Published in final edited form as:

J Am Coll Radiol. 2016 March ; 13(3): 237–241. doi:10.1016/j.jacr.2015.11.009.

NIH Perspective on Reports of Gadolinium Deposition in the Brain

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Introduction

Gadolinium-based contrast agents (GBCAs) are currently approved by the United States Food and Drug Administration (FDA) for use in conjunction with magnetic resonance imaging (MRI). GBCAs are indispensable adjuncts to MRI with numerous studies showing their efficacy in improving accuracy of MRI studies while having a positive cumulative safety record to date. For example, acute adverse reactions are reported in only approximately 0.079% of all administrations, of which 91% are classified as mild reactions (1). Despite the positive safety profile immediately following injections of GBCAs, there has been a recent attention to reports of gadolinium deposition in the brains of patients who received multiple doses of GBCAs (2–6). Although it is not yet known if there is a clinical implication of brain deposition of gadolinium, concerns for patient safety are of paramount importance, and thus internal review of institutional policies on GBCA use are warranted. The purpose of this perspective is to a) summarize the literature regarding GBCA deposition in the brain and b) determine any potential impact of that knowledge on how GBCA-enhanced MRI may be performed in order to minimize patient risk.

Background and Scope

There are nine FDA approved GBCAs for clinical use in the United States; GBCA FDA label indications are given in Table 1. Most of these agents are approved for contrast-enhanced imaging of the central nervous system (CNS). Only two agents – gadoxetate disodium and gadofosveset trisodium – are approved for indications other than CNS pathologies. Gadobutrol is the only agent that is approved by FDA for use in breast imaging and in patients younger than 2 years old. Gadopentetate dimeglumine and gadodiamide are approved for body applications, except for cardiac imaging. Although none of these agents is

approved for cardiac applications, their use is commonly reported in the peer-reviewed literature (7). Off-label use of GBCAs, for body applications, is routinely practiced at imaging centers throughout the United States and Europe (8–10).

The rare-earth metal gadolinium facilitates the relaxation of nearby hydrogen protons. In GBCAs, gadolinium is bound to a chelating agent that should remain bound in vivo. Acute toxic effects of free gadolinium, such as suppression of the reticuloendothelial system, inhibition of phagocytosis, and interruption of the function of smooth and skeletal muscles, have been documented in animal studies (11, 12). GBCAs belong to two structurally distinct groups: linear and macrocyclic. In linear or open-chain GBCAs, the chelating agent is wrapped around the gadolinium ion and fixed in place by attachment to eight of the nine coordination sites on the ion, with the ninth coordination site occupied by an exchangeable water molecule. In the macrocyclic agents, the gadolinium ion is caged at the center of the chelating agent (13, 14). Macrocyclic-type GBCAs are more stable than linear agents in terms of in vivo dissociation from gadolinium (Table 2). The highest degree of dissociation has been observed in non-ionic linear chelates (e.g. gadodiamide and gadoversetamide) followed by ionic linear (gadopentetate dimeglumine and gadobenate dimeglumine). The lowest degree of dissociation has been observed with macrocyclic chelating agents (gadobutrol, gadoterate meglumine, and gadoteridol). In a recent *in vitro* study (15), various gadolinium agents were compared for stability in human serum for 15 days. Non-ionic linear GBCAs showed 20% dissociation, while ionic linear GBCAs demonstrated only 1.1 % – 1.9% gadolinium release. Dissociation from macrocyclic agents was undetectable.

The first report of increased signal intensity in the brain associated with GBCAs emerged from Japan in 2014 (3). In this retrospective study by Kanda et al., the signal intensity ratios of dentate nucleus-to-pons and globus pallidus-to-thalamus in 19 patients who had received at least 6 doses of linear GBCAs (gadopentetate dimeglumine and gadodiamide) were significantly higher compared to 16 patients who received at least 6 MRIs without GBCA. The degree of signal intensity correlated with the number of contrast administrations and had no association with renal function. The authors concluded that the high signal intensity in the brain may be the result of the relatively high number of GBCA administrations. This publication was followed by another report from the same group demonstrating a strong association between the dentate nucleus-to-cerebellum signal intensity ratio and linear GBCA exposure (again, gadopentetate dimeglumine and gadodiamide) (4). There was no correlation between exposure to a macrocyclic GBCA (gadoteridol) and signal intensity within the dentate nucleus. The authors concluded that the hyperintense signal in the dentate nucleus was probably related to prior administration of linear GBCAs.

Radbruch et al. (6) confirmed the reported association between the high signal intensity in the dentate nucleus and prior administration of linear contrast agents. They reported a significant association between administration of a linear agent (gadopentetate dimeglumine) and high signal intensity in the dentate nucleus and globus pallidus. A macrocyclic agent (gadoterate meglumine) was not associated with an increase in signal intensity. Similar findings were reported in patients with multiple sclerosis or brain metastasis who had received multiple doses of a linear agent (gadodiamide), again in the setting of normal renal function (16). There was a direct linear relationship between the

number of contrast injections and intensity of T1 signal in dentate nuclei. Quattrocchi et al. (17) evaluated signal intensity changes in patients with meningioma who had undergone repeat MRIs. They reported an increased T1 signal intensity of the dentate nuclei in patients who had received more than 6 doses of gadodiamide compared to those who had received fewer than 6 doses. In a recent study of two linear agents (gadodiamide and gadobenate dimeglumine), Ramalho et al. (18) demonstrated an increase in T1 signal intensity of the dentate nucleus and globus pallidus in patients who received multiple doses of gadodiamide. While there was no difference in T1 signal intensity of the globus pallidus in patients who received multiple doses of gadobenate dimeglumine, there was a trend toward increasing T1 signal intensity in the dentate nucleus.

Recent autopsy studies have provided pathologic confirmatory evidence that the T1 shortening on MRI is probably the result of gadolinium deposition (2, 5). Kanda et al. (2) used postmortem plasma mass spectroscopy to quantify gadolinium deposition in the whole brain, basal ganglia, dentate nucleus, and globus pallidus in 5 patients who had received linear contrast agents and 5 patients with no gadolinium exposure. None of the patients were known to have chronic severe or acute renal failure as defined by GFR $\leq$ 45. The authors found an increase in the gadolinium concentration in all regions of the brain in those who had received gadolinium compared to gadolinium-naïve patients, as well as a higher concentration of gadolinium in the dentate nucleus and globus pallidus compared to other regions of the brain. A second autopsy study by McDonald et al. (5) found similar results in patients who had received repeated doses of gadodiamide, with an increase in the amount of gadolinium in the basal ganglia, pons, and thalamus compared to other regions of the brain. Furthermore, they demonstrated a dose-response relationship with higher deposition of gadolinium in patients who received more doses of the contrast agent.

In summary, the current body of literature supports the notion that repeated administration of linear GBCAs leads to signal changes within the brain, and that these signal changes can be due to gadolinium deposition. Furthermore, there is some evidence that brain deposition is more likely to occur with linear GBCAs compared to macrocyclic GBCAs. The putative mechanism is the dissociation of the contrast agent into free gadolinium. To date, no consequences for patient health have been identified. Recognizing this, the FDA's Drug Safety Communications Statement regarding the risk of brain deposits with repeated use of gadolinium-based contrast agents for MRI concluded that the available information does not identify any adverse health effects (19).

Recommendations

The long-term impact on public health and safety of deposition of gadolinium in the brain remains unknown. A study group was formed at the National Institutes of Health (NIH) Clinical Center to investigate the existing literature on gadolinium deposition in the brain parenchyma and to provide recommendations for clinical use of GBCAs within our institution in order to minimize the potential long-term side effects of GBCA administration. The references summarized in this report conclude that increased signal intensity within certain regions of the brain parenchyma occurred with the use of linear (ionic and non-ionic) contrast agents and have not been conclusively reported with the use of macrocyclic contrast

agents. Autopsy studies, albeit only exploratory in nature with a small number of patients, support the notion that the increased signal intensity is due to gadolinium deposition. Although further investigation is warranted, it appears prudent at this time to revisit institutional protocols for GBCA administration until additional information is obtained. The ideal GBCA agent for MRI would have a favorable safety profile and a low risk of potential long-term deposition within normal tissue. In this regard, macrocyclic agents are reasonable alternatives to linear agents with higher in-vitro and in-vivo stability and longer dissociation half-lives (Table 2). The choice of contrast agents should be individualized at each imaging center, taking into consideration prior experience with various agents and the specific applications of contrast-enhanced studies.

The following set of recommendations has been adopted at the NIH:

1. GBCAs should only be used when clinically indicated or when specified in an institutional Review Board (IRB)-approved protocol.
2. When GBCAs are required, consider the use of a macrocyclic GBCA (e.g. gadobutrol, gadoteridol, or gadoterate meglumine) rather than a linear agent.
3. For patients with documented sensitivity (e.g. hives) to macrocyclic agents, it is appropriate to use linear agents when clinically indicated.
4. MRI protocols should always consider FDA label indications and dosing schemes for administration of GBCAs.
5. Encourage intra- and inter-departmental research programs to evaluate T1 shortening in the brain and other organs in patients who have received multiple doses of GBCAs.

Conclusion

The current body of evidence supports the hypothesis that shortening of the T1 relaxation time within the brain parenchyma may result from gadolinium deposition following injection of linear GBCAs. It is presumed that the deposited gadolinium is a result of dissociation from the chelating molecule. At present, there is no evidence suggesting that gadolinium deposition in the brain alters neurologic function. Although the studies discussed herein assessed a relatively small number of patients, there is sufficient information to warrant institutional review of policies for gadolinium administration.

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Table 1

FDA labeling and doses of GBCAs.

Trade Name	Other	Label Dose	FDA labeling age	FDA approved indication* (see label for precise labeling information)
Gadavist	Gd-BT-DO3A (gadobutrol)	0.1 mmol/Kg (0.1 mL/Kg)	Any Age	Central Nervous System Pediatrics and adult Breast disease
Dotarem	Gd-DOTA (gadoterate meglumine)	<i>0.1 mmol/Kg (0.2 mL/Kg)</i>	2 years	Central Nervous System
Prohance	Gd-HP-DO3A (gadoteridol)	0.1 mmol/Kg (0.2 mL/Kg) <i>Additional dose of 0.2 mmol/Kg (0.4 mL/Kg)</i>	2 – 18 years and adults	Central Nervous System Extracranial/Extraspinal Tissues
Magnevist VL	Gd-DTPA (gadopentetate dimeglumine)	0.1 mmol/Kg (0.2 mL/Kg)	2 years	Central Nervous System Extracranial/Extraspinal Tissues Body (excluding the heart)
Multihance	Gd-BOPTA (gadobenate dimeglumine)	0.1 mmol/Kg (0.2 mL/Kg)	2 years	Central Nervous System
Eovist	Gd-EOB-DTPA (gadoxetic acid disodium)	0.025 mmol/Kg (0.1 mL/Kg)	Adults	Liver lesions
Ablavar (previously Vasovist)	Gd-DTPA (gadofosveset trisodium, MS-325)	0.03 mmol/Kg (0.12 mL/Kg)	Adults	Aortoiliac occlusive disease
Optimark Omniscan	Gd-DTPA-BMEA (gadoversetamide) ionic Gd-DTPA-BMA (gadodiamide)	0.1 mmol/Kg (0.2 mL/Kg) 0.1 mmol/Kg (0.2 mL/Kg) Kidney: 0.05 mmol/Kg (0.1 mL/Kg)§	18–76 years 2–16 years and adults	Central Nervous System Liver Central Nervous System Body [noncardiac]

Table 2

Biochemical Properties of GBCAs (macrocyclic agents in light green) with FDA approval. Note the significantly longer dissociation half-life of macrocyclic agents compare to linear agents (20, 21).

Trade Name	Other	Molecular Structure	Concentration (mol/L)	Formulation	Dissociation half-life	Elimination Pathway
Gadavist	Gd-BT-DO3A (gadobutrol)	Macrocyclic, non-ionic	0.5	Ca-BT-DO3A (Na+ salt) (1 mmol/liter)	N/A	Kidney
Dotarem	Gd-DOTA (gadoterate meglumine)	Macrocyclic, ionic	0.5	No excess ligand	>1 month	Kidney
Prohance	Gd-HP-DO3A (gadoteridol)	Macrocyclic, non-ionic	0.5	[Ca-HP-DO3A] ₂ (Ca ²⁺ salt) 0.1% (0.5 mmol/liter)	3 hours	Kidney
Magnevist VL	Gd-DTPA (gadopentetate dimeglumine)	Linear, ionic	0.5	Free DTPA 0.2% (1 mmol/liter)	10 min	Kidney
Multihance	Gd-BOPTA (gadobenate dimeglumine)	Linear, ionic	0.5	No excess ligand	N/A	93% kidney, 3% bile
Eovist (Primovist in Europe)	Gd-EOB-DTPA (gadoxetic acid disodium)	Linear, ionic	0.25	Ca-EOB-DTPA (concentration N/A)	N/A	50% kidney, 50% bile
Ablavar (previously Vasovist)	Gd-DTPA (gadofosveset trisodium, MS-325)	Linear, ionic	0.25	Fosveset (concentration N/A)	N/A	91% kidney, 9% bile
Optimark	Gd-DTPA-BMEA (gadoversetamide) ionic	Linear, non-ionic	0.5	Ca-DTPA-BMEA (Na+ salt) (50 mmol/liter)	N/A	Kidney
Omniscan	Gd-DTPA-BMA (gadodiamide)	Linear, non-ionic	0.5	Ca-DTPA-BMA (Na+ salt) 5% (25 mmol/liter)	35 sec	Kidney