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Gadolinium Deposition within the Pediatric Brain: No Increased Intrinsic T1-Weighted Signal Intensity within the Dentate Nucleus following the Administration of a Minimum of 4 Doses of the Macrocyclic Agent Gadoteridol

J.R. Young, W.B. Pope, and M. Bobinski

ABSTRACT

BACKGROUND AND PURPOSE: Our aim was to evaluate whether serial administration of the macrocyclic gadolinium-based contrast agent gadoteridol in children is associated with T1-weighted hyperintensity within the dentate nucleus, an imaging surrogate for gadolinium deposition.

MATERIALS AND METHODS: We identified a retrospective cohort of 10 patients younger than 18 years of age who underwent between 4 and 8 gadoteridol-enhanced MR imaging examinations of the brain from 2016 to 2017. For comparison, we identified a retrospective cohort of 9 pediatric patients who each underwent 6 gadodiamide-enhanced MR imaging examinations. For each examination, both dentate nuclei were contoured on unenhanced images and the mean dentate-to-pons signal intensity ratio was calculated. Dentate-to-pons signal intensity ratios from the first and last scans were compared using paired *t* tests.

RESULTS: In the gadoteridol group, there was no significant change in the mean dentate-to-pons signal intensity ratio from the first to the last scan (0.99 versus 0.99, $P = .59$). In the gadodiamide group, there was a significant increase in the mean dentate-to-pons signal intensity ratio from the first to the last scan (0.99 versus 1.10, $P = .001$).

CONCLUSIONS: Repeat administration of the macrocyclic gadolinium-based contrast agent gadoteridol in children was not associated with T1-weighted dentate hyperintensity, while the repeat administration of the linear gadolinium-based contrast agent gadodiamide was associated with T1-weighted dentate hyperintensity, presumably due to gadolinium deposition.

ABBREVIATIONS: DN-P SI = dentate-to-pons signal intensity; GBCA = gadolinium-based contrast agent

A number of recent studies have shown retention or deposition of gadolinium within multiple organs in the body, including the brain, following the serial administration of gadolinium-based contrast agents (GBCAs) for clinical MR imaging.¹⁻⁹ Intracranial gadolinium deposition has been associated with intrinsic T1-weighted hyperintensity, which is most detectable within the dentate nucleus and globus pallidus. To date, most studies investigating intracranial gadolinium deposition have focused on adults, with few studies evaluating gadolinium deposition in the pediatric brain.¹⁻¹⁶

The clinical significance of intracranial gadolinium deposition has been controversial and remains uncertain. However, the pe-

diatric brain may be more vulnerable to the potentially deleterious effects of gadolinium deposition because the pediatric brain is generally more susceptible to a variety of toxins.^{17,18} Furthermore, the cumulative lifetime dose and duration of exposure to GBCAs may be greater in children than in adults. Thus, it remains important to identify the safest GBCAs for use in children. Recent studies evaluating pediatric intracranial gadolinium deposition have generally focused on the linear GBCA gadopentetate dimeglumine.¹⁰⁻¹³ Few studies have evaluated the effect of the repeat administration of macrocyclic GBCAs in children. Radbruch et al¹⁴ found that the repeat administration of the macrocyclic GBCA gadoterate meglumine in pediatric patients was not associated with T1-weighted dentate hyperintensity. Additionally, Tibussek et al¹⁵ found that the serial administration of 2 macrocyclic agents gadoterate meglumine and gadoteridol was not associated with an increase in T1-weighted signal intensity in the dentate nucleus.

The lack of association between macrocyclic GBCAs and T1-weighted dentate hyperintensity was recently questioned by Rossi Espagnet et al,¹⁶ who found that the repeat administration of gadoterate meglumine was associated with increased T1-weighted

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Patient characteristics^a

Parameter	All Patients (n = 19 Patients)	Gadoteridol Group (n = 10 Patients)	Gadodiamide Group (n = 9 Patients)
Sex (No.)			
Male	11 (58%)	7 (70%)	5 (56%)
Female	8 (42%)	3 (30%)	4 (44%)
Age at first scan (yr) ^a	7.5 (0.5–16.5)	5.6 (0.5–13.4)	9.6 (1.7–16.5)
No. of scans ^a	6.1 (4–8)	6.1 (4–8)	6 (6)
Interval between first and last scans (yr) ^a	0.92 (0.05–1.58)	1.01 (0.31–1.58)	0.81 (0.06–1.35)
History of chemotherapy (No.)	9 (47%)	4 (40%)	5 (56%)
History of radiation (No.)	6 (32%)	1 (10%)	5 (56%)
Diagnosis (No.)			
Tumor	16 (84%)	8 (80%)	8 (89%)
Other ^b	3 (16%)	2 (20%)	1 (11%)

^a Data are means. Ranges are in parentheses.

^b Other diagnoses include a subgaleal abscess, an intracranial abscess, and a cavernous malformation.

hyperintensity within the dentate nucleus by quantitative ROI analysis. However, in the study by Rossi Espagnet et al,¹⁶ there was no visible increase in T1-weighted dentate signal intensity.¹⁹ To date, no published studies have examined the association between the repeat exclusive administration of the macrocyclic GBCA gadoteridol and T1-weighted signal intensity within the pediatric brain. The goal of this study was to determine whether the repeat exclusive administration of the macrocyclic GBCA gadoteridol in pediatric patients is associated with the development of T1-weighted hyperintensity within the dentate nucleus, an imaging surrogate for gadolinium deposition.

MATERIALS AND METHODS

Patients

With UC Davis School of Medicine institutional review board approval for this Health Insurance Portability and Accountability Act-compliant retrospective study and a waiver of informed consent, we queried the PACS of our institution and the electronic medical record to identify all pediatric patients younger than 18 years of age without posterior fossa disease who underwent between 4 and 8 gadoteridol-enhanced MR imaging examinations of the brain performed at our institution from 2016 to 2017 and who had not had prior exposure to any other GBCA. Patients with <4 MR imaging examinations were excluded because prior published studies have shown that at least 4 doses of gadolinium are required before progressively increasing T1-weighted hyperintensity within the brain is identified.⁵ This query resulted in a historical cohort of 10 patients. For comparison, we identified a separate retrospective cohort of 9 patients younger than 18 years of age without posterior fossa disease who each underwent 6 gadodiamide-enhanced MR imaging examinations of the brain performed at our institution from 2008 to 2015 and who had not had prior exposure to any other GBCA. The standard pediatric dose of 0.1 mmol/kg was administered for both gadoteridol and gadodiamide.

Patient characteristics, including age, sex, diagnosis, history of chemotherapy, history of radiation, number of MR imaging examinations, and the time interval between the first and last scans are presented in the Table. Patient diagnoses were classified as tumoral (ganglioglioma, astrocytoma, choroid plexus carcinoma, lymphoma, dysembryoplastic neuroepithelial tumor, craniopharyngioma, germ cell tumor [including germinoma], neuroblastoma,

pineoblastoma, Ewing sarcoma, and Langerhans cell histiocytosis) and nontumoral (subgaleal abscess, intracranial abscess, and cavernous malformation). None of the patients had a history of renal disease.

MR Imaging Examination

All MR imaging examinations were performed on 1.5T (Signa HDxt or Optima MR450w; GE Healthcare, Milwaukee, Wisconsin) or 3T scanners (Signa HDxt; GE Healthcare). Three MR imaging protocols were used to obtain precontrast T1-weighted images of the brain: a routine axial T1-weighted spin-echo sequence (slice thickness = 5 mm, TR =

667 ms, TE = 14 ms, flip angle = 90°), an axial echo-spoiled gradient-echo volumetric sequence (slice thickness = 1 mm, TR = 10 ms, TE = 4 ms, flip angle = 20°), and an axial T1-weighted fluid-attenuated inversion recovery sequence (slice thickness = 5 mm, TR = 3180 ms, TE = 29 ms, TI = 1238 ms, flip angle = 90°). For each patient, the same MR imaging protocol was used for the first and last MR imaging examinations. Fifty-eight percent of patients (11/19) had a routine axial T1-weighted spin-echo sequence on the first and last MR imaging examinations; 21% of patients (4/19) had an axial echo-spoiled gradient-echo sequence on the first and last MR imaging examinations, while 21% of the patients (4/19) had an axial T1-weighted FLAIR sequence on the first and last MR imaging examinations. Furthermore, for 84% of the patients (16/19), imaging was performed on scanners of the same magnetic field strength for the first and last MR imaging examinations. Of these 16 patients, 8 (50%) had the first and last MR imaging examinations performed on a 1.5T scanner and 8 (50%) had the first and last MR imaging examinations performed on a 3T scanner.

Image Analysis

For each axial precontrast T1-weighted examination, the right and left dentate nuclei were manually contoured on a single axial slice using polygonal ROIs on the PACS of our institution. The dentate nucleus was selected because it is the most frequently studied site of progressively increasing T1-weighted hyperintensity in the brain following repeat exposure to GBCAs. Additionally, McDonald et al^{5,6} found that the dentate nucleus contained that highest median concentration of deposited gadolinium in their postmortem cohorts. For each patient, the dentate nuclei were identified on later MR imaging examinations in which the dentate nuclei appeared relatively hyperintense in comparison with surrounding cerebellar tissue. This information was then used to guide the contouring of the dentate nuclei on earlier MR imaging examinations in which the margins of the dentate nucleus were not well-delineated. In addition, T2-weighted images were used to help identify the dentate nuclei in some cases. Subsequently, a circular ROI with a diameter of 8 mm was manually placed in the central pons. The ratio of the mean signal intensity of

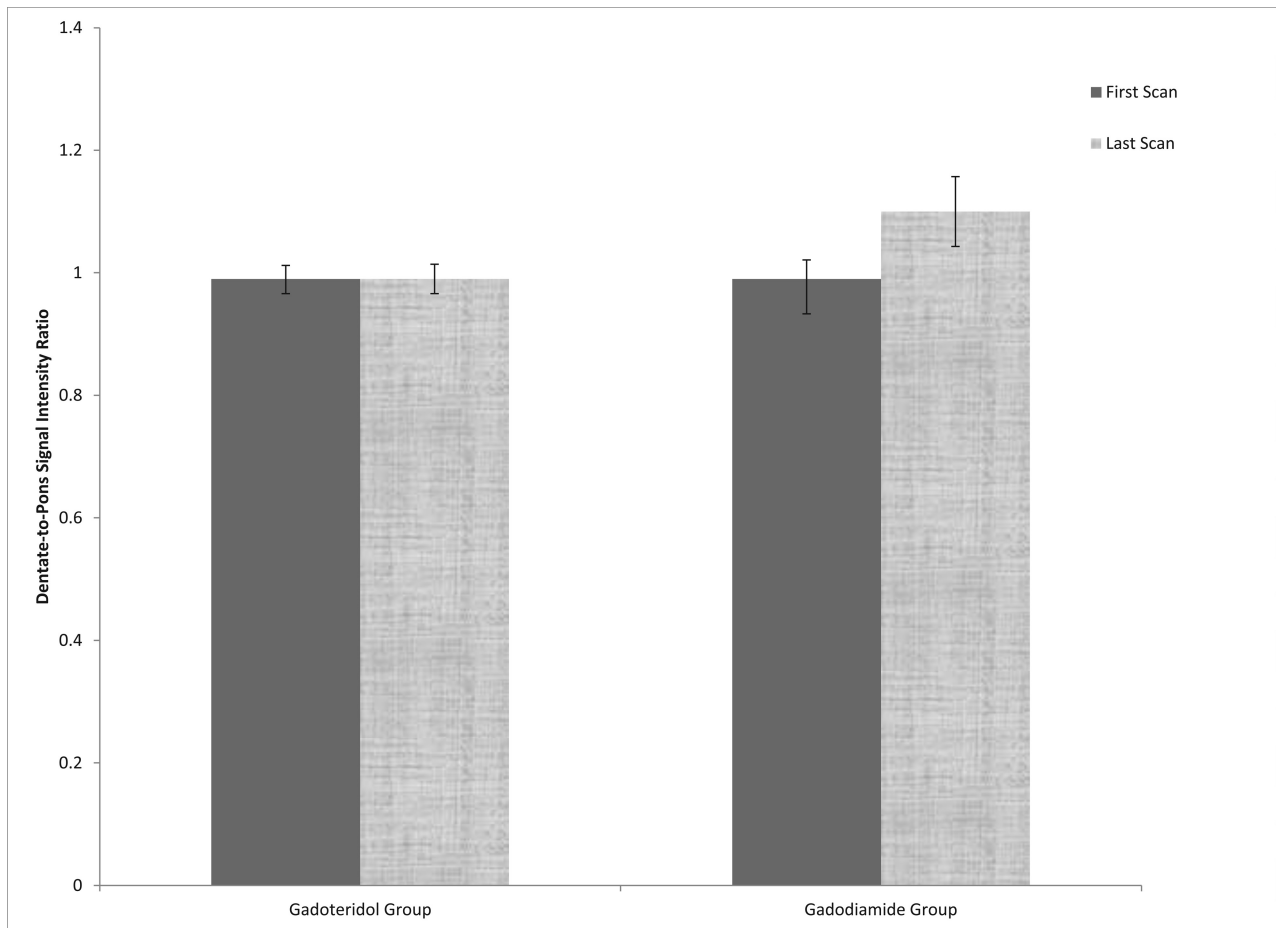


FIG 1. Dentate-to-pons signal intensity ratios on the first and last scans for patients in the gadoteridol and gadodiamide groups. Data are means. Errors bars represent 95% confidence intervals.

the dentate nuclei to the mean signal intensity of the pons was calculated for each MR imaging examination for each patient.

Statistical Analysis

Dentate-to-pons signal intensity (DN-P SI) ratios for the first and last MR imaging examinations were compared using paired *t* tests. The number of doses of gadolinium received and patient age in the gadoteridol and gadodiamide groups were compared using *t* tests. Patient diagnosis (tumoral versus nontumoral), history of chemotherapy, and history of radiation in the gadoteridol and gadodiamide groups were compared using Fisher exact tests. *P* values < .05 were considered statistically significant. Analyses were performed using SPSS 23 for Windows (IBM, Armonk, New York).

RESULTS

Patients

Our study cohort comprised 11 male (58%) and 8 female (42%) pediatric patients (Table). On average, each patient underwent 6.1 MR imaging examinations (range, 4–8 examinations). There was no significant difference in the number of MR imaging examinations between the gadoteridol group and the gadodiamide group (*P* = .85). In the gadoteridol group, each patient underwent an average of 6.1 MR imaging examinations (range, 4–8 examinations). Within the gadodiamide group, each patient underwent 6 MR imaging examinations. Eighty-four percent of the patients (16/19) had brain

tumors. Forty-seven percent of the patients (9/19) had a history of chemotherapy, and 32% (6/19) had a history of radiation therapy. There was no significant difference in the proportion of patients with tumoral diagnoses, history of chemotherapy, and history of radiation between the gadoteridol and gadodiamide groups (*P* = 1.00, .66, .06, respectively). The time elapsed between the first and last MR imaging examinations ranged from 1 month to 1.6 years, which is similar to prior published studies in children with a range of 1.2–12.9 years.¹² There was no significant difference in age between the gadoteridol and gadodiamide groups (*P* = .13).

Dentate Signal Intensity following Repeat Gadoteridol and Gadodiamide Administration

In the gadoteridol cohort, there was no significant change in the mean DN-P SI ratio from the first to the last scan (0.99 versus 0.99, *P* = .59), as shown in Figs 1 and 2. However, in the gadodiamide cohort, there was a significant increase in the mean DN-P SI ratio from the first to the last scan (0.99 versus 1.10, *P* = .001, Figs 1 and 2).

All patients had the same MR imaging protocol on the first and last scans. However, 3 patients in the gadoteridol cohort had differing magnetic field strengths on the first and last scans. All patients in the gadodiamide cohort had the same magnetic field strength on the first and last scans. Thus, we considered the possibility that changes in magnetic field strength could impact T1-

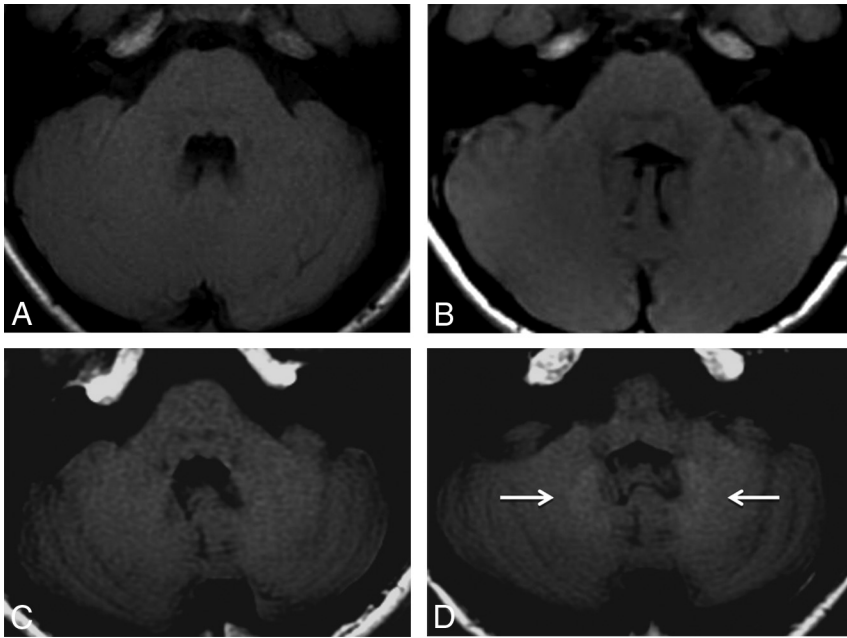


FIG 2. Dentate signal intensity in a patient in the gadoteridol group and in a patient in the gadodiamide group. *A* and *B*, An 11-year-old boy with a subgaleal abscess who underwent 6 gadoteridol-enhanced MR imaging examinations. *A*, Axial T1-weighted image on the first MR imaging examination. *B*, Axial T1-weighted image on the sixth MR imaging examination. *C* and *D*, A 15-year-old boy with a germinoma who underwent 6 gadodiamide-enhanced MR imaging examinations. *C*, Axial T1-weighted image on the first MR imaging examination. *D*, Axial T1-weighted image on the sixth MR imaging examination. There is intrinsic T1-weighted hyperintensity within the dentate nuclei (arrows).

weighted hyperintensity. After we excluded these 3 patients from the analyses, the results were similar. In the gadoteridol cohort, there was no significant change in the mean DN-P SI ratio from the first to the last scan (0.99 versus 0.99, $P = .24$).

DISCUSSION

In this study, we sought to evaluate whether the serial administration of the macrocyclic GBCA gadoteridol in pediatric patients (who received between 4 and 8 doses) was associated with the development of T1-weighted hyperintensity in the dentate nucleus, an imaging surrogate for gadolinium retention. We found that in children who received serial administrations of gadoteridol, there was no significant change in the mean DN-P SI ratio from the first to the last MR imaging examination. However, in children who received serial administrations of the linear GBCA gadodiamide, there was a significant increase in the mean DN-P SI ratio from the first to the last scan, consistent with prior published studies in adults.^{2,3,5,7,9} These findings are also consistent with recently published studies in pediatric patients that found an association between serial administration of the linear GBCA gadopentetate dimeglumine and T1-weighted hyperintensity in the dentate nucleus.¹⁰⁻¹² Our findings suggest that the macrocyclic GBCA gadoteridol may be less likely to deposit within the dentate nucleus in comparison with the linear GBCA gadodiamide. However, an alternative possibility is that gadoteridol may be retained within the dentate nucleus but may result in less T1 shortening than gadodiamide.

Our findings are consistent with those in a prior published study in adults by Kanda et al,⁴ which demonstrated that the mac-

rocyclic GBCA gadoteridol is less likely to deposit within the brain in comparison with the linear GBCA gadopentetate dimeglumine. Our results are also consistent with the results from 2 studies in adults by Radbruch et al,^{8,20} who found that the macrocyclic GBCAs gadoterate meglumine and gadobutrol may be less likely to deposit in the brain in comparison with the linear GBCA gadopentetate dimeglumine.

Furthermore, our findings are consistent with those in a recently published study by Tibussek et al,¹⁵ who evaluated a cohort of 24 pediatric patients who received serial administrations of the macrocyclic GBCAs gadoterate meglumine and gadoteridol and did not find an association with T1-weighted hyperintensity in the dentate nuclei. An important difference between our study and the study by Tibussek et al is that our macrocyclic subcohort received exclusively gadoteridol. The patients in the study of Tibussek et al received both gadoteridol and gadoterate meglumine. Additionally, we compared our gadoteridol subcohort with a subcohort of patients who exclusively received the linear GBCA

gadodiamide. The study by Tibussek et al did not include a linear GBCA subcohort for comparison. Our findings are also consistent with a recent study by Radbruch et al,¹⁴ who found that the serial administration of the macrocyclic GBCA gadoterate meglumine in pediatric patients was not associated with T1-weighted hyperintensity in the dentate nuclei. The conclusions of the Radbruch et al study¹⁴ have recently been called into question because Rossi Espagnet et al¹⁶ found that the repeat administration of gadoterate meglumine was associated with increasing T1-weighted hyperintensity in the dentate nucleus by quantitative ROI analysis. However, in the study by Rossi Espagnet et al, there was no visible increase in the T1-weighted signal intensity in the dentate nucleus.^{16,19} In our study, we found a visible increase in dentate T1-weighted signal intensity in the gadodiamide subcohort, but we did not find a visible increase in dentate T1-weighted signal intensity in the gadoteridol subcohort (Fig 2).

Our study has several potential limitations. First, because of the retrospective nature of this study, all patients were not imaged on the same scanner with the same precontrast T1-weighted protocol. However, in accordance with the recommendations of Ramalho et al,²¹ for each patient, the same MR imaging protocol was used for the first and last MR imaging examinations and thus should allow satisfactory comparison. For 84% of the patients in our cohort (16/19), imaging was performed on scanners of the same magnetic field strength for the first and last MR imaging examinations. The 3 patients who had the first and last MR imaging examinations on scanners of differing magnetic field strengths were from the gadoteridol subcohort. We analyzed the data after

excluding these 3 patients, and the results were similar. In the gadoteridol subcohort, there was no significant change in the mean DN-P SI ratio when comparing the first scan with the last scan. Furthermore, we normalized the dentate signal intensity to the signal intensity of the pons, which should limit the effects of scanner variability (specifically variability in magnetic field strength) and protocol variability.

Second, we used T1-weighted hyperintensity in the dentate nucleus as an imaging surrogate for gadolinium deposition. While the direct measurement of gadolinium in cerebellar tissue is preferable, this is much more challenging to acquire. Additionally, the generation of T1-weighted hyperintensity within the dentate nucleus may potentially depend on factors that may vary between different gadolinium-based contrast agents. As a result, T1-weighted hyperintensity may be an imperfect measure of gadolinium concentration in the brain. A quantitative method based on susceptibility mapping has recently been studied and used by other groups.²²

Third, our study did not include an age-matched control cohort of patients who did not receive any GBCA. However, each patient in our study cohort was followed serially across time, thus serving as his or her own internal control. Fourth, patients in our gadoteridol subcohort received, on average, 6 doses of gadoteridol. We cannot exclude the possibility that T1-weighted hyperintensity within the dentate nucleus may appear after >6 doses of gadoteridol in pediatric patients. Despite these limitations, our results suggest that in children, the macrocyclic GBCA gadoteridol may be less likely than linear GBCAs such as gadodiamide to deposit in the dentate nuclei.

CONCLUSIONS

To our knowledge, our study is the first to demonstrate that the repeat exclusive administration of the macrocyclic GBCA gadoteridol in children is not associated with T1-weighted hyperintensity in the dentate nucleus. Thus, the macrocyclic GBCA gadoteridol may be less likely than linear GBCAs, such as gadodiamide, to deposit within the pediatric brain, consistent with prior published studies in adults.^{4,8,20}

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