

Comparison of Gadolinium Contrast Agent Retention in Patients Receiving Multiple Contrast-enhanced MRI Exams

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Keywords: Magnetic Resonance Imaging, Gadolinium-based Contrast Agents, Gadolinium Retention.

Abstract: Gadolinium-based contrast agents have long been utilized in magnetic resonance imaging (MRI) to enhance image quality. Aside from the few reported cases of Nephrogenic Systemic Fibrosis in patients with severely compromised renal function, these contrast agents have generally been viewed as safe. However, recent studies have shown evidence of the retention of potentially toxic gadolinium well beyond the previously recognized clearing times in patients with normal renal function. This retention has been shown via persistent hyper-intense signal in certain brain regions in unenhanced MRI exams. The exact form of retained gadolinium and its long-term potential health effects remain unknown at this time. Due to concerns over retained gadolinium, our hospital switched to a more stably bound contrast agent in the spring of 2018. This study examined brain MRI images from patients with multiple contrast-enhanced exams using either the older, more unstable, linear agent, and the newer, more stable, macrocyclic agent. Signal intensities were measured in the globus pallidus and dentate nucleus; regions of the brain that have previously been shown to accumulate heavy metals such as gadolinium. Statistically significant increases in signal intensity were seen in the dentate nucleus in the linear contrast agent group, but not in the macrocyclic agent group. No significant signal increases were seen with either agent in the globus pallidus region of the brain. No correlation was seen between signal increase and the volume of contrast agent administered for either region or contrast agent.

1 INTRODUCTION

Intravenous gadolinium-based contrast agents (GBCAs) have been utilized extensively in magnetic resonance imaging (MRI) to enhance image quality. These agents are injected intravenously and contain paramagnetic molecules that act to shorten the T1 relaxation time of protons in surrounding tissues, enhancing signal strength and brightness, which can be especially valuable in locating lesions and tumors in the brain.

GBCAs are produced in various chemical forms and consist of a gadolinium ion bonded to an organic ligand molecule to form a chelate. The ligand can take the form of either a linear or ring-shaped molecule, which is referred to as “macrocyclic.” Depending on the chemical structure, both molecular shapes can be further classified as either “ionic” or “non-ionic” based on the type of bond between the ligand and the Gd^{3+} ion. Linear contrast agents are not as chemically stable as macrocyclic agents, which more tightly bind the Gd^{3+} ion, and ionic bonds are stronger than non-ionic. (McDonald et al., 2018). A more unstable agent

is more likely to dissociate the gadolinium ion from the ligand.

GBCAs have long been considered safe, as the potentially toxic free Gd^{3+} ion is bound to the ligand and most of the agent is excreted within 24 hours of injection in patients with normal kidney function. Nephrogenic systemic fibrosis (NSF), a rare but potentially fatal condition has been reported in a small number of patients with severely compromised renal function who receive GBCAs. Though the exact cause and mechanism for NSF is unknown, longer exposure to gadolinium in patients who can't biologically clear it as quickly is thought to be a factor. Improved screening for patient renal function has largely eliminated instances of NSF in the last decade.

Though thought to be safe for those with normal kidney function, recent studies have shown long term retention of gadolinium contrast in various parts of the body; primarily in the brain (Kanda, Ishii, Kawaguchi, Kitajima, & Takenaka, 2014; Kanda et al., 2015) and bone (Gibby, Gibby, & Gibby, 2004; White, Gibby, & Tweedle, 2006), in patients with otherwise normal renal function. This retention was

first identified visually via persistent increased signal intensity on non-contrast T1-weighted images in certain areas of the brain, primarily in the dentate nucleus and globus pallidus regions (Kanda et al., 2015b; Radbruch et al., 2015). Essentially, residual gadolinium in some form is retained in the body and concentrated in these brain areas, leading to increased MR signal in non-contrast-enhanced images where such signal would not be expected. Gadolinium retention has been verified with inductively coupled plasma mass spectrometry in tissue samples excised from patients and cadavers (Gibby et al., 2004; White et al., 2006; Kanda et al., 2015a).

While the mechanism of retention and exact chemical form of retained gadolinium remains unknown, dose dependent retention in the brain has been demonstrated in patients receiving as few as two doses of linear GBCAs (Kanda et al., 2014, 2015b), with larger signal increases seen in patients with higher cumulative doses. Similar studies have generally shown no such measurable levels of brain retention with ionically bonded macrocyclic agents, which more tightly bind the Gd^{3+} ion to the ligand, pointing to the likelihood that dissociation of Gd^{3+} is involved in the process (Kanda et al., 2015b; Moser et al., 2018, Radbruch et al., 2015). However, there have been recent studies indicating gadolinium retention with macrocyclic agents, though at a lower level than as seen with linear agents (Bjørnerud et al., 2017, Splendiani et al., 2019). Any long-term clinical significance of deposited gadolinium remains unknown, though there are patients who have reported clinical symptoms they attribute to gadolinium toxicity (Ramalho et al., 2016).

Due to concerns over the unknown effects of gadolinium retention, our institution switched from using the linear, non-ionic contrast agent gadodiamide (trade name, Omniscan; GE Healthcare, Piscataway, New Jersey) to the macrocyclic, ionic agent gadoteric acid (trade name, Dotarem; Guerbet, Aulnay-sous-Bois, France) in the spring of 2018. The aim of this work is to investigate differences in signal intensity in non-contrast T1-weighted MR images of the brain from patients who received multiple administrations of GBCA before and after the switch from a linear to a macrocyclic contrast agent. Each patient group received between three and seven administrations of linear or macrocyclic GBCA exclusively, and correlation between increased signal intensity in areas of the brain and the amount of administered contrast agent was explored.

2 METHOD

This study was approved by the hospital Institutional Review Board (IRB), and due its retrospective nature, written informed consent was not required. Prior imaging for patients receiving clinically indicated contrast-enhanced MR scans of the head were used.

A total of eighteen patients were investigated. Two groups of nine patients who received serial administrations of either the linear (Omniscan) or macrocyclic (Dotarem) GBCA were selected based on analysis of records of routine head MRI exams in the department between January 2016 and August 2019. The institution switched from Omniscan to Dotarem in the spring of 2018, and both contrast agents are dispensed in the same concentration (0.5 mmol/mL) using the same weight-based dosage of 0.2 mL/kg.

2.1 Patient Selection

Due to the recent switch to the macrocyclic agent, fewer overall patients with multiple administrations of Dotarem were available for the study, limiting the group size. The nine selected patients had received at least three administrations exclusively with the macrocyclic contrast agent within our radiology department. The mean number of administrations for the group was 3.67 (SD 1.25), with six patients receiving three administrations, two receiving four, and one receiving seven contrast administrations.

Once the patients in the macrocyclic agent group were identified, patients were selected for the linear agent group, attempting to match the characteristics of number of exams, accumulated dose of contrast agent, and mean days between administrations as closely as possible. Nine patients overall were selected, with an average number of exams matching that of the macrocyclic group. The accumulated dose and average number of weeks between contrast administrations for both groups of patients are shown in Table 1. Patient records for both groups were examined back through 2013 to ensure there were no previous contrast-enhanced exams prior to the period used in the study.

Patient medical records for both groups were also screened for signs of abnormal renal function during the period of the study. Aside from a small transient decrease in renal function test results in three patients, all had documented estimated glomerular filtration rates (eGFR) > 60 ml/min per 1.73 m² recent to the date of the last MR exam, indicating no evidence of compromised renal function.

Table 1: Comparison of patient groups.

	Linear GBCA (Omniscan) Group	Macrocytic GBCA (Dotarem) Group
Number of patients	9	9
Female	3	3
Male	6	6
Age (y)	51.0 ± 12.2	54.0 ± 14.64
Mean # of exams	3.67 ± 1.25	3.67 ± 1.25
Mean accumulated dose (ml)	64.3 ± 19.4	60.4 ± 19.4
Mean weeks between exams	4.9 ± 2.1	7.0 ± 3.7

2.2 Imaging

Non-contrast-enhanced T1-weighted axial images taken from each patient's first and most recent clinically indicated whole brain MRI exam were analysed for this study. Images were acquired exclusively on a single Philips Achieva Nova 1.5 tesla scanner in the hospital's radiology department. Image acquisition parameters are summarized in Table 2.

Table 2: MRI scanner image acquisition parameters.

Manufacturer	Philips
Model	Achieva Nova
B0 Strength (tesla)	1.5
T1 Axial Scan Protocol	
Repetition Time (TR) (ms)	450-650
Echo Time (TE) (ms)	15
Slice Thickness (mm)	4
# Signals Acquired	1
Matrix Size	256 x 163
Slice Thickness (mm)	5
T2 Axial Scan Protocol	
Repetition Time (TR) (ms)	6479
Echo Time (TE) (ms)	100
Slice Thickness (mm)	4
# Signals Acquired	2
Matrix Size	384 x 242
Slice Thickness (mm)	5

2.3 Data Collection

Quantitative measurements were taken by two board certified radiologists (V.J. and J.G., with eleven and one years' experience, respectively), who were blinded to the contrast agent in use while making

measurements. Using a method similar to Kanda et al. (2014), each patient's first and most recent unenhanced T1-weighted brain MRI examination was used to measure signal intensity in the globus pallidus (GP) and the dentate nucleus (DN); structures of the brain previously shown to preferentially deposit gadolinium (Kanda et al., 2015b). Circular or oval shaped regions of interest (ROIs) on the order of 20-60 mm² were drawn to cover anatomy in each structure within the Centricity PACS image viewer (GE Healthcare, Barrington, Illinois). As a point of comparison, signal intensity was also measured in surrounding background regions of the brain, including the thalamus and the pons, which have not previously shown deposition of retained gadolinium. As all structures but the pons are bilateral, measurements were taken on both the left and right sides for each structure, with a single central measurement taken in the pons. In instances where anatomy could not be accurately identified in the T1 scan, T2 weighted images from the same examination were used to aid in proper anatomical ROI placement. Clinical scans with ROIs in place are shown in Figures 1 and 2.

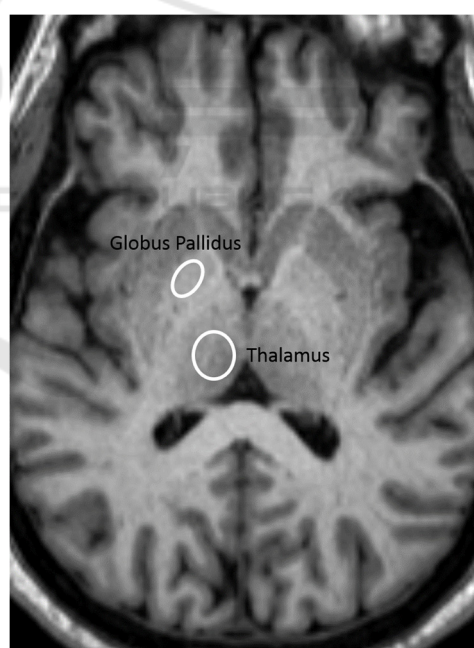


Figure 1: Regions of interest in place in the globus pallidus and thalamus on an unenhanced, axial T1 weighted MR image.

Since there is no standardized intensity scale for pixel signal in MR images, direct comparison between measurements in different images, even

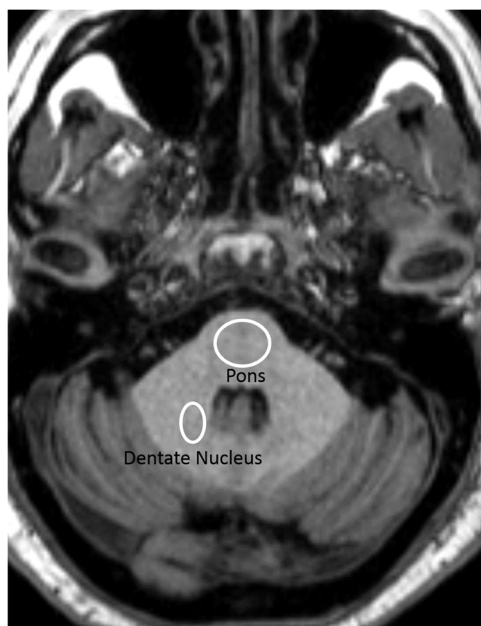


Figure 2: Regions of interest in place in the dentate nucleus and pons in unenhanced axial T1 MRI images.

those obtained on the same scanner with the same imaging sequence, is not meaningful. To compensate for this, the measured signal values from the target and background structures in a given slice image were used to calculate the signal intensity (SI) ratio for the two regions. Absent any outside factors, the signal intensity in the target and background structures should be the same, yielding a ratio of ~ 1 . Any retained gadolinium in the target structure would cause signal in that area to be greater than that of the background structure, increasing the SI in relation to the relative amount of Gd present. Since the SI ratio is relative within a given image, it can be readily compared between exams in order to infer the presence of retained gadolinium in the brain.

The globus pallidus signal intensity ratio for each image was calculated by dividing the average of the signals measured in both sides of the GP by the mean signal, similarly calculated, measured in the thalamus, using the following formula:

$$SI_{GP} = \frac{S_{GP}}{S_{Th}} \quad (1)$$

Similarly, the dentate nucleus signal intensity ratio was calculated by dividing the average of the measured signals on both sides of the DN by the signal measured in the pons, using the following formula:

$$SI_{DN} = \frac{S_{DN}}{S_P} \quad (2)$$

In cases where only one measurement was available due to the presence of tumor, edema, or infarct in the measurement area, only a single side measurement was used. One patient in the Dotarem group had a tumor and associated edema in the area of the dentate nucleus that prevented the SI_{DN} from being calculated.

The GP and DN SI ratios were calculated by both radiologists on each patient's first and most recent MR exam, and the difference between the two exams was calculated to evaluate any changes in signal intensity in the GP and DN over time using the following equation:

$$SI_{diff} = SI_{last\ exam} - SI_{first\ exam} \quad (3)$$

An SI_{diff} of zero indicates no changes in the relative signal intensity of the target structure between the patient's first and last exam, while a SI_{diff} greater than zero indicates signal enhancement in the structure over the course of the patient's care.

2.4 Data Analysis

Data analysis was conducted using Microsoft Excel. Correlation between the two radiologist's ROI measurements was measured using the Lin concordance correlation coefficient.

One-sample t tests were used to determine whether the differences in SI ratios, SI_{diff} , between the first and last MR exam for each patient group were statistically different from zero. $P < 0.05$ was considered indicative of a statistically significant difference.

An independent-sample t test was used to determine whether the differences between the two patient contrast groups were statistically significant.

3 RESULTS

In comparing the radiologist's ROI measurements, the Lin concordance coefficient for both readers was 0.992 (95% confidence interval: 0.989, 0.994) indicating excellent inter-observer correlation.

3.1 Recent Exam SI Ratios

Scatterplots of the SI_{GP} and SI_{DN} measured in the most recent MR exam plotted against the total volume of administered contrast (ml) for each patient are shown in Figures 3 and 4.

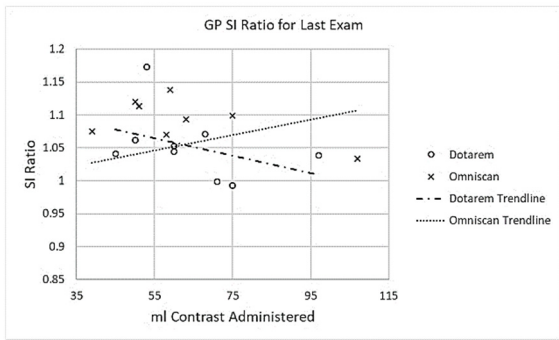


Figure 3: SI Ratio in the globus pallidus vs. administered volume of contrast for both linear (Omniscan) and macrocyclic (Dotarem) agents.

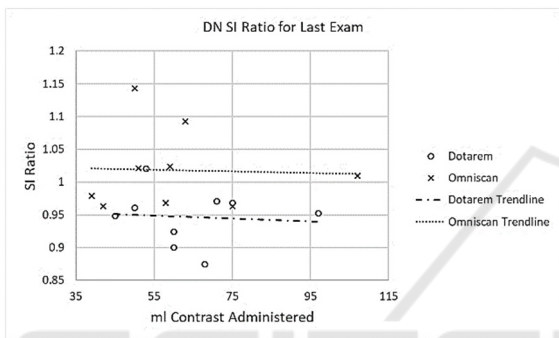


Figure 4: SI Ratio in the dentate nucleus vs. administered volume of contrast agent for both linear (Omniscan) and macrocyclic (Dotarem) agents.

Although previous publications (Kanda et al., 2014) have shown a strong positive correlation between administered linear contrast agent volume and SI ratio in both the GP and DN, our study showed no statistically significant correlation between administered contrast volume and SI ratio for any brain region for either contrast agent. This is likely a result of the small sample size of our study, which was limited in design due to the recent switch to a macrocyclic GBCA. This limited the number of available patients with multiple contrast-enhanced exams, as well as the total volume of contrast administered to those patients. As the linear agent group was chosen to match the macrocyclic group, those same limitations applied. It should be noted that based on previous publications, no correlation between SI ratio and contrast volume administered was expected for the Dotarem group due to that contrast agent's tighter binding of the gadolinium ion.

3.2 Signal Intensity Ratio Changes

Plots of the measured SI ratio from the first exam versus the last exam for both the GP and DN are

shown in Figures 5 and 6. The solid lines represents the hypothetical case where the signal ratio from the first and last exams were equal, indicating no change in the SI ratio over the course of care. Data points above the line indicate an increase in the SI ratio in the last exam compared to the first, while data points below the line indicate a lower SI ratio in the most recent exam.

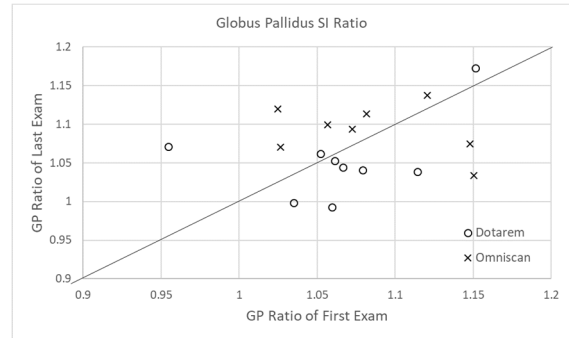


Figure 5: Scatterplot of GP ratio at first study versus last study for both GBCAs. Solid line represents hypothetical instance where the first and last scan have identical SI ratios, indicating no increased signal due to gadolinium retention.

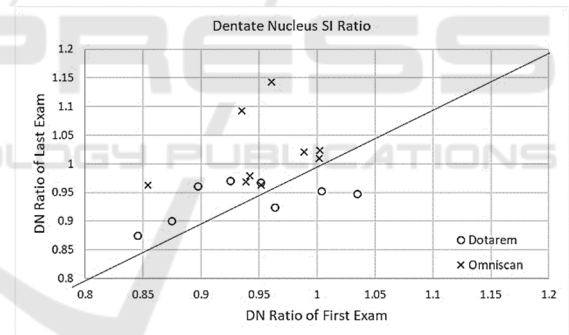


Figure 6: Scatterplot of DN ratio at first study versus last study for both GBCAs. Plots of the Omniscan group are above the line, indicating an increase in signal in later exams.

In both graphs, most data points are located near the line, indicating only small changes in the SI ratio. No statistically significant differences were found in the GP for either contrast agent. However, in the dentate nucleus graph, most Omniscan data points are located above the line, indicating an increase in the SI ratio in the last exam compared to the first. These results were found to be statistically significant ($t(8) = 2.94, p = .019$). The magnitude of the SI ratio in the DN for several of these points aligns with values published by Kanda et al., 2015b.

3.3 Signal Intensity Ratio Differences

The distributions of SI ratio differences, SI_{diff} , for both the globus pallidus and dentate nucleus regions in both patient groups are shown in Figures 7 and 8 as an alternative way of displaying the information in Figures 5 and 6. Grey dots indicate individual data points from each radiologist and the black bar indicates the mean of all measurements.

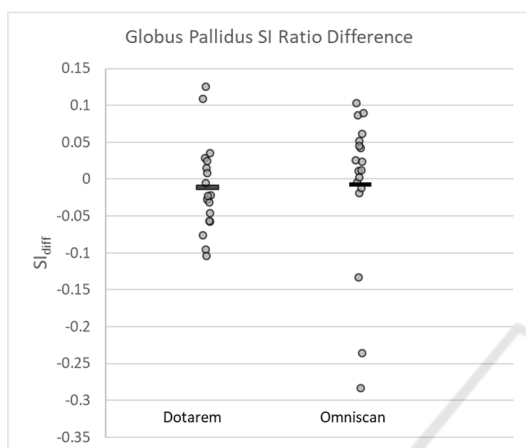


Figure 7: Distribution of SI_{diff} for each GBCA in the GP region.

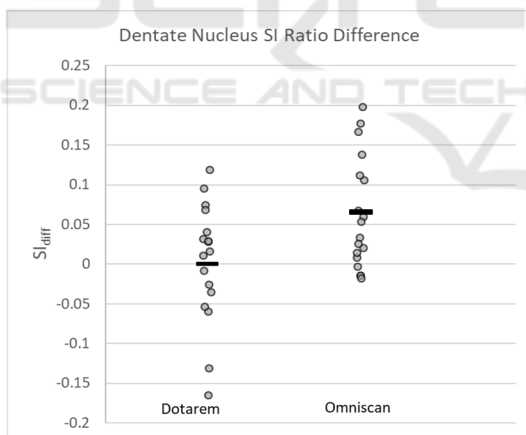


Figure 8: Distribution of SI_{diff} for each GBCA in the DN region.

As in the previous graphs, no statistically significant changes were seen in the GP region for either patient group. In the DN, for the linear GBCA Omniscan, the mean SI_{diff} of 0.065 ± 0.022 between the most recent MR exam and the first exam was found to be significantly larger than zero. ($t(8) = 2.94$, $p = .019$). This indicates an increase in the signal level in the DN after serial administration of the linear GBCA, likely due to the retention of gadolinium in

some form. In the macrocyclic, Dotarem group, the mean SI_{diff} of 0.0002 ± 0.018 in the DN between the most recent MR exam and the first exam was not found to be significantly larger than zero ($t(7) = 0.014$, $p = .989$). When comparing the SI_{diff} in the DN between the two patient groups, they were found to be statistically different from each other ($t(8) = -2.24$, $p = .041$).

In the globus pallidus, neither the Dotarem or the Omniscan group's SI_{diff} was found to be statistically different from zero indicating no significant change in signal intensity between the first and last exam, and likely no measurable deposition of gadolinium in this brain region. In comparing the SI_{diff} in the GP between the two patient groups, they were not found to be statistically different ($t(9) = -0.114$, $p = .911$).

4 CONCLUSIONS

This study set out to compare differences in signal enhancement in structures of the brains of patients given serial administrations of two commercially available gadolinium-based contrast agents in use at our hospital. In reviewing previously obtained clinical MRI images, a statistically significant increase in signal was measured in the dentate nucleus region as compared to the pons region for patients given the linear, non-ionic agent Omniscan. No such increase was seen in patients given the ionic, macrocyclic agent Dotarem, nor was any measurable signal increase seen in the globus pallidus region of the brain for either GBCA. The magnitude of signal increase seen in the DN was in line with that in other published works (Kanda et al. 2015b), though it is noted that neither radiologist noticed any obvious visual signal increase in the images.

Our study did not show any correlation between the magnitude of signal enhancement and the volume of contrast administered, likely due to the previously mentioned small sample size of the study and relatively low volume of contrast administered, compared to other studies. Another possible cause is that despite medical records review, we were unable to account for potential contrast-enhanced exams performed outside of our hospital system.

Many questions surround the long-term retention of gadolinium in patients with healthy renal function, including the mechanism of deposition, exact chemical form of retained gadolinium, and any potential long term negative clinical impact to patients. This study confirms the likelihood of retained gadolinium in a patient population who were

administered linear contrast agents, but shows promise of reduced retention from the newer, more stable macrocyclic contrast agent. In the future, we hope to repeat this study, focusing on the macrocyclic agent, with a larger patient population and with patients having a higher number of contrast injections in order to further study any dose dependent relationship to gadolinium retention.

ACKNOWLEDGEMENTS

The authors would like to thank Holly Frank and the rest of the MRI staff for help in putting together details for this study.

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