Gadolinium based contrast agents in current practice: Risks of accumulation and toxicity in patients with normal renal function

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Abstract

Despite being decked as the most prized compounds in the nugget box of contrast agents for clinical radiologists, and carrying an indisputable tag of safety of the US Food and Drug Administration for close to three decades, all may not be seemingly well with the family of gadolinium compounds. If the first signs of violations of *primum non nocere* in relation to gadolinium-based contrast agents (GBCAs) appeared in the millennium year with the first published report of skin fibrosis in patients with compromised renal function, the causal relationship between the development of nephrogenic systemic fibrosis (NSF) and GBCAs, first proposed by two European groups in 2006, further precluded their use in renocompromised patients. The toxicity, pharmacokinetics, and pharmacodynamics of GBCAs, however, has come under hawk-eyed scrutiny with recent reports that gadolinium tends to deposit cumulatively in the brain of patients with normal hepatobiliary function and intact blood–brain barrier. While the jury on the long-term hazard significance of this critical scientific finding is still out, the use of GBCAs must be guided by due clinical diligence, avoidance of repeated doses, and preferring GBCAs with the best safety profiles.

Key words: Gadolinium-based contrast agents; long-term toxicity; nephrogenic systemic fibrosis; neuronal deposition

Introduction

Considered hugely safe, engined by their water proton relaxation catalyst properties, the unique nine-membered family of gadolinium-based contrast agents (GBCAs) has gained a dominant clinical role in the arena of magnetic resonance imaging (MRI). In clinical harness since 1988, these paramagnetic pharmaceuticals are known to shorten the T1 and T2 relaxation times of the adjoining hydrogen nuclei, thus, enhancing the soft tissue contrast and helping in the characterization of a wide array of pathologies, be it inflammatory or malignant conditions, fibrosis, or perfusion and marrow disorders.

Born out of a free gadolinium ion, which is inherently toxic, GBCAs have been created by chelating with a ligand to form a stable complex, which protects tissues from interactions with Gd^{3+} ions and enables rapid renal clearance of the Gd^{3+} ions to minimize biotransformation or accumulation

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in the body. While eliminating their toxicity, the chelating process also regulates their pharmacokinetics.

The safety record of GBCAs has been extremely impressive. Literature places the incidence of severe adverse reactions with GBCAs to be as low as 0.01%.[1] During the first many years of their usage, until the late 1990s, GBCAs were found to be far less nephrotoxic than the iodinated contrast media.[2] These early favorable results encouraged liberal use of GBCAs as "safe" contrast agents. In addition to their usage in MRI examinations, GBCAs also came to be used as substitutes for iodinated contrast media while carrying out conventional angiographies and contrast computed tomography in patients with deranged renal function.

This trusting belief was, however, soon demolished by a concatenation of studies, which revealed a relationship between the use of GBCAs and the development of nephrogenic systemic fibrosis (NSF). The first report of skin fibrosis in these patients appeared in the year 2000.[3] Six years later, two European groups suggested the causal relationship between the development of nephrogenic systemic fibrosis (NSF) and GBCAs.[4,5] These studies came as a rude shock and necessitated "*The Contrast Media Safety Committee of European Society of Urogenital Radiology*" to establish guidelines on NSF in 2007.[6] Since then, considerable literature has emerged which establishes a linear relationship between insufficient excretion of GBCAs in renocompromised patients and NSF due to retention of dissociated gadolinium. This risk was found to vary with the structure of each GBCA, being much higher in the case of non-ionic linear chelates than the relatively biostable macrocyclic GBCAs owing to the rapid dechelation of the former. These studies led to distinct modifications in the usage of intravenous MRI contrast agents, bringing the villain of NSF to heel.

However, even before the fire of NSF was to go cold, new alarm bells have begun to toll. The more recent scientific literature seems to point that, despite a normal hepatobiliary function and intact blood–brain barrier, patients receiving GBCAs are liable to suffer gadolinium deposition in the neuronal cells. Specific brain regions have been found to demonstrate distinct MR signal changes due to cumulative gadolinium deposition in the wake of usage of GBCAs. Until recent, these changes were erroneously thought of as signs of specific pathologies. Much like NSF, this risk also appears to vary with the structure of GBCA used. The clinical import of this neuronal gadolinium deposition, however, still needs to be defined. Whether this would impair the neuronal function in the long run, or simply reflect a morphological artefact, remains a major clinical enquiry.

Until the long-term clinical significance of this major scientific find is established, it is imperative that, guided by the cardinal principle of *primum non nocere*, the use of GBCAs must be guided by due clinical diligence, avoidance of repeated doses, and preference for GBCAs with best safety profiles. No more should GBCAs be touted as holy contrast agents.

This brief review, while discussing the toxicity, pharmacokinetics, and pharmacodynamics of GBCAs, recapitulates the current literature on tissue deposition of gadolinium, and delves on clinical concerns and prudent recommendations in relation to their clinical usage.

Gadolinium: The Chemistry Behind its Pernicious Behavior

A rare earth element from the lanthanide series, gadolinium carries strong paramagnetic properties which can be exploited to provide enhanced contrast between healthy and diseased tissues. However, gadolinium is toxic to humans in its free form (Gd^{3+}). Free gadolinium is excreted very slowly owing to its insolubility at physiological pH, and has an ionic radius close to calcium allowing it to compete with it various physiological processes. As a result, it can block various calcium-gated channels, act as an agonist on calcium-sensing receptors, and inhibit activity of various enzymes. This necessitates its chemically bonding to an organic ligand so that it can be excreted by the kidneys before the free ion is released in the body. GBCAs are aminopolycarboxylic acid ligands chelated to gadolinium and can be subdivided according to their molecular structure into ionic linear, nonionic linear, and macrocyclic chelates. The macrocyclic chelates are more stable than the linear type and ionic linear chelates more than non-ionic linear chelates in the laboratory. However, all types of chelates have been considered sufficiently stable in the body in patients with normal kidney function.[7-11]

In vivo, the various endogenous cations (e.g., Fe^{3+}, Cu^{2+}, Zn^{2+}, Ca^{2+}) compete with Gd^{3+}ions for the ligand, awhereas the endogenous anions (e.g., phosphate, carbonate, hydroxide) compete for the Gd^{3+}ions. This competition may destabilize the gadolinium complex in biologic fluids and shift the dissociation equilibrium toward its free components, which bind to other agents rapidly. This exchange process is termed "transmetallation."[a11]

GBCAs can also be classified according to their biodistribution as extracellular, combined intracellular–extracellular, and blood pool agents. 98% of the GBCAs are excreted unchanged by the kidneys without any biotransformation. Patients with poor renal function have reduced GBCA excretion. As a result, GBCAs remain in the body for a long time, increasing their probability to dissociate and deposit in the body. Biliary route is also an important pathway of excretion for combined intracellular–extracellular GBCAs in these patients.[11]

The Birth of a Hypothesis: Does Gadolinium Deposit in the Brain?

A significant recent development in the field of GBCAs includes reports of gadolinium retention in brain of patients with normal renal function. First reported in December 2013 by Kanda *et al*., this new finding has raised doubts regarding the long held thought of positive safety of GBCAs.

Kanda *et al*. calculated the dentate nucleus-to-pons and globus pallidus-to-thalamus signal intensity ratio in patients who underwent more than six contrast-enhanced MRI (CE-MRI) examinations in the past. They established a positive correlation between the number of previous GBCAs administrations, and high signal intensity in the dentate nucleus (DN) and globus pallidus (GP) on unenhanced T1-weighted MR images. A significant dose-response relationship was also established.[12] Studies by Erante *et al*. and Weberling *et al*. confirmed these findings with gadodiamide and gadobenate dimeglumine, respectively.[13,14]

Miller *et al*. and Roberts *et al*. published two individual case reports of a pediatric patient with increased signal intensity changes in GP and DN after multiple CE-MRI examinations, similar to those described in adults in previous articles.[15,16]

These groups hypothesised that the high signal intensity found in GP and DN was attributable to gadolinium being dechelated from GBCAs and retained in the brain for a long time irrespective of renal function.[12,13]

Gadolinium accumulation, not pathologies, represent magnetic resonance signal changes

In 2009, hyperintense dentate nuclei were described by Roccatagliata *et al*. in patients with multiple sclerosis (MS) to be associated with secondary progressive disease subtype and with increased clinical disability, lesion load, and brain atrophy.[17] Similar findings were also described by Kashara *et al*.in cases of brain irradiation.[18]

Kanda *et al*.hypothesised that high signal intensity of GP and DN seen in these patients with previous irradiation and MS also could be attributable to previous GBCA administrations only.[12]

Adin *et al*. retrospectively studied multiple longitudinal CE-MR examinations of patients treated with brain radiation. They validated that an increase in the total number of CE-MRI scans (≥4) and hence the total amount of gadolinium administration (total dose of >77ml) significantly increased the risk for developing hyperintense DN. They also found no correlation between brain irradiation and development of hyperintense DN, thus complementing the results of Kanda *et al*.[19]

In view of recent developments, it would be wise to consider a possibility of gadolinium deposition leading to hyperintense DN in patients of MS and brain irradiation.

Molecular structure of gadolinium-based contrast agents and neuronal gadolinium deposition

In 2015, Radbruch *et al*. and Kanda *et al*. stated that signal intensity increase in the DN and GP on T1-weighted images was only seen with serial administration of the linear GBCA (gadopentetate dimeglumine) but not with macrocyclic GBCA (gadoterate meglumine).[20,21] Cao *et al*. in 2016 also published data complementing previous studies. DN T1 hyperintensity was seen after multiple administrations of gadopentetate dimeglumine, a linear ionic agent, but not after gadobutrol, a macrocyclic GBCA.[22] Radbruch *et al*. also found no changes in the signal intensities of GP and DN after serial injections of the macrocyclic GBCA gadobutrol.[23]

Similar results were also published in healthy rats by Robert *et al*. in April 2015. They demonstrated a progressive and significantly increased T1 signal hyperintensity in the deep cerebellar nuclei after linear GBCAs administration (gadodiamide), which was not seen with macrocyclic GBCAs (gadoterate meglumine).[24]

All these studies supported the hypothesis that the molecular structure of a GBCA as either macrocyclic or linear is a crucial factor for its potential to cause gadolinium deposition in the brain.

Later, Stojanov *et al*. published contradicting data that an increase in signal intensity within the DN and GP on unenhanced T1-weighted images in patients with relapsing remitting multiple sclerosis may be a consequence of multiple administrations of gadobutrol (macrocyclic GBCA). Administration of the same amount of gadobutrol over a shorter time period in their study caused a greater increase in signal intensity. This is the only study suggesting a macrocyclic GBCA to be associated with this phenomenon. However, the authors have specifically mentioned that they could not control for or exclude the use of other contrast agents, including linear GBCAs, which could be a confounding factor. Moreover, the correlation mentioned in the study is weak (0.23). Shortly after, Agris *et al*. fuelled concerns over limitations in their study design and confounding factors that do not support any conclusion regarding the role of repeated administrations of GBCAs in general or a specific contrast agent in this particular patient group.[25,26] Therefore, it is yet not clear whether the molecular structure of GBCAs plays a role in their brain deposition or not.

Ramalho *et al*. proved that globus pallidus-to-thalamus signal intensity ratio (GP:T) and Dentate nucleus-to-middle cerebellar peduncle signal intensity ratio (DN:MCP) increased only after serial administrations of gadodiamide, a linear nonionic GBCA but not after gadobenate

dimeglumine, a linear ionic contrast agent. The differences in the stability and elimination of both contrast agents could be implicated as the cause.[27]

Thus, the data from these studies appears to be segregated according to GBCA class, similar to NSF in the past. This lent additional 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.

The Coming True of Hypothesis: Evidence of Gadolinium Deposition in the Brain

The conjecture of deposited gadolinium causing T1 hyperintensity in brain MRI scans lacked histopathological validation.

In June 2015, Mc Donald *et al.* published another study supplementing our current knowledge and proving the hypothesis of neuronal tissue gadolinium deposition in patients with normal renal function. They harvested autopsy brain specimens of patients with relatively normal renal function who had undergone at least four GBCAs (gadodiamide) administration, along with a control group. Formalin-fixed samples of the DN, GP, pons, and thalamus were studied with inductively-coupled plasma mass spectroscopy (ICP-MS), transmission electron microscopy, and light microscopy to quantify, localize, and assess the effects of gadolinium deposition. Gadolinium deposition in the capillary endothelium and neural interstitium was observed only in the contrast group. Significant dose-dependent relationship was found in the test group between tissue gadolinium concentration and previous GBCAs administration that correlated with signal intensity changes on precontrast T1-weighted MRI. The study results were unrelated to renal function, age, or interval between exposure and death. The detected gadolinium was predominantly clustered in the endothelial walls, however, roughly 18–42% of all detected gadolinium had crossed an intact blood–brain barrier and deposited into the otherwise normal neuronal interstitium.[28]

In July 2015, Kanda *et al.* published another similar study complementing the results of Mc Donald *et al.* They found increased tissue gadolinium concentrations in formalin fixed autopsy samples of the DN, inner segment of the GP, cerebellar white matter, frontal lobe cortex, and frontal lobe white matter using ICP-MS, in patients with previous GBCAs administration compared to control group. They also established that higher concentration of gadolinium was found in GP and DN compared to other brain regions in the test group who had been administered GBCAs.[29]

Ionic vs chelated form of deposited gadolinium
Published literature establishes neurodeposition of gadolinium, however, fails to specify the form of deposition as dissociated gadolinium ion or a chelated gadolinium compound. In the case of the former, a shift to the use of a macrocyclic-type GBCA may inhibit gadolinium deposition, as this type is more stable than linear-type GBCA.[28,29] This limitation is because of the currently available tissue-based assays. They are capable only of detecting elemental gadolinium owing to their technical limitations because the extraction method and ionization of these tissues destroys the organic ligand.[30,31]

Gadolinium Deposition in Bone

Gadolinium deposition has been proven in bones of patients with normal renal function by Gibby *et al.*, Darrah *et al.*, and White *et al.*[32-34]

Murata studied the deposition of gadolinium in brain and bone tissues in patients with normal renal function receiving GBCAs. They found that deposition of gadolinium in cortical bone occurs at much higher levels compared with brain tissue with a notable correlation between the two. They proposed the bone as a surrogate to estimate brain deposition if brain gadolinium were to become a useful clinical or research marker.[35]

Clinical Concerns and Recommendations

Far back in 1991, Rocklage *et al.* proposed that minute amounts of chelated or unchelated metals were likely to remain in the body for an extended period and could possibly result in toxic effects. His proposition appears to be true with regard to Gd^{+3} and GBCAs in the light of various recent studies.[36]

Earlier, we had studies describing gadolinium deposition in bone in patients with normal renal function. Now, we have studies establishing gadolinium deposition in brain tissues also. The presence of gadolinium accumulation within nondiseased neuronal tissues despite apparently intact blood–brain barrier challenges our understanding of the biodistribution of GBCAs after intravenous administration.[31,37-39] The true mechanisms of gadolinium retention and neuronal deposition remain unknown despite innumerable studies on the complex pharmacokinetics of GBCAs.

NSF is a well-documented long-term complication of administration of weaker chelates of GBCAs to patients with poor renal function. However, we are unaware of the detrimental long term complications of retained gadolinium in patients with normal renal function. The potential risks and associated clinical significance of this entity have not yet been explicated and merit additional research.

Similar MR signal intensity changes reported in the brain of patients suffering from neurological disorders such as

MS, neurofibromatosis, hypoparathyroidism, inherited metabolic disorders, and Fahr disease suggest that these areas may be vulnerable to metal deposition.[12,13,40]

Brain toxicity of gadolinium has been proven in rats when administered via intraventricluar route or by intravenous route with disrupted blood–brain barrier.[41] It is probable that gadolinium deposited in brains of healthy individualscould bear adverse outcomes. It is imperative that we cannot ignore these new troublesome discoveries and continue prescribing GBCAs as per our current protocols.

In a press release by RSNA in May 2015, Dr.Kanal emphasized that physicians should consider the unknown risks of residual gadolinium when deciding about the need, type, and amount of contrast agent to administer. However, he also affirmed that GBCAs can be extremely valuable in providing crucial, even life-saving medical data, and patients should not be deprived of the same.[42]

The U.S. Food and Drug Administration also made a safety announcement in July 2015 stating that it is investigating the risk of brain deposits following repeated use of GBCAs for MRI. It suggests health care professionals to consider limiting GBCA use to clinical circumstances in which contrast administration provides important additional information, so as to reduce the potential for gadolinium accumulation. It also urged physicians to reassess the necessity of repetitive GBCA MRIs in established treatment protocols.[43]

Conclusion

We now have compelling evidence concerning the accumulation of residual gadolinium in the brain of patients with normal renal function following GBCA administration. This calls for amendments in the current contrast administration protocols.

We recommend a genuine effort to keep the dose of GBCAs to minimal required, acknowledging the significant dose-dependent neuronal accumulation of gadolinium in the studies. The advantages of gadolinium administration should be carefully calculated against the potential risks for every patient before administering any GBCA, instead of following routine imaging protocols. A careful evaluation should be performed for each patient pertaining to the supplemental information that GBCAs can yield.

GBCAs should be administered only when the benefits outweigh the risks. When being administered, the dose of GBCAs should be kept to the minimum possible while providing all important imaging details and repetitive CE MRI scans should be avoided to all extents possible.

Data in literature seems to be segregated according to class of agents. Studies suggest that macrocyclic GBCAs are more stable as compared to their linear counterparts, and hence exhibit lesstendency for neuronal deposition. Therefore, incorporating them as a preferred class of GBCAs in clinical practice could diminish the unforeseen dangers.

The hypothetical cumulative and long-term effects of retained gadolinium warrant special attention while decision making when performing CE-MRI scans in children and young adults, who may have to bear the brunt of any potential side effect life-long.

We are presently oblivious to the probable dangers of retained gadolinium in the brain, and must execute gadolinium administration with wariness. However, GBCAs can impart pivotal life-saving information in numerous circumstances, which our patients should not be deprived of. Thus, we need not be strongly opined against GBCAs, and should rather strike equilibrium in the pros and cons in individual cases.

In the end, we conclude that it is important on the part of the radiological community to critically analyse risk–benefit ratios of contrast administration while performing each MRI scan till the results of further long term studies relating to this subject become available.

Conflicts of interest
There are no conflicts of interest.

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