

Signal changes in dentate nuclei with 10 or more gadolinium-based contrast administrations: comparison of linear versus macrocyclic contrast agents

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Target audience: All radiologists, clinicians, pharmaceutical companies, patients and regulators interested in MR contrast agent safety

Purpose: To investigate any correlation between types of gadolinium-based contrast agents administered and high signal intensity in the dentate nucleus on unenhanced T1-weighted MR images in patients with 10 or more gadolinium-based contrast-enhanced examinations

Methods: 72 patients with 10 or more contrast-enhanced MR exams including an initial and final MRI of brain at our institution were retrospectively reviewed with institutional review board approval. Patients received only gadopentetate dimeglumine (Magnevist)-enhanced exams, only gadobutrol (Gadavist)-enhanced exams, or combination of Magnevist followed by Gadavist exams as our institution switched from Magnevist to Gadavist usage in 1/2013. Two attending radiologists independently measured unenhanced T1 signal of dentate nuclei and pons on the initial MR exams, after all Magnevist injections and after all Gadavist administrations. The dentate nucleus to pons signal intensity ratio (DNP) was calculated for each exam. The difference in DNP ratios from the initial to last MR exams for all patients was then calculated and analyzed using paired t-tests. Reviewers also visually graded signal changes in dentate nuclei relative to pons as positive change, negative change or borderline.

Results: 11 patients received only Magnevist, 52 patients received Magnevist followed by Gadavist and 9 patients received only Gadavist administrations. DNP ratio for patients with only Magnevist exposure increased from 0.99 to 1.06 after an average of 11 Magnevist administrations ($p = 0.0005$). DNP ratio for patients with combination of Magnevist followed by Gadavist increased from 1.05 after the last Magnevist exposure to 1.10 after an average of 7 Gadavist administrations (p -value 0.03). DNP ratio for patients after only Gadavist (averaging 11 Gadavist injections per patient) did not change at 1.01 (p -value 0.33). Visual assessment of DNP changes demonstrated 54% of Magnevist-only patients had a positive change but none of the Gadavist-only patients demonstrated a positive change in DNP.

Reviewer 1 Reviewer 2	Magnevist only	Gadavist only	Gadavist after Magnevist
Number of patients	61	9	52
Average # of contrast administrations	11	12	18
Visually +change DNP	33 / 33	0 / 1	33 / 33
Visually -change DNP	22 / 25	7 / 8	18 / 17
Visually borderline	6 / 3	2 / 0	1 / 2
DNP ratio Initial/Final	0.99 / 1.06 1.00 / 1.08	1.01 / 1.01 0.71 / 1.00	1.05 / 1.10 1.08 / 1.11
P-value	0.0005 / <0.0001	0.33 / 0.09	0.03 / 0.05

Table A: Summary of results both by calculated signal ratio changes and visual assessment method

Discussion: High T1 signal in the dentate nucleus following multiple gadolinium-based contrast administrations has been reported by Kanda et al¹ (19 patients with ≥ 6 injections) and Errante et al² (75 patients with ≥ 2 injections) using Magnevist and gadodiamide. Our data in 70 patients confirms the observation of high dentate nucleus signal following multiple Magnevist injections. However, for patients receiving only a macrocyclic agent, Gadavist (>10 injections), no signal accumulation in the dentate nucleus was observed (Figure 1). We observed cases where the dentate signal increased following multiple Magnevist injections and then disappeared after we switched to using Gadavist as our primary MR contrast agent (Figure 2). It is also interesting that many patients receiving >10 Magnevist injections showed no dentate nucleus signal accumulation.

This suggests that there are factors other than Gd administration that contribute to this effect which we have not yet discovered. We also noticed cases where there was no dentate nucleus signal accumulation after multiple Magnevist injections but then after switching to using Gadavist, dentate signal accumulation was observed (Figure 3).

Different effects on the dentate nucleus signal accumulation with different contrast agents raises the possibility that this may be related to the gadolinium based contrast agent. On the other hand, lack of consistency in this observations indicates that other factors contributing to this effect have not yet been discovered. In particular, absence of dentate signal accumulation in more than one third of patients receiving ≥ 10 Magnevist injections indicates that Magnevist is only associated with this effect and not the primary cause. Differences between Gadavist and Magnevist, which might contribute to differences in dentate signal accumulation include: macrocyclic versus linear molecular structure, nonionic versus ionic, low viscosity/osmolality versus higher viscosity/osmolality as well as differences in non-Gd additives within the solution being injected.

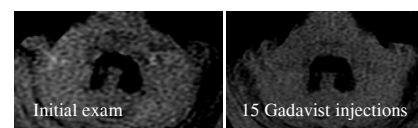


Figure 1: DNP does not change after 15 Gadavist administrations.

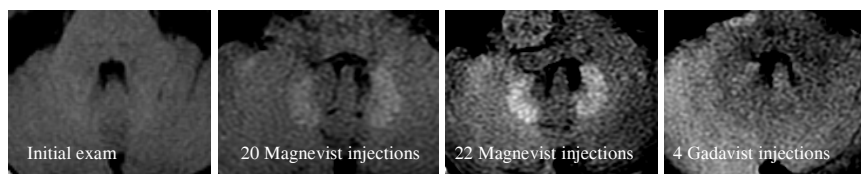


Figure 2: DNP progressively increases during Magnevist administrations, followed by decrease to baseline after Gadavist.



Figure 3: DNP does not change after Magnevist but increases after Gadavist administrations. Perhaps the larger number of Gadavist injections relative to the number of Magnevist injections may play a role in the variable signal appearance.

Conclusion: Our study supports the observation of high dentate nucleus signal following multiple gadolinium-enhanced MRI exams. However, this correlation may not be linear and does not occur in every patient. Patients receiving different gadolinium-based agents also demonstrate variable signal changes, suggesting a multifactorial basis.

References:

1. Kanda T, Ishii K, Kawaguchi H, et al. High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material. *Radiology* 2014; 270 (3): 834-841.
2. Errante Y, Cirimele V, Mallio C. Progressive Increase of T1 Signal Intensity of the Dentate Nucleus on Unenhanced Magnetic Resonance Images Is Associated With Cumulative Doses of Intravenously Administered Gadodiamide in Patients With Normal Renal Function, Suggesting Dechelation. *Investigative Radiology* 2014. 49 (10): 685-690.