Gadolinium Contrast Agent Safety

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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.
Linear Gd Chelates

Gd-DTPA

- Extracellular Non-ionic
  - Gd-DTPA-BMA
  - Gd-DTPA-BMEA

- Hepatobiliary Ionic
  - Gd-BOPTA

- Blood pool Ionic
  - Gd-EOB-DTPA
  - MS-325

a flawed rationale for development & approval
The clinical safety of a gadolinium chelate is to a large extent dependent upon the stability of the chelate in vivo.
Approved MR Contrast Media
(World-wide vs USA only)

• IV contrast media
  – Gadolinium chelates
    • Dotarem (Guerbet)
    • Gadovist (Bayer)
    • Magnevist (Bayer)
    • MultiHance (Bracco)
    • Omniscan (GE Healthcare)*
    • OptiMARK (Covidien)*
    • Primovist (Bayer)
    • ProHance (Bracco)
    • Ablavar (Lantheus)

• Oral contrast media
  • Magnevist enteral*
  • GastroMARK (Lumirem)*

• Other agents
  • Feridex (Berlex)*
  • Resovist (Schering AG)*
  • Teslascan (GE Healthcare)*
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 diethylenetriaminepentaacetic 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).
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 examined at the NIH was pooled with those receiving saline and compared with that obtained, with a system, with a system, with a system, with a system, with a system, with a system.
## Thermodynamic Stability

<table>
<thead>
<tr>
<th>Class</th>
<th>Net Charge</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Short Names</th>
<th>Excess Ligand</th>
<th>Log $K_{therm}$</th>
<th>Log $K_{cond}$ 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>Nonionic</td>
<td>Omniscan</td>
<td>GE Healthcare, Braunshweig, Germany</td>
<td>Gadodiamide Gd-DTPA-BMA</td>
<td>5%</td>
<td>16.9</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Nonionic</td>
<td>Optimark</td>
<td>Mallinckrodt Inc., St. Louis</td>
<td>Gadoversetamide Gd-DTPA-BMEA</td>
<td>10%</td>
<td>16.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Magnevist</td>
<td>Bayer Schering Pharma, Berlin, Germany</td>
<td>Gadopentetate Gd-DTPA</td>
<td>0.1%</td>
<td>22.5</td>
<td>18.4</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Multihance</td>
<td>Bracco Altana, Konstanz, Germany</td>
<td>Gadobenate Gd-BOPTA</td>
<td>0%</td>
<td>22.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Primovist</td>
<td>Bayer Schering Pharma</td>
<td>Gadoxetate Gd-EOB-DTPA</td>
<td>0.5%</td>
<td>23.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Vasovist</td>
<td>Bayer Schering Pharma</td>
<td>Gadofosveset</td>
<td>0.1%</td>
<td>22.1</td>
<td>18.9</td>
</tr>
<tr>
<td>Macrocyclic</td>
<td>Nonionic</td>
<td>Gadovist</td>
<td>Bayer Schering Pharma</td>
<td>Gadobutrol Gd-BT-DO3A</td>
<td>0.1%</td>
<td>21.8</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>Nonionic</td>
<td>Prohance</td>
<td>Bracco Altana</td>
<td>Gadoteridol Gd-HP-DO3A</td>
<td>0.1%</td>
<td>23.8</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>Ionic</td>
<td>Dotarem</td>
<td>Guerbet, Roissy, France</td>
<td>Gadoterate Gd-DOTA</td>
<td>0%</td>
<td>25.6</td>
<td>19.3</td>
</tr>
</tbody>
</table>

The amounts of excess ligand in the marketed formulations are expressed in percentages of the molar concentration of the Gd complex.

Invest Radiol 2008;43:817
The agents can be differentiated on the basis of thermodynamic and kinetic stability, with the latter the overriding factor (slow dissociation is desired).
The more stable an agent is, the less gadolinium is left in the body after injection - data is from animal studies with radiolabeled gadolinium chelate.
Native human serum, % of Gd$^{3+}$ released after 15 days:

- **Macrocyclic agents:** no detectable Gd$^{3+}$ released (<0.1%)
- **Linear ionic:** up to 2%
- **Linear non-ionic:** up to 22%

Courtesy of Bayer
Interference of Gd-Based Contrast Agents With Laboratory Test for Serum Ca

- Determination of serum Ca after administration of Omniscan and OptiMARK
  - May be incorrect when blood is drawn within 12–24 hours after administration\(^1\)
  - Time window prolonged with higher doses and impaired renal function\(^2\)

- Can lead to spurious hypocalcemia
  - Both dry-chemical arsenazo and wet-chemical OCP colorimetric methods are affected

- Potential clinical relevance to patients\(^2\)
  - If not recognized as artifact, unnecessary treatment may be given (7 patients received IV calcium)

Analytical Interference in Serum Iron Determination Reveals Iron Versus Gadolinium Transmettallation With Linear Gadolinium-Based Contrast Agents

Nathalie Fretteller, PhD, Nathalie Poteau, BS, Cécile Factor, PhD, Jean-François Mayer, BS, Christelle Medina, PhD, Marc Port, PhD, Jean-Marc Idev, PharmD, and Claire Corot, PhD

Objectives: The purpose of this study was to evaluate the risk for analytical interference with gadolinium-based contrast agents (GBCAs) for the colorimetric measurement of serum iron (Fe²⁺) and to investigate the mechanisms involved.

Materials and Methods: Rat serum was spiked with several concentrations of all molecular categories of GBCAs, ligands, or “free” soluble gadolinium (Gd³⁺). Serum iron concentration was determined by 2 different colorimetric methods at pH 4.0 (with a Vitros DT60 analyzer or a Cobas Integra 400 analyzer). Second, the cause of interference was investigated by (a) adding free soluble Gd³⁺ or Mn²⁺ to serum in the presence of gadodiamide or gadobutrol and (b) spectroscopy using mass spectrometry.

Results: Spurious decrease in serum Fe⁺⁺ concentration was observed with all linear GBCAs (only with the Vitros DT60 technique occurring at pH 4.0). But not with macrocyclic GBCAs or with free soluble Gd³⁺. Spurious hypochromism was also observed with the free ligand present in the pharmacological solutions of the linear GBCAs gadodiamide and gadobutrol (ie, diethylenetriamine pentaacetic acid and calcium disodium tetrakis (ethylenediamine) tetraacetate acid, respectively), suggesting the formation of Fe⁺⁺ chelate.

Gadodiamide-induced interference was blocked in a concentration-dependent fashion by adding a free soluble Gd²⁺ salt. Conversely, Mn²⁺, which has a lower affinity than Gd²⁺ for the ligand of gadodiamide (ie, hexyloxypolyethyleneimine tetraacetic acid), was less effective (interference was only partially blocked), suggesting an Fe⁺⁺ vs Gd³⁺ transmetallation phenomenon at pH 4.0. Similar results were observed with gadobutrol. Mass spectrometry detected the formation of Fe⁺⁺-ligand with all linear GBCAs tested in the presence of Fe⁺⁺ and the disappearance of Fe⁺⁺ ligand after the addition of free soluble Gd³⁺. No Fe⁺⁺ chelate was found in the case of the macrocyclic GBCA gadodiamide.

Conclusions: Macrocyclic GBCAs induced no interference with colorimetric methods for iron determination, whereas negative interference was observed with linear GBCAs using a Vitros DT60 analyzer. This interference of linear GBCAs seems to be caused by the excess of ligand and/or an Fe⁺⁺ vs Gd³⁺ transmetallation phenomenon.

Keywords: gadolinium-based contrast agents, transmetallation, interference, iron, mass spectrometry

Invest Radiol 2014;49: 766–772

Gadolinium-based contrast agents (GBCAs) are widely used in magnetic resonance imaging (MRI) because of their unique capacity to enhance T₁-weighted images by increasing the longitudinal relaxation rate of extracellular fluid protons (1/T₁).

Some linear GBCAs have been reported to interfere with colorimetric assays for the determination of serum analytes such as total calcium, creatinine, angiotensin-converting enzyme, zinc, magnesium, and iron. The spurious decrease or increase in these analytes could lead to potential risks for the patient, such as wrong diagnosis or treatment.

Interference with colorimetric assays can occur when, during or after GBCA dissociation, “unbound” Gd³⁺ binds to the dye or when the “free” ligand of GBCA associates with the analyte being measured in a dissociation with gadolinium (Gd³⁺). This can be a problem when calcium levels are measured using o-cresolphthalein complexone (OCP). In the presence of the linear GBCA gadodiamide and OCP, they observed a disappearance of gadodiamide as well as an appearance of the free ligand diethylene triamine pentaacetic acid bis(methylamide) (DTPA-BMA) and a new complex, Gd-OCP. The interference of gadodiamide with colorimetric determination of serum calcium is therefore related to dissociation of this GBCA. Nevertheless, some marketed GBCAs, especially macrocyclic chelates, do not generate any interference with analytical methods. This effect is therefore likely related to differences in GBCA thermodynamic and kinetic stability profiles.

Macro cyclic GBCAs are kinetically more stable than linear GBCAs, and linear iron chelates are thermodynamically more stable than linear nonionic GBCAs.

Under physiological conditions, endogenous cations such as Fe⁺⁺, Zn⁺⁺, or Cu⁺⁺ can compete with Gd³⁺ for the ligand and can induce a transmetallation phenomenon (ie, a metal exchange reaction), defined as follows:

$$\text{Gd}^{3+} + M^{2+} \rightleftharpoons \text{Gd}^{2+} + M^{3+}$$

where M is metal and L is ligand.

The probability of transmetallation depends on the affinity of endogenous metal ions for the ligand and is therefore related to the thermodynamic stability of the metal ion chelate (eg, Fe-L, Cu-L). Furthermore, some anions, such as PO₄³⁻, CO₃²⁻, and OH⁻, can also compete with the ligand of GBCA at physiological pH, inducing precipitation of insoluble Gd salts.

In a previous study performed in renally impaired rats, a negative interference with serum iron determination concentrations (spurious decrease in serum iron concentrations) was suspected after interavenous administrations of calcium-diythylene triamine pentaacetic acid (Ca-DTPA), gadodiamide, gadolinium, or gadobutrol. The present study was therefore designed to evaluate the risk for analytical interference with all structural categories of GBCAs for colorimetric determination of serum iron levels by currently used laboratory methods and to investigate the cause of this interference.

MATERIALS AND METHODS

Analytical Interference of GBCAs, Gd Acetate, and Ligands With Colorimetric Determination of Serum Iron

Products

Five commercially available GBCAs were tested: a linear and nonionic GBCA, gadodiamide (Gd-DTPA-BMA, Omniscan; GE Healthcare).
Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy

The FDA has learned of 25 cases of NSF/NFD in patients with kidney failure who received Omniscan®, a gadolinium-containing contrast agent, and took the MRA test.

Gadolinium-containing contrast agents, especially at high doses, should be used only if clearly necessary in patients with advanced kidney failure.

June 8, 2006
FDA Public Health Advisory

Since 2002 around 400 patients with end-stage renal failure with and without replacement therapy has been examined with gadodiaimide. Of those patients a least 20 have developed NSF. An incidence of a severe adverse event around 5% in a well defined group of patients is not acceptable for a contrast medium.

May 29, 2006
Professor Henrik S. Thomsen, MD
Department of Diagnostic Radiology
Copenhagen University Hospital, Denmark
Number of Cases by Agent*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Estimated number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omniscan</td>
<td>327 &gt; 40 million</td>
</tr>
<tr>
<td>Magnevist</td>
<td>43 &gt; 90 million</td>
</tr>
<tr>
<td>Optimark</td>
<td>9 &gt; 6 million</td>
</tr>
</tbody>
</table>

*unconfounded cases

As of July 2008
• “The present study demonstrates that the risk of NSF is unexpectedly and unacceptably high (18%) in CKD5 patients exposed to gadodiamide.”

• “Our results confirm that gadodiamide is associated with an unacceptably high risk of NSF among CKD5 patients, i.e. patients with an eGFR less than 15 mL/min/1.73 m². For safety reasons, we agree that CKD4 patients (i.e. patients with eGFR of 15-30 mL/min/1.73 m²) also should not be exposed to gadodiamide (15). 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.”

18 of 102 patients
GE Failed to Adequately Warn about Dangers of its MRI Dye, Jury Finds

by Jeff Gerth
ProPublica, March 22, 2013, 2:41 p.m.

In a setback for GE Healthcare, a jury today found that the company failed to adequately warn patients and doctors about the dangers of its medical imaging dye. The jurors awarded $5 million to the plaintiff and his wife.
I would like to thank you for your written request and clinical inquiry of February 7, 2003. We appreciate your taking the time to voice your concerns about Omniscan® (gadodiamide; Amersham Health) and hope this written response addresses each of the issues you have enumerated.

We have evaluated the literature regarding the potential for various gadolinium-based products to release free gadolinium ions into the circulation.

The literature has failed to establish a correlation or association between an increased release of gadolinium ions and any adverse effects.

As a result, we cannot grant approval of an exemption from the purchasing requirements for MRI contrast agents.

- The end result
  - 6 NSF cases (IR 2007;42:139)
Update on the etiology of NSF

• “our data suggest that NSF-like skin lesions in rats were induced by an acute reaction to Gd, indicated by the rapid but transient up-regulation of several cytokines involved in fibrotic processes. Without cofactors such as high cytokine expression, the NSF-like lesions were not maintained.”

### Renal Status of NSF Cases

#### Cases With Type or Degree of Renal Status Specified

<table>
<thead>
<tr>
<th>Renal Status</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Renal Impairment (ARF)</strong></td>
<td>72  (9.8%)</td>
</tr>
<tr>
<td><strong>Chronic Kidney Disease (CKD)</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 5 (eGFR &lt; 15 mL/min/1.73m² or dialysis-dependent)</td>
<td>610 (82.5%)</td>
</tr>
<tr>
<td>Stage 4 to 5</td>
<td>41  (5.6%)</td>
</tr>
<tr>
<td>Stage 4 (eGFR 15 to &lt; 30 mL/min/1.73m²)</td>
<td>12  (1.6%)</td>
</tr>
<tr>
<td>Stage 3 to 4</td>
<td>3   (0.4%)</td>
</tr>
<tr>
<td>Stage 3 (eGFR 30 to &lt; 60 mL/min/1.73m²)</td>
<td>1   (0.1%)</td>
</tr>
</tbody>
</table>

#### Cases With History of Renal Dialysis Specified

<table>
<thead>
<tr>
<th>Renal History</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with History of Dialysis</strong></td>
<td>615 (93.0%)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>483 (73.2%)</td>
</tr>
<tr>
<td>Hemodialysis and peritoneal dialysis</td>
<td>25  (3.8%)</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>66  (10.0%)</td>
</tr>
<tr>
<td>Dialysis, type not specified</td>
<td>40  (6.0%)</td>
</tr>
<tr>
<td><strong>Patients with no History of Dialysis</strong></td>
<td>47 (7.1%)</td>
</tr>
</tbody>
</table>
Incidence of Nephrogenic Systemic Fibrosis in Patients Undergoing Dialysis After Contrast-Enhanced Magnetic Resonance Imaging With Gadolinium-Based Contrast Agents

The Prospective Fibrose Nephrogénique Systémique Study

Sabine Amet, PharmD,* Vincent Launay-Vacher, PharmD,* Olivier Clément, MD, PhD,† Camille Frances, MD,‡ Aurore Tricotel, MSc,§ Benedicte Stengel, MD,∥ Jean-Yves Gauvrit, MD,¶ Nicolas Grenier, MD,# Geneviève Reinhardt, MD,** Nicolas Janus, PharmD,* Gabriel Choukroun, MD,†† Maurice Laville, MD,‡‡ and Gilbert Deray, MD§§

Conclusions: The incidence of NSF after a single dose of a macrocyclic GBCA is null in our sample of 268 patients undergoing dialysis (hemodialysis and peritoneal dialysis). This incidence is just lower than 0.5%. When contrast-enhanced MRI can be essential, or even decisive, to the diagnosis, these results are important and reassuring if physicians need to perform contrast-enhanced MRI in patients undergoing dialysis.
As a Result of NSF

**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

* of inducing NSF
These agents are CONTRA-INDICATED in
- patients with CKD 4 and 5 (GFR < 30 ml/min), including those on dialysis
- acute renal insufficiency
- neonates

These agents should be used with CAUTION in
- patients with CKD 3 (GFR 30–60 ml/min)
  - There should be at least 7 days between two injections
- children less than 1 year old

Lactating women: Stop breastfeeding for 24 h and discard the milk.

Serum creatinine (eGFR) measurement and clinical assessment of patient before administration:

**Mandatory**

These agents should never be given in higher doses than 0.1 mmol/kg per examination in any patient
**Lowest risk of NSF**

Gadobutrol (Gadovist®, Gadavist®)

*Ligand*: Non-ionic cyclic chelate (BT-DO3A)

*Incidence of NSF*: A few unconfounded cases have been reported, but there is uncertainty about the histopathological changes.

Gadoterate meglumine (Omniscan®)

*Ligand*: Ionic cyclic chelate

*Incidence of NSF*: A few unconfounded cases have been reported.

Gadoteridol (Prohance®)

*Ligand*: Non-ionic cyclic chelate (HP-DO3A)

*Incidence of NSF*: No unconfounded cases have been reported.

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These agents should be used with CAUTION in:

- patients with CKD 4 and 5 (GFR <30 ml/min)
- There should be at least 7 days between two injections
Iron, Copper, and Zinc Distribution of the Cerebellum

Bogdan F. Gh. Popescu • Christopher A. Robinson • Alex Rajput • Ali H. Rajput • Sheri L. Harder • Helen Nicol

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, dysarthria, and oculomotor impairment [1]. Complex connections between the dentate nucleus, thalamus, basal ganglia, and prefrontal cortex support the hypothesis that the cerebellum is 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.

Histochimistry 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 histochimistry lacks sensitivity and specificity [16, 17], and zinc histochimistry detects only part of the tissue zinc pool [18, 19].

• “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 are known to form chelates with DTPA
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

Yuri Errante, MD, Vincenzo Cirimele, MD, Carlo Augusto Mallo, MD, Vincenzo Di Lazzaro, MD, Bruno Beomonte Zobel, MD, and Carlo Cosimo Quattrorchi, MD, PhD

Objective: The purpose of this study was to assess the association between the serial number of gadolinium-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 38 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 or more enhanced MRI scans or more on a linear regression analysis with age as a covariate.

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 ratio of the last scan in the subgroup of patients with 6 or more scans was significantly higher than those of the first scans in the MS group (P < 0.05) and in the BM group (P < 0.01). A relative increase of the DNP showed a positive correlation with the number of scans (r = 0.54; P < 0.001). In the MS group and that of r = 0.06 (P = 0.001) in the BM group. The analysis of the progressive increase of the DNP ratio showed linear models to best fit the data with r² = 0.35 in the MS group and r² = 0.74 in the BM group.

Conclusion: Our study shows that the increase in the unenhanced T1 signal intensity has a linear relationship with the number of scans in patients with MS and BM. 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, magnetic resonance, cumulative doses, gadodiamide, contraindicated agent

Progressive increase of T1 signal intensity of the dentate nucleus has a role in the planning, initiation, and timing of voluntary movements. Moreover, non–motor functions are attributed to the dentate nucleus, such as rule-based learning and visuospatial integration. Neurons in the dentate nucleus receive input from Purkinje cells in the cerebellar cortex and send output fibers to the contralateral anterior and ventral lateral nuclei of the thalamus as well as to the contralateral red nucleus.

The T1 signal intensity increase of the dentate nucleus has been reported in patients with multiple sclerosis (MS) and in oncological patients who have undergone brain irradiation. Kanda et al recently reported an association between high T1 signal intensity of the dentate nucleus and globus pallidus in patients with cancer and the history of number of gadolinium-enhanced magnetic resonance imaging (MRI) examinations. Similarly, we also observed in our institution that high T1 signal intensity of the dentate nucleus is common in patients with brain metastases (BMs) from various primary cancers who have undergone multiple brain gadolinium-enhanced MRI scans. We hypothesized that, as it has been proposed by Kanda et al for patients with cancer who have BM, the signal intensity on unenhanced T1-weighted images is higher with the increasing number of gadolinium-enhanced MRI examinations also in patients with MS.

The purpose of this study was to assess and quantify the association between the serial number of gadolinium-enhanced MRI examinations and the signal hyperintensity of the dentate nucleus on unenhanced T1-weighted images in patients with MS and BM.

MATERIALS AND METHODS

Patients

This retrospective observational study was conducted in accordance with the Declaration of Helsinki. All patients provided their written informed consent to use their anonymized data for research analyses. In our image database, including data from July 2008 to December 2011, we identified 50 consecutive patients with MS and 200 consecutive patients with BM who had undergone at least 2 consecutive MRI examinations in our institution.

Patients With MS Group

The patients with MS were selected with the following inclusion criteria: (1) clinically defined relapsing-remitting MS according to the 2010 revised McDonald criteria; (2) patients with clinical follow-up exclusively at the neurology unit in our institution; (3) first brain gadolinium-enhanced MRI scan performed in our department; (4) at least 2 consecutive brain gadolinium-enhanced MRI scans performed in our department; and (5) absence of brain stem or cerebellar inflammatory lesions on turbo spin echo (TSE) T2-weighted or fluid attenuated inversion recovery (FLAIR) images. The exclusion criteria were as follows: (1) history of vascular, malignant, or traumatic disease of the central nervous system; (2) comorbidity of congenital metabolic diseases or malformations; (3) history of prophylactic brain irradiation or neurosurgery; (4) history of parenteral nutrition; (5) liver or renal dysfunction detected by means of routine laboratory tests; (6) diagnosis of nephrogenic systemic fibrosis; and
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