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Original contribution

Impact of chelation timing on gadolinium deposition in rats after contrast administration

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ABSTRACT

Objective: To determine if gadolinium (Gd) can be rechelated once released from Gd-based contrast agents (GBCAs) and deposited in vivo. Despite extensive research comparing GBCAs and GBCA formulations as well as the ongoing debate about their risks of deposition and the role of Gd release, it remains unknown if retained Gd can be eliminated by administering chelating agents.

Materials and methods: Rats were injected intravenously with 10 doses of 1 mmol/kg gadodiamide and treated with intravenous Zn-DTPA (30 μmol/kg) concomitantly or 1, 4 or 8 h after GBCA administration ($N = 3$ rats per group). After euthanization, tissues were harvested three days after the last dose of gadodiamide and tissue Gd concentrations were assessed by ICP-MS. Additionally, a simulation of a single 0.1 mmol/kg gadopentetate dose with 30 μmol/kg DTPA given either concomitantly or within the first 24 h after GBCA was run; simulated tissue Gd concentrations were compared with those observed in rats to determine if simulated trends were accurate.

Results: Concomitant DTPA did not produce a significant reduction in Gd concentration in any organ for rats. There was a time-dependent trend in liver Gd reduction. The 1 h timepoint was associated with a non-significant increase in kidney, brain and femur Gd relative to untreated controls. There were no significant deviations from the model-predicted Gd changes.

Discussion: Both the simulation and rat study did not identify major benefits for chelation at the doses given, despite the simulation assuming all Gd deposited in tissues is unchelated. The potential redistribution in the rat study provide a compelling result that may impact the clinical relevance of further work investigating re-chelation of Gd. Future work should further describe the three-dimensional dose-time-response relationship for preventing Gd deposition, and how that relates to long-term Gd toxicities.

1. Introduction

Tissue deposition of gadolinium (Gd) following administration of Gd-based MRI contrast agents (GBCAs) has been widely reported with potentially negative clinical outcomes. Currently there are few preventative strategies [1]. The FDA recently mandated a labeling change for GBCAs to warn patients and clinicians about the possibility of deposition [2], and the EMA removed “high-risk” GBCAs from the European market [3]. Despite common, misleading dichotomization of “high-risk” (linear, less stable) and “low-risk” (macrocyclic, more stable) agents, deposition of Gd in human and animal studies has been reported for all GBCAs [4,5], and the difference in risk is a matter of magnitude of deposition without any known clinical significance. Known toxicities resulting from Gd deposition include nephrogenic systemic fibrosis (NSF) in patients with severe renal dysfunction [6], and gadolinium deposition disease in patients with normal renal function [7]; only the former has sufficient evidence to support a direct relationship between level of deposition and severity of symptoms [8,9], but a conservative approach would be to minimize retained Gd across patient populations.

Approaches to reducing deposition should be generalizable to all GBCAs, and should be rationally developed based on mechanistic understanding of Gd deposition. Though the exact mechanism of Gd deposition has not been identified, there is sufficient evidence to suggest Gd release from GBCAs plays at least a partial role [10,11]. It is also unknown if release from macrocyclic GBCAs occurs in vivo and results in Gd deposition, but considering that the trend in stability and retention continues through the macrocyclic GBCAs [11], there is reasonable support for the hypothesis that Gd deposition is caused in-part by release across all GBCAs.

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If Gd is released from GBCAs in vivo, then it can simply be treated as any other heavy metal intoxication, i.e., with chelation. This approach is complicated by ionized Gd introduced systemically through gradual release from the chelating GBCA ligand, which impacts the sensitive time-efficacy relationship for chelation in heavy metal contaminations. Is earlier chelator administration more efficacious, as in decorporation therapy of heavy radioactive metals [12]? At what point, if ever, does chelation have an impact on Gd tissue levels? To identify if rechelation can reduce Gd deposition and to identify any dose-timing relationship, simulations and animal studies were conducted using clinically-relevant dosing regimens.

2. Materials and methods

2.1. Simulation-based assessment

A previously-described multicompartmental model of GBCA/Gd pharmacokinetics was run with a single, intravenous 0.1 mmol/kg dose of gadopentetate (Gd-DTPA) in a 70 kg reference patient [13]. To assess the impact of chelation timing on retained Gd, the simulation was run with 2 mmol (30 μmol/kg) excess DTPA (pretreatment), or a single 2 mmol dose of DTPA (from the standard 1 g dose of Ca-DTPA used in decontamination) given at 1, 4, 8 or 24 h after the GBCA dose (post-treatment); a control simulation was run without excess DTPA or post-treatment. Gd content in the bone, blood, brain, kidneys and liver were assessed 3 days after the simulated GBCA dose, and normalized to the total mass of each tissue or organ in the ICRP Reference Man [14].

2.2. Animal model

Three separate studies were performed with common treatment groups between them for cross-study comparison. Female Sprague Dawley rats (Charles River Laboratories) weighing approximately 200 g with implanted jugular vein catheters were administered 1 mmol/kg of the linear GBCA gadodiamide (Gd-DTPA-BMA; MedChem Express, Monmouth Junction, NJ) via catheter daily or weekdaily (daily, excluding weekends) for 10 doses (Fig. 1). The rats were divided into treatment groups and two control groups containing $N = 3$ rats each; the sample size was selected as it exceeded the minimum number to determine a difference of 50% in retained Gd between two groups with 10% standard deviation at 80% power. The treatment groups were administered 30 μmol/kg Zn-DTPA via tail vein 15 min before each Gd-DTPA-BMA dose (pretreatment) or 1, 4 or 8 h after each Gd-DTPA-BMA dose (post-treatment). The Gd-DTPA-BMA was administered via jugular catheter to minimize deposition at the injection site over the dosing course, which may bias towards increased benefit of DTPA administered at the same site. Three days after the last Gd-DTPA-BMA dose, rats were euthanized by carbon dioxide asphyxiation, and femurs, blood, brain, kidneys and liver were harvested. Tissues were weighed and homogenized using a PowerGen High Thoughput Homogenizer (Fisher Scientific). Samples were dissolved in different volumes of concentrated nitric acid based on the weight of each tissue sample. Brain (around 1 g) homogenates were then sampled and dissolved in 1 mL of nitric acid. For liver (300–400 mg) and kidneys (100–200 mg), triplicate samples of the homogenate were dissolved in 2 mL and 1 mL of nitric acid, respectively. Bone was not homogenized and dissolved in 5 mL of nitric acid. All samples were diluted to a final concentration of 2% nitric acid for ICP-MS measurement.

An Agilent 7500cx was used for the ICP-MS assays. The analysis was run in no gas mode. Masses scanned were ^{156}Gd for 200 ms, and the internal standard ^{115}In for 100 ms. The Gd concentration in each sample was reported as the mean of 5 replicate scans, and concentrations for sampled homogenates of liver and kidneys were averaged for each animal.

2.3. Statistical analysis

For the animal model, Gd concentration in each organ was compared across groups be one-way ANOVA followed by Sidak-corrected multiple *t*-tests comparing treatment groups to control. Each animal study was analyzed separately, and then the results were synthesized based on common treatment groups for an overall assessment of chelation dose-timing; to assess the validity of these comparisons, organ Gd content for common dosing groups will be compared groupwise with two-way ANOVA and for each organ using Sidak-corrected multiple *t*-tests. Trends observed in the simulation were compared organ-wise to those in the simulation by Sidak-corrected, one-sample *t*-tests. Analyses were performed using GraphPad Prism v. 6.05 (La Jolla, CA).

3. Results

The simulation indicated that only modest reduction in organ Gd content would be observed after a single chelator dose within the first 24 h, regardless of timing. Posttreatment was consistently more effective than pretreatment, with maximum reduction at 4 h across all tissues except blood, which had more reduction at 8 h. No chelation timepoint resulted in over 10% reduction in Gd deposition in the simulation.

In the rat studies, there were few significant differences between the Gd concentrations in any organ for the various chelation times (Table 1). Organ Gd concentrations in pretreated animals were significantly different from control, primarily driven by a decrease in kidney Gd. Neither posttreatment study yielded significant differences in tissue Gd concentrations by two-way ANOVA (study-wide comparisons), but kidney Gd concentrations were significantly higher in the 8 h treatment group than in the 1 h treatment group from the same study. There were only non-significant trends ($p = 0.07$) in the overall change over time with the combined results, suggesting minor reduction in

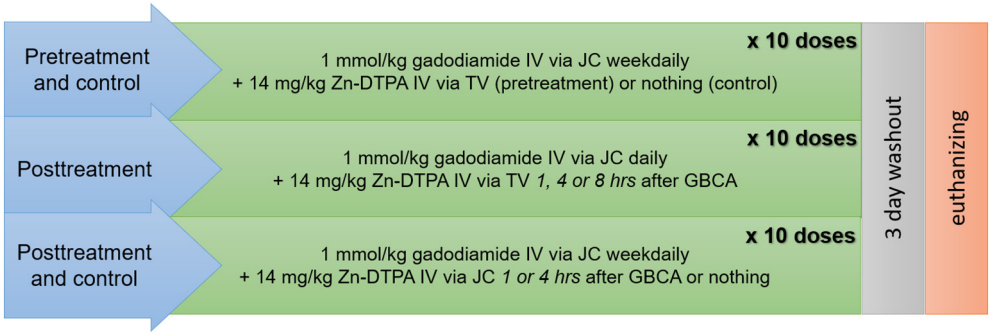

Fig. 1. Treatment protocols for rats administered Zn-DTPA relative to repeated doses of Gd-DTPA-BMA.
Abbreviations: GBCA: Gd-based contrast agent (gadodiamide, in this study); Gd-DTPA-BMA: gadodiamide; IV: intravenously; JC: jugular catheter; TV: tail vein; weekdaily: Monday-Friday.

Table 1
Impact of time of chelation treatment on Gd concentration in various tissues following GBCA administration. The concentration data from rats administered Zn-DTPA/Gd-DTPA-BMA represent the means and standard deviations of 3 animals in μg/g tissue, and the concentration data from the simulation with DTPA/Gd-DTPA dosing are in units of ng/g tissue. Organ comparisons are two-way ANOVA with multiple comparisons to control (concentration data) or simulation results (for relative concentrations) using Sidak-adjusted *t*-tests; significance (p or adjusted $p < 0.05$) is denoted with an (*) in the group header (ANOVA) or value (multiple comparisons). The exact pretreatment and post-treatment protocols are described in Fig. 1.

Time	Bone		Brain		Liver		Kidneys	
	Rats	Sim.	Rats	Sim.	Rats	Sim.	Rats	Sim.
Pretreatment study*								
NA	30.3 ± 0.6	7.53	0.34 ± 0.05	0.027	78.2 ± 5.7	11.5	247.6 ± 39.7	8.36
0 h	29.0 ± 1.0	7.31	0.29 ± 0.03	0.026	79.6 ± 4.1	11.2	187.1* ± 25.9	8.12
Post-treatment study 1								
1 h	25.6 ± 2.0	7.26	0.55 ± 0.15	0.026	78.0 ± 5.4	11.1	230.3 ± 29.4	8.06
4 h	24.2 ± 1.6	7.23	0.36 ± 0.02	0.026	82.4 ± 7.9	11.1	244.0 ± 28.7	8.03
8 h	23.4 ± 1.2	7.26	0.39 ± 0.08	0.026	70.6 ± 6.7	11.1	261.3*[1h] ± 26.1	8.05
Post-treatment study 2								
NA	23.4 ± 3.0	7.53	0.58 ± 0.04	0.027	75.2 ± 10.0	11.5	156.6 ± 31.5	8.36
1 h	30.2 ± 7.1	7.26	0.62 ± 0.12	0.026	66.8 ± 5.0	11.1	176.6 ± 53.6	8.06
4 h	21.1 ± 1.3	7.23	0.47 ± 0.02	0.026	67.6 ± 3.4	11.1	162.4 ± 20.6	8.03
Simulation-only								
24 h	ND	7.40	ND	0.026	ND	11.3	ND	8.20

Abbreviations: GBCA: Gd-based contrast agent; Gd-DTPA-BMA: gadodiamide; NA: not applicable, control group; ND: not determined; Sim.: simulation.

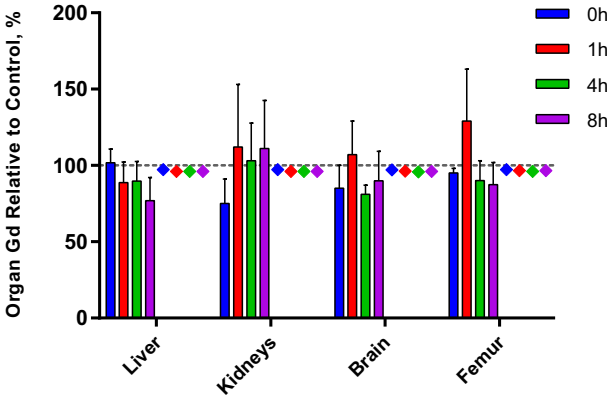

Fig. 2. Relative Gd concentrations in different organs 3 days after GBCA administration with prophylactic chelator dosing within the first 8 h post-GBCA compared to unchelated control. The bars with lines represent the observed trend (and pooled standard deviations) for rats administered Gd-DTPA-BMA while the diamond markers represents the effectiveness of Zn-DTPA in a simulated reference patient administered the GBCA Gd-DTPA. The 8 h timepoint is an extrapolation based on the ratio of 8 h organ Gd to 4 h organ Gd, and 4 h organ Gd to control. Data were analyzed by two-way ANOVA and Sidak-adjusted multiple *t*-tests (comparisons within organs, and to expected means of 100% and the simulation results), but no statistical differences were found.

liver Gd the later the chelator is given, and potential redistribution of Gd to the kidneys, brain and femur if DTPA is given at the 1 h timepoint. No change in organ Gd concentration compared to control was significantly different from the value hypothesized in the simulation study (Fig. 2).

Gd concentrations in the control groups for the pre- and post-treatment studies were significantly different by two-way ANOVA ($F = 11.2$, $p = 0.004$ for the study effect), and the kidney concentrations were significantly different by Sidak-corrected multiple *t*-tests (*t*-stat = 6.047, adjusted $p < 0.0001$). The repeated 1 h dosing group organ Gd concentrations were not significantly different from the first 1 h dosing group by two-way ANOVA ($F = 2.8$, $p = 0.11$), but kidney concentrations were significantly different in multiple comparisons (*t*-stat = 3.005, adj. $p = 0.03$). Like the control group, the repeated 4 h group differed from the first 4 h group significantly overall ($F = 22.38$, $p = 0.0002$), and in kidney concentration (*t*-stat = 7.766, adj. $p < 0.0001$). The ratios of Gd in each organ in the 4 h dosing group to the amount in the 1 h dosing group was not significantly different between studies either overall ($F = 1.2$, $p = 0.28$) or in individual organs; femurs were the closest organ to reach significance in this comparison (mean difference for the ratios was 24.7, adjusted 95% confidence interval for the difference, −15.5–64.9).

4. Discussion

The results of this investigation suggest there is a complex relationship between dose-timing and chelation-based prophylaxis of Gd deposition. Even in a model built upon the hypothesis that Gd deposition is entirely explained by release of Gd from GBCAs, a single, optimally-timed chelator dose was insufficient to prevent even 10% of deposition to any organ (relative to the level of deposition if no chelator is administered). The results of the animal studies provided reasonable corroboration with the predictions of the model, and indicate a potential redistribution phenomena if chelation is administered in the first 24 h. The animal study was also biased towards more released gadolinium by using unformulated gadodiamide (gadodiamide without 5 mol % excess ligand), which is associated with substantially more Gd release than any other GBCA [15], thus a rechelation approach should be more effective for gadodiamide deposition.The pretreatment assessed in the animal studies amounted to using the equivalent of ~3% excess ligand (chelator); in these studies, the “excess ligand” was Zn-DTPA rather than DTPA-BMA, the ligand in the GBCA administered. We have previously considered how excess ligand would influence Gd retention using our simulation, and found that in a reference patient with normal renal function, each percentage of excess ligand would result in ~1% total reduction in total retained Gd [13]. Our animal experiment did not produce results consistent with one comparing 0%, 5% and 10% excess ligand administered with Gd-DTPA-BMA or gadoversetamide, which showed that even 5% excess could reduce liver deposition by at least 10-fold, and femur deposition by more than half [16]; the present animal study did not significantly reduce liver or femur deposition with 3% excess chelator. Both the present and former study involved administering high cumulative GBCA doses to rats week-daily, however, Sieber et al. administered 2.5 mmol/kg of Gd-DTPA-BMA or gadoversetamide for 10 (0% excess ligand) or 20 (5–10% excess ligand) doses, resulting in more than double the cumulative dose of GBCAs than was used in our study; the 1 mmol/kg dose of Gd-DTPA-BMA we used is closer to the surface-adjusted, human-equivalent rat dose of 0.6 mmol/

kg [17], and should thus more accurately reflect the behavior of GBCAs/ligands in humans. Differences may also be explained by the different routes of administration for the GBCA (jugular catheter) and chelator (tail vein in pretreatment and uncontrolled posttreatment), which may result in different levels of extravasation and thus altered pharmacokinetics [18]. We have examined the impact of tail vein injection versus other sites (jugular catheter or subcutaneous) and concluded that serial injections of GBCAs via tail vein result in significantly elevated retention at that site, potentially acting as a depot for Gd that could enhance any perceived benefit of co-formulated excess chelator, or a chelator given separately by tail vein (i.e., by preventing release at the injection site, specifically; Supplementary); we found 0.02% of the cumulative injected dose remains in the tail when given by JC, whereas 0.3% remains when given via tail vein, thus there is 10-fold more Gd available to be either rechelated or redistributed to other tissues. Measuring the benefit of GBCAs co-formulated with excess chelator given via tail vein or jugular catheter may resolve the observed discrepancy. The 15-min delay between DTPA pre-treatment and GBCA doses also does not explain the differences in the reported results, since the two-compartment pharmacokinetics of DTPA in rats would result in at least 50% of the injected dose being present in plasma at 15 min [19], meaning the GBCA had at least 1.5% excess chelator in plasma at the time of administration in the animals. Cacheris et al. showed that the toxicity of unformulated gadodiamide is reduced by adding 5 mol% excess chelator (in the form of caldiamide, the calcium complex), but that the toxicity would increase as more chelator was added because of its effect on endogenous metals [20]. It seems undeniable that the toxicity of the unformulated gadodiamide could only be attributable to released Gd, so perhaps the lack of chelation benefits in our study is due to slow chelation kinetics in vivo for the Zn-DTPA, or the concentrations of available chelator resulted in rechelation being thermodynamically unfavorable.

Our posttreatment data was also not consistent with recent results from Rees et al. [21] and Semelka et al. [22], who adminsitered DTPA to mice and humans, respectively, known to be exposed to Gd. The study from Rees et al. adminstered 100 μmol/kg DTPA intraperitoneally 1 h before or after exposure to a single intravenous dose of ^{153}Gd-citrate and showed significant reduction of retained Gd in both groups compared to control. The differences between the results of our study and their findings can be readily explained by the larger dose of DTPA via a route with 100% bioavailability, delayed absorption and prolonged elimination in rodents [23], along with the administration of a Gd salt rather than a clinically relevant chelate, which likely has a strong impact on the biodistribution of Gd and the amount available for chelation. The study from Semelka et al. treated patients with 1 g Zn- or Ca-DTPA (~30 μmol/kg) intravenously months to years after GBCA exposure and found a 10–30-fold increase in 24-h urine Gd following treatment. Our results do not necessarily differ from those of Semelka et al., because we investigated treatment relatively soon after GBCA administration when change in urine Gd output caused by chelation would be negligible. Earlier work in our lab suggested dosing DTPA more than a week after loading GBCA into a rat over multiple high doses would result in no change in urine or organ Gd levels compared to controls (data not shown). In our simulation, chelation also has a dwindling effect on organ Gd if chelation is given after the first 24-h post-GBCA dose (Table 1), so early treatment should magnify any benefit observed in later treatments. It is unknown if patients environmentally-exposed to Gd but not exposed to GBCAs would also have a 30-fold enhanced Gd urine elimination after treatment with DTPA, or how that would explain the results from Semelka et al.; it may also be that the symptomatic patients used in the study have altered Gd/GBCA biokinetics. If the discrepancy cannot be explained by any of these as-of-yet unknown factors, it may be that the rat is simply a poor model of the behavior of Gd/GBCAs in humans. The rat model was selected simply because it can easily be related to prior research with GBCAs [8], and because the concerns between comparing rat and human GBCA deposition appears to be mainly focused on different glymphatic and brain ECF dynamics [24]. A rodent model in a study such as ours is appropriate because, in general, deposition and potential dechelation/rechelation of Gd in vivo deal more with the components various media into which GBCAs distribute, which are largely the same in humans and rats; the exceptions to that statement are newer GBCAs with modifications to improve protein-binding or non-renal clearance, which would predictably behave differently in non-human circulation [25].

The overall study on dose-timing is confounded by the week-daily and daily dosing for the pre- and post-treatment groups, respectively, potentially impacting the direct comparisons between pre- and post-treatment groups. We attempted to resolve this issue by repeating the 1 h and 4 h dosing group week-daily with another control group for comparison with the original week-daily control group. We identified significant variation between the week-daily and daily dosing groups, but the differences between the control groups that received the same GBCA dosing schedule would suggest these differences are attributable to instrumental variation, variation in organ processing or gadodiamide batch variation. The experimental methodologies were designed to ensure consistency in these elements, so we are still uncertain as to the exact cause of the disparity. Regardless, the lack of significant differences between the ratios of 4 h–1 h organ Gd in the daily versus week-daily administration supports the conclusion that comparisons within each study are still valid, as are comparisons of relative organ Gd among groups.

While no significant trends were observed in the rat study, we did observe a potential redistribution of Gd into the kidneys, brain and bone if DTPA is given 1 h after gadodiamide. This observation may be akin to what is observed in the treatment of lead intoxication with EDTA [26] if it is truly occurring. A redistribution phenomenon was not predicted by the simulation. While these studies were not primarily designed to directly compare the simulation and animal results, the lack of significant deviation from most predicted values suggests that the model may describe what is occurring in vivo to the extent necessary to replicate the observations within the studied time period. Different simulation and animal model conditions may explain observed differences in absolute concentrations, though; in the simulation, Gd-DTPA was used as the GBCA rather than Gd-DTPA-BMA, and chelation therapy was performed with Zn-DTPA in both studies which binds more strongly to Gd than DTPA-BMA and may explain observed differences (i.e., Zn-DTPA was more effective in removing Gd released by the weaker ligand, DTPA-BMA, than the stronger ligand, DTPA). Additionally, the simulation modeled a single dose in a human patient, while the animal study modeled sequential doses in rats.

Extending the simulated chelator administrations to every hour over 16 h after GBCA administration, it was determined that the 4 h administration time provides the optimal reduction in Gd burden in all tissue. In the simulation, the peak released Gd from Gd-DTPA accessible to be re-chelated (in both DTPA-accessible compartments) occurs at 6 h post-GBCA, thus the optimized efficacy at 4 h may be attributable to optimized distribution of DTPA into its two compartments by the time available Gd concentration peaks.

The current investigation was limited by testing the hypothesis that Gd deposition is attributable to release without testing whether retained Gd was intact or released. Such an assessment would be complicated and there are limitations to methods to determine intact GBCAs in tissues described in available literature [27,28], but it would strengthen our conclusions, particularly those drawn from the simulation. Gd release from GBCAs is widely accepted to play some role in Gd deposition and toxicity [11], but there is little consensus on how much deposition is the result of free Gd [29]. Because intact GBCA has been detected in tissues, particularly in deposits containing the more stable macrocyclic agents [19], and intact GBCAs can induce fibrosis-related cytokines without necessarily releasing Gd [30], it is unlikely that Gd release is the sole cause of GBCA-associated adverse outcomes in

patients. However, the simulation demonstrated that a single, standard chelator dose will be insufficient to prevent deposition even if it is resulting from Gd release; because chelation is reversible in the model, this result is likely demonstrating that only a minor fraction of each DTPA dose will bind and renally eliminate released Gd, suggesting a higher cumulative DTPA dose is necessary. Performing the present animal study with macrocyclic GBCAs or stronger linear agents may indicate whether release of Gd that can be re-chelated only occurs with less stable agents like Gd-DTPA-BMA, or if chelation provides broad benefit across GBCA classes.

5. Conclusions

The timing of the administration of a chelating agent has no effect on Gd deposition following administration of a GBCA, but pretreatment and posttreatment with a chelating agent within the first 8 h should be targeted for further investigation. Higher or more frequent chelator doses, or using agents with more prolonged residence time in the body may demonstrate more benefit than the single IV bolus regimens investigated here. Potential redistribution identified in the animal studies but not predicted by the simulation suggests evidence that small molecule Gd complexes (including intact GBCAs) may be important for brain and bone deposition, and the simulation model must be revised if the redistribution is reproducible and clinically significant, rather than a methodological anomaly. Fundamentally, we have not demonstrated that Gd can be re-chelated in rats and further work is required to determine if that is a matter of suboptimal chelator administration, or the translatability GBCA retention data in rats to humans.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mri.2018.10.006.

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