Dose-Lowering in Contrast-Enhanced MRI of the Central Nervous System: A Retrospective, Parallel-Group Comparison Using Gadobenate Dimeglumine

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Background: Concerns over gadolinium (Gd) retention encourage the use of lower Gd doses. However, lower Gd doses may compromise imaging performance. Higher relaxivity gadobenate may be suited to reduced dose protocols.
Purpose: To compare 0.05 mmol/kg and 0.1 mmol/kg gadobenate in patients undergoing enhanced MRI of the central nervous system (CNS).
Study Type: Retrospective, multicenter.
Population: Three hundred and fifty-two patients receiving 0.05 ($n = 181$) or 0.1 ($n = 171$) mmol/kg gadobenate.
Field Strength/Sequences: 1.5 T and 3.0 T/precontrast and postcontrast T1-weighted spin echo/fast spin echo (SE/FSE) and/or gradient echo/fast field echo (GRE/FFE); precontrast T2-weighted FSE and T2-FLAIR.
Assessment: Images of patients with extra-axial lesions at 1.5 T or any CNS lesion at 3.0 T were reviewed by three blinded, independent neuroradiologists for qualitative (lesion border delineation, internal morphology visualization, contrast enhancement; scores from 1 = poor to 4 = excellent) and quantitative (lesion-to-brain ratio [LBR], contrast-to-noise ratio [CNR]; SI measurements at regions-of-interest on lesion and normal parenchyma) enhancement measures. Noninferiority of 0.05 mmol/kg gadobenate was determined for each qualitative endpoint if the lower limit of the 95% confidence interval (CI) for the difference in precontrast + postcontrast means was above a noninferiority margin of −0.4.
Statistical Tests: Student's t-test for comparison of mean qualitative endpoint scores, Wilcoxon signed rank test for comparison of LBR and CNR values; Wilcoxon rank sum test for comparison of SI changes. Tests were significant for $P < 0.05$.
Results: The mean change from precontrast to precontrast + postcontrast was significant for all endpoints. Readers 1, 2, and 3 evaluated 304, 225, and 249 lesions for 0.05 mmol/kg gadobenate, and 382, 309, and 298 lesions for 0.1 mmol/kg gadobenate. The lower limit of the 95% CI was above −0.4 for all comparisons. Significantly, higher LBR and CNR was observed with the higher dose.
Data Conclusion: 0.05 mmol/kg gadobenate was noninferior to 0.1 mmol/kg gadobenate for lesion visualization.
Evidence Level: 2
Technical Efficacy: Stage 3

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Concern over nephrogenic systemic fibrosis (NSF) and the unknown but possible long-term impact on health from retained gadolinium (Gd) in brain and body tissues after routine contrast-enhanced MRI (CE-MRI) procedures has led to a more judicious use of gadolinium-based contrast agents (GBCAs).[1,2] Whereas the risk of NSF has largely been eliminated by contraindication of the linear GBCAs gadopentetate dimeglumine, gadodiamide, and gadoversetamide (group I GBCAs according to the American College of Radiology [ACR] manual on contrast media[3]) in patients with severe renal insufficiency, Gd retention remains a concern. Although no signs, symptoms, or adverse clinical outcomes associated with Gd retention in the brain have yet been reported,[4–8] the widespread tendency in recent years has been to limit the GBCA dose administered whenever practicable if a CE-MRI exam is considered essential for diagnosis.

Among the GBCAs available for CE-MRI in the United States, gadobenate dimeglumine (MultiHance, Bracco) has the highest longitudinal relaxivity (R1)[9] and has been shown to provide significantly better lesion conspicuity and diagnostic performance in CE-MRI of the CNS when compared intraindividually to lower relaxivity GBCAs administered at equivalent dose under identical conditions.[10–15] Furthermore, a half dose of gadobenate has been shown to provide similar lesion conspicuity and diagnostic performance when compared to a full dose of lower relaxivity GBCA.[14] Reducing the dose of GBCA for routine clinically indicated studies while maintaining diagnostic performance would be an important strategy to address concerns related to Gd retention. In this setting, gadobenate might be the most suitable of the currently available GBCAs for reduced dose applications.

The aim of our study was to determine whether a half-dose of gadobenate (0.05 mmol/kg bodyweight) can be considered noninferior to a full dose of gadobenate (0.1 mmol/kg bodyweight) for lesion visualization on combined precontrast and postcontrast (precontrast + postcontrast) T1-weighted images in patients undergoing CE-MRI of the CNS.

Materials and Methods

This retrospective study of MR data from patients at seven sites was reviewed and approved by the Institutional Review Board (IRB) at each center, and the requirement for informed consent was waived by each local Ethics Committee/Institutional Review Board. The study was conducted in accordance with the International Congress on Harmonization, Good Clinical Practice, United States FDA regulations, and ethical principles outlined in the Declaration of Helsinki and all applicable local regulations. The study protocol was compliant with the Health Insurance Portability and Accountability Act and was registered at www.clinicaltrials.gov (NCT03147989).

Patients

Patients eligible for inclusion were at least 2 years of age, had full demographic data available, and underwent contrast-enhanced MRI with gadobenate dimeglumine at a documented dose of 0.1 mmol/

kg or 0.05 mmol/kg bodyweight (±20% in volume administered) for known or suspected enhancing disease of the CNS. Eligibility also required the acquisition of pulse sequence and parameter-matched precontrast and postcontrast T1-weighted spin echo/fast spin echo (SE/FSE) and/or gradient echo/fast field echo (GRE/FFE) images and precontrast T2-weighted FSE and, optionally, fluid-attenuated inversion recovery (FLAIR) images. Patients were included consecutively from January 20, 2017 and enrolled in reverse chronological order until the prospectively designed enrollment (at least 320 patients) had been achieved (examination performed July 18, 2012). Patients were enrolled into one of four groups based on the gadobenate dose received (0.1 mmol/kg or 0.05 mmol/kg bodyweight) and field strength of the magnet (1.5 T or 3.0 T). Each group included at least 80 patients (160 in each dose group [80 at 1.5 T, 80 at 3.0 T]).

A total of 352 subjects were enrolled. Of these 181 (109M/72F; 97 [53.6%] at 1.5 T, 84 [46.4%] at 3.0 T) received 0.05 mmol/kg gadobenate and 171 (79M/92F; 86 [50.3%] at 1.5 T, 85 [49.7%] at 3.0 T) received 0.1 mmol/kg gadobenate (Table 1). Overall, 40 of the 181 (22%) patients who received 0.05 mmol/kg gadobenate were <18 years of age, whereas 0 of the 171 (0%) patients who received 0.1 mmol/kg gadobenate were <18 years of age. Eight (4.4%) subjects who received 0.05 mmol/kg gadobenate and five subjects (2.9%) who received 0.1 mmol/kg gadobenate had protocol violations and were excluded from primary efficacy analysis (nine patients did not have precontrast T2-weighted or postcontrast T1-weighted images available; two patients in the 0.05 mmol/kg group received a gadobenate dose that deviated by ±20% of the stated dose; two patients in the 0.1 mmol/kg group had inadvertently been enrolled previously in the study). The final per-protocol efficacy populations, therefore, comprised 173 subjects (91 at 1.5 T, 82 at 3.0 T) who received 0.05 mmol/kg gadobenate and 166 subjects (84 at 1.5 T, 82 at 3.0 T) who received 0.1 mmol/kg gadobenate. The mean (±standard deviation) doses administered across all enrolled patients was 0.051 mmol/kg ± 0.006 mmol/kg for the 0.05 mmol/kg gadobenate group, and 0.1 mmol/kg ± 0.01 mmol/kg for the 0.1 mmol/kg gadobenate group.

Demographic data collected for each patient included sex, age, and weight. Similarly, the medical history of each enrolled patient and final lesion diagnosis was recorded. Lesions recorded at final diagnosis were categorized as nontumor or tumor. Tumors were further categorized as extra-axial or intra-axial, the latter further classified as benign or malignant. All clinical information at the time of the examination (e.g., serum creatinine levels) were recorded.

Imaging

Contrast-enhanced MRI was performed using the standard neuroimaging protocols in place at each investigational center. All patient exams were conducted using commercially available MRI equipment and software packages, and all major MRI scanner manufacturers were represented. MR imaging at 1.5 T was performed in 97 and 86 patients with 0.05 mmol/kg and 0.1 mmol/kg gadobenate, respectively (Siemens Magnetom Avanto, Espree, Essenza, Symphony or Aera [Siemens, Erlangen, Germany] in 37 and 48 patients, respectively; GE Signa HDxt, Exite or Optima MR450 [GE Healthcare, Milwaukee, Wisconsin] in 54 and 20 patients, respectively; Toshiba MRT200SP8 [Tustin, California] in 5 and

TABLE 1. Demographic Characteristics of Enrolled Patients

Characteristic		Overall Population		Field Strength 1.5 T		Field Strength 3.0 T	
		0.05 mmol/kg (N = 181)	0.1 mmol/kg (N = 171)	0.05 mmol/kg (N = 97)	0.1 mmol/kg (N = 86)	0.05 mmol/kg (N = 84)	0.1 mmol/kg (N = 85)
Sex	Male	109 (60.2)	79 (46.2)	57 (58.8)	33 (38.4)	52 (61.9)	46 (54.1)
	Female	72 (39.8)	92 (53.8)	40 (41.2)	53 (61.6)	32 (38.1)	39 (45.9)
	P-value*	0.103		0.008		0.351	
Age (years)	Mean (SD)	53.5 (26.82)	60.4 (14.92)	54.9 (26.53)	59.4 (15.61)	51.8 (27.22)	61.3 (14.22)
	Range	(2, 93)	(24, 93)	(2, 93)	(24, 92)	(2, 90)	(26, 93)
	P-value*	0.003**		0.157		0.005**	
Age group N (%)	<18 years	40 (22.1)	0	18 (18.6)	0	22 (26.2)	0
	18–64 years	54 (29.8)	99 (57.9)	31 (32.0)	55 (64.0)	23 (27.4)	44 (51.8)
	≥65 years	87 (48.1)	72 (42.1)	48 (49.5)	31 (36.0)	39 (46.4)	41 (48.2)
	P-value*	<0.001**		<0.001		<0.001**	
Weight (kg)	Mean (SD)	79.07 (29.21)	82.13 (19.35)	78.87 (29.15)	82.07 (19.22)	79.30 (29.45)	82.18 (19.60)
	Range	(13.0, 179.5)	(42.2, 128.4)	(13.6, 179.5)	(45.5, 125.0)	(13.0, 156.0)	(42.2, 128.4)
	P-value*	0.245**		0.377		0.455**	

*P-values are for the comparison of two doses using the t-test for continuous variables and the Fisher's Exact test for categorical variables.
**Forty subjects in the 0.05 mmol/kg dose group were < 18 years of age while no subjects were < 18 years of age in the 0.1 dose group. Due to this imbalance, some demographic characteristics show significant differences.

13 patients, respectively; Philips Achieva [Philips Healthcare, Best, The Netherlands] in 1 and 5 patients, respectively). MR imaging at 3.0 T was performed in 84 and 85 patients with 0.05 mmol/kg and 0.1 mmol/kg gadobenate, respectively (Siemens Skyra or Verio in 44 and 79 patients, respectively; GE Discovery 3 T MR750 in 23 and 1 patients, respectively; Toshiba Vantage Titan 3 T in 6 and 0 patients, respectively, Philips Ingenia in 11 and 5 patients, respectively). Images required for the study were precontrast and postcontrast T1-weighted SE/FSE and/or GRE/FFE images and precontrast T2-weighted FSE images. T2-weighted FLAIR images of the brain were included when available. Pulse sequence and parameters (Supplemental Material) varied with scanner type but were identical for all precontrast and postcontrast acquisitions in each patient. All precontrast and postcontrast T1-weighted images were acquired in the same plane.

Efficacy Assessments

MR images were evaluated independently by three experienced neuroradiologists (readers 1 [C.C.], 2 [J.V.], and 3 [Z.W.] with 41, 33, and 31 years of experience, respectively) who were unaffiliated with the enrollment centers and blinded to all patient clinical profiles, to the dose of gadobenate dimeglumine utilized, and to the field strength of the MR scanner. Evaluation was performed using the thin client of TeraRecon AquariusNet server (v 4.4.5.36) (San Mateo, California). Precontrast images and combined precontrast + postcontrast images were randomized and presented individually in separate image blocks for assessment. Evaluation was performed in two separate sessions separated by at least 2 weeks to avoid/minimize recall bias. In the first session, either precontrast images alone or precontrast + postcontrast images from each patient were evaluated. In the second session, the other image set from each patient was evaluated. Each reader initially evaluated all images for technical adequacy. Patients with images considered technically inadequate (i.e., with artifacts totally compromising image quality and interpretability) were excluded from subsequent assessment by that reader.

QUALITATIVE ASSESSMENTS. Assessment of lesion visualization on technically adequate precontrast and precontrast + postcontrast images was performed for lesion border delineation, visualization of lesion internal morphology, and lesion enhancement. Each blinded reader was instructed to evaluate up to five lesions (the five largest) per patient for patients with multiple lesions. Assessments were performed using 4-point scales for each parameter from 1 (poor), through 2 (moderate), 3 (good) to 4 (excellent). A score of zero was assigned by default whenever a lesion was not identified on either image set after lesion matching. Lesion matching was

performed after completion of the blinded readings by a fourth experienced, unaffiliated neuroradiologist (D.D.M.L. with 15 years of experience) to enable comparison of the same lesion across different image sets. If a lesion was not detected on one of the image sets (e.g., a lesion was detected on precontrast + postcontrast images but not on precontrast images alone) then a score of 0 was imputed for the analysis of the three co-primary visualization endpoints.

Additional assessment during evaluation of the precontrast + postcontrast image sets was performed to determine whether the postcontrast images provided additional information over precontrast images, as described elsewhere.[16] Additional information included whether enhancement revealed an abnormality not seen on the precontrast images, whether it improved visualization of the size, extent and/or margins of a lesion (better conspicuity) or whether the pattern of enhancement was useful in predicting the grade, histologic type, vascularity, and/or aggressiveness of a lesion or documented the activity or aggressiveness of non-neoplastic processes.

QUANTITATIVE ASSESSMENTS. Each reader independently performed quantitative measurements on the T1-weighted SE/FSE image data and, when available, T1-GRE image data. Measurement of signal intensities from regions of interest (ROIs) were calculated for image background (noise), normal brain or spinal cord parenchyma, and for up to three lesions identified. To standardize the placement of the ROIs within a patient, circular ROIs were placed on the image slice that provided the best visualized lesions (if possible, larger than 1 cm in diameter) in the largest most conspicuous areas. ROIs were as large as possible and included only homogeneous areas. The lesion-to-brain ratio (LBR) and contrast-to-noise ratio (CNR) were calculated for precontrast and postcontrast images using the following formulae, where SI_{lesion} is the SI of the lesion, $SI_{brain/spine}$ is the SI of the normal brain or spine parenchyma, and SD_{Noise} is the standard deviation of ROI pixels in the image background (noise):

$$LBR = SI_{Lesion}/SI_{Brain/Spine}$$

$$CNR = (SI_{Lesion} - SI_{Brain/Spine})/SD_{Noise}$$

Statistical Analysis

Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA). Continuous measurements were reported as mean ± standard deviation (SD), while categorical assessments were described as number (%). All analyses compared the two doses across all patients as well as for subgroups of patients imaged at 1.5 T and 3.0 T. Demographic characteristics of the two dose groups were compared using Student's t-test for continuous variables and Fisher's Exact test for categorical variables. All statistical tests were considered significant for $P < 0.05$.

The primary efficacy evaluation determined whether a gadobenate dose of 0.05 mmol/kg was noninferior to a dose of 0.1 mmol/kg across the three co-primary endpoints: lesion border delineation, lesion internal morphology, and lesion contrast enhancement. The mean scores for each endpoint for the two dose groups were compared using Student's t-test, and a 95% confidence interval

(CI) for the difference between the groups was determined. A gadobenate dose of 0.05 mmol/kg was considered noninferior to a dose of 0.1 mmol/kg if the lower limit of the 95% CI for the difference in the mean visualization score (0.05 mmol/kg − 0.1 mmol/kg) was greater than a noninferiority margin of −0.4, described below. If two of the three readers met this criterion for noninferiority, 0.05 mmol/kg gadobenate was considered noninferior to 0.1 mmol/kg gadobenate for lesion visualization. The noninferiority margin of −0.4 was determined assuming an average visualization score of 2.43 for the 0.1 mmol/kg dose group (Bracco unpublished data; data on file), a conservative reduction of 16.5% from this average score, and that an average visualization score of 2 (moderate visualization) would be clinically meaningful for the 0.05 mmol/kg dose group (i.e. noninferiority margin $-\delta$ = 2.43*16.5% = −0.4). Secondary analyses evaluated the change in visualization endpoint scores from precontrast to precontrast + postcontrast between the two dose groups. Student's t-test was used and a 95% CI for the difference in change from precontrast between the two dose groups calculated. Comparisons were performed for all patients combined and for sub-groups of patients by sex and age group (<18 years, 18–64 years, ≥65 years).

Inter-reader agreement was evaluated by the intraclass correlation coefficient (ICC) for the three co-primary variables based on the patient-level averaged results of precontrast and precontrast + postcontrast assessments. Two sources of variance were considered in the calculation of inter-reader agreement: patient (treated as a random effect) and residual. The ICC (ranging from 0 to 1) was computed from the mixed model as the ratio of the variance attributable to the patient effect to the total variance (patient plus residual) and was interpreted as: ICC < 0.20 "slight agreement"; 0.21–0.40 "fair agreement"; 0.41–0.60 "moderate agreement"; 0.61–0.80 "substantial agreement"; >0.80 "almost perfect agreement".[17]

Lesion-level analyses were performed for LBR and CNR measured by the blinded off-site readers for T1wSE/FSE and, when available, T1wGRE sequences. Differences between means and the two-sided 95% CIs were determined. The Wilcoxon signed rank test was used to compare precontrast and postcontrast image values within each dose group. Comparison of the change from precontrast to postcontrast in signal intensity enhancement between the two groups was analyzed using the Wilcoxon rank sum test. Comparison of postcontrast image signal intensity enhancement between two dose groups was also performed using the Wilcoxon rank sum test.

The required sample size for statistical demonstration of noninferiority was based on an average visualization score of 2.43 for the 0.1 mmol/kg dose group with a common SD of 1.1, considering slightly higher variability due to the two field strengths. Given a noninferiority margin of 0.4, an expected difference between the two dose groups of zero, and a two-group one-sided t-test at an alpha level of 0.025, a total sample size of 320 (n = 160 in each dose group [80 at 1.5 T, 80 at 3.0 T]) would provide 90% power to reject the null hypothesis that the 0.05 mmol/kg dose is inferior to the 0.1 mmol/kg dose in terms of lesion visualization (H0: $\mu_{0.05}-\mu_{0.1} \leq -0.4$), in favor of the alternative hypothesis that the 0.05 mmol/kg dose is noninferior to the 0.1 mmol/kg dose (H1: $\mu_{0.05}-\mu_{0.1} > -0.4$).

Results

The medical history and final diagnoses of enrolled patients are summarized in Table 2. At least one finding was reported for all 181 patients who received 0.05 mmol/kg gadobenate and for 169 of the 171 (98.8%) patients who received 0.1 mmol/kg gadobenate. The most commonly reported medical history findings were oncologic, occurring in 168 of the 352 (47.7%) subjects with available information (68/181 [37.6%] and 100/169 [58.5%] subjects in the 0.05 and 0.1 mmol/kg dose groups, respectively). Among subjects with confirmed tumors, 128 of the 141 (90.8%) and 99 of the 126 (78.6%) subjects who received 0.05 mmol/kg and 0.1 mmol/kg gadobenate, respectively, had extra-axial tumors while 13 of the 141 (9.2%) and 27 of the 126 (21.4%) subjects had intra-axial tumors, respectively. All but one subject with confirmed intra-axial tumors were imaged at 3.0 T. Consequently, analysis of efficacy by field strength was performed for subjects with both extra-axial and intra-axial tumors at 3.0 T but only for subjects with extra-axial tumors at 1.5 T.

Serum creatinine values were available for 141 and 123 patients in the 0.05 mmol/kg and 0.1 mmol/kg dose groups, respectively. The average creatinine levels at the time of the examination were 1.08 ± 0.355 (range: 0.3 mg/dL– 2.2 mg/dL) and 0.91 mg/dL $\pm$ 0.219 mg/dL (range: 0.5 mg/dL–1.6 mg/dL) for the 0.05 mmol/kg and the 0.1 mmol/kg dose groups, respectively.

QUALITATIVE ASSESSMENTS. Readers 1, 2, and 3 considered 7 (2.0%), 4 (1.1%), and 1 (0.3%) precontrast image sets and 5 (0.14%), 6 (1.7%), and 2 (0.6%) precontrast + postcontrast image sets to be technically inadequate. All other image sets in both reading sessions were technically adequate and included in the analysis of efficacy.

Readers 1, 2, and 3 evaluated 304, 225, and 249 lesions, respectively, in the 0.05 mmol/kg group (52, 43, and 48 lesions, respectively, in patients aged <18 years; 57, 55, and 58 lesions, respectively, in patients aged 18–64 years; and 195, 127, and 143 lesions, respectively, in patients aged ≥65 years), and 382, 309, and 298 lesions, respectively, in the 0.1 mmol/kg group (0, 0, and 0 lesions, respectively, in patients aged <18 years; 215, 197, and 177 lesions, respectively, in patients aged 18–64 years; and 167, 112, and 121 lesions, respectively, in patients aged ≥65 years). Significant improvement in mean lesion visualization score from precontrast to precontrast + postcontrast was noted by all three blinded readers for both the 0.1 mmol/kg and 0.05 mmol/kg dose groups for all qualitative endpoints (delineation of lesion border, visualization of internal lesion morphology, and lesion contrast enhancement) for all lesions combined and for sub-analysis by gender and age group. Overall, the mean scores for lesion border delineation increased for the 0.05 mmol/kg group from 2.45, 2.13, and

1.86 (readers 1, 2, and 3, respectively) on precontrast images alone to 3.39, 3.00, and 3.56, respectively, on combined precontrast + postcontrast images. Mean scores for the 0.1 mmol/kg group increased from 2.54, 2.14, and 1.80 on precontrast images alone to 3.52, 3.10, and 3.57 on combined precontrast + postcontrast images. Similar improvements were reported for visualization of internal lesion morphology (mean scores of 2.49, 2.04, and 1.86 on precontrast images alone and 3.39, 2.90, and 3.65 on precontrast + postcontrast images for the 0.05 mmol/kg group; mean scores of 2.54, 2.06, and 1.79 on precontrast images alone and 3.55, 3.02, and 3.64 on precontrast + postcontrast images for the 0.1 mmol/kg group) and qualitative assessment of lesion contrast enhancement (mean scores of 2.51, 2.01, and 1.86 on precontrast images alone and 3.45, 2.94, and 3.69 on precontrast + postcontrast images for the 0.05 mmol/kg group; mean scores of 2.58, 1.99, and 1.88 on precontrast images alone and 3.59, 3.07, and 3.68 on precontrast + postcontrast images for the 0.1 mmol/kg group).

Analogous findings were reported for subanalysis of patients aged 18–64 years and for patients aged >65 years. Unfortunately, comparison of the two doses in subjects <18 years of age could not be performed since no patients in this age group received the higher dose. However, analysis of 52, 43, and 48 (readers 1, 2, and 3, respectively) lesions in the pediatric sub-group who received 0.05 mmol/kg gadobenate revealed significant improvement in lesion visualization from precontrast to precontrast + postcontrast for all endpoints and readers (delineation of lesion border: improvements from mean scores of 1.64, 1.79, and 1.66 on precontrast images alone to 3.19. 2.66, and 3.28, respectively, on combined precontrast + postcontrast images; visualization of internal lesion morphology: improvements from mean scores of 1.77, 1.79, and 1.76 on precontrast images alone to 3.19. 2.59, and 3.36, respectively, on precontrast + postcontrast images; lesion contrast enhancement: improvements from mean scores of 1.77, 1.81, and 1.70 on precontrast images alone to 3.25. 2.61, and 3.44, respectively, on precontrast + postcontrast images) indicating the efficacy of 0.05 mmol/kg gadobenate among pediatric patients with CNS diseases.

Analysis of the 0.05 mmol/kg and 0.1 mmol/kg dose groups for all lesions evaluated (Table 3), extra-axial lesions at 1.5 T (Table 4), and both intra- and extra-axial lesions at 3.0 T (Table 5) revealed significant increases in mean lesion visualization score from precontrast to precontrast + postcontrast for all endpoints and readers. In all cases, the lower limit of the 95% CI of the difference between the gadobenate 0.05 mmol/kg dose minus the gadobenate 0.1 mmol/kg dose was greater than the noninferiority margin value of −0.4. Examples of extra-axial lesions (meningiomas) imaged at 1.5 T with 0.1 and 0.05 mmol/kg gadobenate are

TABLE 2. Medical History of Enrolled Patients

Medical History Finding[a]		Overall Safety Population		Field Strength			
				1.5 T		3.0 T	
		0.05 mmol/kg N = 181[b] n (%)	0.1 mmol/kg N = 171[b] n (%)	0.05 mmol/kg N = 97[b] n (%)	0.1 mmol/kg N = 86[b] n (%)	0.05 mmol/kg N = 84[b] n (%)	0.1 mmol/kg N = 85[b] n (%)
Number of subjects with at least one finding		181 (100.0)	169 (98.8)	97 (100.0)	86 (100.0)	84 (100.0)	83 (97.6)
Number of subjects by finding	Oncology	68 (37.6)	100 (58.5)	35 (36.1)	42 (48.8)	33 (39.3)	58 (68.2)
	Metabolic	76 (42.0)	58 (33.9)	36 (37.1)	17 (19.8)	40 (47.6)	41 (48.2)
	Congenital	9 (5.0)	2 (1.2)	4 (4.1)	1 (1.2)	5 (6.0)	1 (1.2)
	Other	169 (93.4)	157 (91.8)	92 (94.8)	78 (90.7)	77 (91.7)	79 (92.9)
Final diagnosis	Nontumor	40 (22.1)	45 (26.3)	22 (22.7)	33 (38.4)	18 (21.4)	12 (14.1)
	Tumor[c]	141 (77.9)	126 (73.7)	75 (77.3)	53 (61.6)	66 (78.6)	73 (85.9)
	Extra-axial	128 (90.8)	99 (78.6)	75 (100.0)	52 (98.1)	53 (80.3)	47 (64.4)
	Intra-axial	13 (9.2)	27 (21.4)	0	1 (1.9)	13 (19.7)	26 (35.6)
	Benign	88 (62.4)	39 (31.0)	50 (66.7)	14 (26.4)	38 (57.6)	25 (34.2)
	Malignant	39 (27.7)	50 (39.7)	13 (17.3)	22 (41.5)	26 (39.4)	28 (38.4)
	Not available	14 (9.9)	37 (29.4)	12 (16.0)	17 (32.1)	2 (3.0)	20 (27.4)

[a]Subjects may have findings in more than one category.
[b]Denominator for subject-related percentages.
[c]Denominator for tumor-related percentages.

TABLE 3. Precontrast vs. Precontrast + Postcontrast Lesion Visualization for All Lesions

		Reader 1		Reader 2		Reader 3	
	Dose group	0.05 mmol/kg	0.1 mmol/kg	0.05 mmol/kg	0.1 mmol/kg	0.05 mmol/kg	0.1 mmol/kg
Assessment	Number of Subjects / Number of Lesions	$N = 163$ / $n^a = 304$	$N = 158$ / $n^a = 382$	$N = 165$ / $n^a = 225$	$N = 161$ / $n^a = 309$	$N = 164$ / $n^a = 249$	$N = 160$ / $n^a = 298$
Lesion border delineation	Precontrast	1.9 ± 1.1	1.9 ± 1.2	1.7 ± 1.0	1.6 ± 1.1	1.6 ± 0.9	1.4 ± 0.9
	Precontrast + postcontrast	3.1 ± 1.2	3.0 ± 1.3	2.8 ± 1.0	2.7 ± 1.2	3.2 ± 1.2	3.1 ± 1.3
	Mean change ± SD[b]	1.1 ± 1.7	1.1 ± 2.0	1.0 ± 1.5	1.2 ± 1.7	1.6 ± 1.5	1.7 ± 1.8
	Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	0.03 (−0.2, 0.3); P = 0.66		0.04 (−0.2, 0.2); P = 0.81		0.1 (−0.05, 0.4); P = 0.12	
Lesion internal morphology	Precontrast	2.0 ± 1.1	2.0 ± 1.2	1.7 ± 1.0	1.5 ± 1.1	1.6 ± 0.9	1.4 ± 0.9
	Precontrast + postcontrast	3.1 ± 1.2	3.1 ± 1.3	2.7 ± 1.0	2.7 ± 1.1	3.3 ± 1.2	3.1 ± 1.4
	Mean change ± SD[b]	1.1 ± 1.7	1.1 ± 2.0	1.0 ± 1.5	1.2 ± 1.6	1.7 ± 1.6	1.7 ± 1.9
	Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	−0.006 (−0.2, 0.2); P = 0.9		0.02 (−0.2, 0.2); P = 0.94		0.2 (−0.02, 0.5); P = 0.03	
Lesion contrast enhancement	Precontrast	2.0 ± 1.1	2.0 ± 1.2	1.7 ± 0.9	1.5 ± 1.0	1.6 ± 0.9	1.5 ± 1.0
	Precontrast + postcontrast	3.1 ± 1.2	3.1 ± 1.4	2.7 ± 1.0	2.7 ± 1.2	3.3 ± 1.2	3.2 ± 1.4
	Mean change ± SD[b]	1.1 ± 1.7	1.1 ± 2.0	1.1 ± 1.5	1.3 ± 1.6	1.7 ± 1.6	1.7 ± 1.9
	Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	0.009 (−0.2, 0.2); P = 0.81		0.005 (−0.2, 0.2); P = 0.89		0.02 (−0.02, 0.4); P = 0.08	

[a]Up to 10 largest lesions were assessed per subject.
[b]All P-values from the paired t-test for mean change from precontrast to precontrast + postcontrast were $P < 0.0001$.
[c]Difference in means of precontrast + postcontrast between dose 0.05 mmol/kg and 0.1 mmol/kg.
[d]P-value and confidence intervals for the difference in means between dose groups are obtained from the mxed model: precontrast + postcontrast score = precontrast score. A lower 95% CI margin that is greater than the non-inferiority margin −0.4 implies that gadobenate 0.05 mmol/kg is non-inferior to gadobenate 0.1 mmol/kg.

shown in Fig. 1 while examples of intra-axial lesions (metastases) imaged at 3.0 T with 0.1 and 0.05 mmol/kg gadobenate are shown in Fig. 2.

The ICC values for the three co-primary variables (delineation of lesion border, visualization of internal lesion morphology, and lesion contrast enhancement) across all patients in the 0.05 mmol/kg group (1.5 T and 3.0 T combined) were 0.3, 0.27, and 0.27, respectively, for precontrast images and 0.26, 0.25, and 0.25, respectively, for precontrast + postcontrast images, indicating fair agreement between the three blinded readers. Similar ICC values indicating fair agreement (0.33, 0.29, and 0.28 for precontrast images and 0.36, 0.32, and 0.34 for precontrast + postcontrast images) were obtained across all patients (1.5 T and 3.0 T combined) in the 0.1 mmol/kg group. Fair agreement (ICC values between 0.21 and 0.40) was obtained for sub-analysis of all images acquired at 1.5 T (both 0.05 mmol/kg and 0.1 mmol/kg gadobenate) and for images acquired at 3.0 T with 0.1 mmol/kg gadobenate. Slightly lower ICC values (0.18, 0.15, and 0.19, respectively [slight agreement]) were determined for the three visualization endpoints only for the evaluation of the precontrast + postcontrast image sets at 3.0 T in patients who received 0.05 mmol/kg gadobenate.

The 0.05 mmol/kg dose of gadobenate provided additional information for lesion diagnosis in similar proportions of patients to that of the 0.1 mmol/kg dose at both 1.5 T (76/90 [84.4%] vs. 81/83 [97.6%], 89/90 [98.9%] vs. 79/81 [97.5%], and 87/91 [95.6%] vs. 81/83 [97.6%]; readers 1, 2 and 3, respectively) and 3.0 T (77/81 [95.1%] vs. 77/80 [96.3%], 80/81 [98.8%] vs. 81/81 [100%], and 77/82 [93.9%] vs. 79/81 [97.5%]; readers 1, 2, and 3, respectively). In subjects with enhancing lesions, the reasons most frequently reported across all readers for the benefit of enhancement following gadobenate administration were similar for the two doses and occurred in similar proportions of patients for all readers: 1) enhancement provided improved visualization of the size, extent and/or margins of a lesion (better conspicuity); 2) the pattern of enhancement was useful in predicting the grade, histologic type, vascularity and/or aggressiveness of a lesion; and 3) enhancement revealed an abnormality not seen on the precontrast MR images (Table 6).

QUANTITATIVE ENHANCEMENT. LBR and CNR values calculated from measurements made on precontrast and postcontrast T1wSE/FSE images at 1.5 T or 3.0 T are shown in Figure 3. Readers 1, 2, and 3 evaluated 40, 32, and 64 lesions, respectively, in patients who received 0.05 mmol/kg gadobenate (22, 13, and 31 lesions, respectively, at 1.5 T; 18, 19, and 33 lesions, respectively, at 3.0 T) and 36, 22, and 41 lesions, respectively, in patients who received 0.1 mmol/kg gadobenate (20, 13, and 22 lesions, respectively,

at 1.5 T; 16, 9, and 19 lesions, respectively, at 3.0 T). The change from precontrast to postcontrast was significant for both parameters and both doses at both field strengths. All three readers measured significantly higher LBR for the 0.1 mmol/kg dose compared to the 0.05 mmol/kg dose, while two of three readers measured significantly higher CNR for the 0.1 mmol/kg dose compared to the 0.05 mmol/kg dose (Fig. 3).

Quantitative determinations of LBR and CNR based on precontrast and postcontrast T1wGRE images were made by readers 1, 2, and 3 for 1, 0 and 0 lesions, respectively, in patients who received 0.05 mmol/kg gadobenate, and for 11, 13 and 20 lesions, respectively, in patients who received 0.1 mmol/kg gadobenate (0, 1 and 4 lesions, respectively at 1.5 T; 11, 12, and 16 lesions, respectively at 3.0 T). The limited number of evaluations made on T1wGRE images precluded meaningful comparison between doses for these image sets.

Discussion

Our study shows that a gadobenate dose of 0.05 mmol/kg is noninferior to a full 0.1 mmol/kg dose for delineation of lesion borders, visualization of lesion internal morphology, and qualitative assessment of lesion contrast enhancement, for both extra-axial lesions imaged at 1.5 T and for extra-axial and intra-axial lesions imaged at 3.0 T. In confirming noninferiority, our findings support the results of previous smaller scale studies that demonstrated diagnostic efficacy of half dose gadobenate for CE-MRI applications in the CNS[18–21] and other body regions.[22–26] Although patients were enrolled retrospectively into our study, prospective image evaluation was performed by three experienced neuroradiologists who were unaffiliated with the investigational centers and fully blinded to all clinical and radiological information, including the dose of gadobenate used.

While noninferiority was confirmed for qualitative lesion visualization endpoints, quantitative assessments of LBR and CNR unsurprisingly revealed significantly greater enhancement with 0.1 mmol/kg gadobenate. This is to be expected based on the physical principals governing contrast enhancement of MR signal and has been demonstrated previously in very early studies of gadobenate in CE-MRI of cerebral metastases.[27,28] However, while the 0.1 mmol/kg dose of gadobenate provided significantly greater quantitative enhancement compared to the 0.05 mmol/kg dose, a previous study[14] has shown that the enhancement achieved with 0.05 mmol/kg gadobenate is still sufficiently high as to be not significantly different to that obtained with a full 0.1 mmol/kg dose of gadoteric acid (Dotarem; Guerbet, Aulnay-sous-Bois, France) in CE-MRI of CNS lesions.

The greater signal intensity enhancement achieved with gadobenate reflects the higher longitudinal (R1) relaxivity of

TABLE 4. Precontrast vs. Precontrast + Postcontrast Lesion Visualization for Extra-axial Lesions at 1.5 T

		Reader 1		Reader 2		Reader 3	
Assessment	**Dose group** **Number of Subjects Number of Lesions**	**0.05 mmol/kg** N = 86 n^a = 169	**0.1 mmol/kg** N = 80 n^a = 165	**0.05 mmol/kg** N = 86 n^a = 122	**0.1 mmol/kg** N = 81 n^a = 142	**0.05 mmol/kg** N = 85 n^a = 136	**0.1 mmol/kg** N = 81 n^a = 149
Lesion border delineation	Precontrast	2.0 ± 1.1	1.9 ± 1.3	1.7 ± 1.1	1.6 ± 1.1	1.7 ± 0.9	1.4 ± 0.9
	Precontrast + postcontrast	3.0 ± 1.1	3.1 ± 1.2	2.6 ± 1.1	2.6 ± 1.2	3.1 ± 1.2	2.9 ± 1.4
	Mean change ± SD[b]	1.0 ± 1.6	1.2 ± 1.9	0.9 ± 1.7	1.0 ± 1.8	1.4 ± 1.6	1.5 ± 1.8
	Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	−0.1 (−0.3, 0.2); P = 0.79		−0.03 (−0.3, 0.3); P = 0.97		0.2 (−0.1, 0.5); P = 0.14	
Lesion internal morphology	Precontrast	2.0 ± 1.1	1.8 ± 1.3	1.7 ± 1.0	1.5 ± 1.1	1.7 ± 0.9	1.5 ± 0.9
	Precontrast + postcontrast	3.0 ± 1.1	3.1 ± 1.2	2.6 ± 1.1	2.6 ± 1.2	3.2 ± 1.3	3.0 ± 1.4
	Mean change ± SD[b]	1.0 ± 1.6	1.3 ± 1.9	0.9 ± 1.7	1.1 ± 1.7	1.5 ± 1.8	1.6 ± 1.9
	Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	−0.1 (−0.3, 0.2); P = 0.61		−0.05 (−0.3, 0.3); P = 0.99		0.2 (−0.1, 0.6); P = 0.11	
Lesion contrast enhancement	Precontrast	2.1 ± 1.1	1.9 ± 1.3	1.6 ± 1.0	1.5 ± 1.0	1.7 ± 0.9	1.6 ± 1.0
	Precontrat + postcontrast	3.1 ± 1.1	3.2 ± 1.2	2.6 ± 1.1	2.6 ± 1.2	3.3 ± 1.2	3.1 ± 1.4
	Mean change ± SD[b]	1.0 ± 1.5	1.3 ± 1.9	1.0 ± 1.7	1.2 ± 1.7	1.6 ± 1.7	1.5 ± 1.9
	Difference in means of precontrast + postcontrast[c]; (95% CI of difference); p-value[d]	−0.1 (−0.3, 0.2); P = 0.54		−0.04 (−0.3, 0.3); P = 0.83		0.2 (−0.1, 0.5); P = 0.13	

[a]Up to 10 largest lesions were assessed per subject.
[b]All P-values from the paired t-test for mean change from precontrast to precontrast + postcontrast were $P < 0.0001$.
[c]Difference in means of precontrast + postcontrast between dose 0.05 mmol/kg and 0.1 mmol/kg.
[d]P-value and confidence intervals for the difference in means between dose groups are obtained from the mixed model: precontrast + postcontrast score = precontrast-score. A lower 95% CI margin that is greater than the noninferiority margin −0.4 implies that gadobenate 0.05 mmol/kg is noninferior to gadobenate 0.1 mmol/kg.

TABLE 5. Precontrast vs. Precontrast + Postcontrast Lesion Visualization for Intra- and Extra-Axial Lesions at 3.0 T

	Reader 1		Reader 2		Reader 3	
Dose group	0.05 mmol/kg	0.1 mmol/kg	0.05 mmol/kg	0.1 mmol/kg	0.05 mmol/kg	0.1 mmol/kg
Number of Subjects / Number of Lesions	$N = 77$ / $n^a = 135$	$N = 78$ / $n^a = 217$	$N = 79$ / $n^a = 103$	$N = 80$ / $n^a = 167$	$N = 79$ / $n^a = 113$	$N = 79$ / $n^a = 149$
Assessment						
Lesion border delineation						
Precontrast	1.8 ± 1.1	2.0 ± 1.2	1.8 ± 1.0	1.5 ± 1.1	1.5 ± 0.9	1.4 ± 0.9
Precontrast + postcontrast	3.1 ± 1.3	3.0 ± 1.4	3.0 ± 0.9	2.8 ± 1.1	3.3 ± 1.1	3.2 ± 1.3
Mean change $\pm$ SD[b]	1.3 ± 1.8	1.0 ± 2.1	1.2 ± 1.2	1.3 ± 1.6	1.9 ± 1.5	1.8 ± 1.7
Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	$0.1\ (-0.2,\ 0.4)$; $p = 0.51$		$0.2\ (-0.2,\ 0.3)$; $p = 0.72$		$0.1\ (-0.2,\ 0.4)$; $p = 0.38$	
Lesion internal morphology						
Precontrast	1.9 ± 1.2	2.0 ± 1.2	1.7 ± 0.9	1.5 ± 1.1	1.5 ± 0.9	1.4 ± 1.0
Precontrast + postcontrast	3.1 ± 1.3	3.0 ± 1.4	2.8 ± 0.9	2.7 ± 1.1	3.4 ± 1.1	3.2 ± 1.3
Mean change $\pm$ SD[b]	1.2 ± 1.8	1.0 ± 2.1	1.1 ± 1.2	1.2 ± 1.6	1.9 ± 1.4	1.9 ± 1.9
Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	$0.1\ (-0.3,\ 0.4)$; $P = 0.66$		$0.1\ (-0.3,\ 0.3)$; $P = 0.87$		$0.2\ (-0.1,\ 0.5)$; $P = 0.14$	
Lesion contrast enhancement						
Precontrast	1.9 ± 1.2	2.0 ± 1.2	1.7 ± 0.8	1.4 ± 1.0	1.5 ± 1.0	1.4 ± 1.0
Precontrast + postcontrast	3.2 ± 1.3	3.1 ± 1.4	2.8 ± 0.9	2.8 ± 1.1	3.4 ± 1.1	3.3 ± 1.3
Mean change $\pm$ SD[b]	1.3 ± 1.8	1.0 ± 2.1	1.2 ± 1.2	1.3 ± 1.5	1.9 ± 1.5	1.9 ± 1.8
Difference in means of precontrast + postcontrast[c]; (95% CI of difference); P-value[d]	$0.1\ (-0.2,\ 0.4)$; $P = 0.52$		$0.1\ (-0.3,\ 0.2)$; $P = 0.69$		$0.1\ (-0.2,\ 0.5)$; $P = 0.31$	

[a]Up to 10 largest lesions were assessed per subject.

[b]All P-values from the paired t-test for mean change from precontrast to precontrast + postcontrast were $P < 0.0001$.

[c]Difference in means of precontrast + postcontrast between dose 0.05 mmol/kg and 0.1 mmol/kg.

[d]P-value and confidence intervals for the difference in means between dose groups are obtained from the mixed model: precontrast + postcontrast score = precontrast-score. A lower 95% CI margin that is greater than the noninferiority margin −0.4 implies that gadobenate 0.05 mmol/kg is noninferior to gadobenate 0.1 mmol/kg.
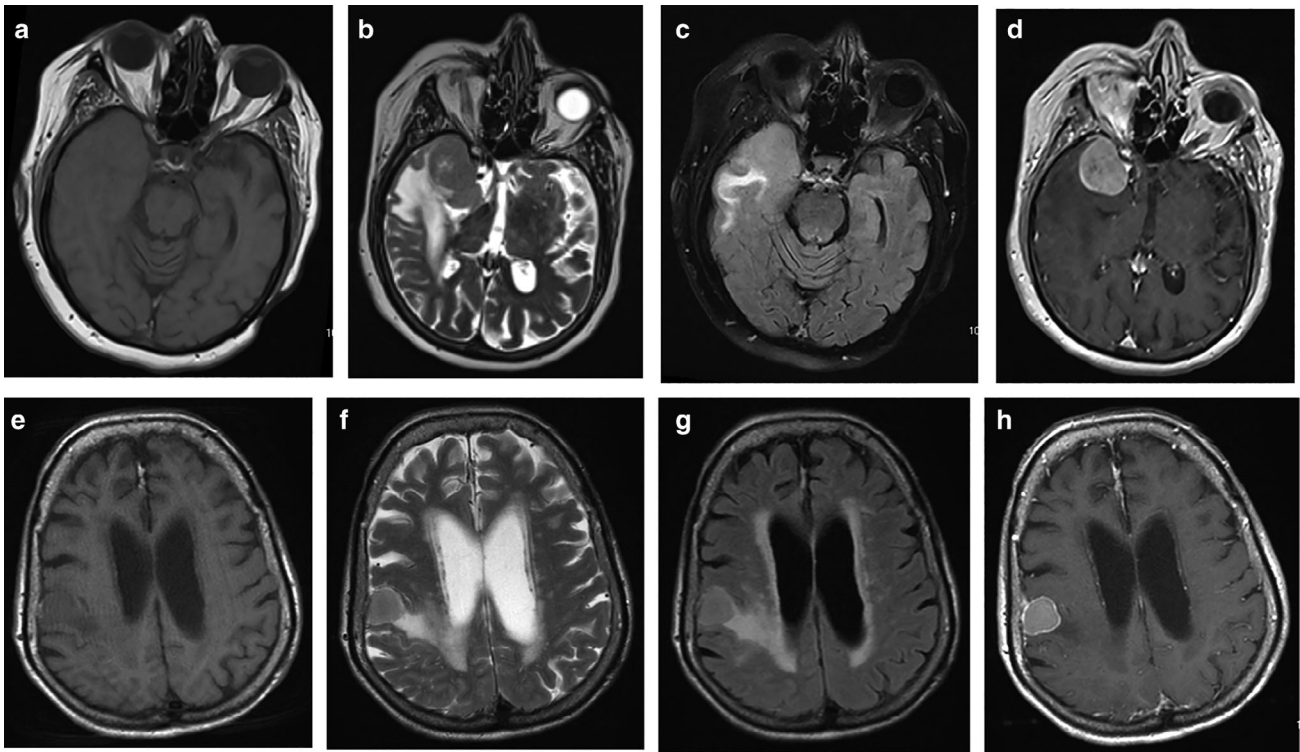
FIGURE 1: Meningiomas imaged at 1.5 T after administration of 0.1 mmol/kg gadobenate dimeglumine (18 mL; 77-year old female [83 kg]; Siemens Espree; Top Row) and after administration of 0.05 mmol/kg gadobenate dimeglumine (7.5 mL; 91-year-old female [68.1 kg]; Philips Achieva; Bottom row). The MR images in the top row (0.1 mmol/kg gadobenate) show right temporal pole sulcal effacement on precontrast T1 (a), with abnormal hypointensity on T2 (b), and with surrounding vasogenic edema on T2 FLAIR (c). The postcontrast T1 image (d) shows a right temporal pole enhancing mass with well-defined borders and a dural tail. The postcontrast T1 image (d) clearly demonstrates that this abnormality is an extra-axial neoplasm. Similarly, the MR images in the bottom row (0.05 mmol/kg gadobenate) show right frontal parietal sulcal effacement with area of faint hypointensity on precontrast T1 (e), and a mildly hyperintense lesion on T2 (f) and T2 FLAIR (g). The postcontrast T1 image (h) shows a solid enhancing mass with well-defined borders. The postcontrast T1 image (h) shows that this abnormality is an extra-axial neoplasm. The mass is better delineated on the postcontrast T1 image (h) than on the precontrast T1 image (e). A diagnosis of meningioma is readily achievable with a half dose of gadobenate.

this GBCA[9] and raises an interesting clinical choice regarding the appropriate dose to use in clinical routine. On the one hand, the imaging and diagnostic performances achievable with 0.1 mmol/kg gadobenate are significantly superior to those achievable with other GBCAs administered at the same dose under identical conditions.[10–15] On the other hand, the higher dose may result in greater levels of retained Gd in brain and body tissues compared with a lower dose. While there is no evidence of harm associated with retained Gd,[4–8] the current widely accepted recommendation is to reduce the dose of GBCA administered whenever possible while not denying a CE-MRI examination when clinically indicated.[1] Clearly, the levels of retained Gd would be minimized if a lower dose were practicable for routine CE-MRI procedures. Given the current concern over the use of GBCAs in clinical practice, a practical rule-of-thumb might be to utilize a full dose whenever greater contrast enhancement is likely to markedly improve diagnostic performance and improve therapeutic outcomes and a reduced dose for other scenarios, such as disease monitoring and surveillance.

Applications for which a full dose might be appropriate include scenarios both where a high degree of confidence in the predictive value of a negative test has impact and those where detection of early disease has major impact. This might be particularly important for the exclusion or detection of metastases for stereotactic radiosurgery in oncologic patients and presurgical planning and follow-up of patients with intra-axial tumors (e.g., gliomas) for whom prognosis and longer-term survival are improved if macroscopically complete tumor removal is achieved.[29] In this latter setting, a full dose would be especially relevant for aggressive tumors such as high-grade gliomas to detect disease progression earlier so that treatment can be adjusted. The value of full dose gadobenate in these patients would be in improving the detection and delineation of small or poorly enhancing lesions and improving the visualization of enhancing regions of glioma which are known to correspond histologically to the hypervascular tissue of viable tumor.[29] In such cases, the short-term risk to patients from undetected lesions or of incomplete resection is undoubtedly of greater concern than any potential long-term risks associated with Gd
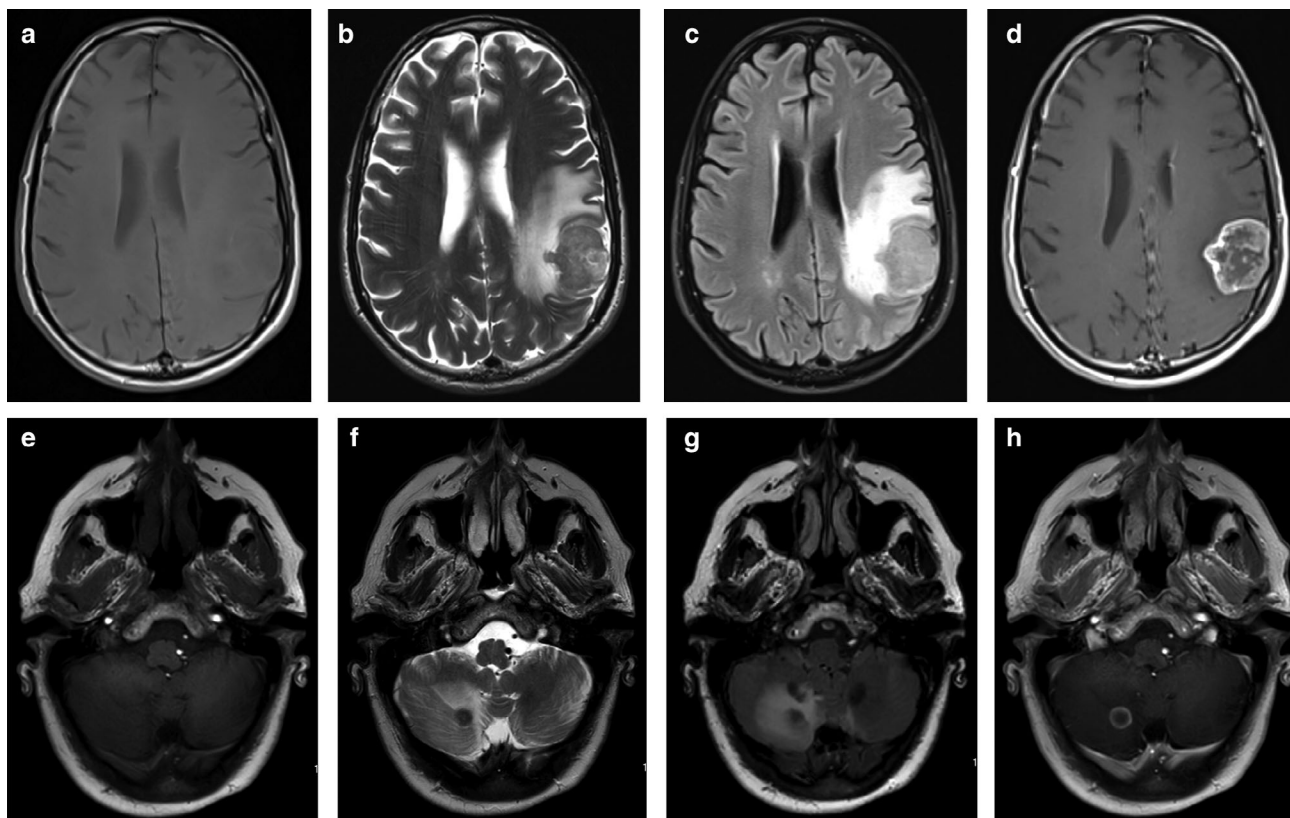
FIGURE 2: Metastases from non-small cell lung cancer imaged at 3.0 T after administration of 0.1 mmol/kg gadobenate dimeglumine (10 mL; 66-year-old male [51.1 kg]; Siemens Skyra; top row) and from endometrial cancer after administration of 0.05 mmol/kg gadobenate dimeglumine (8 mL; 77-year-old female [81.1 kg]; Philips Ingenia; Bottom Row). The MR images in the top row (0.1 mmol/kg gadobenate) demonstrate a left parietal lobe mass, isointense on precontrast T1 (a), hypointense on T2 (b), and surrounded by moderate vasogenic edema on T2 FLAIR (c). The postcontrast T1 image (d) clearly delineates an enhancing necrotic mass with well-defined borders. The mass and its extent are better delineated on the postcontrast T1 image (d) than on the precontrast T1 image (a). The MR images in the bottom row (0.05 mmol/kg gadobenate) show a left cerebellar hemisphere mass, isointense on precontrast T1 (e), hypointense on T2 (f), and with surrounding vasogenic edema on T2 FLAIR (g). The postcontrast T1 image (h) clearly delineates a rim-enhancing lesion with well-defined borders. This finding is not well seen on the precontrast T1 image (E). Overall, better delineation of lesion borders, visualization of internal lesion morphology, and lesion contrast enhancement are achieved with the full dose of gadobenate, although the lesion is visualized with half dose gadobenate.

retention. For the same reason, a full dose might also be appropriate for follow-up examinations in these patients to look for residual or recurrent tumor following resection.

Conversely, a lower dose might be practicable for imaging extra-axial tumors, routine monitoring of patients with known benign lesions or conditions such as multiple sclerosis (MS) which require regular follow-up CE-MRI, post-operative spinal imaging, and imaging of pediatric patients. Unfortunately, the absence of pediatric patients imaged with 0.1 mmol/kg gadobenate in this study precluded a comparison in this age group. However, previous studies have shown that 0.05 mmol/kg gadobenate is safe in patients as young as 4 days[30,31] and that no significant differences in diagnostic accuracy are apparent between gadobenate doses of ≤0.08 mmol/kg and >0.08 mmol/kg in neonates and infants undergoing CE-MRI of the CNS.[31] Notably, gadobenate is approved by the U.S. Food & Drug Administration for CE-MRI of the CNS in children younger than 2 years at volumes of 0.1–0.2 mL/kg bodyweight, corresponding to doses of 0.05–0.1 mmol/kg bodyweight.[32]

In common with other group II GBCAs classified by the ACR,[3] gadobenate has not been associated with any unconfounded cases of NSF and is considered safe for use in patients with chronic kidney disease (CKD). A recent meta-analysis of studies investigating the incidence of NSF in patients with stage 4 or 5 CKD following administration of group II GBCAs showed that by far the greatest number of investigated high-risk patients received gadobenate (3167/4931 [64.2%] included patients) and that the incidence of NSF was 0%.[33] Another recent study in patients who received predominantly half dose gadobenate confirmed the absence of NSF in 860 patients with impaired renal function and additionally showed that Gd levels in the skin following as many as nine gadobenate administrations were extremely low (<0.05 μg/g to 1.1 μg/g) and consistent with background values.[34] Importantly, these levels were distinctly lower than levels typically measured in skin biopsies of patients with NSF (4.8 μg/g–106 μg/g) who received other GBCAs.[34] In this regard, it should be noted that Gd

TABLE 6. Additional Enhancement Information For All Lesions

Additional Information	0.05 mmol/kg			0.1 mmol/kg		
	Reader 1 N (%)	Reader 2 N (%)	Reader 3 N (%)	Reader 1 N (%)	Reader 2 N (%)	Reader 3 N (%)
Subjects with enhancement of lesions[a]	130	129	155	134	145	151
Enhancement revealed an abnormality not seen on precontrast images	27 (20.8)	18 (14.0)	152 (98.1)	35 (26.1)	43 (29.7)	147 (97.4)
Enhancement provided improved visualization of the size, extent and/or margins of a lesion (better conspicuity)	88 (67.7)	108 (83.7)	155 (100)	86 (64.2)	112 (77.2)	151 (100.0)
The pattern of enhancement was useful in predicting the grade, histologic type, vascularity and/or aggressiveness of a lesion	18 (13.8)	78 (60.5)	136 (87.7)	7 (5.2)	82 (56.6)	127 (84.1)
Enhancement suggested residual tumor in an operative site not distinguishable from post-surgical changes on precontrast images	1 (0.8)	2 (1.6)	26 (16.8)	2 (1.5)	5 (3.4)	23 (15.2)
Enhancement documented the activity or aggressiveness of certain non-neoplastic processes, including multiple sclerosis, vasculitis and infection	2 (1.5)	1 (0.8)	0	7 (5.2)	2 (1.4)	1 (0.7)
Enhancement proved the subacute nature of a lacuna or infarct when the age of such lesion was clinically and radiologically indeterminate	1 (0.8)	1 (0.8)	0	0	0	0
Other diagnostic benefits of enhancement	7 (5.4)	2 (1.6)	0	6 (4.5)	4 (2.8)	1 (0.7)

[a]Denominator for percentages.
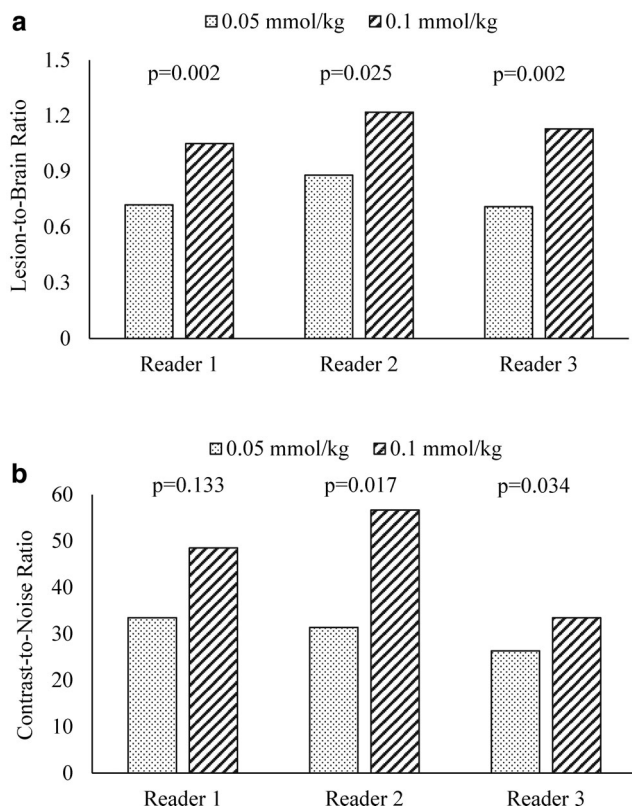Subjects may have finding in more than one category.

a

b

FIGURE 3: Quantitative analysis of LBR and CNR for enhancing lesions in patients who received 0.05 mmol/kg and 0.1 mmol/kg doses of gadobenate. Columns represent the change (postcontrast minus precontrast) for each dose. Data based on SI measurements made on precontrast and postcontrast T1wSE/FSE images acquired at 1.5 T or 3.0 T.

retention has been observed to a greater or lesser extent with all GBCAs regardless of molecular structure[35–38] and appears an unavoidable consequence of GBCA use. Although studies to assess the impact of Gd retention on human development and neurologic function are difficult to perform, studies in animals have revealed no impact of gadobenate on growth, maturation, behavior or cognitive function of neonatal and juvenile rats, even after very high cumulative doses (15 mmol/kg; corresponding to about 25 injections of a standard 0.1 mmol/kg dose in humans).[39] Certainly, the possibility to lower the GBCA dose wherever possible would result in lower levels of retained Gd which might help to allay concerns about possible long-term effects of Gd retention. Interestingly, more patients with a higher degree of renal impairment received the lower 0.05 mmol/kg dose in our study. Although an assessment of renal impairment was not an objective of the study, the use of a half dose in patients with greater renal impairment might reflect a more widespread tendency toward GBCA dose lowering.

Limitations

First, the retrospective design may have introduced selection bias. To minimize any possibility of bias, patient recruitment

was performed backward chronologically to identify all the MR examinations stored in the local site Picture Archiving and Communication Systems (PACS) of the enrollment centers. All subjects were consecutively screened to verify whether they met the inclusion criteria of the study. Not meeting the inclusion criteria in terms of age, pathology, field strength, and dose of GBCA administered were the only reasons for a patient not to be enrolled. Hence, the possibility of selection bias was minimized as much as possible. Concerning the evaluation of study images, this was carried out according to a defined protocol, using a rigorous off-site blinded read methodology. Second, the parallel-group design of the study is less suited to showing differences in contrast enhancement and lesion visualization compared with a crossover, intraindividual study design. However, the sample size of the study was large enough to allow meaningful conclusions of potential differences between the two doses tested. Third, we were unable to compare the two doses of gadobenate for visualization of intra-axial lesions at 1.5 T or for imaging of pediatric subjects. Nevertheless, the data acquired in this study were considered sufficient and adequate for the approval of half dose gadobenate in Canada in patients with extra-axial lesions imaged at 1.5 T and in all CNS examinations performed at 3.0 T.[40] Further work should be performed to confirm the efficacy of reduced dose gadobenate across all indications and field strengths particularly in comparison with higher doses of alternative, lower relaxivity GBCAs.

Conclusion

Our study revealed no significant differences between 0.05 mmol/kg and 0.1 mmol/kg doses of gadobenate for qualitative lesion visualization of extra-axial lesions at 1.5 T and both intra-axial and extra-axial lesions at 3.0 T. These findings suggest that a half dose of gadobenate might be a practicable solution to concerns over Gd retention for certain CE-MRI applications in the CNS.

Acknowledgments

REFERENCES

1. Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB, International Society for Magnetic Resonance in Medicine. Gadolinium deposition in the brain: Summary of evidence and recommendations. Lancet Neurol 2017;16:564-570.

2. Mathur M, Jones JR, Weinreb JC. Gadolinium deposition and nephrogenic systemic fibrosis: A radiologist's primer. Radiographics 2020;40:153-162.

3. American College of Radiology. Manual on Contrast Media. Version 2020. http://www.acr.org. Accessed September 18, 2020.

4. Welk B, McArthur E, Morrow SA, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. JAMA 2016;316:96-98.

5. Ackermans N, Taylor C, Tam R, et al. Effect of different doses of gadolinium contrast agent on clinical outcomes in MS. Mult Scler J Exp Transl Clin 2019;5(1):2055217318823796.

6. Cocozza S, Pontillo G, Lanzillo R, et al. MRI features suggestive of gadolinium retention do not correlate with expanded disability status scale worsening in multiple sclerosis. Neuroradiology 2019;61:155-162.

7. Zivadinov R, Bergsland N, Hagemeier J, et al. Cumulative gadodiamide administration leads to brain gadolinium deposition in early MS. Neurology 2019;93:e611-e623.

8. Vymazal J, Krámská L, Brožová H, Růžička E, Rulseh AM. Does serial administration of gadolinium-based contrast agents affect patient neurological and neuropsychological status? Fourteen-year follow-up of patients receiving more than fifty contrast administrations. J Magn Reson Imaging 2020;51:1912-1913.

9. Shen Y, Goerner FL, Snyder C, et al. T1 Relaxivities of gadolinium-based magnetic resonance contrast agents in human whole blood at 1.5, 3, and 7 T. Invest Radiol 2015;50:330-338.

10. Maravilla KR, Maldjian JA, Schmalfuss IM, et al. Contrast enhancement of central nervous system lesions: Multicenter intraindividual crossover comparative study of two MR contrast agents. Radiology 2006;240:389-400.

11. Rumboldt Z, Rowley HA, Steinberg F, et al. Multicenter, double-blind, randomized, intra-individual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 tesla. J Magn Reson Imaging 2009;29:760-767.

12. Rowley HA, Scialfa G, Gao PY, et al. Contrast-enhanced MR imaging of brain lesions: A large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. AJNR Am J Neuroradiol 2008;29:1684-1691.

13. Seidl Z, Vymazal J, Mechl M, et al. Does higher gadolinium concentration play a role in the morphologic assessment of brain tumors? Results of a multicenter intraindividual crossover comparison of gadobutrol versus gadobenate dimeglumine (the MERIT study). AJNR Am J Neuroradiol 2012;33:1050-1058.

14. Vaneckova M, Herman M, Smith MP, et al. The benefits of high relaxivity for brain tumor imaging: Results of a multicenter intraindividual crossover comparison of gadobenate dimeglumine with gadoterate meglumine (the BENEFIT study). AJNR Am J Neuroradiol 2015;36:1589-1598.

15. Kanal E, Maravilla K, Rowley HA. Gadolinium contrast agents for CNS imaging: Current concepts and clinical evidence. AJNR Am J Neuroradiol 2014;35:2215-2226.

16. Elster AD, Moody DM, Ball MR, Laster DW. Is Gd-DTPA required for routine cranial MR imaging? Radiology 1989;173:231-238.

17. Montgomery AA, Graham A, Evans PH, Fahey T. Inter-rater agreement in the scoring of abstracts submitted to a primary care research conference. BMC Health Serv Res 2002;2:8-12.

18. Huang B, Liang CH, Liu HJ, et al. Low dose contrast-enhanced magnetic resonance imaging of brain metastases at 3.0T using high-relaxivity contrast agents. Acta Radiol 2012;51:78-84.

19. Khouri Chalouhi K, Papini GD, Bandirali M, Sconfienza LM, Di Leo G, Sardanelli F. Less is better? Intraindividual and interindividual comparison between 0.075 mmol/kg of gadobenate dimeglumine and 0.1 mmol/kg of gadoterate meglumine for cranial MRI. Eur J Radiol 2014;83:1245-1249.

20. Crisi G, Filice S, Erb G, Bozzetti F. Effectiveness of a high relaxivity contrast agent administered at half dose in dynamic susceptibility contrast MRI of brain gliomas. J Magn Reson Imaging 2017;45:500-506.

21. Filice S, Crisi G, Erb G. T2*-correction in dynamic contrast-enhanced magnetic resonance imaging of glioblastoma from a half dose of high-Relaxivity contrast agent. J Comput Assist Tomogr 2017;41:816-821.

22. Rehnitz C, Do T, Klaan B, et al. Feasibility of using half-dose Gd-BOPTA for delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at the knee, compared with standard-dose Gd-DTPA. J Magn Reson Imaging 2020;51:144-154.

23. Cheong BY, Duran C, Preventza OA, Muthupillai R. Comparison of low-dose higher-relaxivity and standard-dose lower-relaxivity contrast media for delayed-enhancement MRI: A blinded randomized crossover study. AJR Am J Roentgenol 2015;205:533-539.

24. Balci NC, Inan N, Anik Y, Erturk MS, Ural D, Demirci A. Low-dose gadobenate dimeglumine versus standard-dose gadopentate dimeglumine for delayed contrast-enhanced cardiac magnetic resonance imaging. Acad Radiol 2006;13:833-839.

25. Bauner KU, Reiser MF, Huber AM. Low dose gadobenate dimeglumine for imaging of chronic myocardial infarction in comparison with standard dose gadopentetate dimeglumine. Invest Radiol 2009;44:95-104.

26. Schneider G, Maas R, Schultze Kool L, et al. Low-dose gadobenate dimeglumine versus standard dose gadopentetate dimeglumine for contrast-enhanced magnetic resonance imaging of the liver: An intra-individual crossover comparison. Invest Radiol 2003;38:85-94.

27. Balériaux D, Colosimo C, Ruscalleda J, et al. Magnetic resonance imaging of metastatic disease to the brain with gadobenate dimeglumine. Neuroradiology 2002;44:191-203.

28. Schneider G, Kirchin MA, Pirovano G, et al. Gadobenate dimeglumine-enhanced magnetic resonance imaging of intracranial metastases: Effect of dose on lesion detection and delineation. J Magn Reson Imaging 2001;14:525-539.

29. Kuhn MJ, Picozzi P, Maldjian JA, et al. Evaluation of intraaxial enhancing brain tumors on magnetic resonance imaging: Intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for visualization and assessment, and implications for surgical intervention. J Neurosurg 2007;106:557-566.

30. Schneider G, Schürholz H, Kirchin MA, Bücker A, Fries P. Safety and adverse effects during 24 hours after contrast-enhanced MRI with gadobenate dimeglumine (MultiHance) in children. Pediatr Radiol 2013;43:202-211.

31. Enterline DS, Martin KW, Parmar HA, Triulzi FM, Colosimo C. Safety and diagnostic efficacy of gadobenate dimeglumine in MRI of the brain and spine of neonates and infants. AJNR Am J Neuroradiol 2019;40:2001-2009.

32. MultiHance prescribing information in the USA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021357s016s017,021358s015s016lbl.pdf. Accessed 22 September, 2020.

33. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a group II gadolinium-based contrast agent: A systematic review and meta-analysis. JAMA Intern Med 2020;180:223-230.

34. Kanal E, Patton TJ, Krefting I, Wang C. Nephrogenic systemic fibrosis risk assessment and skin biopsy quantification in patients with renal disease following gadobenate contrast administration. AJNR Am J Neuroradiol 2020;41:393-399.

35. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: Preliminary results from 9 patients with Normal renal function. Invest Radiol 2016;51:447-453.

36. Stanescu AL, Shaw DW, Murata N, et al. Brain tissue gadolinium retention in pediatric patients after contrast-enhanced magnetic resonance exams: Pathological confirmation. Pediatr Radiol 2020;50:388-396.

37. Fingerhut S, Sperling M, Holling M, et al. Gadolinium-based contrast agents induce gadolinium deposits in cerebral vessel walls, while the neuropil is not affected: An autopsy study. Acta Neuropathol 2018;136:127-138.

38. Kiviniemi A, Gardberg M, Ek P, Frantzén J, Bobacka J, Minn H. Gadolinium retention in gliomas and adjacent normal brain tissue:

Association with tumor contrast enhancement and linear/macrocyclic agents. Neuroradiology 2019;61:535-544.

39. Bussi S, Penard L, Bonafè R, et al. Non-clinical assessment of safety and gadolinium deposition after cumulative administration of gadobenate dimeglumine (MultiHance®) to neonatal and juvenile rats. Regul Toxicol Pharmacol 2018;92:268-277.

40. MultiHance Product Monograph, Canada. https://pdf.hres.ca/dpd_pm/ 00053801.PDF. Accessed 30 December 2020