Safety of the Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging, Focusing in Part on Their Accumulation in the Brain and Especially the Dentate Nucleus

Val M. Runge, MD

Abstract: The established class of intravenous contrast media for magnetic resonance imaging is the gadolinium chelates, more generally referred to as the gadolinium-based contrast agents (GBCAs). These can be differentiated on the basis of stability in vivo, with safety and tolerability of the GBCAs depending upon chemical and biologic inertness. This review discusses first the background in terms of development of these agents and safety discussions therein, and second their relative stability based both on in vitro studies and clinical observations before and including the advent of nephrogenic systemic fibrosis. This sets the stage for the subsequent focus of the review, the current knowledge regarding accumulation of gadolinium in the brain and specifically the dentate nucleus after intravenous administration of the GBCAs and differentiation among agents on this basis. The information available to date, from the initial conception of these agents in 1981 to the latest reports concerning safety, demonstrates a significant difference between the macrocyclic and linear chelates. The review concludes with a discussion of the predictable future, which includes, importantly, a reassessment of the use of the linear GBCAs or a subset thereof.

Key Words: cerebellar nuclei, contrast media, magnetic resonance, dentate nucleus, safety, toxicity, gadolinium-based contrast agents, gadopentetate dimeglumine, gadoversetamide, gadodiamide, gadobenate dimeglumine

Received for publication January 19, 2016; and accepted for publication, after revision, February 3, 2016.

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Conflicts of interest and sources of funding: Activities related to the present article: acceptance of educational grants (to Inselspital, Bern) for partial support of this research from Guerbet and Bracco Diagnostics. Activities not directly related to the present article: the author is a paid consultant for Bayer Healthcare.

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ISSN: 0020-9996/16/5105–0273
DOI: 10.1097/RL1.0000000000002073

STABILITY (AND NEPHROGENIC SYSTEMIC FIBROSIS)

The first public presentation concerning paramagnetic metal ion chelates as contrast media for MR occurred at the 1982 Radiological Society of North America meeting in Chicago, Illinois, with parts therein published in the journal Radiology in mid-1983. Advanced in this presentation, and emphasized throughout the developmental history of the gadolinium chelates, is that the clinical safety of these agents is a large extent dependent upon their metabolic stability in vivo (specifically their...
TABLE 1. The Clinically Approved GBCAs—Names, Incidence of NSF, and Occurrence of Dentate Nucleus Hyperintensity

<table>
<thead>
<tr>
<th>Trade Name*</th>
<th>Generic Name</th>
<th>Acronym</th>
<th>Incidence of NSF† (No. US Cases)‡</th>
<th>Dentate Nucleus Hyperintensity§</th>
<th>No Dentate Hyperintensity§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnevist</td>
<td>Gadopentetate dimeglumine</td>
<td>Gd-DTPA</td>
<td>0.1%–1% (195)</td>
<td>Kanda et al,1 Radbruch et al2</td>
<td>Radbruch et al2</td>
</tr>
<tr>
<td>Dotarem</td>
<td>Gadoterate meglumine</td>
<td>Gd-DOTA</td>
<td></td>
<td></td>
<td>Kanda et al3</td>
</tr>
<tr>
<td>ProHance</td>
<td>Gadodiamide</td>
<td>Gd-HP-D03A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omniscan</td>
<td>Gadoteridol</td>
<td>Gd-DTPA-BMA</td>
<td>3%–18% (382)</td>
<td>Kanda et al,1 Errante et al4, McDonald et al,5 Quattrocchi et al6</td>
<td></td>
</tr>
<tr>
<td>Gadovist/Gadavist</td>
<td>Gadobutrol</td>
<td>Gd-D03A-Butrol</td>
<td>Unknown (35)</td>
<td>Weberling et al7</td>
<td></td>
</tr>
<tr>
<td>Optimark</td>
<td>Gadoversetamide</td>
<td>Gd-DTPA-BMEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MultiHance</td>
<td>Gadobenate dimeglumine</td>
<td>Gd-BOPTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primovist/Eovist</td>
<td>Gadodete disodium</td>
<td>Gd-EOB-DTPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablovak</td>
<td>Gadofosveset trisodium</td>
<td>MS-325</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Listed in order of initial clinical approval. †In at risk patients, data from the ESUR. ‡†Fda adverse event reporting system 2009. §§Primary author listed for confirming report, with reference provided. ¶Presented data on a second than indirectly suggested dentate nucleus hyperintensity with gadobenate dimeglumine. *Stojano et al11 presented data concerning gadobutrol that the 2 subsequent publications call into question.*

GBCA indicates gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

kinetic and thermodynamic stability—concepts that were clarified in later years), to avoid release of the gadolinium ion from the chelate.18 For example, a chelate such as Gd EDTA, which has low stability, has a much lower LD50—0.3 mmol/kg IV in mice—than the commercial GBCAs, and is thus much more toxic.19 More explicitly, the use of multidentate ligands to obtain a highly stable chelate complex constitutes a fundamental safety basis for this group of contrast media.13,20 Since chemical bonds in the GBCAs chelates are predominantly ionic, stable chelates are formed with multidentate polyaza-carboxylate chelates. Three main structural factors influencing the stability of GBCAs have been described: (a) the basicity of the ligand; (b) the number of 5-membered rings (N-Gd-N and N-Gd-O); and (c) the rigidity, cavity size, and conformation of the ligand.21

Two additional early developments in the field (macrocyclic agents—including a nonionic macrocylic, and nonionic linear agents) are important to note, which followed the initial research in 1981 performed at Schering with gadopentetate dimeglumine. Gadoterate meglumine (a macrocylic agent) was first presented in an abstract from Guerbet in 1985,22 with subsequent initial European approval in 1989 (the original "Diagnostic media" US patent with priority date July 24, 1981 from Schering indeed also listed “the sodium salt of the gadolinium [III] complex of 1,4,7,10-tetraazacyclododecanetetraacetic acid,” thus Gd-DOTA or gadoterate meglumine). In the US, clinical trials were completed by Squibb Diagnostics for gadoteridol (a second macrocylic agent) before 1991, leading to its approval in 1992.23 Approval for gadobutrol, the third macrocylic agent, occurred in 1998.

The development of gadoterate meglumine and gadoteridol followed gadopentetate dimeglumine rapidly in temporal sequence, but featured a chelate design (macrocylic as opposed to linear) that was substantially improved in terms of kinetic stability both in vitro and in vivo. As detailed in the 1991 clinical trial publication, “the chelate (ligand) in gadoteridol is ring-shaped and chemically rigid, as opposed to the linear, flexible structure of diethylenetriaminepentaacetic acid (DTPA) in gadopentetate dimeglumine.” “Transmetallation reactions in vivo occur very slowly with sterically rigid chelates such as gadoteridol, causing high in vivo stability and thus low toxicity.” Earlier basic science publications demonstrated transmetallation involving Cu2+ and Zn2+ with the DTPA chelate, but not with the macrocyclic chelates, also clearly stating the concept of transmetallation and the difference between linear and macrocycles in vivo, and the reason therein.24–27

The second important development to note was the pursuit of the nonionic linear Gd chelates, for clinical use, and attempts therein to justify their safety.19 This occurred despite knowledge that such derivatives of DTPA were susceptible to gadolinium dissociation, in addition to the possibility of decomposition reactions (breakdown of the chelate itself into separate compounds).28 The clinical development and safety in terms of potential transmetallation was justified by formulation with large amounts of excess chelate, 12 mg/mL for gadodiamide (5 mol% of excess ligand) and 28.4 mg/mL for gadoversetamide. Early research showed the LD50 for gadodiamide to be markedly improved with the addition of large amounts of excess ligand.19

Excess ligand, in very small amounts, has been used in the formulation of both gadoteridol and gadobutrol (macrocyclic agents) for a very different reason, unrelated to the stability of the compound. In this instance, the excess chelate ensures “that metal traces from the glass vials can be trapped during the process of heat sterilization,” specifically in the commercial production of the agent.29 In comparison to the very large amounts of excess chelate in the formulations for gadodiamide and gadoversetamide (linear, nonionic agents), gadopentetate dimeglumine (a linear, ionic agent) is formulated with only 0.4 mg/mL excess chelate. It should be noted, however, that this is double that in the original formulation, a change made to reduce the transient, dose-dependent elevation in serum iron and bilirubin seen after injection of this agent.30

Publications continued in the 1990s and 2000s detailing the difference in stability between the linear and macrocyclic agents, as revealed by transmetallation,31 biodistribution,32 and subchronic toxicity—the latter in animals.33 A transmetallation study with zinc citrate demonstrated major differences between GBCAs, unexplained by equilibrium thermodynamics or selectivity constants, with the order of kinetic stability being macrocyclic > linear ionic > linear nonionic.34 Research using radiotracers in animals elegantly demonstrated that the more stable agent is—with the ranking of stability from most to least being the macrocyclic agents > gadopentetate dimeglumine > gadoversetamide...
As of the January 21, 2011 FDA Regulatory update regarding NSF risk, there were 438 cases globally due to gadodiamide injection (where this was the only agent injected), 7 due to gadoversetamide, and 135 due to gadopentetate dimeglumine. Given the number of administrations of these 3 agents (47 vs 0.8 vs 95 million), data also provided in the FDA update, the incidence with gadodiamide and gadoversetamide is relatively equivalent, with that of gadopentetate dimeglumine lower. There is a discrepancy in reporting, which should be noted, as the FDA adverse event reporting system states that domestic single-agent NSF reports were 382 for gadodiamide, 195 for gadopentetate dimeglumine, and 35 for gadoversetamide. In addition, as of April 2010, in the adverse event reporting system database, there were a total of 1381 reported cases of NSF, the majority confounded (when 2 or more different GBCAs have been injected, and thus it is impossible to determine with certainty which agent triggered the development of NSF). The association of NSF with GBDA injection is irrefutable, given that new cases of NSF have virtually ceased after a change in clinical practice regarding their administration.

In a landmark article by Thomas Frenzel in 2008,\textsuperscript{44} the kinetic stability of the clinically approved GBCAs was evaluated in human serum, together with a complete description of their respective structures, characteristics, and published stability constants. It was observed that the release of Gd\textsuperscript{3+} from the linear gadolinium complexes was orders of magnitude higher than with macrocyclic complexes. Key to this research was the identification by high pressure liquid chromatography of dechelated gadolinium. As well, the release from the nonionic linear GBCAs (gadodiamide and gadoversetamide) was determined to be 10 times that of the other ionic linear GBCAs. After 15 days incubation, 20\% of the Gd\textsuperscript{3+} had been released from gadodiamide, and 21\% from gadoversetamide. The amounts released by gadofosveset trisodium, gadopentetate dimeglumine, and gadobenate dimeglumine ranged from 1.8\% to 1.9\%, whereas only 1.1\% was released from gadodextrate disodium. Under these conditions, human serum at 37°C evaluated with both normal and elevated phosphate levels, all 3 macrocyclic chelates remained stable.

Sieber et al\textsuperscript{45} in 2008 was able to develop an animal model for NSF, concluding that the NSF-like signs observed were most likely due to the Gd\textsuperscript{3+} ion, after dechelation. The release of Gd was shown to correlate with the kinetic stability of the agents, with the least stable agent evaluated (gadodiamide) leading to significantly higher Gd levels, particularly in the skin, with the occurrence of macroscopic and microscopic skin lesions. In clinical studies performed in the years immediately after the advent of NSF, skin biopsies demonstrated Gd in all NSF patients (in some cases at very high levels, >100 \( \mu g/g \)), with no Gd found in patients who received GBCAs but did not have NSF.\textsuperscript{46} Fretellier et al\textsuperscript{47} in 2011 also demonstrated in vivo dechelation in renally impaired rats receiving gadodiamide, with induction of skin lesions and higher gadolinium concentration in both skin and bone. These findings were not seen with gadoterate meglumine, which remained stable over the study period. Recent updates include a general review article (2014) that exhaustively discusses the mechanism of NSF.\textsuperscript{48} A landmark article published the next year (2015) subsequently elegantly confirmed the binding of GBCAs by peptides in vivo, inducing release of the gadolinium ion.\textsuperscript{49}

As a result of NSF, the FDA guidelines for the use of GBCAs were revised on several occasions. Gadopentetate dimeglumine, gadodiamide, and gadoversetamide are now, as of the latest safety guidelines (September 2010), contraindicated in patients with chronic severe kidney disease or acute kidney injury. In addition, all patients are to be screened for kidney disease before possible GBDA injection. However, withdrawal of the approval for a supplemental injection of 0.2 mmol/L kg gadodiamide (for a total dose of 0.3 mmol/L/kg) did not occur until August 27, 2013. In the European community, the recommendations by the European Health Authorities and the European Society of Urological Radiology (ESUR) are more specific and detailed. Agents are
classified, relative to the risk of NSF, as high, medium (intermediate), or low. The final Committee for Medicinal Products for Human Use opinion was issued in November 2009 and ratified by European Commission decision in July 2010. Gadodiamide, gadoversetamidate, and gadopentetate dimeglumine are deemed high risk (due to NSF). These agents are contraindicated in renal insufficiency (glomerular filtration rate <30 mL/min) and liver transplant patients, in neonates younger than 4 weeks of age, with mandatory laboratory testing to screen all patients before injection for renal dysfunction. In reference to the ESUR guidelines (version 9.0, 2014, http://www.esur.org/esur-guidelines/), the 3 high-risk agents (group 1), gadodiamide, gadopentetate dimeglumine, and gadoversetamidate, are contraindicated in patients with CKD stage 4 and 5, acute renal insufficiency, pregnant women, and neonates. Measurement of estimated glomerular filtration rate (eGFR) is mandatory before contrast administration. It is also stated that these agents should be stored separately to prevent inadvertent use of a high-risk agent in a patient with poor renal function. The incidence of NSF is reported by the ESUR as 3% to 18% in at-risk patients with gadodiamide, and 0.1% to 1% in at-risk patients with gadopentetate dimeglumine (Table 1). The agents classified as intermediate risk are gadobenate dimeglumine, gadofosveset trisodium, and gadoxetate disodium. Those classified as having the lowest risk of NSF are gadobutrol, gadoterate meglumine, and gadoteridol (the 3 macrocyclic agents). In the ESUR report, it is also stated that no unconfounded cases of NSF (NSF cases occurring after the sole administration of only 1 specific GBCA) have been reported with either gadoterate meglumine or gadoteridol, and that for gadobutrol there are a few unconfounded cases, but that there is uncertainty about the histopathologic changes. No unconfounded NSF cases have occurred with the first agent, a linear chelate, and not with the second, a macrocyclic chelate. All patients underwent at least 6 consecutive contrast administration, but due to prior GBCA administration, are discussed in chronological order relative to e-publication date. The second article by Kanda et al3 compared findings with a linear contrast agent to that with a macrocyclic agent. Hyperintensity in the dentate nucleus on precontrast T1-weighted images was determined to be associated with prior administration of gadopentetate dimeglumine but not gadoteridol. McDonald et al1 then published the definitive first article with tissue samples. Postmortem specimens in 13 patients with at least 4 contrast-enhanced brain examinations (using exclusively gadodiamide) were compared with patients who had not received intravenous contrast. Neuronal tissue from the contrast group demonstrated up to 59 μg gadolinium per gram of tissue (ppm), with a significant dose-dependent relationship correlating with precontrast T1-weighted SI changes (obtained antemortem). Tissue deposition of gadolinium, determined by transmission electron microscopy, was localized to the capillary endothelium and neural interstitium. No gadolinium was detectable in the neuronal tissue of control patients. The second article from Rome, with Quattronechi as first author and Errante as coauthor, included 102 patients that had multiple follow-up brain MRs for evaluation of incidentally noted meningeomas.6 In patients with a history of at least 6 enhanced studies using gadodiamide, a significant increase in the SI of the dentate nucleus on T1-weighted precontrast studies was noted, clarifying that this finding was not related to medical therapy (as could have been the case with the prior studied patient populations). Radbruch et al7 then published a comparison of gadopentetate dimeglumine and gadoterate meglumine, with 50 patients in each group (in individuals with a suspicion of a brain tumor), demonstrating that on average a change occurred with the first agent, a linear chelate, and not with the second, a macrocyclic chelate. All patients underwent at least 6 consecutive MR examinations with exclusive use of either the linear or macrocyclic GBCA. In June, Ramalho et al8 published a study evaluating 23 patients who received gadodiamide (5 ± 2.4 injections) and 46 who received gadobenate dimeglumine (4.6 ± 2.1 injections). Their findings were that a significant increase was seen in the dentate nucleus to middle cerebellar peduncle ratio with gadodiamide but not gadobenate dimeglumine. However, the rate of change data suggested gadolinium deposition in the dentate nucleus with gadobenate dimeglumine (with this change statistically significant), although less than with gadodiamide.

In mid-2015, the first animal model of this disease process was published by Robert et al.55 Repeated doses of gadodiamide (a linear chelate) were associated with progressive and persistent T1 signal hyperintensity in the deep cerebellar nuclei, with no effect for gadoterate meglumine (a macrocyclic chelate). Tissue samples were assayed by inductively coupled plasma mass spectrometry, with quantitative data showing a statistically significant difference between gadolinium concentrations in the gadodiamide animal group in the cerebellum (3.66 ± 0.91 nmol/g) versus that with gadoterate meglumine (0.26 ± 0.12 nmol/g).

### ACCUMULATION IN THE BRAIN (AND SPECIFICALLY THE DENTATE NUCLEUS)

Two articles in 2014 identified for the first time abnormal high signal intensity (SI) in the dentate nucleus and globus pallidus on unenhanced T1-weighted imaging and its correlation with increasing cumulative dose of specific GBCAs. It is important to note that this phenomenon is seen in patients with normal renal function, as opposed to NSF, which occurs in patients with renal insufficiency. The first article appeared in the journal Radiology by Kanda et al,1 and reported 19 patients who received 6 or more doses of contrast media, most of whom had a brain tumor. The 2 agents used at the site were gadopentetate dimeglumine and gadodiamide. The dentate nucleus to pons (DN/pons) SI ratio correlated with the number of prior contrast agent doses. The SI changes in the dentate nucleus were more prominent than that in the globus pallidus, where this finding was also seen (hyperintensity of the nucleus on precontrast T1-weighted images), leading to a focus in this and later articles on the dentate nucleus. The article left open the question as to whether the findings might be due to the patient’s primary pathology or treatment therein. The second article appeared in the journal Investigative Radiology by Errante et al.4 It reported findings with gadodiamide in 2 different patient populations, 38 patients with multiple sclerosis and 37 patients with brain metastases. A progressive increase in SI (DN/pons SI ratio) was seen in both patient populations. This article was crucial as it demonstrated that the findings were not related to a specific pathology, in addition to confirming the observations of the first publication.

The following publications, all appearing in 2015, relating to the dentate nucleus and high SI on T1 weighted scans before contrast administration, but due to prior GBCA administration, are discussed in chronological order relative to e-publication date. The second article by Kanda et al3 compared findings with a linear contrast agent to that with a macrocyclic agent. Hyperintensity in the dentate nucleus on precontrast T1-weighted images was determined to be associated with prior administration of gadopentetate dimeglumine but not gadoteridol. McDonald et al1 then published the definitive first article with tissue samples. Postmortem specimens in 13 patients with at least 4 contrast-enhanced brain examinations (using exclusively gadodiamide) were compared with patients who had not received intravenous contrast. Neuronal tissue from the contrast group demonstrated up to 59 μg gadolinium per gram of tissue (ppm), with a significant dose-dependent relationship correlating with precontrast T1-weighted SI changes (obtained antemortem). Tissue deposition of gadolinium, determined by transmission electron microscopy, was localized to the capillary endothelium and neural interstitium. No gadolinium was detectable in the neuronal tissue of control patients. The second article from Rome, with Quattronechi as first author and Errante as coauthor, included 102 patients that had multiple follow-up brain MRs for evaluation of incidentally noted meningeomas.6 In patients with a history of at least 6 enhanced studies using gadodiamide, a significant increase in the SI of the dentate nucleus on T1-weighted precontrast studies was noted, clarifying that this finding was not related to medical therapy (as could have been the case with the prior studied patient populations). Radbruch et al7 then published a comparison of gadopentetate dimeglumine and gadoterate meglumine, with 50 patients in each group (in individuals with a suspicion of a brain tumor), demonstrating that on average a change occurred with the first agent, a linear chelate, and not with the second, a macrocyclic chelate. All patients underwent at least 6 consecutive MR examinations with exclusive use of either the linear or macrocyclic GBCA. In June, Ramalho et al8 published a study evaluating 23 patients who received gadodiamide (5 ± 2.4 injections) and 46 who received gadobenate dimeglumine (4.6 ± 2.1 injections). Their findings were that a significant increase was seen in the dentate nucleus to middle cerebellar peduncle ratio with gadodiamide but not gadobenate dimeglumine. However, the rate of change data suggested gadolinium deposition in the dentate nucleus with gadobenate dimeglumine (with this change statistically significant), although less than with gadodiamide.

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Investigative Radiology • Volume 51, Number 5, May 2016

an important question is whether the findings in the dentate nucleus cause clinical symptomatology. To date, only a single case report hints at this possibility (with severe joint contractures observed), with further research including animal models of disease (and potential changes in behavior) critical. Anecdotal reports, and more recently a case report, reveal dentate nucleus hyperintensity in the NSF patient population (in addition to that, as reported in 2014 and 2015, in patients with normal renal function). In terms of the cerebellum, it is known that the dentate nucleus—having in normal subjects high levels of zinc, iron, and copper—is a major repository of metals essential to normal function. These metals are also known to form chelates with DTPA. Thus transmetallation with the GBCAs is very much a possibility, in particular with the less stable MR agents. Relevant to the importance of these transmetallation with the GBCAs is very much a possibility, in particular with the less stable MR agents. Relevant to the importance of these transmetallation with the GBCAs is very much a possibility, in particular with the less stable MR agents. Relevant to the importance of these
benefit when compared with the approved macrocyclic agents.7,71 A recent opinion piece published from the National Institutes of Health, Radiology and Imaging Sciences, confirms this shift, specifically recommending when GBCAs are required that consideration should be made in terms of use of a macrocyclic rather than a linear agent.72

REFERENCES


