CASE REPORT

Longitudinal Assessment of Dentate Nuclei Relaxometry during Massive Gadobutrol Exposure

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We report the assessment of Dentate Nuclei (DN) R1 ($1/T_1$) and R2* ($1/T_2^*$) values in a patient with relapsing-remitting Multiple Sclerosis, exposed to 22 standard (0.1 mmol/kg) doses of gadobutrol, who underwent eight relaxometric MR measurements within 2 years. DN R1 did not significantly increase nor correlated with cumulative gadobutrol administration, even after a total dose of 130 ml. Likewise, DN R2* relaxometry remained unchanged. In conclusion, massive gadobutrol exposure did not induce significant DN relaxometry changes.

Keywords: *gadolinium, magnetic resonance imaging contrast media, dentate nucleus, multiple sclerosis, relaxometry*

Introduction

Since the pioneering work of Kanda et al.[1] Gadolinium-based contrast agents (GBCA) have been associated with dentate nuclei (DN) increased signal intensity (SI) in T_1-weighted images in patients who received previous multiple intravenous GBCA administrations, even if with normal renal function (for updated reviews[2–4]). This effect, and the deposition of Gadolinium (Gd) in brain tissues, has been clearly demonstrated for linear GBCA,[5–8] while this is less straightforward for the macrocyclic GBCA gadobutrol.[9–13]

In fact, one study reported increased dentate nucleus-to-pons SI ratio in multiple sclerosis (MS) patients receiving an average of 33.3 ± 11.3 ml of Gadobutrol,[12] but also showed an inappreciable SI increase in the presented images and lacked a control population. On the contrary, no increased SI in T_1-weighted images was found in one animal[10] and five human studies assessing multiple doses of this GBCA.[6,9,11,13–14] Finally, variable Gd deposition has been observed in the brain of two patients exposed to gadobutrol only, who had received 5 and 20 ml before death, respectively.[15]

Recently, quantitative, unbiased alternatives to the previous qualitative SI assessments have been presented.[16–17] In particular, longitudinal R1 ($1/T_1$) relaxation rates of DN were found positively correlated with the number of previous linear GBCA administrations, while R2* ($1/T_2^*$) values were unaffected, thereby excluding a role of pathological iron accumulation in determining the observed R1 increase.[18]

In this case report we aimed to assess whether multiple administrations of gadobutrol as the only GBCA were associated with changes in R1 and R2* relaxometry, along with a "standard" SI evaluation in T_1-weighted images, in a patient repeatedly studied during massive gadobutrol exposure.

Case Report

A 32-year old female was diagnosed with relapsing-remitting MS at our institution, where she has been followed thereafter. No history of cardiovascular or metabolic disorders, alcoholism, substance dependence or abuse, total parenteral nutrition containing manganese, previous head injuries, or any brain disease other than MS were reported, nor any contrast-enhanced magnetic resonance scans (CE-MRIs) prior to diagnosis. Within a 10-year period, the patient underwent four brain CE-MRI at 1.5 Tesla in our center, each with the administration of a standard dose (0.1 mmol/kg body weight) of gadobutrol (Gadovist, Bayer Pharma AG). Renal and hepatic function were always normal; in particular, the glomerular filtration rate, estimated using the blood creatinine value and the CKD-EPI formula, was over 60 ml/min/1.73 m^2 at all timepoints. She was then enrolled in a MR relaxometry study on neuro-inflammatory diseases, which was approved by our local ethics committee, and underwent, beside a standard brain MRI (including a 2D T_1-weighted Spin Echo with TR =

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700 ms, TE = 9 ms and voxel size = 0.5 × 0.5 × 4 mm³), her first MR relaxometry measurement at 3 Tesla (Trio, Siemens, Erlangen, Germany) using two unenhanced 3D double-echo fast low angle shot (FLASH) sequences (TR = 28 ms; TE_1 = 7.63 ms; TE_2 = 22.14 ms; Bandwidth = 190 Hz/pixel; voxel size = 0.65 × 0.65 × 1.3 mm³; 128 axial slices; acquisition time: 5.08 minutes) sequentially acquired with different flip angles (θ_1 = 3° and θ_2 = 20°). The theoretical bases and the image processing for calculation of R1 and R2* maps have been already described in detail.[18,19] Briefly, in these FLASH sequences the decay of signals at different echo times allows for the derivation of R2* values, while the responses of the tissues at the different RF excitations (*i.e.* variable flip angle), with a fixed TR, are exploited for R1 calculation.

In the following 2 years, she developed a life-threatening natalizumab-associated Progressive Multifocal Leukoencefalopathy (PML) and subsequent Immune Reconstitution Inflammatory Syndrome (IRIS), requiring a close neuroradiological follow-up. The patient therefore underwent further 18 brain CE-MRI, always using the standard dose of gadobutrol as a GBCA, which in seven instances also included relaxometry measurements on the same 3T scanner. After the acute PML-IRIS stage, her clinical status gradually improved, and she is currently followed-up in our center. Thus, we had the opportunity to measure R1 and R2* DN values after 4, 8, 9, 10, 11, 13, 16 and 22 CE-MRI, and to correlate them with the amount of gadobutrol administered (Table 1).

In these eight scans, bilateral ROIs were hand-drawn independently by two neuroradiologists (with 10 and 25 years of experience, respectively) on the DN and in the normal-appearing white matter in the pons, on the same 1.3 mm-thick axial slice, as previously described.[18] Possible relaxometry and SI changes associated with GBCA administrations were evaluated by simple linear regression analyses, comprehensive of both point estimates and confidence intervals for the model coefficients. The significance of the measured MR changes was assessed by testing the null hypothesis for the slope coefficient of the estimated linear model.

The corresponding DN R1 values, normalized by the pons and averaged between the two observers (nR1), showed no significant changes with time (Table 1); in fact, they ranged from 1.13 at the first relaxometry measurement (after a cumulative gadobutrol dose of 24 ml) to 1.14 (after a cumulative gadobutrol dose of 130.1 ml), and did not significantly correlate with the cumulative dose of gadobutrol administered (P = 0.22; slope of the affine fit b = [0.34 ± 0.61] l⁻¹ at a 95% confidence interval-confidence interval [CI]), although a slight, non-significant trend toward increased values was observed (Fig. 1). This relationship excluded (at a 95% CI) any potential Gd build-up that may account for a b value bigger than 0.83 l⁻¹, well below the value of 1.30 l⁻¹ that can be inferred for mixed (linear and macrocyclic) GBCA from a previous study.[18] Likewise, the DN R2* values showed no significant changes (P = 0.35) at an increasing total gadobutrol dose (Table 1). The R1 and R2* maps of the first and last relaxometry scan are displayed in Fig. 2. Also, the visual and semi-quantitative assessment (i.e. the SI ratio between DN and pons) on the corresponding T_1-weighted Spin-Echo images, acquired at the same time-points of the relaxometry scans, disclosed no significant differences (P = 0.11) at increasing total gadobutrol dose (Table 1 and Fig. 2).

Discussion

Our findings, albeit limited to one patient, contribute to shed some light on the controversy about the effects of gadobutrol on DN MR properties and, indirectly, on the brain deposition of Gd induced by this macrocyclic agent. In fact, the absence of a significant increase in nR1 after 22 CE-MRI (corresponding to a cumulative dose of 130 ml of gadobutrol) in our patient lends further support to the hypothesis that this molecule does not reach a DN concentration high enough to induce relevant changes in tissue relaxometry. Conversely, the same technique proved capable of identifying a positive

Table 1. Relaxometry measurements and cumulative gadobutrol doses in the 2-year observation period

Relaxometry Scan #	Patient age (yr)	Cumulative Gd dose (ml)	Time from previous relaxometry scan	Time from previous GBCA administration	Normalized DN R1	DN R2* (s-1)	Normalized DN T_1w-SI
1	42	24.0	-	6 years	1.13	30.87	0.96
2	43	46.0	16 months	7 days	1.06	32.68	0.98
3	43	51.5	7 days	7 days	1.12	34.43	0.97
4	43	57.0	14 days	14 days	1.11	31.96	0.98
5	43	62.8	14 days	14 days	1.12	31.76	0.96
6	43	74.8	28 days	14 days	1.13	32.10	0.98
7	44	92.8	28 days	7 days	1.14	28.72	0.93
8	44	130.1	6 months	40 days	1.14	31.09	0.94

Normalized DN R1 and DN T_1w-SI: Longitudinal relaxation rate (1/T_1) and T_1-weighted Signal Intensity (SI) values of the dentate nuclei (DN), normalized by a reference ROI in the normal-appearing white matter of the pons. DN R2*: Transverse relaxation rate (1/T_2^*) of the dentate nuclei (DN); Gd, Gadolinium; GBCA, Gadolinium-based contrast agent.

correlation between nR1 values and the administration of mixed (linear and macrocyclic) GBCA in number ranging from 1 to 15.[18]

**nR1 = 1.09 + 0.34 * Cumulative Gadobutrol dose**
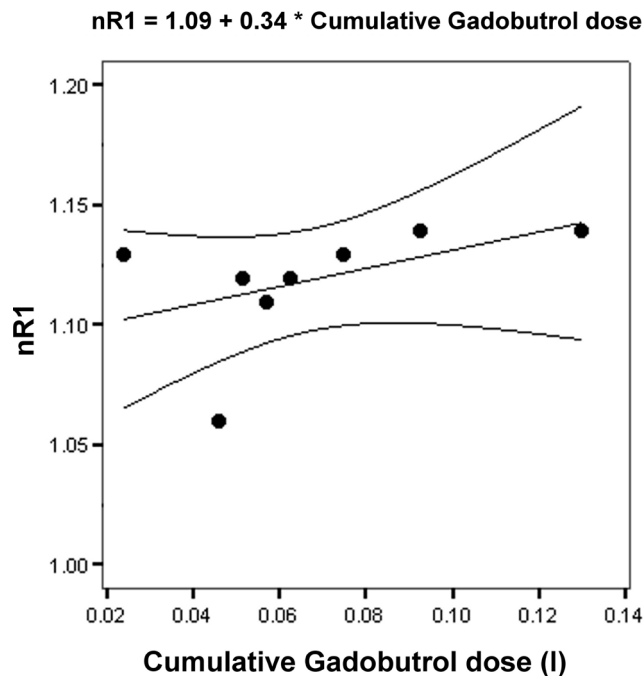
Fig. 1 Relationship between normalized dentate nuclei R1 (nR1) and the cumulative gadobutrol dose. The regression line and the 95% confidence limits are displayed, showing no significant temporal change of nR1 during the prolonged gadobutrol exposure (P = 0.22).

Further confirmation stems from the observation that even the 95% CI upper limit of the slope *b* is smaller than the value corresponding to mixed GBCA administration, which can be calculated from the data of a previous work,[18] thus suggesting very low, if any, gadobutrol retention in DN. The variable gadobutrol accumulation in brain tissue recently reported in two decedents after 1-2 gadobutrol injections[15] is likely too small to induce significant relaxometry changes, let alone be detected by SI qualitative assessment. Also, in this study the time intervals between gadobutrol exposure and tissue measurement were: 5 days in a terminally ill patient in septic shock with possible multiple organ failure, and 392 days in the other patient with liver cirrhosis. Thus, as the authors state, no firm conclusions can be drawn from this small sample size.[15]

The estimate of longitudinal relaxation rates is preferable to signal intensity evaluation, as it allows for quantitative comparisons in longitudinal studies and does not depend on sources of potential inaccuracy that instead affect T_1w signal intensity measurements, such as inhomogeneity of receiver coil sensitivity profile, transverse relaxation rates and proton density. In fact, relaxation rates are physical parameters intrinsically related to tissue microstructure, not affected by acquisition-related confounding factors[16,19] and, thus, possibly more reliable than signal intensity ratios.

The usefulness of a relaxometric approach to evaluate and monitor the local Gd concentration in the brain was recently demonstrated in patients exposed to linear GBCAs only, in whom a significant T_1 shortening in several grey
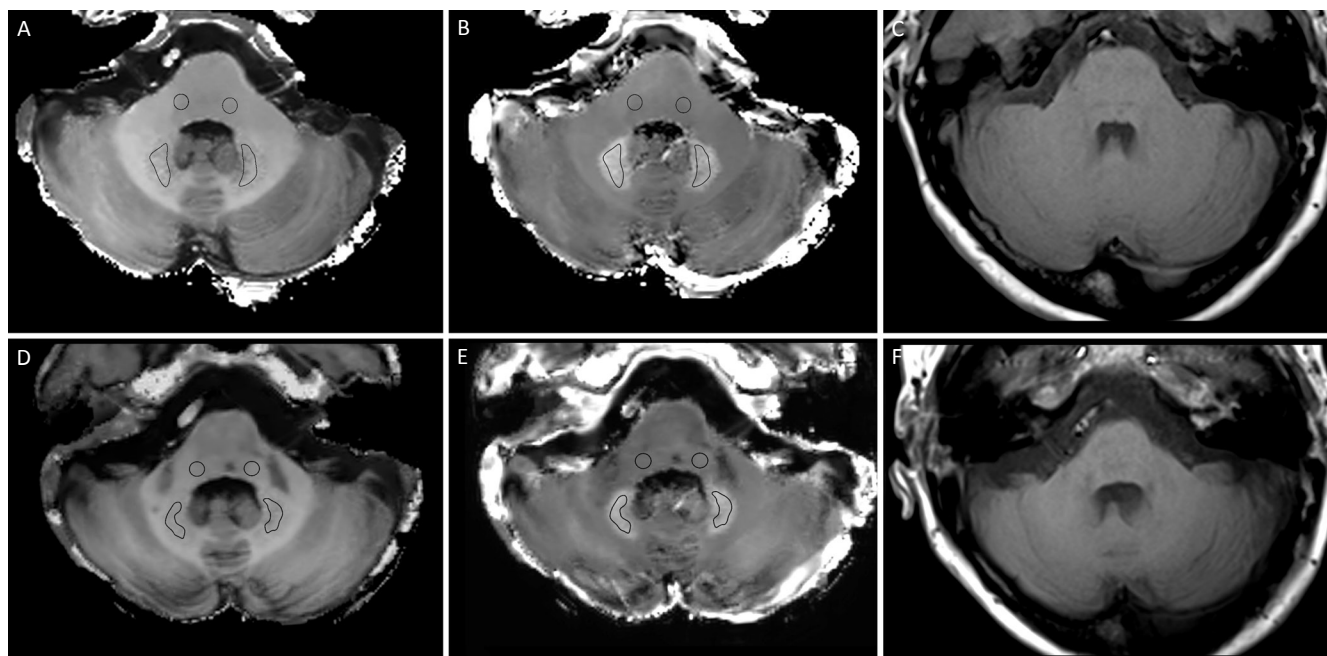
Fig. 2 R1 (**A**, **D**) and R2* map (**B**, **E**) with ROIs placement, of the 1st (upper row) and 8th (lower row) relaxometry measurement (*i.e.* after 24 and 130 ml of gadobutrol administered, respectively), showing no changes in R1 and R2* of dentate nuclei. 4 mm-thick T_1-weighted Spin-Echo images at corresponding levels in both scans (**C**, **F**) are also displayed, for visual confirmation of unchanged T_1 signal intensity in the dentate nuclei.

matter regions was observed, correlated with the number of prior GBCA injections.[17] Instead, to our knowledge, the repeated evaluation of brain relaxometry during prolonged exposure to macrocyclic GBCA only, as in the present case, has not been described before.

To corroborate our relaxometric measurements, we also performed a longitudinal "conventional" semi-quantitative SI assessment, using the methodology described by others,[5,9,14] which detected no signal increase in T_1-weighted images after multiple gadobutrol administrations.

The present case thus confirms and provides quantitative support to the findings of unchanged SI reported in the literature regarding patients exposed to gadobutrol as the only GBCA,[9,11,12,20,21] furthermore assessing T_1 relaxometry after a larger total gadobutrol dose administered (130 ml in 22 CE-MRI). In fact, Radbruch et al.[11] studied 30 patients (12 of whom actually exposed to gadobutrol only) receiving a cumulative gadobutrol dose of 54 ± 30 ml in 5-19 CE-MRI, Cao et al.[9] reported on 25 patients undergoing 6-16 CE-MRI (no cumulative dose available), the patients of Stojanov et al.[12] received gadobutrol doses about four times lower than our case, Kromrey et al.[20] evaluated 271 healthy subjects who had received, 5 years earlier, one single dose (1.5 mmol/kg) of gadobutrol, and Schlemm et al.[21] described 50 patients exposed to 2–5 standard (0.1 mmol/kg) gadobutrol administrations (no cumulative dose available). Most recently, Radbruch et al.[22] demonstrated no DN SI increase in 33 patients who underwent at least 20 CE-MRI using gadobutrol or gadoterate meglumine (mean cumulative Gd dose for the gadobutrol group: 71 ± 30 mmol). In all these studies, a relaxometric evaluation has not been performed.

Besides in humans, T_1 relaxometry has also been shown to be useful in animal studies, being capable to differentiate the pure T_1 effect of gadolinium accumulation on deep cerebellar nuclei in rats after administration of different linear GBCA compared to saline and gadoterate meglumine.[23] As Robert at al. pointed out, R1 maps may help to estimate the local relaxivities of Gd, and therefore investigate the form of Gd in brain tissue, once the tissue Gd concentration has been precisely determined.[23]

An obvious limitation of the present report is the lack of histopathological confirmation; however, our aim was not to assess the presence of Gd in the patient's brain, but rather the study of a possible effect of large cumulative doses of gadobutrol on DN relaxometry. Also, we feel confident that the measured relaxometry changes were not influenced by potential circulating Gd, since our relaxometry measurements were always performed at least 7 days after the previous GBCA administration. In patients with normal renal function, the terminal half-life for blood elimination is about 1.5 hours for GBCAs, which are in fact recovered >90% from urine after 12 hours.[24]

Conclusion

This case report suggests that massive exposure to gadobutrol (130 ml) does not induce significant changes in R1 and R2* of the dentate nuclei at 3T, paralleling the absence of increased signal intensity reported in other studies with this macrocyclic contrast agent.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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