Comparison of Gadolinium Concentrations within Multiple Rat Organs after Intravenous Administration of Linear versus Macrocyclic Gadolinium Chelates

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Purpose: To compare gadolinium tissue concentrations of multiple linear and macrocyclic chelates in a rat model to better understand the scope and extent of tissue deposition following multiple intravenous doses of gadolinium-based contrast agent (GBCA).

Materials and Methods: In this Institutional Animal Care and Use Committee-approved study, healthy rats received 20 intravenous injections of 2.5 mmol gadolinium per kilogram (gadolinium-exposed group) or saline (control group) over a 26-day period. Unenhanced T1 signal intensities of the dentate nucleus were measured from magnetic resonance (MR) images obtained prior to GBCA injection and 3 days after final injection. Rat brain and renal, hepatic, and splenic tissues were harvested 7 days after final injection and subjected to inductively coupled plasma mass spectrometry and transmission electron microscopy for quantification and characterization of gadolinium deposits.

Results: Gadolinium deposition in brain tissue significantly varied with GBCA type ($F = 31.2; P < .0001$), with median concentrations of 0 µg gadolinium per gram of tissue (95% confidence interval [CI]: 0, 0.2) in gadoteridol-injected rats, 1.6 µg gadolinium per gram of tissue (95% CI: 0.9, 4.7) in gadobutrol-injected rats, 4.7 µg gadolinium per gram of tissue (95% CI: 3.3, 6.1) in gadobenate dimeglumine–injected rats, and 6.9 µg gadolinium per gram of tissue (95% CI: 6.2, 7.0) in gadodiamide-injected rats; a significant positive dose–signal intensity correlation was identified ($r = 0.93; P < .0001$). No detectable neural tissue deposition or MR imaging signal was observed in control rats ($n = 6$). Similar relative differences in gadolinium deposition were observed in renal, hepatic, and splenic tissues at much higher tissue concentrations ($P < .0001$). Gadolinium deposits were visualized directly in the endothelial capillary walls and neural interstitium in GBCA-injected rats, but not in control rats.

Conclusion: Tissue deposition of gadolinium was two- to fourfold higher following administration of the linear agents gadodiamide and gadobenate dimeglumine compared with the macrocyclic agents gadobutrol and gadoteridol. These findings suggest that organ tissue deposition is reduced but not eliminated following administration of macrocyclic GBCA chelates in lieu of linear chelates.

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Recent human and animal model studies have revealed the presence of gadolinium deposits in various central nervous system structures following repeated administration of intravenous gadolinium-based contrast agents (GBCAs) (1–6). These studies demonstrated a strongly positive dose-dependent relationship with tissue concentration based on cumulative lifetime GBCA dose. Such deposition appears to occur in the absence of renal or hepatobiliary dysfunction and, based on limited data, is durable with deposits remaining years after administration of GBCAs. Although the toxicity of GBCAs is low in their chelated form, concern exists that such gadolinium deposits represent a free (dechelated) form, which is of concern given the cytotoxic effects of free gadolinium (7,8). These findings prompted the U.S. Food and Drug Administration and European Medicines Agency to issue safety warnings in 2015 and 2016, respectively, with the intent to more closely examine the risks and biologic effects of these deposits (9,10).

Following these initial reports, Radbruch et al and Kanda et al published imaging evidence that this deposition is limited to linear GBCA chelates and is not observed with macromolecular GBCAs (11–14). Differences in deposition propensity between GBCA classes have been attributed to the higher intrinsic stability and gadolinium-binding affinity of macromolecular agents compared with linear agents. Similar mechanistic interpretations have been used to explain the higher incidence of nephrogenic systemic fibrosis following administration of linear agents compared with macrocyclic agents. To date, the mechanistic understanding of nephrogenic systemic fibrosis and gadolinium deposition in neural tissues remains relatively undefined. Further, it remains unclear if chelate stability alone accounts for the relative differences in deposition observed in humans and animal models.

In the current study, we compared elemental gadolinium tissue concentrations of multiple linear and macrocyclic chelates in a rat model to better understand the scope and extent of tissue deposition following multiple intravenous GBCA doses.

Materials and Methods

Design and execution of this single-center retrospective study from August 2015 to December 2015 was subject to Institutional Animal Care and Use Committee oversight.

Study Design and Animals

Healthy male Wistar rats (Charles River Laboratories, Wilmington, Mass) were treated with either intravenous injections of GBCA or saline to assess the extent and significance of gadolinium deposits in various rodent tissues. The dosing scheme consisted of 2 intravenous injections of 2.5 mmol gadolinium per kilogram (gadolinium-exposed group).

Implications for Patient Care

- Neuronal tissue deposition of gadolinium appears to take place with both macrocyclic and linear GBCAs, albeit at lower concentrations than with macrocyclic agents.
- Gadolinium deposition is substantially higher in nonneural tissues; some of these tissues may act as a long-term biologic reservoir.
- At high doses, all GBCAs appear to have varying degrees of nephrotoxicity.
- The clinical significance of gadolinium deposition in neural, hepatic, and splenic issues remains poorly understood.

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Abbreviations:
GBCA = gadolinium-based contrast agent
ICP-MS = inductively coupled plasma mass spectrometry

Author contributions:
Guarantors of integrity of entire study, R.J.M., J.S.M., R.K., D.F.K.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, R.J.M., J.S.M., D.D., M.E.J., D.L.M., R.K., L.J.E.; experimental studies, R.J.M., J.S.M., D.D., D.S., M.E.J., D.L.M., R.K., D.F.K.; statistical analysis, R.J.M.; and manuscript editing, all authors
Conflicts of interest are listed at the end of this article.
See also the editorial by Kang and the article by McDonald et al in this issue.
Results

Animal Population
A total of 30 healthy rats were included in this study, with six rats in each treatment group (control, gadobenate dimeglumine–exposed, gadobutrol–exposed, gadopentetate dimeglumine–exposed, gadodiamide–exposed, and gadoteridol–exposed). Two rats in the gadobenate dimeglumine–exposed group acquired a tail infection during their injection series and were
Euthanized according to standard Institutional Animal Care and Use Committee protocols. Three additional rats (gadodiamide-exposed, gadobenate dimeglumine–exposed, and gadobutrol-exposed) died during MR imaging due to complications from anesthesia administration. In total, 25 of 30 rats (83.3%; six control, six gadoteridol-exposed, five gadobutrol-exposed, three gadobenate dimeglumine–exposed, and five gadodiamide-exposed) completed their injection series and were euthanized for further analysis.

Effect of GBCA Exposure on MR Imaging Signal Intensities

Qualitative changes in T1-weighted imaging within the rat dentate nucleus following multiple intravenous saline and GBCA doses are shown in Figure 1, B and C, respectively. The effects of intravenous administration of GBCA on normalized T1-weighted imaging signal changes in the dentate nucleus are shown in Figure 2. Among the GBCAs studied, gadodiamide had the greatest mean T1 signal increase and gadoteridol had the least amount of signal change. Compared with saline-injected rats that had minimal normalized changes in dentate nucleus signal intensity (<4%), gadolinium-exposed rats had significantly higher normalized T1 signal increases in their dentate nuclei compared with saline-injected control rats (Fig E1 [online]) \( (\chi^2 = 25.0, P < .0001) \) with significant pairwise differences between each contrast group \( (P \leq .0135) \).

**Effect of GBCA Exposure on Neural and Nonneural Tissue Deposition**

Comparisons of the amount of elemental gadolinium detected in neural tissues by ICP-MS are shown in Figure 3, A and the Table. In descending order, gadodiamide had the highest mean amount of gadolinium deposition in neural tissues, followed by gadobenate dimeglumine, gadobutrol, and gadoteridol (Table). Relative to control rats that had undetectable levels of elemental gadolinium, all GBCA-exposed rats had significantly elevated levels of elemental gadolinium in their dentate nuclei ranging from 0.1 to 6.9 \( \mu \)g gadolinium per gram of tissue (Fig 3, A) \( (H = 22.1; P = .0002) \). Mean elemental gadolinium concentrations within cerebellar tissues were also significantly different between GBCAs \( (P = .0459 \text{ to } P = .0038) \) and demonstrated a significant positive dose–signal intensity correlation in the dentate nucleus \( (\rho = 0.93; P < .0001) \).

Comparison of the amount of elemental gadolinium detected in hepatic, splenic, and renal tissues by ICP-MS is shown in Figure 3, B and the Table. Relative to control rats, GBCA-exposed rats had significantly elevated levels of elemental gadolinium (liver: \( H = 30.0, P < .0001 \); spleen: \( H = 21.4, P = .0003 \); kidney: \( H = 23.5, P < .0001 \)). Low levels of elemental gadolinium in hepatic, splenic, and renal tissues of control rats were noted and likely reflect rare earth metal groundwater contamination \( (18,19) \). In these tissues, elemental gadolinium concentrations were several orders of magnitude higher in GBCA-exposed rats compared with the concentrations observed in neural tissues (liver, 8.9–511.6 \( \mu \)g gadolinium per gram of tissue; spleen, 11.9–647.8 \( \mu \)g gadolinium per gram of tissue; kidney, 49.5–2179.7 \( \mu \)g gadolinium per gram of tissue). For each unique GBCA, median elemental gadolinium tissue concentration was significantly higher in the liver, spleen, and renal tissue compared with the dentate nucleus (gadoteridol: \( H = 23.1, P < .0001 \)).
linium deposits were identified in the... of contrast agents–exposed rats (Fig 5, H).

In the gadoteridol-exposed group, the histologic changes of renal injury were more extensive, with diffuse dilation and cast deposition in the renal tubules, focal tubular epithelial hyperplasia, and mononuclear inflammatory cell infiltration with peritubular inflammation and glomerular sclerosis (Fig 6, E). These histologic changes were not identified in control rats (Fig 5, D, Fig 6, A).

When compared with renal tissue harvested from control rats (Fig 6, B–D), gadoteridol-exposed renal tissues demonstrated advanced ultrastructural changes that were less severe with other GBCAs and included advanced loss of normal cytoarchitecture of the proximal convoluted tubule (Fig 6, E), alterations in glomerular structure and filling of Bowman space with matrix and cellular debris (Fig 6, G), and complete loss of the outer mitochondrial membrane (Fig 6, H) that is often associated with early cellular apoptosis (20).

**Discussion**

The results of this prospective animal model study reveal a significant association between intravenous GBCA administration, chelate subtype, and the extent of deposition in neuronal, hepatic, splenic, and renal tissues. While macroyclic agents had diminished elemental gadolinium tissue deposition compared with linear agents, significant differences in tissue concentrations were noted between macroyclic agents. Further, all GBCAs with the exception of gadoteridol were associated with significantly elevated levels of elemental gadolinium in neural and other tissues over animals exposed to saline alone. Our current findings refute current assumptions that gadolinium deposition in neural tissues is limited to linear GBCAs.

Our current findings complement the preliminary animal model findings of Robert et al and expand on these prior studies by including a larger number of linear and macroyclic GBCAs. Further, our study...
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**Table: Mass Spectrometry Results**

<table>
<thead>
<tr>
<th>Group</th>
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<th>Kidney</th>
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<th>Spleen</th>
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<td>1.9</td>
<td>1.7</td>
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<td>4.6 (1.8–12)</td>
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<tr>
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<td>192.6</td>
<td>18.1</td>
<td>15.5</td>
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<td>17</td>
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<td><strong>Median</strong></td>
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<td>168 (73–193)</td>
<td>16 (12–18)</td>
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<td><strong>Median</strong></td>
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<td>124 (101–176)</td>
<td>190 (119–236)</td>
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<td>388.4</td>
<td>354.1</td>
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<td>2179.7</td>
<td>492.9</td>
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<td><strong>Median</strong></td>
<td>6.9 (6.2–7.0)</td>
<td>2134 (1174–2157)</td>
<td>388 (310–503)</td>
<td>354 (299–587)</td>
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</table>

*Note.—Data are tissue gadolinium concentrations detected with ICP-MS (in micrograms of gadolinium per gram of tissue.) Data in parentheses are the interquartile range.*

provides more robust evidence of elemental gadolinium tissue deposition via ICP-MS and transmission electron microscopy compared with prior work. The larger complement of GBCAs in our study permits comparison of differences in tissue deposition potential between GBCAs with similar stability and chelate subtype. Furthermore, our study utilized more extensive methods to characterize the location and distribution of gadolinium deposits in neural tissues and quantified tissue deposition in other organs. Such findings add to the collective knowledge of the evolving field of GBCA-mediated gadolinium tissue deposition.

Overall, our data support the initial findings of Kanda and Radbruch to the extent that linear agents have higher tissue concentrations of elemental gadolinium compared with macrocyclic agents from equivalent intravenous GBCA doses (11–14). However, juxtaposition of the deposition propensities of several linear and macrocyclic agents facilitates comparison of observed data with predicted gadolinium tissue concentrations. One prevailing theory posits that deposition is related to chelate stability as defined by absolute and relative thermodynamic binding constants that quantify the binding strength of the gadolinium ion to the chelate ligand. For our investigation, the predicted stability of studied GBCAs in descending order is as follows: gadoteridol, gadobenate dimeglumine, gadobutrol, and gadodiamide. In agreement with these predicted trends, we report that gadoteridol and gadodiamide have the lowest and highest elemental gadolinium tissue concentrations, respectively. However, the relative tissue concentrations of gadobenate dimeglumine and gadobutrol deviate from predicted trends because we observed significantly higher deposition of gadobenate dimeglumine in all studied organs compared with gadobutrol. Such findings suggest that chelate stability alone does not define the deposition potential of these GBCAs and that other physiochemical properties such as lipophilicity and dissociation kinetics may play a role in tissue deposition (21,22). Further, the large variation in tissue deposition between macrocyclic agents expands on the existing work by Tweedle et al, Radbruch et al, Kanda et al, and others (11–14,21) and provides new data to suggest that whereas gadolinium tissue deposition is somewhat class-dependent, macrocyclic contrast agent deposition is not universally lower than linear agents, with some macrocyclic agents apparently demonstrating higher tissue gadolinium deposition than what has been previously described in skin biopsy samples and recent reports of T1-weighted signal intensity changes (23).

The observation of significantly higher gadolinium accumulation in nonneural tissues (liver, spleen, kidney), compared with neural tissues, conforms with our understanding of the capillary structure of these organs. Unlike the continuous capillary
structure that constitutes the blood-brain barrier in neural tissues, the hepatic and splenic tissues contain permeable, discontinuous capillaries that permit the free flow of blood products into these organs. Likewise, renal tissue capillaries are fenestrated, permitting smaller molecules to freely exchange into the kidney parenchyma. As noted previously, the presence of gadolinium deposits within the neural interstitium challenges our understanding of the apparent impermeability of the blood-brain barrier (3). Although much of the gadolinium appears to be sequestered in deposits that border the endothelium, possibly near tight junctions of the blood-brain barrier, the small fraction that is detected within the neural interstitium and cells suggests that this fraction of gadolinium deposits has either directly crossed or indirectly circumvented the blood-brain barrier. These
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Histologic abnormalities in the neural tissues of gadolinium-exposed rats, despite the elevated doses and dose frequency used in this study. By adjusting for body surface area differences between humans and rats where a remains undefined, yet the considerable attention to these deposits is warranted due to their cytotoxic potential (7,8). Similar to our previous report on human tissues (3), we did not detect histologic abnormalities in the neural tissues of gadolinium-exposed rats, despite the elevated doses and dose frequency used in this study. By adjusting for body surface area differences between humans and rats where a

Figure 5

Cerebellum    Liver    Spleen    Kidney

Control

E

Gd Exposed

E

Figure 5: Representative photomicrographs from light microscopy (hematoxylin-eosin stain; original magnification, ×100) of dentate nucleus, liver, spleen, and kidney are shown for, A–D, control group and, E–H, gadodiamide-exposed rats. Gd = gadolinium.

Figure 6

Renal Cortex    PCT    Bowman’s Capsule    Mitochondria

Control

E

ProHance Exposed

E

Figure 6: Renal histology and transmission electron microscopy results. Representative images of renal tissues of, A–D, control and, E–H, gadoteridol-exposed rats for, A, E, light microscopy samples (hematoxylin-eosin stain; original magnification, ×100) and for, B–D and F–H, transmission electron microscopy samples (hematoxylin-eosin stain; original magnification, ×10 000). Transmission electron micrographs show, B, F, proximal convoluted tubule (PCT), C, G, Bowman capsule of the glomerulus, and D, H, mitochondria.
standard human dose of 0.1 mmol/kg is roughly equivalent to 0.6 mmol/kg in a rat, each animal in this study received the equivalent of a total of approximately 80 human doses (2.5 mmol/kg × 20 doses) (5). Even at these supratherapeutic doses, we were unable to identify gadolinium-mediated damage to the liver or spleen. However, we did observe renal injury in all gadolinium-exposed rats, particularly in gadoteridol-exposed rats in which there were early findings of apoptosis. Because gadoteridol had the least amount of tissue deposition, these effects are likely unrelated to the extent of deposition but do suggest small amounts of gadolinium or gadolinium chelate are entering the cell and causing renal injury. The mechanism of gadolinium-mediated renal toxicity remains undefined and merits additional investigation.

Additional study limitations persist. First, the rats in this study were subjected to higher and more frequent dosing than what humans experience in typical clinical practice. The effects of these high doses, particularly those observed in the kidneys, may be significantly attenuated or absent in human patients exposed to these agents at clinically-relevant doses and dosing schedules. Likewise, the low levels of elemental gadolinium detected following intravenous administration of macrocyclic agents at this dosing schedule is expected to be considerably lower, and possibly below the detection limit of most analytical instrumentation, by using typical human doses. Additional studies examining lower doses and less frequent administrations of GBCAs are needed. Second, the chelation state of these gadolinium deposits cannot be assessed by using the analytical methods utilized within this article; however, recent work by Birka et al using hydrophilic interaction liquid chromatography–ICP-MS has demonstrated an effective means of gadolinium tissue deposit speciation (18). Third, although no neurologic symptoms or sequelae appear to be associated with gadolinium deposition in humans or rodents, the expected cellular and physiologic effects and ultimate clinical significance of lanthanide metal deposition within neuronal tissues is unknown and may confound our ability to identify these abnormalities.

In conclusion, our findings demonstrate that intravenous administration of high doses of GBCAs is associated with extensive multigorgan deposition that is reduced but not eliminated by use of macrocyclic GBCA chelates in lieu of linear chelates. Although no histologic changes to neural, hepatic, or splenic tissues were identified at this supratherapeutic dose, renal tissue exposure to this dosing schedule of GBCAs appear to sustain significant injury that merits additional investigation. Our findings strongly argue for future research to assess the in vivo stability and safety of GBCAs.

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nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015;275(3):783–791.


