in clinical use today (21,22). Because NSF is associated predominantly with GBCAs that more rapidly dissociate free gadolinium under stress, the “transmetalation theory” conjectures that gadolinium chelate dissociation in vivo participates with unknown other factor(s) to begin the chain of events that ultimately lead to clinical NSF.

The different brands of GBCA available for clinical use today differ primarily in the chelating ligand molecule used to form the gadolinium chelate. The macrocyclic gadolinium chelates are considerably more resistant to dechelation in vivo than are the linear gadolinium chelates, particularly the nonionic linear chelates. The technical arguments that explain these facts, including transmetalation or other theories, are less relevant to the current discussion than are the facts themselves: Gadolinium released and retained in vivo in animals (22), in human serum (21), and in humans to the growing extent measured with past and present studies increases by GBCA class from barely to undetectable in macrocyclic GBCA, to greater amounts detected for ionic linear GBCA, to the greatest amounts in nonionic linear GBCA. NSF is associated with the

previous unconfounded administration of gadodiamide and gadoversetamide (nonionic, linear GBCA) and is present but less so with gadopentetate dimeglumine (a linear ionic GBCA) but rarely or not at all following the previous unconfounded administration of macrocyclic GBCAs (23,24).

It should be stressed, however, that the transmetalation theory in and of itself seems insufficient to account for all that we know about NSF. For example, gadopentetate dimeglumine and gadobenate are both linear ionic GBCAs, yet there have been roughly 100 cases of NSF following the previous unconfounded administration of gadopentetate dimeglumine and none following the previous unconfounded administration of gadobenate (23,24). Furthermore, despite its macrocyclic structure, gadobutrol seems to have been associated with at least two cases of NSF that were associated with its previous unconfounded administration (25).

One of the self-stated limitations of the study by McDonald et al (11) is that “...it remains unclear if the gadolinium detected in neuronal tissues remains in a chelated state or free ionic form.” Similarly, Kanda et al (12) stated that “...our results show only gadolinium deposition; its specific form (ie, as a dissociated gadolinium ion or a chelated gadolinium compound) was not determined.” Although this remains true in studies of brain biopsies, the same question has been recently answered in skin biopsies from a patient with apparent NSF. Using an ingenious and coordinated approach combining inductively coupled plasma mass spectrometry, laser ablation inductively coupled plasma mass spectrometry to quantify and provide high-resolution histologic gadolinium spatial localization information, and hydrophilic interaction liquid chromatography inductively coupled plasma mass spectrometry to identify the form in which the gadolinium is found, Birka et al (26) examined a 25-year-old woman with renal failure who was on dialysis (after two renal transplants) with signs and symptoms characteristic of

NSF. This patient had received gadopentetate dimeglumine in 2002 as well as gadoteridol in 2005. Their studies of skin biopsies from affected regions in this patient revealed the presence of gadolinium in the biopsy specimens at concentrations ranging from 3.02 to 4.58 mg/kg. They reported finding the highest levels of gadolinium in the walls of blood vessels in the subcutis, consistent with the results of McDonald et al (11), with additional but lower levels in the connective tissue of subcutaneous tissue septae and deeper connective tissue. These spatial distributions of gadolinium also paralleled the spatial distribution maps of calcium and phosphorus. They also reported that the predominant form of gadolinium in the skin sample was gadolinium phosphate, $GdPO_4$. Remarkably, they also reported for the first time in the peer-reviewed literature the presence of intact gadoteridol in the skin biopsy at a concentration of $1.76 \text{ nmol/L} \pm 0.05$ 8 years after the last administration of gadoteridol in that patient. No intact gadopentetate dimeglumine could be identified in the specimen, presumably, as per the conjecture of the authors, due to the lower in vivo stability of this agent (compared to gadoteridol) and its presumed dechelation by the time of biopsy. Two other forms of gadolinium were also detected in the skin biopsy, but their molecular form or species could not be identified. The presence of considerable quantities of $GdPO_4$ as well as other still-unidentified molecular gadolinium-containing moieties supports what must be considered definitive evidence of dechelation and release of the Gd^{3+} ion from administered GBCA. The presence of intact gadoteridol molecules more than 8 years after its last administration is itself unanticipated, albeit at a nanomolar level in compromised tissue in a patient undergoing dialysis with presumed NSF.

The findings of Kanda et al (6), Errante et al (5), McDonald et al (11), and others are restricted to those patients demonstrating significant intracranial T1 shortening. As suggested or documented by the work of Gibby

et al (27), White et al (28), Darrah et al (29), Birka et al (26), and others, $GdPO_4$ and other insoluble forms of gadolinium may make up a significant percentage of all residual gadolinium in humans after the administration of at least some of the GBCAs in use today. It is interesting to note that insoluble $GdPO_4$ or soluble protein-bound gadolinium would not have, a priori, a known effectiveness at T1 shortening. As such, the possibility exists that MR imaging may significantly underestimate how much gadolinium may be retained in human tissues where it is detected, and by omission also in which tissues it may be found. MR imaging alone is not a reliable analytical tool for the detection of gadolinium of unknown composition and environment.

Recommendations

At this stage, we now have clear evidence that the administration of various GBCAs results in notably varied levels of accumulation of residual gadolinium in the brain and bones of patients, even those with normal renal function. What we still do not know is the clinical significance, if any, of this observation. The present data now confirm that long-term multi-year residual gadolinium at these observed levels is a reality for some, but not all, of the GBCAs.

As we are now discovering new information regarding the biodistribution and pharmacokinetic behavior of at least some of these GBCAs, we suggest that the radiology community should consider these findings when using these agents. We must first and foremost confirm that the requested contrast material-enhanced MR examination is truly indicated. We must now also consider the unknown risks of previously unanticipated residual gadolinium in our decisions as to which agent to administer, how much to administer, and whether to administer it at all.

Gadolinium administration has only been approved under the assumptions that (a) the potential substantial benefits outweigh any known risks, (b) the risks of administration are relatively well established, and

(c) the administered GBCA will be effectively excreted from the body in a rapid and timely fashion and pose no serious long-term or lasting deleterious effects. Because new data are now becoming available regarding the basic underlying pharmacokinetics of at least a small but unknown fraction of administered GBCAs, it seems most appropriate to ensure that we re-review all that we now know about GBCAs and affirm what we consider to be their appropriate uses and indications. Research is needed to confirm the existing findings, particularly to confirm whether the use of a given GBCA will avoid or minimize the residual gadolinium. Extension of the elegant separations of Birka et al (26) to brain biopsies would inform on chemical speciation of the residual intracranial gadolinium. Postmortem biopsy studies should be extended to other organ systems in animals and humans. Most difficult, but highly important, would be studies to determine whether there are indeed any toxic effects of residual gadolinium in organs where it is detectable, including the brain, and here such studies should include cognitive ones. Finally, the search for more effective MR imaging agents should continue to occupy scientists in both academic and commercial laboratories. How our funding agencies and commercial partners spend money on research should be important to us, especially as the safety of at least some of these vital GBCAs is being called into question.

GBCAs are extremely valuable to patients worldwide and have been so for decades. Our use of these and other exogenous agents has always been guided by risks and benefits, and new knowledge will inevitably affect both the numerator and the denominator of the equation. Of all of the possible endings to this story, one of the worst would be for us to unnecessarily deprive our patients of crucial, even life-saving, medical data from GBCA-enhanced MR imaging. Another would be for us to ignore these new findings and continue prescribing them as we have until now, without change.

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