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

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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 dependent 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

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S lightly more than 30 million enhanced magnetic resonance (MR) imaging procedures are performed worldwide each year (as of 2014), utilizing gadolinium-based contrast agents (GBCAs), with continued growth year to year (source: Arlington Medical Resources, Inc, https://decisionresourcesgroup.com). Overall, in both Europe and the United States, approximately 40% of all MR examinations are performed with intravenous contrast administration (the remainder are performed without the use of a contrast agent). Utilization varies by anatomic region, from slightly less than 50% for the central nervous system, to greater than 70% for the heart and liver, to greater than 90% for the breast (source: Arlington Medical Resources, Inc). Although half of all doses are for central nervous system imaging, the rest are scattered among the different types of examinations, led by MR angiography followed by abdominal imaging.

The 9 agents currently approved for clinical use (in 1 or more of the major clinical markets worldwide) include—listed in order relative to their initial approval—gadopentetate dimeglumine (Magnevist; Bayer HealthCare), gadoterate meglumine (Dotarem; Guerbet Group),

gadoteridol (ProHance; Bracco Imaging), gadodiamide (Omniscan; GE Healthcare), gadobutrol (Gadovist/Gadavist; Bayer HealthCare), gadoversetamide (Optimark; Guerbet Group), gadobenate dimeglumine (MultiHance; Bracco Imaging), gadoxetate disodium (Primovist/Eovist; Bayer HealthCare), and gadofosveset trisodium (Ablavar; Lantheus Medical Imaging) (Table 1). Although no gadolinium chelate to date has been withdrawn from the market, in several regions of the world, there have been recent major market shifts, leading to the less stable gadolinium chelates having a markedly lower to—in some instances—near-nonexistent use. It is important to note that the history of intravenous contrast agents for MR also includes 3 agents, none gadolinium chelates, that are no longer available, at least in the United States and Europe. This group includes Feridex (ferumoxides), Resovist (ferucarbotran), and Teslascan (mangafodipir). Giving more specific data for one of these agents, Teslascan was withdrawn from the United States market in 2003 and from the European market in 2012. Among concerns with this agent was developmental toxicity with maternal administration (teratogenicity).[12] All 3 agents were narrowly indicated with very small markets, as well as having a far greater minor adverse event profile.

The approved GBCAs can be differentiated, in terms of chemical design, on the basis of ligand type and charge. Gadoterate meglumine, gadoteridol, and gadobutrol are macrocyclic in type, whereas gadopentetate dimeglumine, gadodiamide, gadoversetamide, gadobenate dimeglumine, gadoxetate disodium, and gadofosveset trisodium are linear in type. Gadopentetate dimeglumine, gadoterate meglumine, gadobenate dimeglumine, gadoxetate disodium, and gadofosveset trisodium are ionic, whereas gadoteridol, gadodiamide, gadobutrol, and gadoversetamide are nonionic. Other features that differentiate the agents include formulation with excess ligand (and the amount therein), osmolality, viscosity, thermodynamic and kinetic stability constants, clearance (renal, hepatic), and relaxivity. The readers are referred to an in-depth review for a better understanding of these important characteristics.[13]

Hypersensitivity reactions after intravenous administration of GBCAs have been well studied over the years since the introduction of gadopentetate dimeglumine in the late 1980s, the first approved agent. For the agents that do not interact with proteins (thus excluding gadofosveset trisodium, gadobenate dimeglumine, and gadoxetate disodium), all have the same incidence of mild adverse reactions, as well as severe hypersensitivity reactions.[14] Nausea is seen in approximately 1.5% of patients, hives in 0.2%, and severe reactions in less than 0.001%. Anecdotal information has often been alleged to differentiate the agents on the basis of adverse reactions, although all studies performed for agency approval report similar values, as do well controlled large prospective trials, irrespective of the class of the agent (macrocyclic or linear, ionic, or nonionic).[15,16]

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.[17] Advanced in this presentation, and emphasized throughout the developmental history of the gadolinium chelates, is that the clinical safety of these agents is to 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

Trade Name*	Generic Name	Acronym	Incidence of NSF† (No. US Cases)‡	Dentate Nucleus Hyperintensity§	No Dentate Hyperintensity§
Magnevist	Gadopentetate dimeglumine	Gd-DTPA	0.1%–1% (195)	Kanda et al,[1] Radbruch et al[2]	
Dotarem	Gadoterate meglumine	Gd-DOTA			Radbruch et al[2]
ProHance	Gadoteridol	Gd-HP-DO3A			Kanda et al[3]
Omniscan	Gadodiamide	Gd-DTPA-BMA	3%–18% (382)	Kanda et al,[1] Errante et al,[4] McDonald et al,[5] Quattrocchi et al[6]	
Gadovist/Gadavist	Gadobutrol	Gd-DO3A-Butrol			Radbruch et al,[7] Cao et al[8]¶
Optimark	Gadoversetamide	Gd-DTPA-BMEA	Unknown (35)		
MultiHance	Gadobenate dimeglumine	Gd-BOPTA		Weberling et al[9]‖	
Primovist/Eovist	Gadoxetate disodium	Gd-EOB-DTPA			
Ablavar	Gadofosveset trisodium	MS-325			

*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.

‖Ramalho et al[10] presented data that only indirectly suggested dentate nucleus hyperintensity with gadobenate dimeglumine.

¶Stojanov et al[11] 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 LD_{50}—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 macrocyclic, and nonionic linear agents) are important to note, which followed the initial research in 1981 performed at Schering with gadopentetate dimeglumine. Gadoterate meglumine (a macrocyclic 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 macrocyclic agent) before 1991, leading to its approval in 1992.[23] Approval for gadobutrol, the third macrocyclic agent, occurred in 1998.

The development of gadoterate meglumine and gadoteridol followed gadopentetate dimeglumine rapidly in temporal sequence, but featured a chelate design (macrocyclic 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 Cu^{2+} and Zn^{2+} with the DTPA chelate, but not with the macrocyclic chelates, also clearly stating the concept of transmetallation and the difference between linear and macrocylics 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 LD_{50} 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.[31] Research using radiotracers in animals elegantly demonstrated that the more stable an agent is—with the ranking of stability from most to least being the macrocyclic agents > gadopentetate dimeglumine > gadoversetamide

~ gadodiamide, the less gadolinium is left in the body after injection.[32] A subchronic toxicity study in mice confirmed zinc transmetallation (by measurement of urinary zinc) with gadodiamide, together with unexplained weight loss, hair loss, ulcerative dermatitis, and necrotizing vasculitis, together with a reduction in number of ovarian follicles.[33] It is of historical interest to also note that the original preclinical safety assessment of gadodiamide, published in 1993, included the observation of skin desquamation and ulceration in the highest dose group (subchronic toxicity),[34] findings not reported with the other agents.

During the 1990s, it became known that gadodiamide interfered with measurement of serum calcium from blood samples when colorimetric reagent kits were used.[35] Subsequently, this was also shown for gadoversetamide, with the other agents having no interference.[36,37] The interference observed in the measurement of serum calcium by the linear GBCAs was demonstrated to be due to transmetallation, which was subsequently reported as well in the colorimetric measurement of serum iron.[37,38] Despite the recommendation in the 1995 publication that colorimetric kits should not be used for determination of serum calcium in blood within 24 hours after gadodiamide injection, in the United States other analytical methods were generally not employed. This led eventually to a report in 2003 documenting inappropriate intravenous calcium administration in 7 patients, due to the incorrect diagnosis of critical hypocalcemia from blood samples obtained soon after gadodiamide injection.[39] Subsequently, it has also been shown that linear agents in general interfere with the analytical determination of serum iron and that the macrocyclic agents do not.[38]

The world of MR owes thanks to Thomas Grobner for his identification of the link between nephrogenic systemic fibrosis (NSF) and intravenous GBCA administration.[40] In a report published January 23, 2006, Dr Grobner described 5 patients in his dialysis unit who underwent contrast-enhanced MR angiography and then developed, within 2 to 4 weeks, thickening and induration of the skin, starting in the lower extremities and progressing to the trunk and upper extremities (with concomitant pain). Unfortunately, in his *Interesting Case* report, the agent was identified as Gd-DTPA (Magnevist), whereas in reality it was gadodiamide.

"NSF is an uncommon but serious acquired systemic skin disorder affecting patients with renal insufficiency, specifically patients on dialysis or approaching dialysis."[41,42] Systemic manifestations include involvement of the muscles, liver, and lungs. Pruritus and sharp pain are often reported with skin lesions. Fibrosing effects can progress rapidly, leading to limb contractures and decreased mobility—and the disease can be fatal. Examination of the patient files of Shawn Cowper in 2006 quickly revealed that gadopentetate dimeglumine was also a causative agent, although implicated in fewer cases than gadodiamide. Dissemination of this information and change in practice was slow, despite the mailing of a letter by GE Healthcare on June 6, 2006, informing health care professionals concerning the development of NSF after administration of gadodiamide in chronic renal failure patients and publication of a Public Health Advisory by the FDA on June 8, 2006. These events, and the slow recognition of the disease and its implications, served as motivation for reporting 6 additional cases of NSF, all temporally related to gadodiamide injection, in order both to emphasize the need for a change in clinical practice and to explain the likely etiology, that being dechelation.[41] This publication went further to describe for the medical community the difference in stability of the available agents and the implications therein with the less stable agents. A subsequent more in-depth study in 2008 revealed an incidence of NSF of 18% in renal dialysis, chronic kidney disease (CKD) stage 5, patients administered 1 to 2 doses of gadodiamide.[43]

A large number of cases of NSF occurred in the United States. However, due to the legal system, and the use of sealed court cases, little information is available regarding the actual number of patients and the contrast media involved. It is known that more than 400 lawsuits were filed in US federal courts, with the majority involving gadodiamide.

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 GBCA 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,[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^{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^{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 gadoxetate 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[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^{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 μg/g), with no Gd found in patients who received GBCAs but did not have NSF.[46]

Fretellier et al[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.[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.[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 GBCA injection. However, withdrawal of the approval for a supplemental injection of 0.2 mmol/kg gadodiamide (for a total dose of 0.3 mmol/kg) did not occur until August 27, 2013. In the European community, the recommendations by the European Health Authorities and the European Society of Urogenital 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, gadoversetamide, 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 gadoversetamide, 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 been reported as well with gadobenate dimeglumine, gadofosveset trisodium, and gadoxetate disodium. Two recent articles provide a further overview of current knowledge concerning NSF, which is estimated to have affected up to 10,000 patients with renal dysfunction.[50,51]

Three subsequent studies have evaluated whether NSF might occur after administration of GBCAs that were categorized by the European Medicines Agency as either intermediate or low risk. The incidence of NSF after a single dose (0.1 mmoL/kg) of gadoterate meglumine in 255 patients on either hemodialysis or peritoneal dialysis was zero.[52] This included 106 doses less than 0.1 mmoL/kg, 106 doses between 0.1 and 0.2 mmoL/kg, and 42 doses above 0.2 mmoL/kg. For reference, CKD stage 4 is defined as an eGFR of 15 to 29 mL/min per 1.72 m^2 and stage 5 as eGFR less than 15 mL/min per 1.72 m^2 or on dialysis. In a cohort of 85 patients with severe renal impairment (defined by the authors as eGFR less than 30 mL/min per 1.72 m^2 or individuals on dialysis), no patient developed NSF after administration of 0.025 mmoL/kg gadoxetate disodium (standard dose for this agent).[53] In addition, in 1423 patients with severe renal dysfunction (defined as eGFR <30 mL/min per 1.72 m^2) administered gadobenate dimeglumine, there were no cases of NSF. The majority of the latter patients received 0.1 mmoL/kg, and there were 428 patients with an eGFR less than 15 mL/min per 1.72 m^2.[54] Thus, in the patient populations and with the doses evaluated, the incidence of NSF in chronic renal failure with gadoterate meglumine, gadoxetate disodium, or gadobenate dimeglumine (single injection) was shown to be zero.

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 their e-publication date. The second article by Kanda et al[3] 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 al[5] 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 Quattrocchi as first author and Errante as coauthor, included 102 patients that had multiple follow-up brain MRs for evaluation of incidentally noted meningiomas.[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 al[2] 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 al[10] 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,

at the limit of detectability). Two additional basic science articles were first available in November 2015, both pursuing further investigation in animal models of this disease process. Robert et al[56] published his second article, now comparing a larger group of GBCAs. All the linear contrast agents evaluated (gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide) produced a significant increase in SI in the deep cerebellar nuclei, which was not seen with gadoterate meglumine or the control (saline). Confirmation of the increased levels of total gadolinium in tissue was performed with inductively coupled plasma mass spectrometry. From an evaluation of the figures, both on MR images and for tissue analysis, results with gadopentetate dimeglumine and gadobenate dimeglumine are similar, whereas those with gadodiamide are of greater magnitude. In the article from Jost et al,[57] gadopentetate dimeglumine, gadobenate dimeglumine, and gadodiamide were compared with gadoterate meglumine and gadobutrol, confirming the increase in SI on T1-weighted imaging in the deep cerebellar nuclei with the 3 linear agents, and the absence therein with the 2 evaluated macrocyclic GBCAs.

After publication of the initial Robert research, an article appeared in *European Radiology*, focusing on a 58 patient group with relapsing-remitting multiple sclerosis, that reported both the globus pallidus/thalamus and the dentate pons SI ratios to correlate with the administration of gadobutrol, one of the macrocyclic agents.[11] However, in the only figure published, no increase in SI of the dentate nucleus can be seen, and the article did not include a control group.

The group of Radbruch then added 2 important articles, clarifying and expanding the findings to date. In the first article, Weberling et al[9] showed in 50 patients with 5 or more doses that patients receiving gadobenate dimeglumine also demonstrated precontrast an increased DN/pons SI ratio, not differentiable from that of gadopentetate dimeglumine. The second article refuted the findings published in *European Radiology*,[11] showing in 30 patients receiving 5 or more doses of gadobutrol no increase in dentate nucleus or globus pallidus SI, despite that the cumulative doses were higher than in the prior publication.[7] The last article on the dentate nucleus issue, available electronically in 2015, by Cao et al[8] confirmed further the findings of Radbruch, that no statistically significant increase in SI was seen for gadobutrol (in distinction to their gadopentetate dimeglumine group) in the DN/pons SI ratio.

In summary, dentate nucleus high SI on T1-weighted scans precontrast has been documented after gadodiamide, gadopentetate dimeglumine, and gadobenate dimeglumine administration (linear chelates) and is not seen after gadoterate meglumine, gadobutrol, and gadoteridol administration (macrocyclic chelates; Table 1).

Putting these findings in perspective, that gadolinium remains in tissues after administration of a GBCA has been known since 1986.[26,58,59] 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),[60] with further research including animal models of disease (and potential changes in behavior) critical. Anecdotal reports, and more recently a case report,[61] 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.[62] 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 metals for normal function is a recent report documenting their redistribution in the dentate nucleus in patients with Friedreich's ataxia.[63]

In regard to the brain, and specifically the nuclei therein, there is much that we do not understand about essential metals as well as the effects of administration of the less stable GBCAs. It will be important to establish in what form the deposited gadolinium occurs in tissue. Is the chelate intact? This is likely with the more stable agents,

such as demonstrated in the skin with gadoteridol in a patient 8 years after injection.[64]

What symptoms are associated with the high levels of gadolinium demonstrated in patients in the dentate nucleus after administration of the less stable agents, such as gadodiamide? Retrospective clinical studies are unlikely to be helpful in this regard, with animal experiments potentially of high value, mandating close cooperation between clinicians and preclinical researchers. In the literature there is a study evaluating the neurotoxicologic effect of long-term exposure to lanthanum (used to treat chronic renal failure)—one of the transition metals with properties similar to gadolinium.[65] Despite oral as opposed to intravenous administration, long-term exposure to lanthanum was shown to cause in rats a decline in neurobehavioral performance.

Concerning medical practice with the GBCAs, it is suggested that the use of extremely high numbers of doses in a single patient be reevaluated. Cumulative dose may need to be considered in terms of risk benefit for the patient, particularly in view of recent data. As recently reported, on the basis of a patient receiving 61 contrast-enhanced scans over an 11-year period—who on this basis had substantial gadolinium deposition in the skin despite normal renal function, caution advocates avoiding such large cumulative doses of GBCAs, in particular with the linear agents.[60] From a recent editorial by Henrik Thomsen,[66] who was heavily involved in the identification and clarification of the link between NSF and the GBCAs, "current knowledge suggests that it is safe to do multiple enhanced MR examinations with all 3 macrocyclic agents (gadoterate, gadoteridol, and gadobutrol)."

CONCLUSIONS

The established class of contrast media today for MR is that of the Gd chelates (GBCAs). These agents can be differentiated on the basis of stability (safety) and effective enhancement (relaxivity and formulation). Concerning the latter, the reader is referred to several excellent reviews.[13,67,68]

It is important to keep in mind that "the gadolinium chelates are critical to disease diagnosis by MR, indeed to clinical medicine worldwide, and have proven to be overall a very safe class of contrast media."[69] Given the observations concerning the dentate nucleus, a greater understanding of stability in vivo, together with the role of essential metals in the brain, is needed. Clearly, there is great need for in-depth, well-performed, scientific investigations in this area, to clarify the mechanisms therein and possible adverse effects, or lack thereof to determine risk benefit in GBCA use.

Considering NSF, the safest and simplest course of action at any individual site is simply not to stock the high-risk agents. Failures in screening are known, as they depend upon technologist education and require a completely secure system to prevent inadvertent administration.[70]

Due to the finding of T1 hyperintensity in the dentate nucleus after administration of the less stable gadolinium chelates—including specifically gadodiamide, gadoversetamide, gadopentetate dimeglumine, and gadobenate dimeglumine, in patients with normal renal function, whether clinical practice should continue with these agents, and with what justification, is important to address. A similar but slightly different question is what regulatory actions will occur, and at what time? It has been known in the printed literature since 1989 (and to the dedicated researchers in the field before then)[28]—in the very early days of development of the GBCAs, that macrocyclic chelates were substantially more stable than linear agents, and indeed it was suggested at that time that the macrocyclic agents should and would—on the basis of safety—replace the latter.

It is difficult to predict the future. However, one likely scenario is the withdrawal from clinical use of 3 agents—gadodiamide, gadoversetamide, and gadopentetate dimeglumine. Whether the remaining linear agents will be affected remains to be seen, in particular for agents and applications thereof that offer no additional clinical

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]

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