Review Article

Gadolinium Retention in the Human Body after Administration of Magnetic Resonance Contrast Agents: Where We are Now

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Abstract

In the last 3 years, clinical and pre-clinical studies demonstrated a progressive increase in the concentration of Gadolinium in the brain of patients with normal renal function, following repeated injections of some of the commercially approved Gadolinium Based Contrast Agents (GBCA). Till now no association has been demonstrated between Gadolinium presence in the brain and any kind of neurological signs or symptoms, but there’s need to modify the current approach in using Gadolinium contrast media in daily clinical practice, in order to reduce unknown possible risks for patients. On 21 July 2017, the European Medicines Agency (EMA) confirmed the suspension of the authorisations for the European market for four GBCAs, due to Gadolinium deposition in brain tissue. Recently, some recommendations are produced on behalf of the International Society for Magnetic Resonance in Medicine, an attempt to balance the potential harm of Gadolinium deposition with the proven clinical utility of GBCA.

Introduction

The use of Gadolinium as MRI contrast agent is due to its strong ability to reduce T1 in tissues, inducing a high contrast efficiency. With more than 360 million procedures performed to date, contrast-enhanced MRI is a well-established and safe diagnostic imaging technique that is used worldwide [1].

Free Gadolinium (Gd) ions can have adverse biological effects. Therefore, the Gd ion needs to be chelated to a polyamino-carboxylic-acid agent when used as a contrast medium. On the basis of the chemical structure of the chelating molecule, GBCAs can be divided into 2 classes: linear and macrocyclic, and each class can be subdivided into ionic and non-ionic (Figure 1).

Macroyclic and linear agents show a different trend to release free Gd, due to their different thermodynamic, kinetic and conditional stability. Macroyclic GBCA are more stable and inert, whereas linear GBCA are characterized by a lower complex stability and a faster trend to release free Gd; the difference in stability can be explained by the intrinsic physicochemical properties of the molecules: it has been proven that the molecular geometry of macrocyclic agents, the presence of basic polyaminocarboxylates and the higher number of coordination sites for Gd ion provide a better stability and thus a lower trend to release free Gd than linear.

Figure 1: Commercially available GBCA, classified according to molecular structure and charge (From JM Ideé et al., Role of thermodynamic and kinetic parameters in Gadolinium chelate stability, Journal of Magnetic Resonance Imaging, 2009).
agents [2]; the lower stability of linear GBCA has been proven to play an essential role in the pathogenesis of Nephrogenic Systemic Fibrosis (NSF) in patients at high risk [2,3].

In the last 3 years several retrospective studies in patients with normal renal function, who underwent multiple administrations of GBCA, have reported increased T1 signal intensity in the dentate nucleus and globus pallidus [4-6,9-13], thus leading research to focus on Gd retention and on possible long-term effects of GBCA in patients without kidney impairment.

**Evaluation of Gd Deposits with MRI Studies**

Research about Gd retention started with a paper published by Kanda et al., [4] in which authors reported a linear increase of dentate nucleus and globus pallidus T1 signal intensity and its correlation with the number of previous GBCA injections. This study showed for the first time that hyperintensity in the dentate nucleus could be related not only to a history of brain irradiation or secondary progressive subtype of multiple sclerosis, but to the number and the total amount of GBCA administered.

Errante et al., [5] reported T1 signal intensity increase in the *dentate nuclei* and *globi pallidi* in 2 different groups of normal renal function patients (multiple sclerosis and brain metastases patients), and the correlation of the hyperintensity with the total number of gadodiamide (linear non-ionic) administrations.

Tedeschi et al., [6] reported a correlation between GBCA administration and in vivo T1 and T2* relaxometry of *dentate nucleus*, showing that hyperintensity was related to the presence of Gd and not to other metals (e.g., Fe).

Further studies demonstrated that hyperintensity may be also seen in other anatomical sites: Zhang et al., [7] have demonstrated that after 46 injections many other brain structures are involved (*substantia nigra*, thalamus, colliculi, etc.); Khant et al., [8] showed that after 86 injections of linear GBCA the T1 signal intensity was increased also in the grey matter of brain cortex.

After establishing the relationship between hyperintensity and the number of GBCA administrations, the aim of MRI studies was to prove if there was a relationship between the signal intensity change and the subtype of GBCA.

Kanda et al., [9] reported that hyper-intensity in the dentate nucleus was associated with repeated administrations of gadopentetate dimeglumine (linear ionic), but not gadoteridol (macrocyclic non-ionic). Radbruch et al., [10] also reported that repeated administration of gadopentetate dimeglumine (linear ionic) caused hyperintensity of the *dentate nucleus*, whereas gadoterate meglumine (macrocyclic ionic) did not.

Weberling et al., [11] reported that MRI signal intensity change of the *dentate nucleus* was more evident in subjects with multiple administrations of gadopentetate dimeglumine (linear ionic), less evident but still present with gadobenate dimeglumine (linear ionic) and no evident with gadoterate meglumine (macrocyclic non-ionic).

Same results were shown by Cao et al., [12] and Schlemm et al., [13] who demonstrated increase in signal intensity with gadopentetate dimeglumine (linear ionic,) but not with gadobutrol (macrocyclic non-ionic).

Almost all studies showed that T1 signal intensity increase was associated with high- and moderate- NSF risk GBCA injections, according to the classification of the Contrast Medium Safety Committee of the European Society of UroRadiology (ESUR) in 2008.

An exception has been reported by Stojanov et al., [14]: they showed increasing T1 signal intensity in the *dentate nucleus* and *globus pallidus* after multiple administrations of gadobutrol (macrocyclic non-ionic); however, this study had some limitations: no hyperintensity in the dentate nucleus on T1 weighted images could be visually noted in their images and they did not include a control group.

In 3 studies, Radbruch et al., [15-17] didn’t find any signal intensity increase in *dentate nucleus* after serial injections of macrocyclic GBCA. Same results were obtained by Eisele et al., [18].

All these imaging studies still have certain limitations: they are all retrospective single-centre studies, there is a lack of longitudinal data, in some papers there is an exposure to different classes of contrast agents, many papers do not have a control group and data analysis are not controlled for confounding variables (like age, sex, interval between administrations). There probably could be also a pathophysiological mechanism related to the patient’s disease, to the drugs used to treat it, there could be an effect related to the age of the patients and to the pulse sequences used. What is needed at the moment is a standardized protocol, with the use of quantitative T1 mapping techniques, that would allow to do correct and comparable studies.

**Tissue Samples Studies in Humans**

T1 hyperintensity can be caused not only by Gadolinium, but also by Calcium, Manganese, Iron, lipids and other substances. To determine the real cause of signal intensity increase, histological analysis was needed. McDonald et al., [19] and Kanda et al., [20] detected retention of Gd in patients presenting hyperintensities in the brain examining tissue samples using Inductively-Coupled-Plasma Mass Spectrometry (ICP-MS). In addition, McDonald et al., [19] showed that Gadolinium accumulates mainly within the endothelial wall, but also in the neural tissue, passing through a normal Blood Brain Barrier.

Although there was direct evidence of Gadolinium deposition within tissues, no histological change of neural tissues was detected.

Regarding deposition in organs different from the brain, Murata et al., [21,22] have reported the presence of Gd in skin and bones.
in patients with normal renal function, who underwent several administrations of gadoteridol (macrocyclic non-ionic), gadobutrol (macrocyclic non-ionic), gadobenate (linear ionic) and gadoxetate (linear ionic). Bone levels measured a concentration 23 times higher (median) than brain levels.

Roberts et al., [23] described the presence of Gd in the skin of a pediatric patient who underwent 61 contrast enhanced MRIs.

This direct evidence of Gd presence in human tissues confirms the hypotheses that were proposed with the results of the imaging studies.

Pre-clinical evaluation of Gd deposition

Findings on clinical studies, regarding comparison between macrocyclic and linear GBCA, were confirmed in several studies conducted in rats.

Robert et al., [24,25] demonstrated in two studies that repeated administrations of gadodiamide (linear non-ionic) in healthy rats is associated with progressive and persistent T1 signal hyperintensity in the deep cerebellar nuclei, with Gd deposition in the cerebellum, in contrast with gadoterate meglumine (macrocyclic ionic) for which no effect was observed.

Similar results were obtained by Jost et al., [26]: in this study in rats, increased signal intensity in the deep cerebellar nuclei was found up to 24 days after multiple, extended doses of linear GBCA. The elevated signal intensities remained persistent over the entire observation period. In contrast, no changes of signal intensities were observed for macrocyclic GBCA. However, all GBCA investigated, were able to pass the Blood-Cerebro Spinal Fluid (CSF) barrier in rats to a certain, not well quantified, extent.

Regarding the role of renal function, Rasscheart et al., [27] demonstrated the impact of renal failure on Gd retention in animal models: renal insufficiency in rats potentiates Gd uptake in the cerebellum, brain and bones.

Recently Lohrke et al., [28] clearly demonstrated that the skin and brain accumulation of Gd in healthy rats, following consecutive administrations of GBCA, occurs with both linear and macrocyclic agents, although the average residual brain Gd detected was 15-fold higher for linear than for macrocyclic GBCA. The highest amounts of Gd found in brain rats, as published in a different article, corresponds to 0.00019 % of the injected dose, 1 week after dosing [29]. In another study, published by McDonald et al., [30], using both macrocyclic and linear chelates, the Gd deposition in rat organs was confirmed in the brain but also in the kidneys, liver and spleen, with linear agents able to reach from two to fourfold higher concentration than macrocyclic ones.

The Gadolinium Anomaly

Geologists use the term “anomaly” to indicate that somewhere there is a deviation of the normal level of a specific chemical element or compound. High concentrations of Gd were detected, since 1996, in river and superficial waters [31] and recent evaluations found very high level of Gd in the surface waters of Berlin [32], with an enrichment by a factor of 103, compared to the background level, and in both Tokyo bay [33] and San Francisco bay [34]. The abnormal presence of Gd in tap water has been reported also for London [32] and for Prague [35]. The problem with the GBCA is that most of them are excreted through the kidneys while a small amount of them are eliminated through the biliary system in the intestine. So, more than 99.99 % of the injected GBCA reaches the sewer and because of their high stability and water solubility, go through the waste water treatment plants largely unchanged. Recent measurements indicate that the ordinary sewage treatment are able to remove only the 10 % of the Gd input enters [36]. Therefore, in recent decades a large amount of the Gd entering the sewage treatment process was not removed but entered the environment leading to a very high load of anthropogenic Gd in surface waters. Although the Gd concentration observed in the contaminated waters are probably still too low to pose a serious risk to health, nothing is yet known about the possible long-term effects. For a complete analysis of this aspect, a deep assessment was published by Thomsen [37].

Discussion

The results of clinical and pre-clinical studies provide evidence that the multiple administrations of linear GBCA are associated with T1 hyperintensity in brain regions and that hyperintensity is directly linked to the presence of Gd. Currently there’s not a clear evidence that macrocyclic subtypes of GBCA have the same effect, but we know that rats’ brain and other tissues deposition, like skin, kidneys, liver, spleen and more than all bones, is reduced but not eliminated by the administration of macrocyclic GBCA instead of linear chelates.

Gd deposited in bones reaches very high concentration and can persist for long term. It could be possible that a small fraction of injected GBCA may be taken up by bone matrix that can act as a reservoir, releasing slowly Gd with subsequent uptake in other tissues [38].

There are still open questions about how Gadolinium enters the brain; a possible pathway has been shown in a study by Jost et al., [39] in healthy rats using fluid-attenuated MR images, up to 4h after high dose of 6 marketed and one experimental GBCA. Authors found that a signal enhancement of CSF spaces was observed with all available GBCA, first in the inner CSF cavities and later in the subarachnoid spaces: this study suggests that all GBCA, regardless of their chemical structure, can pass the Blood-CSF barrier. The main question is how Gd can reach the brain parenchyma; a possible pathway could be the perivascular fluid circulation through the Virchow-Robin spaces [40] or via the lymphatic system [41].

Once in the brain, Gd may dissociate from its ligand with different kinetics, as shown by Frenzel et al., [2] then bind to a macromolecule and thus cause hyperintensity.

What remains to clarify is the form in which Gd deposits in tissues (chelated or unchelated or both) and what happens to deposi-
ed-Gd during time, especially to the brain-retained Gd. Smith et al., [29] in a rat model, studied if Gd deposited in the brain after administration of a linear GBCA could undergo to clearance. They found that the deposition of Gd decreased by approximately 43% from 1 week to 20 weeks after injection. Radbruch et al., [16] found an increase in signal intensity after administration of linear GBCA, which is consistent with already published data, and a slight but significant decrease in the same group of patients after the suspension of linear and a shift to macrocyclic. This result and also the results of Frenzel et al., [42] in rats, demonstrate that Gd in tissues could be found at least in three different forms: soluble small molecules, including the intact GBCA, soluble macromolecules and insoluble salts. The first two forms are chelated and could be the origin of a washout, through the elimination with urine during time, while the precipitation with phosphate or carbonate (insoluble salts) probably not. It is not yet known the kind of relationship among the different forms, but the results from the study of McDonald [19], who found a strong correlation between the amount of injected GBCA and Gd found in tissues, makes the hypothesis of precipitation the favorite one in terms of percentage.

Regarding clinical aspects of Gd retention, it remains unclear today if Gd deposition could lead to potential long-term toxicity. Till now, there aren’t clear long-term adverse effects reported in patients with normal renal function. In 2015, Gathings et al., [43] reported two cases of Gadolinium-associated skin plaques in patients without severe renal dysfunction. This plaque was reported as the sclerotic body that had been linked to NSF.

Semelka et al., [44] described “Gd deposition disease” in 4 patients, but the paper has important limitations: 1) the very small number of patients: 2) the absence of a control group and 3) the fact that reported symptoms are quite non-specific: these limitations make it difficult to draw any final conclusion about the association between symptoms and the administration of Gd.

There are still no clear data about the effects of Gd retention in young patients and pregnant women [45]; the administration of multiple doses of GBCA in children and adolescents for monitoring therapy (in multiple sclerosis, e.g.,) can lead to exposure to high doses of Gd during bone growth and brain development, with still unknown risks. Brain has proven to be particularly vulnerable to toxic agents during this period of development. [46,47].

Also, the serial administration of GBCA, and consequent Gd retention in young women, who may become pregnant, needs caution; pregnancy can lead to transmetallation and mobilization of Gd from the bone [48,49]; Gd can penetrate through the placenta into the foetal blood circulation, then be released to the different organs, in a developmental phase, and, through the kidneys of the foetus, into the amniotic fluid, which the foetus continuously swallows during gestation [50].

A retrospective study by Ray et al., [49] found that GBCA-enhanced MRI, at any time during pregnancy, was associated with an increased risk of a broad set of rheumatological, inflammatory or infiltrative skin conditions.

In March 2017, the Pharmacovigilance Risk Assessment Committee (PRAC) of European Medicines Agency (EMA) has recommended the suspension of the marketing authorisations for four linear Gadolinium contrast agents because of evidence that small amounts of the Gadolinium they contain are deposited in the brain. Some of the marketing authorisation holders, concerned by this referral procedure, have requested a re-examination. But on the 21st of July 2017, the European Medicine Agency (EMA) confirmed the suspension of the authorisations for the European market for four linear GBCA.

On May 22 2017, the US Food and Drug Administration (FDA) has published a review according to which there is no evidence that Gadolinium remaining in the body, after MRI contrast administration, has any negative health effects.

Since no clear and conclusive data are available regarding clinical aspects of Gd retention, further research is needed to understand long term effects of GBCA deposition.

In the meantime, there are some recommendations produced on behalf of the International Society for Magnetic Resonance in Medicine, that we can consider for the near future [51]: 1) per standard practice, use of GBCA should be avoided when not necessary. The physician responsible for the administration of a contrast agent should understand the benefits and risk of the agents; 2) the clinical indication, the specific contrast agent used, its dosage and other pertinent information should be documented in the patient’s medical record; 3) some commercially available macrocyclic agents might deposit less Gadolinium than some linear agents, however evidence shows that Gadolinium deposition in the brain and in other tissues can also occur after the administration of macrocyclic agents; 4) because at the present no risks are known to be associated with Gadolinium deposition, each institution must decide whether inclusion on information on Gadolinium deposition is necessary and should be a part of the consent form; 5) investigators reporting studies on Gadolinium deposition should exercise meticulous disclosure of financial, consulting and advising relationships with industries as potential conflicts of interest; 6) due to potential confounding of disease-related signal intensity changes with Gadolinium deposition, future studies should explicitly describe all relevant clinical history of participants, including the treatment.

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