Published in final edited form as:

Invest Radiol. 2020 October ; 55(10): 636–642. doi:10.1097/RLI.0000000000000681.

Human Hair as a Possible Surrogate Marker of Retained Tissue Gadolinium: A Pilot Autopsy Study Correlating Gadolinium Concentrations in Hair with Brain and Other Tissues Among Decedents who Received Gadolinium-based Contrast Agents

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Abstract

Objectives: We employed laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS) to quantify gadolinium in hair samples from autopsy cases with gadolinium based contrast agent (GBCA) exposure. Hair gadolinium data was correlated with gadolinium concentrations in brain, skin, and bone tissues from the same case to investigate a potential non-invasive method for gadolinium quantification and monitoring.

Materials and Methods: Medical records from autopsy cases at our institution were screened for history of GBCA exposure. Cases with exposure to a single type of GBCA with the most

recent injection occurring within one year were identified and included in the study. The concentration of gadolinium in hair samples was analyzed by LA-ICP-MS, and brain (globus pallidus, dentate nucleus, white matter), bone and skin tissues were analyzed by bulk ICP-MS. The mean of the maximum value in the hair samples was used to generate a representative measurement of the hair gadolinium concentration for each case. A linear regression analysis between each tissue type and hair was conducted to assess for possible correlation.

Results: Tissue and hair samples from 18 autopsies (16 cases with exposure to GBCA, 2 controls) were included in the study. Comparing the different tissues revealed good correlation between some tissue types. The best model fit occurred between white matter and hair ($R^2 = 0.83$; $p\text{-value} < 0.0001$) followed by the comparison between dentate nucleus and hair ($R^2 = 0.72$; $p\text{-value} < 0.0001$) and dentate nucleus and skin ($R^2 = 0.70$; $p\text{-value} < 0.0001$).

Conclusions: A significant correlation in this study between hair gadolinium concentrations and brain and skin gadolinium concentrations suggests that hair may serve as a safe and effective biomonitoring tissue for patients who receive GBCA injections.

Keywords

LA-ICP-MS; gadolinium; GBCA; MRI; hair; brain; bone; skin; biomonitoring; postmortem

Introduction:

Gadolinium based contrast agents (GBCAs) are used in magnetic resonance imaging (MRI) to increase diagnostic performance. Gadolinium in its elemental form is toxic to humans since the ionic radius of gadolinium is close to that of calcium and, thus, it may act as an inorganic blocker of calcium channels¹. Additionally, gadolinium ion substitution for calcium in biological sites may stay bound for long periods due to the +3 charge on the gadolinium ion. To prevent this, gadolinium in contrast agents is administered in a chelated form (i.e., incorporated into a ligand) and in this form it is considered safe^{2,3}. The first indication for concern with GBCAs came in 2006 with the discovery of nephrogenic systemic fibrosis (NSF). NSF is a rare debilitating condition that occurred in patients with renal failure and has been associated with the use of GBCAs², primarily certain linear GBCAs that more readily release unchelated gadolinium in vivo.

To further underscore concerns of potential adverse effects from gadolinium use, Kanda, et al.⁴ reported an increasing T1-weighted image (WI) hyperintensity within the brain in the globus pallidus and dentate nucleus related to cumulative doses of linear GBCA, even in patients with normal renal function. This observed hyperintense T1 was confirmed to be associated with retention of small amounts of gadolinium from an autopsy study by McDonald, et al.⁵. A subsequent autopsy study by our group⁶ demonstrated the variability in retained gadolinium among different contrast agents. Significance of these small amounts of retained gadolinium in human tissue is not fully understood, however the potential for toxicity remains of great concern. Although several observational studies have failed to show a toxic effect from these small amounts of retained gadolinium, there is a small group of patients who reportedly suffer from various maladies including pain and debilitation, which they attribute to GBCA exposure. Although controversial and, as yet, unproven, these

patients have been referred to as having “gadolinium deposition disease” by Semelka, et al.⁷ who is currently studying this patient group and continuing to evaluate them.

Although, to date, no proven adverse effect from administered gadolinium exists there is still considerable detail that is not known regarding GBCAs and their biologic behavior. We do know that small amounts of gadolinium are retained in the human body but we do not know the speciated form(s) of these deposits. We also have evidence that different GBCAs are retained and eliminated at different rates in rats⁸, though this is not directly transferable to humans. Bower et al. (2019) showed evidence of GBCA toxicity in neuronal cell culture that was directly related to GBCA concentration and inversely related to kinetic stability of the various agents⁹. Additionally, Bower et al. (2019) pointed out that any clinical effect was likely to be related to factors such as the amount of retained gadolinium, the rate of elimination, and the integral of the amount retained over a long period of time. Thus, in order to begin to accumulate these types of data to evaluate for possible subtle long term effects, a noninvasive method is needed to quantify tissue gadolinium.

A major impediment in evaluating patients with possible gadolinium toxicity is that we lack a reliable method to non-invasively sample, quantify, and monitor gadolinium in humans in vivo. One possible biological material that is known to concentrate heavy metals, is readily accessible, and can be obtained non-invasively is hair. The purpose of this study is to use laser ablation (LA) ICP-MS to evaluate gadolinium levels in hair obtained from decedents that were exposed to GBCA during life and to determine if there is a possible correlation with concentrations in other body tissues obtained at autopsy including brain, bone and skin.

Materials and Methods:

Subjects:

This study was approved by our institution’s Human Subjects Review Board for retrospective review of medical records and was Health Insurance Portability and Accountability Act compliant. Additionally, autopsy consent from each case granted authorization for use of tissues for research purposes.

Cases were identified and their electronic medical records (EMR) screened when they presented for autopsy between December 2017 and May 2019 at the pathology department in our institution. If they met inclusion criteria, brain, bone, skin, and hair samples were collected. Inclusion criteria included having complete and accessible medical records, a history of one or more GBCA injection(s), exposure to a single type of GBCA, and most recent exposure within one year before death. Medical records were thoroughly reviewed, to the best of our ability, to make a determination as to the completeness of those records. The time limitation (i.e., one year before death) was implemented due to the shorter hair lengths in received samples. For example, an injection one year ago would require approximately 12 cm of hair to capture the exposure period. Exclusion criteria included inaccessible or incomplete medical records, and exposure to multiple GBCA types. Initially, a total of 42 cases with gadolinium exposure and two controls were identified from the consecutive autopsy review.

EMRs were subsequently more thoroughly searched for exposure to GBCA. The type of GBCA administered, dose, and date of injection for all recorded injections were compiled for all cases with exposure. Subjects documented without exposure to GBCAs were included as controls. Age, sex, and estimated glomerular filtration rate (eGFR) were recorded for all subjects. For subjects with eGFR values above 60, autopsy records report “> 60.” For subjects with eGFR values below 60, the actual numeric value is reported.

A tiered screening methodology was employed to identify cases that did not meet inclusion criteria. Nine subjects received injections of more than one GBCA type, 12 received injections more than a year before their death, 1 had very short hair that was too short to capture the exposure period, 1 did not have a hair sample, and 1 more was missing required information in the EMR. In total, 24 potential cases were excluded from this initial study group. Eighteen cases with a history of exposure to a single type of GBCA with the most recent injection occurring within one year were identified for inclusion. Two of those cases did not have hair long enough to capture the exposure period (e.g., hair length representative of one month of growth, but exposure period was six months prior) and were excluded. Human scalp hair, on average, grows at the rate of 1 cm/month¹⁰. Final inclusion was 16 cases and two controls in this study. Table 1 summarizes subject characteristics for the subset included here.

Sample Analysis:

Hair-bearing scalp samples as well as brain sections including the globus pallidus (GP), dentate nucleus (DN), and white matter (WM) were collected for all subjects. Skin and bone (rib) samples were also collected at the time of autopsy for most subjects. Brain, bone and skin tissue samples were stored in a 10% formalin solution. After receipt from the pathology department, all tissue samples were cut using stainless steel surgical instruments (e.g., scalpel blades, scissors), which were cleaned with distilled water and dried between each sample to prevent cross contamination of gadolinium. Brain, bone and skin tissue samples were cut, weighed using an analytical balance (AG104; Mettler Toledo, Greifensee, Switzerland). Samples underwent microwave assisted nitric acid digestion before inductively coupled plasma mass spectrometry (ICP-MS) analysis following a modified version of the U.S. Environmental Protection Agency (EPA) method 6020a (revision 1, 2007).

Hair from the scalp samples were plucked, including the root when possible, using carbon fiber (non-metal) tweezers and placed in microfuge tubes (one per subject); these tubes were filled with acetone and the caps closed. Tweezers were cleaned with methanol between subjects to prevent cross contamination. The microfuge tubes with hairs and acetone were sonicated for 30 minutes in water at room temperature. The hairs were then removed from the acetone and placed in Kim Wipe pouches to be dried in an incubator at 37°C for one hour. This washing process has been used previously¹¹ and removes exogenous contamination from the hair shaft. The cleaned hairs are then mounted onto glass slides covered in double stick tape, which adheres the hair to the slide without damaging the shaft. The slides were placed on the laser stage along with calibration gels and a glass pellet standard reference material (SRM; National Institute of Standards and Technology [NIST])

612) with trace metals. The calibration gels were bovine skin-based gelatin amended with selected isotope concentrations between 0 and 2,000 ug/g.

For LA analysis, the laser path along each hair was traced as a single line scan from root to tip in the instrument software (Agilent NWR ESI ActiveView). After the material was ablated it was transported through a teflon tube to the ICP-MS via a stream of He for analysis. Between four and 18 hairs were analyzed from cases and two hairs were analyzed from the controls. Calibration gels and SRM were included in each batch run to assess instrument stability over time. After samples were analyzed, counts per second (cps) data was output from the ICP-MS software (MassHunter).

Instrument Parameters:

The instrumentation used for analysis of the hairs included an Elemental Scientific, Inc. (ESI) New Wave Research (NWR) 213 (Nd:YAG [neodymium: yttrium aluminum garnet]) laser interfaced to an Agilent 7900 ICP-MS. The laser operated at a 213 nanometer (nm) wavelength¹². The laser ablation instrument was outfitted with a two volume sample cell which minimized material lost during ablation as well as signal broadening. The helium flow through the laser was 800 mL/min with 1.07 L/min of argon makeup gas T-ed in between the laser and ICP-MS. The sampling period for all isotopes and materials was 0.515 seconds and integration time for gadolinium-157 (157Gd) was 0.4 seconds. The ICP-MS was set to helium mode without collision cell gas and a radiofrequency power of 1550 watts. Laser parameters for the hair and gel analysis were as follows: spot size of 30 um; firing rate of 20 Hz; scan speed of 100 um/sec; and energy of 60%. Brain, skin, and bone tissue were analyzed using the same ICP-MS instrument listed above, except that argon carrier gas flow was 1.03 L/min with no makeup gas.

Data Processing and Analysis:

Laboratory-reported gadolinium concentrations were used for the brain (globus pallidus, dentate nucleus, and white matter), skin, and bone samples. The time series of $m/z157$ intensities for each hair profile was processed using a rolling mean centered on five values. Similar data reduction techniques (i.e., rolling average and/or median) have been employed by previous LA-ICP-MS analysis of hair¹³, corals¹⁴, and otoliths¹⁵. Mass-based concentrations (i.e., ug/g) of 157Gd in each hair line scan were calculated using a linear regression calibration curve derived from the gels. The distance along the hair shaft (in millimeters [mm]) was derived from the scan speed of the laser (100 um/sec for hair) and the acquisition time of each data point. An example plotted line scan for an individual hair showing a 157Gd peak is provided in Figure 1a; an example of a hair from one of the control subjects with no peak is shown in Figure 1b.

For each hair line scan with an identified peak, the portion along the shaft (excluding the root) that included a 157Gd peak was isolated and the maximum concentration was selected as the representative measure for the individual hair. These maximum values were averaged for all hairs analyzed for a specific subject to generate a representative measure of the hair gadolinium concentration for that subject. Hair from control subjects showed no 157Gd peaks and the average of the hair line scan was used as the representative concentration for

each hair; an average of all hairs analyzed was used as the representative concentration for a control. Concentrations below the LA-ICP-MS method detection limit (0.05 ug/g) were set to 0.05 ug/g.

Statistical Analysis:

Using the 'lm()' function in RStudio (version 3.4.0), a linear regression between each tissue type was conducted to assess the relationship between tissue concentrations. Significance was determined as $p < 0.05$. Due to the small sample size, no adjustments were made (i.e., did not use controlling variables).

Results:

There were 16 cases with exposure to GBCAs and two controls included in this study. Approximately a quarter of the cases received linear GBCAs (gadoxetate or gadobenate) and the remaining three quarters received macrocyclic GBCAs (gadobutrol or gadoteridol). There is some variability in the concentration of injectable gadolinium agents. Thus, gadoxetate contains 0.25 mmol/mL, gadobenate and gadoteridol contain 0.5 mmol/mL, and gadobutrol contains 1.0 mmol/mL. Total GBCA dose for each case was calculated as the total number of mL injected multiplied by the GBCA molarity of the agent received. Two cases (subjects 3 and 6) received three injections and the other 14 cases received only one injection. For the two cases that received multiple GBCA injections, subject 3 received injections at 51, 70 and 75 days before death, and subject 6 received injections at 5, 6 and 106 days before death. Days between the last injection and death were between two and 69. For two subjects (2 and 3), brain and hair samples were received for analysis, but no skin or bone samples.

Cases had higher ^{157}Gd concentrations than controls by at least a factor of five (conservative estimate due to detection limit) and up to a factor of 100. Among the brain tissue samples, the GP results were generally the highest with an average concentration of 0.11 ug/g compared to the DN and WM, which had average concentrations of 0.046 and 0.027 ug/g, respectively. Skin concentrations ranged from 0.0154 to 0.21 ug/g and bone concentrations ranged from 0.11 to 2.3 ug/g. The highest tissue concentrations were present in the hair samples at 5.3 ug/g for subject 9. This was consistent with previously published articles^{16,17} noting that metals concentrations in hair can be one to two orders of magnitude higher compared to other tissues. Summaries of the subjects and tissue concentrations are in Table 2.

Comparison of the different tissues using linear regression revealed good agreement (i.e., correlation) between some tissue types. The best model fit was the comparison between WM and hair concentrations ($R^2 = 0.83$; $p\text{-value} < 0.0001$) followed by the comparison between DN and hair ($R^2 = 0.72$; $p\text{-value} < 0.0001$) and DN and skin ($R^2 = 0.70$; $p\text{-value} < 0.0001$). The correlation between DN and hair is shown in Figure 2. The dentate nucleus is of particular interest as it plays an important role in planning and initiation of voluntary movement, and is also a known location of high gadolinium deposition in the brain^{5,6}.

Increasing hair concentrations correlated significantly with increasing concentrations in DN, WM, and skin tissues. Though the linearity between hair and bone was low ($R^2 = 0.30$), this relationship was still statistically significant at an alpha of 0.05. Figure 3 displays the linear regression results' R^2 values and associated p-values for all tests.

All regressions that included GP results were generally not linearly related (i.e., low R^2 values) indicating high variability between GP concentrations and other tissue concentrations. The GP results for subject 7 were almost twice as high as the next highest GP concentration. The other tissue concentrations for this subject did not reflect the same degree of elevated gadolinium concentrations. This result was considered an outlier in the GP results and if it were to be excluded from the regression analysis the linearity of the relationship between GP and hair is improved from an R^2 of 0.049 (p-value = 0.19) to 0.22 (p-value <0.05). Figure 4 shows the comparison between GP and hair with the outlier.

Discussion:

GBCAs are administered intravenously and most are excreted in urine³. Two of the GBCAs included in this study, gadoxetate and gadobenate, are not solely excreted in urine, but also excreted through the liver. There are two general types of GBCAs, the first are linear agents in which the structure of the ligand includes an open chain linked to the gadolinium atom. The second are macrocyclic agents, where the gadolinium atom is enclosed within a cyclic ligand². Linear agents are less stable than macrocyclic agents and thus are more likely to release the gadolinium into the body¹⁸. Multiple studies have demonstrated higher levels of retained tissue gadolinium associated with linear compared to macrocyclic agents^{6,19}.

Using T1 hyperintensity in the globus pallidus and dentate nucleus to quantify gadolinium can be unreliable because other metals (e.g., iron and copper) can accumulate in these tissues and contribute to T1 hyperintensity²⁰. The method used to quantify gadolinium in most studies using human autopsy tissue is ICP-MS, which is a destructive process^{5,6,21}. These studies have found that compared to cases without exposure to GBCAs, brain specimens including globus pallidus and dentate nucleus with history of GBCA use have statistically significant increased concentrations of gadolinium. The highest levels of retained gadolinium in the brain are found in deep grey nuclei including the GP and DN although lesser amounts can also be found in other brain structures including WM. It should also be noted that control subjects without exposure to GBCA may still show trace levels of gadolinium but at much lower levels (usually one to two orders of magnitude lower) compared with exposed patients. This presumably represents accumulation from exogenous background contamination in water or other sources of gadolinium.

As patients continue to receive GBCAs for diagnostic imaging procedures, development of appropriate monitoring strategies is crucial to better understand the natural history and to assess possible toxic effects of the small amounts retained in human tissue. The recent revelation that gadolinium deposition occurs in various tissues and the limited research on relationships between gadolinium deposition and reported adverse outcomes underscore this need for effective, noninvasive monitoring. The analyses presented here were chosen to

include tissues with presumed different gadolinium kinetics (i.e. deposition and washout/elimination).

Hair fibers are proteinaceous fibers with an outer cuticle, inner cortex, and sometimes a central medulla²². Figure 5 shows the general anatomy of the two primary hair components: the hair shaft (i.e., the fiber) and the hair follicle (i.e., the structure embedded within the skin). The cortex is the thickest layer of the hair shaft and is largely composed of keratin, which contains sulfhydryl groups of amino acids^{17,23}. The sulfhydryl groups show high affinity for metals, which can facilitate their deposition into the hair shaft¹⁷. However, the mechanism by which metals are incorporated into hair during fiber synthesis is still not well characterized¹⁷. Concentrations of metals in hair are generally higher (by an order of magnitude or more) than concentrations in blood and urine^{16,17}. Hair samples are stable and thus, make storage and transport considerably simpler than other tissue samples. Additionally, the non-invasiveness of sample collection is very attractive¹⁷.

Recently, techniques linking LA with ICP-MS analysis have been developed to produce highly spatially resolved data of trace metals in biological samples. When a hair is analyzed using LA, the result is that numerous data points are continuously compiling as the hair is ablated and material is sent to the ICP-MS. Depending on the optimized instrument parameters (e.g. laser pulse rate) and the length of the hair, each hair may have hundreds to thousands of discrete data points.

High resolution quantitative elemental distributions with LA-ICP-MS have been produced in brain tissues²⁴, *D. magna* (planktonic crustaceans) and *D. rerio* (zebrafish) embryos²⁵, skin tissues²⁶, and at our own University of Washington laboratory in mouse brain tissue²⁷ and nasal rosettes from Coho salmon²⁸. Application of this micro-destructive technique²⁹ has also been used to quantify metals content in hair. This includes animal and human research on single point and time-resolved temporal frames^{13,30-35}.

Previous studies have used ICP-MS to quantify gadolinium in hair for target subject populations including cancer patients³⁶, patients receiving GBCAs³⁷, and residents living near rare earth mining areas³⁸. Measurement of gadolinium using LA-ICP-MS on the whiskers of mice exposed to GBCAs was recently reported³⁹. This study employed line scan analysis techniques that showed higher doses of GBCA resulted in higher gadolinium concentrations within the whiskers.

LA-ICP-MS has been established as a powerful and sensitive analytical technique for trace metals quantification and distribution at micrometer resolution. Unfortunately, this method is destructive, and is difficult to employ on live tissue. Using this technique on hair strands has allowed monitoring of toxic metals and drugs, and has the potential to monitor gadolinium in patients after administration of GBCAs. However, this technique has not been fully investigated for gadolinium, and no study to date has correlated gadolinium concentrations in hair with other tissues such as brain, bone, and skin.

The measure used for the hair concentration in this study is representative of a maximum signal from a single dose, whereas the brain, skin, and bone concentrations may reflect accumulation from multiple doses for some subjects. Although two of our cases were

exposed to more than one dose of GBCA, there was still a very good correlation between the measured hair concentration especially in brain WM and DN. However, this was not adequately tested with our small pilot study sample size. In addition, this study tested one method of hair concentration quantification using a single maximum signal measure. There are other methods such as analyzing low levels of steady-state hair gadolinium concentration that may be useful but were not tested in this initial study. Independent of the hair measure, other tissue concentrations will presumably be attenuated over time, differentially for each tissue, and based on the tissue-specific excretion kinetics for gadolinium and/or the gadolinium chelates. The effect this will have on the measured tissue correlations with hair remains to be determined.

Other papers^{19,40,41} have reported higher tissue gadolinium concentrations (either through T1-WI or ICP-MS) in humans and animals who received linear GBCAs, compared to macrocyclic GBCAs. However, the data derived from this study did not show a difference in linear regression between these two types of GBCA. Although the case study group included roughly two thirds macrocyclic agents and one third linear agents, they defined a single continuous regression line. This likely reflects the fact that, although the two different types of GBCA retain gadolinium at different rates, the mechanism of tissue retention or, at least of hair accumulation, is similar for both GBCA types. In a way, this supports the potential for hair analysis since it further suggests the ability to measure gadolinium retention independent of GBCA type or types (in the case of multiple exposures) the patient may have been exposed to.

Study Limitations:

There are many limitations to this initial pilot study. Gathering relevant autopsy cases is difficult and precludes typical recruitment methods. One is subject to the limitations of which cases come to autopsy and what their past history of GBCA exposure is. Thus a small sample size was analyzed. In addition, the GBCA agents studied were limited for similar reasons.

Despite this we were able to study a reasonable distribution of linear and macrocyclic agents that included two cases with multiple exposures. Although we employed our best efforts to thoroughly review each subject's medical records this study was a retrospective one and, thus, there is the potential that some pertinent information was not available. Only one LA-ICP-MS hair analysis method was tested in this study and future work with alternative analysis types are being pursued.

Conclusions:

This research study shows significant correlation between hair gadolinium concentrations and brain and skin gadolinium concentrations suggesting that hair may serve as a safe and effective biomonitoring tissue for patients who receive GBCA injections. This was an initial pilot study with a small sample size from a non-ideal study population. Nevertheless, the results are promising and should prompt further research.

Acknowledgments

Sources of Support:

Research supported in part by a grant from the National Institute of Environmental Health Sciences and in part by a grant from Guerbet, LLC.

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Figure 1.
Example hair plots showing: a) hair profile with a ^{157}Gd peak; and b) hair profile without ^{157}Gd peak

Figure 2.
Linear regression between DN and hair

Figure 3.
Summary of linear regression results comparing tissue concentrations

Figure 4.

Linear regression between GP and hair, including the outlier (subject 7)

Figure 5.
General anatomy of a hair follicle (sub-dermal) and fiber

Table 1.

Study population characteristics

Characteristic (Units)	Controls	Cases
Subjects (N)	2	16
Male (N)	0	8
Female (N)	2	8
Age (years, min–max [mean])	70–79 (75)	19–79 (57)
eGFR <60 mL/min/1.73 m ² (N)	1	4
eGFR >60 mL/min/1.73 m ² (N)	1	12
Linear agent (N)	NA	5
Macrocyclic agent (N)	NA	11
Time between last injection and death (days, min–max [mean])	NA	2–69 (22)

Notes:

NA - not applicable

Table 2.

GBCA summary and tissue concentrations for cases and controls

Subject No.	GBCA Type	GBCA Name (Dose [mL])	GBCA Dose (mmol)	Days From Injection to Death	Brain-GP (ug/g)	Brain-DN (ug/g)	Brain-WM (ug/g)	Skin (ug/kg)	Bone (ug/g)	Hair (ug/g)
Cases										
1	Macrocytic	Gadobutrol (10)	10	29	0.050	0.030	0.0084	0.017	0.41	0.4
2	Macrocytic	Gadoteridol (20)	10	25	0.036	0.029	0.029	No data	No data	2.4
3	Macrocytic	Gadoteridol (20)	10	51	0.12	0.024	0.0044	No data	No data	0.39
		Gadoteridol (20)	10	70						
		Gadoteridol (20)	10	75						
4	Macrocytic	Gadoteridol (15)	7.5	5	0.015	0.016	0.013	0.018	0.2	0.27
5	Macrocytic	Gadoteridol (17)	8.5	4	0.060	0.047	0.043	0.065	1.1	3.3
6	Macrocytic	Gadoteridol (15)	7.5	5	0.018	0.017	0.018	0.022	0.13	0.95
		Gadoteridol (14)	7	6						
		Gadoteridol (11)	5.5	106						
7	Macrocytic	Gadoteridol (16)	8	9	0.519	0.056	0.053	0.035	0.59	1.4
8	Macrocytic	Gadoteridol (18)	9	69	0.012	0.0050	0.0031	0.015	0.41	0.69
9	Macrocytic	Gadoteridol (40)	20	2	0.11	0.10	0.099	0.18	0.45	5.4
10	Macrocytic	Gadoteridol (12)	6	7	0.31	0.15	0.070	0.187	2.34	4.4
11	Macrocytic	Gadoteridol (20)	10	16	0.0075	0.0056	0.0043	0.017	0.11	0.4
12	Linear	Gadobenate (16)	8	19	0.128	0.0615	0.019	0.21	2.0	2.1
13	Linear	Gadobenate (17)	8.5	17	0.30	0.080	0.025	0.11	2.1	1.8
14	Linear	Gadobenate (14)	7	7	0.055	0.065	0.031	0.097	1.4	2.9
15	Linear	Gadobenate (13)	6.5	52	0.048	0.035	0.0062	0.042	0.50	0.68
16	Linear	Gadoxetate (10)	2.5	30	0.063	0.013	0.0057	0.017	0.54	0.27
Average			8.6	22	0.11	0.046	0.027	0.073	0.88	1.73
SD			3.3	20	0.14	0.039	0.027	0.070	0.77	1.58
Controls										
17	NA	NA	NA	NA	0.0012	0.0030	0.0011	0.0080	0.0040	0.067
18	NA	NA	NA	NA	0.0006 U	0.0008	0.0003	0.0004	0.0016	0.05 U

Notes:

NA - not applicable

U - below detection limit