A Safety Update on the Gadolinium Chelates

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Allergic Reactions to the Gadolinium Chelates

• “to the best of current scientific knowledge, all of the gadolinium chelates approved clinically for use in the United States … have the same incidence of severe anaphylactoid reactions”
• “this is also true for minor adverse reactions, the two most notable being nausea and hives”
• “let us not add to the problem … by permitting unsubstantiated rumors to circulate … but continue to promote science”

Runge VM
AJR 2001;177:944

nausea ≈ 1.5%

hives ≈ 0.2%

severe reactions < 0.001%
Sils-Maria, Switzerland

Today, worldwide, there are 9 approved MR contrast agents.
Chemical Structures for the Linear Gd Chelates

Gd-DTPA

Gd-DTPA-BMA

Gd-DTPA-BMEA

Gd-BOPTA

Gd-EOB-DTPA

MS-325

Extracellular Non-ionic

Hepatobiliary Ionic

Blood pool Ionic
The clinical safety of a gadolinium chelate is to a large extent dependent upon the stability of the chelate in vivo.
Macrocyclic Gd Chelate

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Clinical Safety and Efficacy of Gd Chelate:
A Study in 411 Patients with Strokes, Intracranial and Spinal Diseases

It was known by the late 1980s that the macrocyclic chelates were more stable in vivo. What about structure and potential safety advantages? Gadoteridol is a neutral (nonionic) agent with low osmolality (0.63 osm/kg of water, as opposed to 1.94 osm/kg of water for gadopentetate dimeglumine, when both are prepared as 0.5 mol/L solutions). The chelate (ligand) in gadoteridol is ring-shaped and chemically rigid, as opposed to the linear, flexible structure of diethylenetriaminepentaaacetic acid (DTPA) in gadopentetate dimeglumine. The solubility of gadoteridol in water is 1.32 mol/L at 25°C (manufacturer’s recommendation, Squibb Diagnostics). Transmetallation reactions in vivo occur very slowly with sterically rigid chelates such as gadoteridol, causing high in vivo stability and thus low toxicity. Although the selectivity of DTPA is high for the gadolinium ion, a comparison of the DTPA ligand and 12-membered 1,4,7,10-tetraaza macrocycles in vitro shows markedly higher release of the gadolinium ion from the DTPA ligand in competition with Cu²⁺ and Zn²⁺ ions (29). However, the enhancement characteristics of gadopentetate dimeglumine and gadoteridol should be comparable because of similar T1 relaxivity and excretion (predominantly renal).
By 1996 it was known that zinc could substitute for gadolinium in vivo with the weaker chelates, leading to release of the gadolinium (transmetallation). This was observed with Gd DTPA-BMA and to a lesser extent Gd DTPA, both linear chelates.
By the early 2000s, studies using radiolabeled gadolinium chelate had demonstrated increased Gd retention with the linear chelates, being greatest with the two linear non-ionic chelates.

Invest Radiol 2002;37:107
Subchronic Toxicity of the Gadolinium Chelates

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INTRODUCTION:

Differences in safety profile between the four gadolinium chelates approved for clinical use by the Food and Drug Administration (FDA) are known, but have received in general little attention.[1, 2] The research subsequently

Shortly thereafter, a study in mice showed unexplained toxicologic findings with the two non-ionic linear chelates, not seen with a macrocyclic agent
In 2006, the link between gadolinium chelate administration and the development of NSF in renal dialysis patients was finally made.

**Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermatopathy and nephrogenic systemic fibrosis?**

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**Keywords:** end stage renal disease; gadolinium–DTPA; metabolic acidosis; nephrogenic fibrosing dermatopathy

**Introduction**

Nephrogenic fibrosing dermatopathy (NFD) is an acquired, idiopathic disorder that is observed in patients with renal disease. Most patients with NFD have undergone dialysis for renal failure [1,2]. It tends to affect mostly the middle-aged. An association of NFD with coagulation abnormalities, recent vascular surgery or intervention (e.g. shunt/fistula and angioplasty), and presence of antiphospholipid antibodies has been discussed by several authors thus far [1,3], but the origin of the disease is still unknown. A more widespread variant of this fibrosing skin disease with involvement of other organs (e.g. lungs, liver, muscles and the heart) is described as nephrogenic systemic fibrosis (NSF) by Leboit ...
High Prevalence of Nephrogenic Systemic Fibrosis in Chronic Renal Failure Patients Exposed to Gadodiamide, a Gadolinium-Containing Magnetic Resonance Contrast Agent

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Objective: Nephrogenic systemic fibrosis (NSF) is a serious disease affecting renal failure patients. It may be caused by some gadolinium (Gd)-containing contrast agents, including gadodiamide. The study aimed at estimating the prevalence of NSF after gadodiamide exposure for patients with chronic kidney disease (CKD).

Materials and Methods: Retrospective cohort study of 190 consecutive nephrological patients in different categories of kidney function referred for gadodiamide-enhanced magnetic resonance imaging in the period January 1, 2004 to March 21, 2006.

Results: Eighteen patients (18/190; 10%, 95% CI: 6%–15%) were diagnosed with NSF within a mean follow-up period of 29 months (range 16–43 months). All 18 cases had stage 5 CKD (ie, estimated glomerular filtration rate less than 15 mL/min/1.73 m² or in dialysis therapy) at the time of their gadodiamide exposure. The prevalence of NSF among patients with stage 5 CKD at exposure (n = 102) was 18% (95% CI: 11%–27%). No cases were seen among 88 gadodiamide-exposed patients who had milder degrees of renal insufficiency (prevalence 0%, 95% CI: 0%–4%).

Conclusions: The risk of NSF is unacceptably high among stage 5 CKD patients exposed to gadodiamide.

Key Words: cohort study, epidemiology, gadodiamide, nephrogenic systemic fibrosis

(Invest Radiol 2008;43: 141–144)

“the risk of NSF is unexpectedly and unacceptably high (18%) in CKD5 patients exposed to gadodiamide.”

“In order to eliminate the risk for accidental gadodiamide exposure and minimize the risk of NSF in renal failure patients in the future, we chose to totally abandon the use of gadodiamide in our institution in March 2006.”
A landmark study in 2008 demonstrated 20% of the gadolinium to be released from the linear non-ionic chelates simply with incubation for 15 days in human serum, as compared to 2% or less with linear ionic chelates and no detectable release with macrocyclic chelates.
Link with Gd-based Agents

- Gd-deposits have been identified in tissues of patients with NSF
  - largest series to date examined 57 skin biopsies
  - all biopsies of histologically confirmed cases contained gadolinium

Number of NSF Cases by Agent

- “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.”
As a result of NSF, drug labeling changes were mandated.

**EMA (Europe)**
- **High risk***
  - Omniscan, Optimark, Magnevist
- **Intermediate risk**
  - Primovist, Vasovist, MultiHance
- **Low risk**
  - Gadovist, Dotarem, ProHance

**FDA (United States)**
Omniscan, Optimark, and Magnevist are contraindicated in patients with acute kidney injury or chronic, severe kidney disease.
Progressive Increase of T1 Signal Intensity of the Dentate Nucleus on Unenhanced Magnetic Resonance Images Is Associated With Cumulative Doses of Intravenously Administered Gadodiamide in Patients With Normal Renal Function, Suggesting Dechelation

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Objective: The purpose of this study was to assess the association between the total number of gadodiamide-enhanced magnetic resonance imaging (MRI) examinations and the signal hyperintensity of the dentate nucleus on unenhanced T1-weighted images in patients with multiple sclerosis (MS) and those with brain metastases (BMs).

Materials and Methods: A group of 36 patients with MS and 37 patients with BM who had undergone at least 2 consecutive enhanced MRI examinations in our institution were examined for this retrospective observational study. The average T1 signal intensity of the dentate nuclei and the pons was obtained, and the dentate nuclei-to-pons (DNP) signal intensity ratio was calculated. These values were compared between patients with less than 6 and 6 enhanced MRI scans or more (≥6 MRIs). Relative changes of the DNP were plotted against the number of enhanced MRI scans (nMRIs).

Results: A progressive increase in the T1 signal intensity of the DNP ratio was observed both in the MS group and in the BM group. The DNP ratios of the last 6 MRIs in the subgroup of patients with ≥6 MRI scans were significantly higher than those of the first 6 MRIs in the MS group (p < 0.001) and in the BM group (p = 0.01). The relative changes of the DNP showed a positive correlation with the nMRIs of Spearman ρ = 0.94 (p = 0.001) in the MS group and of 0.08 (p = 0.001) in the BM group. Curve regression analyses of the relative change of DNP ratios showed linear models to best fit the data with a ρ of 0.99 in the MS group and a ρ of 0.74 in the BM group.

Conclusions: Our study shows that the increase in the unenhanced T1 signal intensity has a linear relationship with the number of enhanced MRI scans. Indeed, we estimated a linear regression model to fit the progressive increase in T1 signal intensity of the dentate nucleus after multiple enhanced MRI scans. This finding suggests substantial dechelation of gadodiamide in patients with normal renal function, raising further concerns regarding the stability of this agent. Further comparative studies with other gadolinium chelates, specifically both linear and macrocyclic, are strongly recommended.

Key Words: signal intensity, dentate nucleus, gadolinium, correlation, gadolinium-based MRI imaging agent

These two papers appeared in 2014 and demonstrated the correlation between number of Omnisin injections and dentate nucleus hyperintensity on T1-weighted scans, a finding seen in patients with normal renal function.
Gadodiamide and Dentate Nucleus T1 Hyperintensity in Patients With Meningioma Evaluated by Multiple Follow-Up Contrast-Enhanced Magnetic Resonance Examinations With No Systemic Interval Therapy

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Abstract: The dentate nucleus of the cerebellum may appear as hyperintense on unenhanced T1 magnetic resonance images (MRI) of the brain. Recently, T1 signal hyperintensity has received attention owing to its association with the buildup of gadodiamide-based contrast agents specifically gadodiamide, in patients not receiving any therapy. Across a time interval of 18-month follow-up, T1 hyperintensity of the dentate nucleus was observed in patients whose medical history showed that they were not receiving any medication. The finding was associated with the histological and microstructural appearance of the dentate nucleus and multiple intraventricular injections of gadodiamide. The findings raised the question of whether gadodiamide would be a useful agent in patients with normal renal function.

Key Words: dentate nucleus, magnetic resonance, contrast agent, gadodiamide, gadodiamide, meningioma, neurology

The dentate nucleus of the cerebellum may appear as hyperintense on unenhanced T1 magnetic resonance images (MRI) of the brain. The reason for T1 signal hyperintensity has received attention in recent years and is still unresolved. More recently, studies have shown that the association between high T1 signal intensity of the dentate nucleus and multiple intraventricular injections of gadodiamide is significant. The finding was associated with the histological and microstructural appearance of the dentate nucleus and multiple intraventricular injections of gadodiamide. The findings raised the question of whether gadodiamide would be a useful agent in patients with normal renal function.

Two Early 2015 Publications

High Signal Intensity in Dentate Nucleus on Unenhanced T1-weighted MR Images: Association with Linear versus Macroyclic Gd Chelate Administration

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Purpose: To assess whether an association exists between hyperintensity in the dentate nucleus (DN) on unenhanced T1-weighted magnetic resonance imaging (MRI) images and the administration of gadodiamide-based contrast agents (GBCAs) that contain different types of gadolinium chelates.

Materials and Methods: A total of 100 patients were included. Two different GBCAs were administered: gadodiamide (Omniscan) and gadoversetamid (Magnevist). T1-weighted images were obtained before and after each administration. The association between hyperintensity in the DN and the type of GBCA administered was assessed using paired t tests and the Lin correlation coefficient.

Results: The images of nine patients (7.1%) showed hyperintensity in the DN. Twenty-two patients (18.1%) received linear GBCAs (median, two patients; maximum, 11 patients), 36 patients (28.3%) received macrocyclic GBCAs (median, two patients; maximum, 15 patients), 14 patients (11.0%) received both types of GBCA (linear, two patients; maximum, five patients) and macrocyclic (median, three patients; maximum, eight patients), and 54 patients (42.5%) had no history of administration of gadolinium chelates. Interobserver correlation was almost perfect (0.982 [95% confidence interval: 0.960, 0.994]). The DN-cerebellar ratio was associated with linear GBCA (P < 0.001), but not with macrocyclic GBCA exposure (P > 0.875). According to the Aikake information criterion, only linear correlation coefficient was significantly different from zero.
Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging

To determine if repeated intravenous exposures to gadolinium-based contrast agents (GBCAs) are associated with neuronal tissue deposition.

In this institutional review board-approved single-center study, signal intensities from T1-weighted magnetic resonance (MR) images and postmortem neuronal tissue samples from 12 patients who underwent at least four GBCA-enhanced brain MR examinations between 2000 and 2014 (contrast group) were compared with those from 10 patients who did not receive GBCA (control group). Autopsy consent was obtained from all study participants. Neuronal tissues from the dentate nucleus, pons, globus pallidus, and thalamus of these 23 deceased patients were harvested and analyzed with inductively coupled plasma mass spectrometry (ICP-MS), transmission electron microscopy, and light microscopy to quantify, localize, and assess the effects of gadolinium deposition. Associations between cumulative gadolinium dose, changes in T1-weighted MR signal intensity, and ICP-MS-derived tissue gadolinium concentrations were examined by using the Spearman rank correlation coefficient (ρ).

Compared with neuronal tissues of control patients, all of which demonstrated undetectable levels of gadolinium, neuronal tissues of patients from the contrast group contained 0.1–58.8 μg gadolinium per gram of tissue, in a significant dose-dependent relationship that correlated with signal intensity changes on precontrast T1-weighted MR images (ρ = 0.48–0.95). All patients in the contrast group had relatively normal renal function at the time of MR examination. Gadolinium deposition in the capillary endothelium and neural interstitium was observed only in the contrast group.

Intravenous GBCA exposure is associated with neuronal tissue deposition in the setting of relatively normal renal function. Additional studies are needed to investigate the clinical significance of these findings and the generalizability to other GBCAs.

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Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Gadobenate Dimeglumine Administration

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Objectives: The aim of this study was to compare changes in signal intensity (SI) ratios of the dentate nucleus (DN) to pons and cerebrospinal fluid (CSF) on unenhanced T1-weighted magnetic resonance imaging (MRI) scans between the first and last MRI using the linear gadolinium-based contrast agent gadobenate dimeglumine.

Materials and Methods: The study was approved by the University of Heidelberg (S-324/2014), waived due to the retrospective character underwent at least 5 consecutive MRI ex MRI for reference) with the exclusive use analyzed retrospectively. The difference of SI ratios was calculated on unenhanced T1 and last examination. Results were compared gadopentetate dimeglumine and gadodate dimeglumine.

Results: Signal intensity ratio differences for DN-to-pons and DN-to-CSF were significantly greater than 0 (pons: 0.039 ± 0.020, P < 0.001; CSF: 0.143 ± 0.152, P < 0.001). No control variable consistently predicted the SI ratio difference for the DN-to-pons and the DN-to-CSF ratio. Compared with previously published data, the difference in SI increase between gadopentetate dimeglumine and gadobenate dimeglumine 0.096. In contrast, the DN-to-gadobenate dimeglumine: E (P = 0.017) ratios were both than for gadodate dimeglumine.

Conclusions: The present study found an increase in SI in the DN after serial injections of gadobenate dimeglumine. Further studies are needed to clarify the potential of different linear gadolinium-based contrast agents to cause SI increase in the DN.

A further study on Kamenko et al. compared the amikacin-IGBCA gadodiamide to the amikacin-IGBCA gadodiamide. The authors found a “significant trend toward relative change” for the DN but not for the globus pallidus after serial applications of gadobenate dimeglumine. This effect was, however, smaller than that found for gadodiamide.12

The current study assessed changes in SI ratios of the DN to

FIGURE 4. Finding of hyperintensities in the DN on unenhanced T1-weighted MRI scans. The DN is shown prior (A) and after 15 administrations with the IGBCA gadobenate dimeglumine (B, arrows) in a SE sequence at 1.5 T.
High-Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-Weighted Images
Evaluation of the Macro cyclic Gadolinium-Based Contrast Agent Gadobutrol

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Objective: The aim of this study was to compare changes in the signal intensity (SI) ratio of the dentate nucleus (DN) to the pons, DN to cerebrospinal fluid (CSF), and globus pallidus (GP) to thalamus on unenhanced T1-weighted magnetic resonance imaging (MRI) scans after serial injections of the macro cyclic gadolinium-based contrast agent gadobutrol.

Materials and Methods: Thirty patients who had received at least 5 MRI examinations (plus an additional last MRI for reference) with the exclusive use of gadobutrol, resulting in a total cumulative dose of 54.1 ± 36.4 mL gadobutrol, were analyzed retrospectively. Signal intensity ratio differences were calculated for DN-to-pons, DN-to-CSF, and GP-to-thalamus ratios by subtracting the SI ratio at the first MRI from the SI ratio at the last MRI scan on each sample. The tests were employed to examine if they differed from 0. Regression and correlation analysis were performed to examine whether the SI ratio differences were predicted by a number of control variables.

Results: Signal intensity ratio differences did not differ significantly from 0, neither for the DN-to-pons ratio (0.035 ± 0.0476, P = 0.69), the DN-to-CSF ratio (−0.54 ± 0.3217, P = 0.37), nor the GP-to-thalamus ratio (−0.0020 ± 0.0211, P = 0.60). None of the control variables predicted changes in SI ratios.

Conclusions: In contrast to a recently published study, we did not find signal increases in the DN or in the GP after serial injections of gadobutrol, even though the total dose applied here was considerably larger than in the respective study. This finding adds further support to the hypothesis that the molecular structure of a gadolinium-based contrast agent such as macro cyclic or linear is a crucial factor for its potential to cause gadolinium deposition in the brain. Future studies should further assess this hypothesis by additional animal investigations as well as histopathological and clinical correlation studies.

(Invest Radiol 2015;50: 805–810)

The study of Radbruch et al provides further evidence supporting a significant difference between macro cyclic and linear chelates in terms of safety profile. As the authors state in their conclusion, for linear GBCAs—specifically those that have no benefit in terms of improved diagnosis in comparison to the approved macro cyclic GBCAs—their ongoing clinical use should be reassessed. Let us remember, as physicians, above all to do no harm.

Macrocyclic Versus Linear Gadolinium Chelates
Val M. Runge, MD

The article “High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evaluation of the macro cyclic gadolinium-based contrast agent gadobutrol” by Radbruch et al1 provides critical new information regarding gadolinium deposition in the dentate nucleus. The conclusion, from a study of 30 patients, is that no signal intensity increase is seen with gadobutrol. This is in sharp distinction to a prior publication2 and, as stated in the conclusion of Radbruch et al, “adds further support to the hypothesis that the molecular structure of a gadolinium-based contrast agent (GBCA) as either macro cyclic or linear is the crucial factor for its potential to cause gadolinium depo sition in the brain.”

History is important, in particular, to avoid the mistakes of the past. Publication and dissemination of well-performed, scientifically valid research are also crucial. Unfortunately, the scientific literature contains errors, many accidental, which in most cases are corrected with time. A prominent example was the belief that peptic ulcers were caused by acid. Indeed, this was part of my instruction, along with contemporaries across the world, while at Stanford Medical School in the late 1970s. It took years of dedicated research by Barry Marshall and Robin Warren,3 beginning in 1983, to dispel this belief. Because of their work, which was awarded a Nobel Prize in 2005, treatment today is simple and effective, with the enormous costs (both financial and in human terms) of surgery and lifelong medical treatment so avoided.

Unfortunately, scientific fraud also occurs, although rare. In the radiology literature, the best known example is that of Dr Robert A. Slutzky at the University of California San Diego in the 1980s. Of the 137 articles published by Dr Slutzky (over only a 6-year period), it was eventually concluded that 77 were valid, 48 were questionable, and 12 were fraudulent.4 Yet, despite the attention that this case received, even articles that were retracted continued to be cited.

Regarding the publication in European Radiology5 that the current results call into question, it is important to note that the European Radiology study was previously rejected by Investigative Radiology. A decision on rejection was made in part due to the only figure provided not showing an increase in dentate nucleus signal intensity and the absence of a control patient population. After the decision by the Investigative Radiology editors, the Radiology authors submitted a revised version of the manuscript to the European Radiology editors, who accepted the manuscript on the basis of its scientific merit. The European Radiology editors have also issued a statement regarding the publication, noting that the manuscript had undergone a thorough peer review process. The editors have also stated that they have reviewed the manuscript and found it to be scientifically sound.

The study of Radbruch et al provides further evidence supporting a significant difference between macro cyclic and linear chelates in terms of safety profile. As the authors state in their conclusion, for linear GBCAs—specifically those that have no benefit in terms of improved diagnosis in comparison to the approved macro cyclic GBCAs—their ongoing clinical use should be reassessed. Let us remember, as physicians, above all to do no harm.
Modeling the Disease

T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats

Difference Between Linear and Macro cyclic Agents

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Objectives: To prospectively compare in healthy rats the effect of multiple injections of macrocyclic (gadoterate meglumine) and linear (gadodiamide) gadolinium-based contrast agents (GBCAs) on T1-weighted signal intensity in the deep cerebellar nuclei (DCN), including the dentate nucleus.

Materials and Methods: Healthy rats (n = 7/group) received 20 intravenous injections of 0.6 mmol of gadolinium (Gd) per kilogram (4 injections per week during 5 weeks) of gadodiamide, gadoterate meglumine, or hyperosmolar saline (control group). Brain T1-weighted magnetic resonance imaging was performed before and once a week during the 5 weeks of injections and during 5 additional weeks (treatment-free period). Gadolinium concentrations were measured with inductively coupled plasma mass spectrometry in plasma and brain. Blinded qualitative and quantitative evaluations of the T1 signal intensity in DCN were performed, as well as a statistical analysis on quantitative data.

Results: A significant and persistent T1 signal hypersignal in DCN was observed only in gadodiamide-treated rats. The DCN-to-cerebellar cortex signal ratio was significantly increased from the 12th injection of gadodiamide (1.070 ± 0.024) compared to the gadoterate meglumine group (1.000 ± 0.033; P < 0.001) and control group (1.019 ± 0.022; P < 0.001) and did not significantly decrease during the treatment-free period. Total Gd concentrations in the gadodiamide group were significantly higher in the cerebellum (3.66 ± 0.91 nmol/g) compared with the gadoterate meglumine (0.26 ± 0.12 nmol/g; P < 0.05) and control (0.06 ± 0.10 nmol/g; P < 0.05) groups.

Conclusions: Repeated administrations of the linear GBCA gadodiamide to healthy rats are associated with progressive and persistent T1 signal hypersignal in the DCN, with Gd deposition in the cerebellum in contrast with the macrocyclic GBCA gadoterate meglumine for which no effect was observed.

Key Words: signal intensity, dentate nucleus, deep cerebellar nuclei, magnetic resonance, cumulative doses, gadolinium, contrast agent, gadoterate meglumine, gadodiamide

Gadolinium (Gd)-based contrast agents (GBCA) are widely used in magnetic resonance (MR) examinations for detection of a large variety of brain pathologic processes, including inflammation, infection, and malignancy.† The efficacy of the GBCAs approved for central nervous system imaging has been amply demonstrated since the end of the 80s, and these agents are generally associated with an excellent safety profile.

However, in the past decade, two major clinical studies questioned this safety profile. First, in 2006, Grobner‡ linked the occurrence of nephrogenic systemic fibrosis and the administration of GBCAs in patients with severe renal impairment. After nearly 10 years of extensive research, this link is now accepted and associated with the relatively lower in vivo stability of some linear GBCA leading to the risk of Gd release. Second, in 2014, Kanda et al reported a significant relationship between T1-weighted (T1w) signal hypersignal observed in specific brain regions (globus pallidus and dentate nucleus) in patients with normal renal function and the number of prior contrast-enhanced MR imaging (MRI) scans.‡ To date, 5 other studies confirmed this correlation for patients exposed to more than 6 contrast-enhanced MRI examinations.‡–‡ Notably, Kanda et al and, more recently, Radbruch et al§ reported that the T1w signal hypersignal was observed after repeated administrations of linear GBCA (gadodiamide and meglumine gadopentetate, respectively) but not with macrocyclic GBCA (gadoteridol and gadoterate meglumine, respectively).

These results strongly suggest long-term Gd deposit in cerebellar regions (especially in the dentate nucleus) but failed to provide any evidence of Gd retention in brain owing to the absence of Gd assays. Very recently, the presence of elemental Gd was demonstrated in various sites of the autopsied brains of patients exposed to at least 4 gadodiamide-enhanced MR examinations.‖ This effect was significantly correlated with the cumulative Gd dose received. The gadodiamide-treated patients demonstrated a significant dose-T1 signal intensity positive cor-

(Invest Radiol. 2015;50: 473–480)
Conclusions: Repeated administrations of the linear GBCAs gadodiamide, gadobenate dimeglumine, and gadopentetate dimeglumine to healthy rats were associated with progressive and significant T1 signal hyperintensity in the DCN, along with Gd deposition in the cerebellum. This is in contrast with the macrocyclic GBCA gadoterate meglumine for which no effect was observed.
Literature Summary

• Omniscan, Magnevist, and MultiHance have been established to be associated with dentate nucleus hyperintensity
• Dotarem, Gadovist and ProHance (the macrocyclics) are not
• The finding has been shown to be present in the absence of therapy

• Initial tissue studies show correlative Gd deposition
• The first animal models have been published, with additional studies ongoing
Iron, Copper, and Zinc Distribution of the Cerebellum

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Abstract Synchrotron rapid-scanning X-ray fluorescence (RS-XRF) is employed for the first time to simultaneously map iron, copper, and zinc in the normal cerebellum. The cerebellum is a major repository of metals that are essential to normal function. Therefore, mapping the normal metal distribution is an important first step towards understanding how multiple metals may induce oxidative damage, protein aggregation, and neurotoxicity leading to cerebellar degeneration in a wide range of diseases. We found that cerebellar white and grey matter could be sharply defined based upon the unique metal content of each region. The dentate nucleus was particularly metal-rich with copper localized to the periphery and iron and zinc abundant centrally. We discuss how RS-XRF metal mapping in the normal brain may yield important clues to the mechanisms of degeneration in the dentate nucleus.

Keywords Iron - Copper - Zinc - Cerebellum - X-ray fluorescence - Dentate nucleus

Introduction

The cerebellum serves as a major integrative center for the coordination of muscular activity, facilitation of movement, and motor planning. Cerebellar lesions result in ataxia, dysmetria, dysdiadochokinesis, and oculomotor impairment [1]. Complex connections between the dentate nucleus, thalamus, basal ganglia, and prefrontal cortex support the hypothesis that the cerebellum is also involved in cognitive functions [2, 3], and indeed, cognitive impairment is associated with cerebellar pathology [4]. Many disorders presenting with cerebellar degeneration are members of the continually growing family of neurodegenerative diseases involving excess central nervous system accumulation of metals. These include Friedreich’s ataxia, Wilson’s disease, Huntington’s disease, and aceruloplasminemia [5–9]. Metal deficiency can also lead to neurodegeneration involving the cerebellum, as exemplified by Menkes’ disease [10].

Although an active area of research, many questions remain about how metal imbalance contributes to neurodegeneration [11–13]. Knowing the macroscopic metal distribution of the normal cerebellum is an important step towards better understanding the role metals play in the pathogenesis of cerebellar degeneration and how neurodegenerative diseases change cerebellar metal distribution and metabolism.

Histochemistry has long been the gold standard for localizing metals in brain slices. However, Perl’s and Turnbull’s methods are not able to detect heme iron [14, 15], copper histochemistry lacks sensitivity and specificity [16, 17], and zinc histochemistry detects only part of the tissue zinc pool [18, 19].

Possible Clinical Consequences

- “the cerebellum is a major repository of metals that are essential to normal function”
- the dentate nucleus is known to be high in Zn, Fe, and Cu
- these metals have the potential to exchange with gadolinium
- however, to date, no definite clinical symptoms have been attributed to dentate nucleus hyperintensity
I would also caution against relying too heavily on screening to identify all patients with advanced renal failure. As we have learned with cardiac pacemakers, some patients inadvertently get past rigorous screening for MRI each year, despite each site’s best attempts. This again argues for a renewed emphasis on the safety profile of the gadolinium chelates and specifically their stability in vivo.  

Runge, AJR 2009

Commentary on T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats

Difference Between Linear and Macroyclic Agents

Val M. Runge, MD

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In this landmark article by Robert et al, an animal model is presented for the T1 signal hyperintensity in the deep cerebellar nuclei, including specifically the dentate nucleus, after intravenous administration of the linear gadolinium-based contrast agent gadodiamide (Omniscan) in normal renal function. This change was further demonstrated to correlate with higher gadolinium concentration in the brain, as determined by inductively coupled plasma mass spectrometry. No abnormality was noted after administration of a macrocyclic agent, gadoterate meglumine (Dotarem). The study provides a scientific basis for previous clinical observations, together with a platform for rigorous further investigation. In-depth study, using this model or similar models, of all of the approved gadolinium-based contrast agents (GBCAs) is warranted.

Coming to a Close

“The gadolinium chelates (the GBCAs) 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. However, the article of reference … should serve as a call for further research as well as reevaluation … This could lead, and if so appropriately, to the reassessment of the approval status of the least stable agents. As physicians, let us remember, above all, to do no harm.”
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 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 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 specifically and 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 dentate nucleus; safe gadopentetate dimeglumine gadobenate dimeglumine

TABLE 1. The Clinically Approved GBCAs—Names, Incidence of NSF, and Occurrence of Dentate Nucleus Hyperintensity

<table>
<thead>
<tr>
<th>Trade Namea</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.</td>
<td>Radbruch et al.</td>
</tr>
<tr>
<td>Dotarem</td>
<td>Gadoterate meglumine</td>
<td>Gd-DOTA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProHance</td>
<td>Gadoteridol</td>
<td>Gd-HP-D03A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omniscan</td>
<td>Gadodiamide</td>
<td>Gd-DTPA-BMA</td>
<td>3%–18% (382)</td>
<td>Kanda et al.</td>
<td>Errante et al.</td>
</tr>
<tr>
<td>Gadovist/Gadavist</td>
<td>Gadobutrol</td>
<td>Gd-D03A-Butrol</td>
<td></td>
<td></td>
<td>Radbruch et al.</td>
</tr>
<tr>
<td>Optimark</td>
<td>Gadoversetamide</td>
<td>Gd-DTPA-BMEA</td>
<td>Unknown (35)</td>
<td>Weberling et al.</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>Gadovetate disodium</td>
<td>Gd-EOB-DTPA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablavars</td>
<td>Gadofosveset trisodium</td>
<td>MS-325</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 (Ablavars; 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 (ferumoxtran-10), 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). All 3 agents were narrowly indicated with very small markets, as well as having a far greater minor adverse event profile.

- This recent review article is on line, open access
- It details the current knowledge concerning NSF and accumulation of Gd in the brain
Conclusion

• The established class of contrast media today for MR is that of the Gd chelates
• These can be differentiated on the basis of stability (safety) and effective enhancement (relaxivity and formulation)
• A greater understanding of stability in vivo, together with the role of essential metals in the brain, is needed

Runge VM, et al. The developmental history of the gadolinium chelates as IV contrast media for MR. Invest Radiol 2011; 46:807