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REVIEW

Brain gadolinium deposition after administration of gadolinium-based contrast agents

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Abstract Gadolinium-based contrast agents (GBCAs) consist of gadolinium ions and a chelating agent that binds the gadolinium ion tightly so that its toxicity is not manifested. However, in 2013, an association between brain MRI abnormalities and a history of GBCA administration was first reported. Even in patients with normal renal function, increased signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images showed a positive correlation with previous exposure to linear chelate type GBCAs, but not to macrocyclic chelate type ones. This difference of GBCAs is speculated to reflect the stability of GBCAs, and de-chelated gadolinium deposition has been strongly suspected. Using inductively coupled plasma mass spectroscopy, gadolinium was detected from patients' brains with a history of repeated GBCA administration. In some cases, the gadolinium concentration of a patient's brain with normal renal function exceeded the gadolinium concentration of the skin in nephrogenic systemic fibrosis patients, but without any histological change. The actual risk has not been documented yet, but it seems important to consider the potential unknown risks of residual gadolinium in our decisions regarding GBCA administration, and to make efforts to minimize any residual gadolinium in the patient's body.

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Introduction

Gadolinium is a heavy metal with atomic number 64 that belongs to the lanthanide family. Like other lanthanide metals, the most common oxidation state of gadolinium is +3 and the ionic radius is 0.99 Å. The ionic radius of gadolinium is almost equal to that of Ca^{2+}, and Gd^{3+} can compete with Ca^{2+} and become toxic in biological systems. To reduce the toxicity of Gd^{3+}, it has to be administered to humans in chelated forms to avoid the presence of free gadolinium [1, 2]. A gadolinium-based contrast agent (GBCA) was first introduced by Runge at the Radiologic Society of North America meeting in Chicago in 1982 [3, 4]. GBCAs were soon produced commercially, gadopentetate dimeglumine (Gd-DTPA, Magnevist) being the first approved for clinical use in 1988, followed by gadoterate meglumine (Gd-DOTA, Dotarem), gadoteridol (Gd-HP-DO3A, ProHance), and gadodiamide (Gd-DTPA-BMA, Ominiscan) [5]. GBCAs have been used internationally for more than a quarter century in more than 100 million patients.

Concept of the gadolinium-based contrast agents

GBCAs were anticipated to have high contrast efficiency, safety due to their high stability and rapid excretion, low viscosity, and low osmolality. To obtain a high contrast image with a low dose of GBCA, high contrast efficiency of GBCA is needed. The contrast efficiency was evaluated with the ability to reduce *T*1 and/or *T*2

in tissue. Each agent's fundamental ability to reduce $T1$ and $T2$ is referred to as its "relaxivity" $R1$ ($=1/T1$) and $R2$ ($=1/T2$). High $R1$ agents induce a shorter $T1$ and higher contrast efficiency. Because the gadolinium ion is toxic, GBCAs consist of gadolinium ions and a chelating agent that binds the gadolinium ion tightly so that its toxicity is not manifested. To maintain the GBCA's low toxicity, the dissociation of gadolinium ion should be minimal in vivo and gadolinium should be rapidly excreted from the body [2, 3, 5]. The stability of GBCA has been evaluated with kinetic stability and thermodynamic stability in the laboratory. The thermodynamic stability is the ratio of free gadolinium ions in equilibrium, and is evaluated with the thermodynamic stability constant (K_{therm}) and conditional stability constant (K_{cond}). These factors reflect the affinity of gadolinium ion for its ligand at high basic pH and 7.4 in equilibrium in a water solution. The kinetic stability reflects the rate of gadolinium dissociation, in other words, how fast the gadolinium ion is released from GBCAs. Kinetic stability is evaluated with the dissociation half-life time ($T_{1/2}$) of GBCA in various conditions. Both thermodynamic stability and kinetic stability reflect the stability of GBCA to some extent, but the stability in vivo cannot be evaluated exactly with these parameters [5–7]. To perform rapid infusion without inducing an acute reaction, low viscosity and osmolality are needed.

Various types of GBCA have been developed to satisfy these conditions. GBCAs are divided into linear and macrocyclic, and subdivided into ionic and non-ionic types according to their chelate structure. Generally, macrocyclic GBCAs are more stable than linear GBCAs. The ionic GBCAs are generally slightly more stable than non-ionic GBCAs, but have higher osmolality. A large amount of excess chelate was added to unstable GBCAs to minimize the release of free gadolinium. The characteristics of GBCAs are summarized in Table 1 [2, 3, 5].

Gadolinium deposition in patients with normal renal function

Since the first reports on GBCAs, there has been concern about gadolinium deposition in tissue. Tweedle and colleagues [8–11] evaluated gadolinium retention in rats and mice after injection of ^{153}Gd-labeled GBCAs and free gadolinium, such as $GdCl_3$ gadolinium acetate. When ''free gadolinium'' is administered, most of the gadolinium deposits in the liver and bone. Very little is excreted and clearance has been reported to be approximately 1–3 % per day. When different chelate types of GBCA are administered, the distribution of gadolinium is very similar during the first 24 h. At 7 and 14 days, the remaining gadolinium is found mainly in kidney, liver, and bone. The amount of remaining gadolinium differs among the chelate types of GBCA [gadodiamide (linear non-ionic GBCA) > gadopentetate dimeglumine (linear ionic GBCA) ≈ gadoterate meglumine (macrocyclic ionic GBCA) ≈ gadoteridol (macrocyclic ionic GBCA)] [11]. Sieber [12] also evaluated the gadolinium retention in rats by inductive coupled plasma atomic emission spectroscopy (ICP-AES) and found that the gadolinium deposition differed among the chelate types of GBCA [gadodiamide (linear non-ionic GBCA) > gadoversetamide (linear non-ionic GBCA) > gadopentetate dimeglumine (linear ionic GBCA) > gadobenate dimeglumine (linear ionic GBCA) ≈ gadobutrol (macrocyclic non-ionic GBCA) ≈ gadoterate meglumine (macrocyclic ionic GBCA)]. This difference was attributed to greater gadolinium release from the chelate.

Studies on gadolinium deposition in humans with normal renal function are limited. Gibby [13], White [14], and Darrah [15] analyzed the gadolinium deposition in femoral bone specimens from total hip arthroplasties, and Xia [16] analyzed it in brain tumor tissue. Their data suggested that gadolinium is deposited even in persons without renal dysfunction. Moreover, Gibby and White [13, 14] found 4-fold higher levels of gadolinium in the bone of subjects who received gadodiamide (linear non-ionic GBCA) than for those who received gadoteridol (macrocyclic non-ionic GBCA) by using inductively coupled plasma mass spectroscopy (ICP-MS). Frenzel [17] evaluated the dissociation of 9 types of GBCA in human serum at 37 °C. This was an in vitro study, but the release of gadolinium from linear GBCA was confirmed. The initial gadolinium dissociation rate of linear GBCAs was 0.07–0.44 %, and that of macrocyclic GBCAs was less than 0.007 %. After a 15-day incubation period, the released rate of gadolinium linear nonionic GBCAs was 20–21 %, in contrast to 1.1–1.9 % for linear ionic GBCAs, and under 0.1 % for macrocyclic GBCAs.

Nephrogenic systemic fibrosis (NSF)

GBCAs are considered very safe in general with severe adverse effects only rarely observed. However, in 1997, Cowper [18] reported "scleromyxoedema-like cutaneous diseases in renal-dialysis patients". In 2006, Grobner [19] and Marckmann [20] suggested a link between these skin lesions and a history of exposure to GBCAs, and this condition was named nephrogenic systemic fibrosis (NSF) [2]. The common presentation of NSF is acute to subacute onset of limb swelling, redness and pain, particularly in the lower limbs, leading in severe cases to joint contractures and immobility. Additionally, NSF may contribute to death through scarring of the body organs. Gadolinium

Table 1 The characteristics of gadolinium-based contrast agents [2, 3, 5]

Acronym	Gd-DTPA	Gd-DOTA	Gd-HP-DO3A	Gd-DTPA-BMA	Gd-DO3A-butrol	Gd-DTPA-BMEA	Gd-BOPTA	Gd-EOB-DTPA	MS-325
Trade name	Magnevist	Dotarem	ProHance	Omniscan	Gadovist	OptiMARK	MultiHance	Primovist Eovist	Vasovist Ablavarr
Generic name	Gadopentetate dimeglumine	Gadoterate meglumine	Gadoteridol	Gadodiamide	Gadobutrol	Gadoversetamide	Gadobenate dimeglumine	Gadoxetic acid disodium	Gadofosveset trisodium
Company	Bayer	Guerbet	Bracco	GE-healthcare	Bayer	Covidien	Bracco	Bayer	Lantheus
First approval	1986, EU	1989, EU	1992, USA	1993, USA	1998, EU	1999, USA	1997, EU	2004, EU	2005, EU
Doses in Japan (mmol/kg)	0.1–0.2	0.1	0.1–0.2	0.1	0.1	–[a,b]	–[a,b]	0.025	–[a,b]
Excess chelate	0.1 %	0 %	0.1 %	5 %	0.1 %	28.4	0 %	0.5 %	0.1 %
Structure	Linear	Macrocyclic	Macrocyclic	Linear	Macrocyclic	Linear	Linear	Linear	Linear
Ionicity	Ionic	Ionic	Nonionic	Nonionic	Nonionic	Nonionic	Ionic	Ionic	Ionic
Stability	Intermediate	High	High	Low	High	Low	Intermediate	Intermediate	Intermediate
NSF risk	High	Low	Low	High	Low	High	Intermediate	Intermediate	Intermediate
Osmolality	1960	1350	630	789	1603	110	1970	688	825
Viscosity	2.9	2.0	1.3	1.4	5.0	2.0	5.3	12	2.1
Log K_{therm}	22.1	25.6	23.8	16.9	21.8	16.6	22.6	23.5	22.1
Log K_{cond}	17.7	19.3	17.1	14.9	14.7	15.0	18.4	18.7	18.9
$T_{1/2}$	<5 s	338 h	3.9 h	<5 s	43 h	<5 s	<5 s	<5 s	<5 s
Relaxivity[a,b] (*R*1/*R*2, 1.5T)	3.9–4.1/4.6–5.3	3.6/4.3	4.1/5.0	4.3/5.2	4.7–5.2/6.1–7.5	4.7/5.2	6.3–7.9/8.7–18.9	6.9/8.7	19.0/34.0
Relaxivity[a,b] (*R*1/*R*2, 3T)	3.7–3.9/5.2	3.5/4.9	3.7/5.7	4.0/5.6	4.5–5.0/6.3–7.1	4.5/5.9	5.5–5.9/11.0–17.5	6.2/11.0	9.9/60.0
Clearance	Renal	Renal	Renal	Renal	Renal	Renal	96 % renal 4 % hepatic	50 % renal 50 % hepatic	79 %–94 % renal 5 % hepatic

K_{therm} thermodynamic stability constant, K_{cond} conditional stability constant, $T_{1/2}$ dissociation half-time at pH 1.0 and 25 °C, *EU* Europe, *USA* United States of America

[a] Not commercially available in Japan

[b] Values in l $mmol^{-1}s^{-1}$ (plasma, 37 °C)

can be detected from the skin tissue of NSF [21–23]. Because the development of NSF symptoms takes several years, the true incidence of NSF has been difficult to determine. According to the database of unconfounded NSF cases [24], the incidence of NSF differs according to the chelate structure of various GBCAs. Approximately 75 % of NSF was associated with gadodiamide (linear non-ionic GBCA), around 23 % with gadopentate dimeglumine (linear ionic GBCA) and only a few cases with other GBCAs. Most cases of NSF were associated with linear chelate GBCAs, with instability of the chelate compound implicated as the factor inducing NSF [25–30]. The European Society of Urogenital Radiology (ESUR) [29] and European Medicines Agency (EMA) [24] classified the NSF risk of GBCAs into three groups (high risk, intermediate risk, low risk), and recommended that high risk GBCAs not be administered to patients on hemodialysis, with eGFR (estimated glomerular filtration rate) under 30, or acute renal dysfunction. The American College of Radiology (ACR) [30] identified the GBCAs associated with the greatest apparent NSF-associated risk (gadodiamide, gadopentetate dimeglumine and gadoversetamide), and recommended that their administration be avoided in such patients. Until now, no definitive treatment for NSF has been devised and radiologists play an essential role in preventing its occurrence [24–30].

Evaluation of gadolinium deposition with brain MRI

In 2013, the association of brain MRI abnormality and a history of GBCA administration was first reported by Kanda et al. [31, 32]. Increased signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images (T1WI) showed a positive correlation with previous exposure to linear chelate type GBCAs (gadopentetate dimeglumine or gadodiamide) even in patients with normal renal function. Their observation revealed an apparent dose-response relationship wherein the greater the number of previous GBCA administrations the greater was the degree of observed intracranial T1 hyper-intensity. The hyper-intensity appeared with more than 5 past administrations of GBCA. Previously, hyper-intensity in the dentate nucleus on T1WI had been attributed to a secondary progressive subtype of multiple sclerosis [33] or irradiation [34]. However, Kanda et al.'s report showed that the cause of hyper-intense dentate nucleus on T1WI was not irradiation, but multiple GBCA administrations. Shortly thereafter, Errate et al. [35–37] also reported the presence of hyper-intensity in the dentate nucleus in parallel with the frequency of past gadodiamide administration. The same phenomenon was also reported in children by Roberts et al. [38]. The next step was the need to clarify the relationship between the signal intensity change and chelate type of GBCAs. In 2014, Kanda et al. [39] reported that hyper-intensity in the dentate nucleus was associated with previous repeated administration of gadopentetate dimeglumine (linear GBCA), but not gadoteridol (macrocyclic GBCA). Radbruch [40] also reported that repeated administration of gadopentetate dimeglumine (linear GBCA) caused hyper-intensity of the dentate nucleus whereas gadoterate meglumine (macrocyclic GBCA) did not.

In these results, dentate nucleus hyper-intensity was caused by high NSF risk GBCAs, and not by low NSF risk ones. Gadobenate dimeglumine is a linear nonionic GBCA, which seldom causes NSF [41], and is classified as an intermediate NSF risk GBCA. Ramalho et al. [42] compared gadodiamide (linear non-ionic GBCA, high NSF risk) and gadobenate dimeglumine (linear ionic GBCA, intermediate NSF risk) using the MRI signal intensity change of the dentate nucleus, and noted such a change only with gadodiamide. Weberling et al. [43] reported that MRI signal intensity change of the dentate nucleus occurred even in subjects with multiple administration of gadobenate dimeglumine (linear ionic GBCA, intermediate NSF risk), but the signal change was gadopentetate dimeglumine (linear ionic GBCA, high NSF risk) > gadobenate dimeglumine (linear ionic GBCA, intermediate NSF risk) > gadoterate meglumine (macrocyclic GBCA, low NSF risk). The intermediate NSF risk GBCAs may be less likely to cause intracranial gadolinium deposition, though other intermediate NSF risk GBCAs need to be evaluated to confirm this.

An exception has also been reported by Stojanov et al. [44]. They evaluated the relationship between the number of past gadobutrol (non-ionic macrocyclic GBCA, low NSF risk) administrations and signal change of the dentate nucleus, with the signal change detectable in the dentate nucleus with ROI analysis. However, no hyper-intensity in the dentate nucleus on T1WI could be visually noted in their presented figure, despite being seen in all other previous reports [32, 35–40, 42, 43]. In addition, they did not rule out the effect of confounding factors, or include control subjects [45]. Radbruch [46] also evaluated the relationship between the number of past gadobutrol administrations and signal change of the dentate nucleus and globus pallidus, but there were no signal increases, even though the total dose applied here was considerably larger than Stojanov et al. reported [44]. The macrocyclic GBCA may also cause hyper-intensity in the dentate nucleus, but this must be confirmed by further investigations.

Evaluation of gadolinium deposition by histological analysis

Hyper-intensity on T1WI is caused not only by gadolinium, but also by calcium, manganese, iron, lipid, and other substances [47]. To determine the cause of signal change on T1WI, the detection of gadolinium by histological analysis was needed. McDonald et al. [48] and Kanda et al. [49] confirmed the considerably higher gadolinium deposition in these hyper-intensity regions as compared to other brain regions using ICP-MS. In addition, McDonald [48] confirmed that gadolinium accumulated mainly within the endothelial wall, but also in the neural tissue, passing through the blood brain barrier (BBB). Despite direct evidence of gadolinium deposition within neuronal tissues, no histologic change of neural tissues was detected.

Robert and colleagues [50] injected 0.6 mmol of gadolinium per kilogram per injection (4 injections per week for 5 weeks) of gadodiamide (linear GBCA), gadoterate meglumine (macrocyclic GBCA), or hyperosmolar saline into rats, and evaluated the gadolinium deposition. Signal change of the dentate nucleus on T1WI was observed only in the gadodiamide-exposed rats, and the total gadolinium concentration of gadodiamide-exposed rat brain was 14-fold higher than in the gadoterate meglumine exposed rats as determined by ICP-MS. Since the effect of repeated GBCA administration had not been evaluated before, Runge [51] recommended that all of the currently approved

GBCAs be evaluated by the same methods as Robert's to better determine their safety.

On the other hand, these studies focused only on the relationship between the dose of gadolinium and residual gadolinium, and further study was needed to verify that the residual gadolinium was actually responsible for the signal change.

Mechanism of gadolinium deposition

The mechanism of gadolinium deposition in the brain has not yet been well clarified. Since the degree of brain gadolinium deposition was shown to vary according to its chelate structure, the degree of de-chelation probably plays a role. Frenzel et al. [52] evaluated the de-chelation rate of GBCA after a 15-day incubation period at 37 °C in human serum in vitro. The de-chelation rates were non-ionic linear GBCAs (20–21 %) > ionic linear GBCAs (1.1–1.9 %) ≫ macrocyclic GBCAs (<0.1 %).

In vivo, the presence of other metal ions that compete with gadolinium for chelation could result in transmetallation, that is, de-chelation of gadolinium assisted by another endogenous metal ion. Endogenous ions present in the body that induce transmetallation include Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}, Fe^{3+}, and Zn^{2+}. Free Fe^{3+} and Cu^{2+} are present in very small amounts in the blood and Na^{+}, K^{+}, Mg^{2+}, and Cu^{2+} have a weak ability to chelate GBCAs. Therefore, Zn^{2+} was surmised to play an important role in transmetallation [1, 5]. Puttagunta et al. [53] and subsequently Kimura et al. [54] showed that Zn^{2+} levels were elevated in the urine of subjects administered linear GBCAs (gadopentetate dimeglumine and gadodiamide), but not in those administered macrocyclic GBCAs (gadoterate meglumine or gadoteridol). It was unclear whether the Zn^{2+} excretion was due to the transmetallation or excess chelation of GBCAs, but this study indicated that Zn^{2+} promoted in some way the chelation of GBCAs.

The results of MRI and autopsy analysis demonstrated that gadolinium can pass through the BBB and accumulate in the brain with a concentration gradient. High concentration areas of gadolinium were the dentate nucleus, inner segment of the globus pallidus, and pulvinar of the thalamus [48, 49], with iron or calcium also showing relatively higher concentrations in these regions [55, 56]. Gadolinium is probably not transported passively, but rather by some biological mechanism(s) such as metal transporter(s) [57, 58].

Safety and GBCAs

With repeated GBCA administration, gadolinium accumulates in the brain and in bone even with normal renal function. However, the risk of gadolinium deposition is unproven. NSF is fatal and no consistently successful treatment is available, but NSF develops only in patients with severe renal dysfunction. McDonald et al. [48] analyzed the dentate nucleus of 13 patients without severe renal dysfunction, and found a gadolinium concentration of 0.1–58.8 μg/g. Christensen et al. [23] analyzed 13 NSF patients' skin and found a gadolinium concentration of 6.3–348.7 μg/g. Some of the gadolinium concentrations in the dentate nucleus were higher than those in NSF patients' skin. In 2015, Gathings et al. [59] 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 [60–62]. The gadolinium-associated plaques caused only mild symptoms, and were associated with few problems clinically.

GBCA has been used for over 30 years, and gadolinium deposition causes no severe problems except for NSF. Even though the potential risk of gadolinium deposition should not be ignored, GBCA administration should not be restricted when truly indicated. And efforts should be made to minimize any residual gadolinium in the patient's body [63]. The American Food and Drug Administration (FDA) began to evaluate the risk of gadolinium deposition in July 2015 [64], and it is anticipated that the magnitude of the potential risk of gadolinium deposition will become gradually apparent. EMA [24], ACR [30], ESUR [29] and the Japan Radiological Society [65] have not proposed any new guidelines concerning gadolinium deposition yet. Radiologists should continue to keep in mind the risks of residual gadolinium.

Conclusion

Knowledge regarding gadolinium deposition in patients with normal renal function has dramatically increased since 2013. Gadolinium is now known to gradually accumulate in brain and bone, even in patients with normal renal function. The amount of residual gadolinium differs markedly among the chelate type of GBCAs, but there have been no reports of severe complications due to gadolinium deposition except for NSF. The actual risk has not been proven yet, but the potential unknown risks of residual gadolinium should be considered in our decisions regarding GBCA administration, and continuous efforts should be made to minimize the frequency of GBCA administration whenever possible.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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