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Philippe Robert, Véronique Vives, Anne-Laure Grindel, Stéphane Kremer, Guillaume Bierry, et al.. Contrast-to-Dose Relationship of Gadopiclenol, an MRI Macrocylic Gadolinium-based Contrast Agent, Compared with Gadoterate, Gadobenate, and Gadobutrol in a Rat Brain Tumor Model. *Radiology*, 2019, 294 (1), 10.1148/radiol.2019182953 . hal-04608911

HAL Id: hal-04608911

<https://hal.science/hal-04608911>

Submitted on 11 Jun 2024

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Contrast-to-Dose Relationship of Gadopiclenol, an MRI Macrocytic Gadolinium-based Contrast Agent, Compared with Gadoterate, Gadobenate, and Gadobutrol in a Rat Brain Tumor Model

Philippe Robert, PhD • Véronique Vives, BS • Anne-Laure Grindel, MS • Stéphane Kremer, MD, PhD • Guillaume Bierry, MD, PhD • Gaëlle Louin, PharmD, PhD • Sébastien Ballet, PhD • Claire Corot, PharmD, PhD

From the Department of Research and Innovation, Imaging and Biological Research Division, Guerbet Group, BP57400, 95943 Roissy CDG, France (P.R., V.V., A.L.G., G.L., S.B., C.C.); and Radiologie 2, CHU de Strasbourg, I-Cube, Université de Strasbourg, Strasbourg, France (S.K., G.B.). Received December 28, 2018; revision requested March 7, 2019; final revision received August 7; accepted August 21. Address correspondence to P.R. (e-mail: philippe.robert@guerbet.com).

Conflicts of interest are listed at the end of this article.

See also the editorial by Tweedle in this issue.

Radiology 2020; 294:117–126 • <https://doi.org/10.1148/radiol.2019182953> • Content codes: **NR** **MR**

Background: Detection of cerebral lesions at MRI may benefit from a chemically stable and more sensitively detected gadolinium-based contrast agent (GBCA). Gadopiclenol, a macrocyclic GBCA with at least twofold higher relaxivity, is currently undergoing clinical trials in humans.

Purpose: To determine the relationship between MRI contrast enhancement and the injected dose of gadopiclenol in a glioma rat model compared with those of conventional GBCA at label dose.

Materials and Methods: Between April and July 2012, 32 rats implanted with C6 glioma received two intravenous injections at a 24-hour interval. The injections were randomly selected among five doses of gadopiclenol (0.025, 0.05, 0.075, 0.1, and 0.2 mmol/kg) and three reference GBCAs (gadoterate meglumine, gadobutrol, and gadobenate dimeglumine) at 0.1 mmol/kg. MRI tumor enhancement was assessed on T1-weighted images before and up to 30 minutes after injection. Two blinded radiologists visually and qualitatively scored contrast enhancement, border delineation, and visualization of tumor morphology. Quantitatively, variations in contrast-to-noise ratio (Δ CNR) between tumor and contralateral parenchyma were calculated at each time point and were compared for each treatment at 5 minutes by using a mixed model after normality test.

Results: A total of 24 rats underwent the complete protocol ($n = 5-7$ per group). A linear dose-dependent Δ CNR relationship was observed between 0.025 and 0.1 mmol/kg for gadopiclenol ($R^2 = 0.99$). No difference in Δ CNR was observed between the three reference GBCAs ($P \geq .55$). Gadopiclenol resulted in twofold higher Δ CNR at 0.1 mmol/kg ($P < .001$ vs gadobutrol and gadoterate, $P = .002$ vs gadobenate) and similar Δ CNR at 0.05 mmol/kg ($P = .56$, $P > .99$, and $P = .44$ compared with gadobutrol, gadobenate, and gadoterate, respectively). For both readers, 0.05 mmol/kg of gadopiclenol improved contrast enhancement, border delineation, and visualization of tumor morphology (scores > 3 compared with scores between 2 and 3 for the marketed GBCA).

Conclusion: Gadopiclenol at 0.05 mmol/kg yielded comparable change in contrast-to-noise ratio and morphologic characterization of brain tumors compared with gadobenate, gadoterate, or gadobutrol at 0.1 mmol/kg.

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Online supplemental material is available for this article.

After brain metastasis, primary central nervous system (CNS) tumors are the most common malignant brain lesions (1); more than 40 000 are malignant, and 60% of all malignant CNS tumors are gliomas (2). With less than 10% of patients surviving at 5 years, early and accurate diagnosis of brain tumors is crucially important. Glioblastoma multiforme leads to 255 000 deaths per year worldwide (3).

With gadolinium-based contrast agents (GBCA), contrast material-enhanced MRI is the first-line diagnostic approach for the detection and characterization of primary CNS tumors. This technique dramatically improves the diagnostic accuracy of brain MRI. Clinical management of brain tumors is highly dependent on

the information provided by contrast-enhanced MRI, including the location, the size, and the precise border delineation of the lesion. Moreover, contrast material uptake is a surrogate marker for distinguishing between low-grade glioma (no contrast material uptake) and high-grade glioma (contrast enhancement).

The common clinical dosage for GBCAs is 0.1 mmol per kilogram of body weight, which has a very high benefit-to-risk ratio (4). A higher GBCA dose leads to better brain lesion detection (5), but a concern is the dose-dependent long-term retention of gadolinium in tissue, especially after injection of less thermodynamically stable (ie, linear) GBCAs (6). Thus, medical agencies (the European Medical Agency, the

Abbreviations

CNR = contrast-to-noise ratio, CNS = central nervous system, GBCA = gadolinium-based contrast agent

Summary

Gadopictenol had approximately twofold higher T1 relaxivity at MRI compared with the gadolinium-based contrast agents gadoterate, gadobenate, and gadobutrol; 0.1 mmol/kg of gadopictenol had approximately twofold higher tumor T1 contrast enhancement compared with gadoterate, gadobenate, and gadobutrol.

Key Results

- For detection of brain glioma in a rat model, 0.05 mmol/kg of high-relaxivity macrocyclic gadopictenol was comparable with currently marketed gadolinium-based contrast agents (gadoterate, gadobenate, and gadobutrol) at 0.1 mmol/kg (contrast-to-noise ratio [CNR], 6.6 for gadopictenol vs 5.3 [$P = .35$], 7.1 [$P > .99$], and 6.6 [$P = .44$] for gadobutrol, gadobenate, and gadoterate, respectively).
- At 0.1 mmol/kg, gadopictenol provided 1.8-to-2.4-fold greater CNR than gadobutrol, gadobenate, and gadoterate (CNR, 12.9 ± 3.1 for gadopictenol vs 5.3 ± 1.5 [$P < .001$], 7.1 ± 3.0 [$P = .002$], and 6.6 ± 2.3 [$P < .001$] for gadobutrol, gadobenate, and gadoterate, respectively).
- Gadopictenol had a similar residual level of gadolinium in the cerebellum as the macrocyclic gadobutrol (5 months after repeated administration: 0.07 and 0.09 nmol/g, respectively, $P > .99$), and a 29-fold lower level compared with linear gadodiamide (2.0 nmol/g, $P = .04$).

Food and Drug Administration in the United States, the Pharmaceutical and Medical Devices Agency in Japan) have recommended limiting the injected dose (7).

These limitations in dose can be overcome by designing a contrast agent with high T1-relaxivity (4). Higher relaxivity is classically obtained by using a higher molecular weight of the molecule to reduce the tumbling rate of the gadolinium chelate. However, because of the larger molecular weight, the distribution volume of these compounds is reduced (8), and this leads to reduced accessibility to the tumors (9).

Gadopictenol is a new nonspecific, non-protein-binding, nonionic macrocyclic GBCA characterized by a low molecular weight (<1 kDa), high kinetic stability, and two-to-three-fold the longitudinal relaxivity from 1.5 T to 3.0 T (Table 1) with similar extracellular distribution volume and renal excretion as currently marketed GBCAs (10–13). A phase I clinical trial demonstrated the excellent safety and pharmacokinetic profile of gadopictenol in humans (11).

Investigating the potential benefits of this high-relaxivity contrast agent to improve the detection and characterization of brain tumors at the same or even lower dose is of interest. The current preclinical study evaluated the contrast-to-dose relationship of gadopictenol in brain tumors in a rat model of glioma and compared it with that of three reference GBCAs at the current clinical dose. We hypothesized that the higher longitudinal relaxivity of gadopictenol would lead to better brain tumor visualization (in terms of contrast-to-noise ratio [CNR], border delineation, and internal morphology visualization) than the reference GBCAs, even at a lower dose.

Table 1: In Vitro Relaxivities at 1.5 and 3.0 T for Gadobutrol, Gadobenate, Gadoterate, and Gadopictenol

Contrast Agent	1.5 T		3.0 T	
	r1	r2	r1	r2
Gadobutrol	5.2 ± 0.3	6.1 ± 0.9	5.0 ± 0.3	7.1 ± 0.9
Gadobenate	6.3 ± 0.3	8.7 ± 0.9	5.5 ± 0.3	11.0 ± 1.0
Gadoterate	3.6 ± 0.2	4.3 ± 0.9	3.5 ± 0.2	4.9 ± 0.9
Gadopictenol	12.8 ± 1.3	15.1 ± 1.5	11.6 ± 1.2	14.7 ± 1.5

Note.—Data are mean relaxivities (as $\text{mM}^{-1} \cdot \text{sec}^{-1}$) ± standard deviations (data given in reference 10). For gadobutrol, gadobenate, and gadoterate, data were measured in plasma at 37°C (13). For gadopictenol, data were from nuclear magnetic relaxation dispersion profiles and MR relaxometry at 37°C in reconstituted lyophilized human plasma (27) standard deviations.

Materials and Methods

Animal experiments were conducted in accordance with European Union Directives 2010/63/EU. Animals were randomly allocated to the various groups. This study was performed between April and July 2012 by the Guerbet research department using a blinded and randomized method. Qualitative data analysis was performed by two radiologists (S.K. and G.B.) who had no conflicts of interest and who had independent and full control of data inclusion and information.

Animal Model

Brain gliomas were induced in 32 female Sprague-Dawley rats (SPF/OFA rats; Charles River, L'Arbresle, France) as described previously (14). Briefly, we implanted C6 glioma tumor cells extracted from *Rattus norvegicus* tissue (ATCC, Manassas, Va) (15) with the animals in a state of general anesthesia (mixture of 3.8 mL ketamine, 2 mL xylazine, and 2.2 mL NaCl 0.9%) in the right caudate nucleus, 3.5 mm to the right of the bregma, by referring to a rat brain atlas (16,17). All rats received the same number of cells (4×10^4 cells/ μL ; volume, 5 μL). Animals were imaged at 12 and 13 days after tumor induction. All experiments were performed by V.V. and G.L. (with 15 and 5 years of experience, respectively, in in vivo preclinical research, including MRI).

Contrast Agent Injection

Gadopictenol (Guerbet, Roissy Charles de Gaulle, France; 0.5 M) was compared with gadoterate meglumine (Dotarem; Guerbet; 0.5 M), gadobutrol (Gadavist; Bayer Pharmaceuticals, Berlin, Germany; 1 M), and gadobenate dimeglumine (Multihance; Bracco, Milan, Italy; 0.5 M). Rats were randomized into eight groups ($n = 8$ per group); each rat received two intravenous injections at a 24-hour interval of a dose randomly selected from among five doses of gadopictenol (0.025, 0.05, 0.075, 0.1, or 0.2 mmol/kg) and the three reference GBCAs at 0.1 mmol/kg. Twenty-four hours was considered a sufficient delay to avoid any interaction between the two injections (18). To ensure blinded injection, products were diluted to be injected at the same volume (0.4 mL/kg).

Imaging Protocol

MRI was performed with the animal in a state of general anesthesia (3%–3.5% isoflurane) at 2.35 T (BioSpec, Bruker, Germany). T1 enhancement of the brain tumor was assessed before and up to 30 minutes after injection with a two-dimensional spin-echo sequence (repetition time msec/echo time msec, 500/10; field of view, 40 × 40 mm²; matrix, 192 × 192; two averages; acquisition time, 3 minutes 12 seconds). Three images and 10 images were acquired before and after injection, respectively.

Image Analysis

First, all images were qualitatively evaluated by two independent and experienced radiologists (S.K. and G.B., with 15 years of experience in clinical radiology). The 624 images (24 rats, 13 images per rat per injection, two injections) were randomized and anonymized for scoring. Readers were blinded to the type of contrast agent, dose, and delay time between the start of the injection and start of the MRI acquisition. Precision in border delineation, quality of internal morphology depiction, and visual degree of contrast enhancement were evaluated with a score of 1 to 4 (from "none" to "excellent") (Table 2). The mean scores given by the two readers were then reported. Interreader variability was determined by counting the percentages of the 624 images for which the quotations of the two readers differed by zero points (ie, both readers gave the same score) and by one, two, or three points.

Second, the paired overall diagnostic preference assessment was performed blindly on crossover images obtained 5 minutes after injection. The two readers had to decide independently which of the two images from the same animal they preferred. Images were rated as equivalent in the case of no preference. Scores of the two readers are reported.

Next, signal intensities of the tumor and contralateral healthy brain were measured by positioning regions of interest (ROIs) on the tumor (V.V. and A.L.G. [with 2 years of experience in preclinical MRI]). The ROIs for noise were drawn outside the brain. Results are expressed as the change in CNR (Δ CNR), as described below:

$$\Delta\text{CNR}(t) = \text{CNR}(t) - \text{CNR}(\text{mean_pre}),$$

with $\text{CNR}(t) = \frac{\text{SI}_{\text{tumor}}(t) - \text{SI}_{\text{brain}}(t)}{\text{SD}_{\text{noise}}(t)}$, where SI is the signal

intensity, SD the standard deviation, and $\text{CNR}(\text{mean_pre})$ is the mean of the three preinjection images.

Contrast-to-dose relationship of gadopichlenol was evaluated with a linear equation by fitting the Δ CNR at approximately 5 minutes in function of dose (5 minutes is inside the 4–8-minute recommended window for postcontrast T1-weighted image analysis, according to Ellingson et al [1]). The increase in Δ CNR at 5 minutes (ie, the ratio of the mean Δ CNR at 5 minutes of the gadopichlenol at different doses to the mean Δ CNR at 5 minutes for the three reference GBCAs) was then calculated.

Table 2: Quantitative Analysis Scoring System

Score	Border Delineation	Internal Morphology	Contrast Enhancement
1	None: No or unclear delineation	Poor: Poorly seen	None: No enhancement
2	Moderate: Some areas of clear delineation but not all	Moderate: Minor parts of lesion visible	Moderate: Weakly enhanced
3	Good: Almost clear but not complete delineation	Good: Majority of lesion is clearly seen but with minor parts of lesion nonvisible	Good: Clearly enhanced
4	Excellent: Border outline is sharp with clear delineation	Excellent: Lesion is well seen and complex heterogeneous areas can be seen	Excellent: Clearly and brightly enhanced

Histopathologic Analysis

Nine brains from 24 rats were randomly selected and analyzed histologically with hematoxylin-eosin staining. Slices were analyzed for the localization of the tumor within the brain parenchyma, the infiltrating status, and the level of necrosis.

Statistical Analysis

Data are expressed as means \pm standard deviations. Statistical analysis was performed with SAS 9.4 software (SAS Institute, Cary, NC). A mixed model with Δ CNR at 5 minutes as response and the injected product as factor was performed. To take into account the repeated measurements on the same rats, a random effect on rats was added to the model. Comparisons of the five doses of gadopichlenol were tested against the three reference products. *P* values were adjusted by means of the Dunnett bilateral adjustment with regard to the multiple comparisons to each of the three references. Moreover, pairwise comparisons between the three references were performed by using a Tukey adjustment. Normality and homogeneity of the variance of the residuals were checked. *P* \leq .05 was considered to indicate a significant difference.

Results

Tumor Model

A total of 24 rats completed the full protocol. All of the observed lesions were confirmed to be malignant, with a mean surface area of 13.6 mm² \pm 4.3. Tumors were localized mainly in the septo-diencephalon region and were associated with a low level of necrosis; clinically significant necrosis was observed in only one rat, with 13% (42 of 320) necrosis area within the tumor (Fig 1, A). In all rats, tumors had clear boundaries, and few tumor cells were found in the tumor margins (Fig 1, B). Good visual correspondence was found between contrast-enhanced MRI and histologic findings (Fig 1, C).

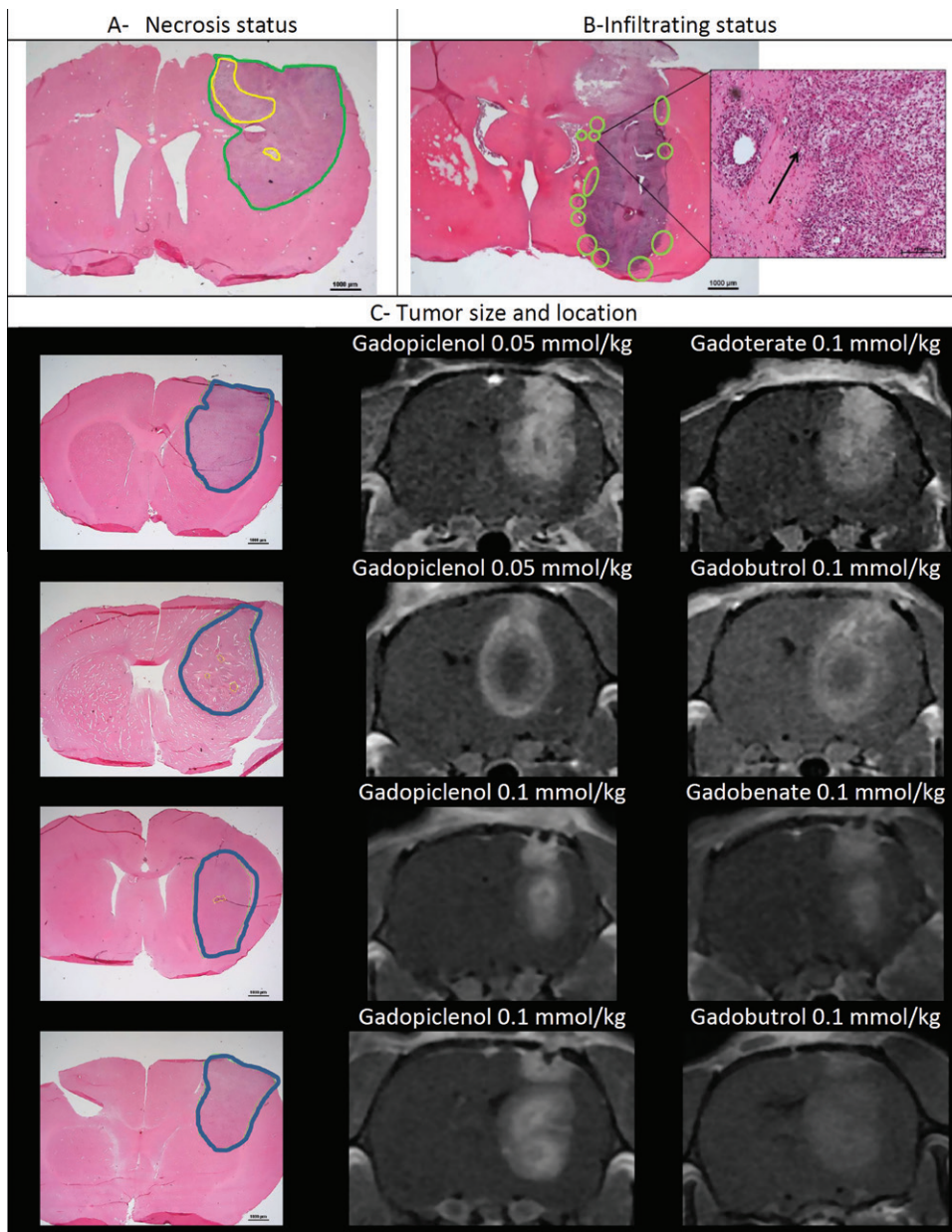


Figure 1: Histologic findings of brain glioma. A, Necrosis level is indicated by yellow circle. B, Infiltrating status of the tumor (green circles = area of infiltrating tumor cells). C, Examples of correspondence between histologic findings and images from contrast-enhanced MRI (repetition time msec/echo time msec, 500/10).

Qualitative Analysis

Examples of crossover images are given in Figure 2. An example of scoring is shown in Figure 3, and results are summarized in Figure 4. A gadoplicenol dose of 0.025 mmol/kg was poorly rated and led to worse diagnosis than the reference GBCAs administered at 0.1 mmol/kg. In the case of 0.05 mmol/kg gadoplicenol and higher, qualitative analysis revealed diagnostic superiority over the control GBCAs with respect to the three qualitative parameters. At 0.05 mmol/kg gadoplicenol or higher, border delineation, internal morphology, and contrast enhancement were rated as 3 or higher, demonstrating good-to-excellent tumor delineation with good enhancement and most of the lesion being clearly seen, with minor parts of the lesion invisible. Interestingly, 0.1 and 0.2 mmol/kg gadoplicenol

provided unique information on complex areas within the tumor, with scores equal or close to 4, especially after 10 minutes (Fig 4, B). Qualitatively, gadoplicenol at 0.05 mmol/kg or higher provided the best performance from 5 minutes after injection and during the 30-minute follow-up. As with the control GBCAs, images became less contrasted from 10 minutes, with diminished border and internal morphology delineation, except for 0.2 mmol/kg gadoplicenol. Focusing on 5 minutes after injection, groups could be separated into the following three categories (Table 3): 0.025 mmol/kg gadoplicenol, with the lowest diagnostic performance (score < 2); the three control GBCAs, with an intermediate level of performance (score between 2 and 3); and the gadoplicenol doses of 0.05, 0.075, 0.1, and 0.2 mmol/kg, with the highest level of performance (score > 3).

The overall diagnostic preferences of the two readers are reported in Figure 4, D. When comparing the overall diagnostic preference 5 minutes after injection, 0.025 mmol/kg gadoplicenol was never preferred compared with the standard dose for GBCAs. However, at 0.05 mmol/kg, gadoplicenol was superior or equal to standard-relaxivity GBCAs in 75% (six of eight) of rats for both readers. At

0.075 mmol/kg, gadoplicenol was superior to standard-relaxivity GBCAs in 100% (five of five) of rats for reader 1 and in 80% (four of five) of rats for reader 2. Finally, gadoplicenol at 0.1 and 0.2 mmol/kg was always preferred for both readers (five of five). Interreader variability was very small: for more than 94% of the images, quotations of the two readers for the three qualitative parameters were the same or differed by only one point (95% [593 of 624], 94% [585 of 624], and 96% [598 of 624] for border delineation, internal morphology, and contrast enhancement, respectively), as reported in Figure 4, E.

Quantitative Analysis

The higher CNR of the tumor compared with the contralateral healthy brain was plotted as a function of time for all groups

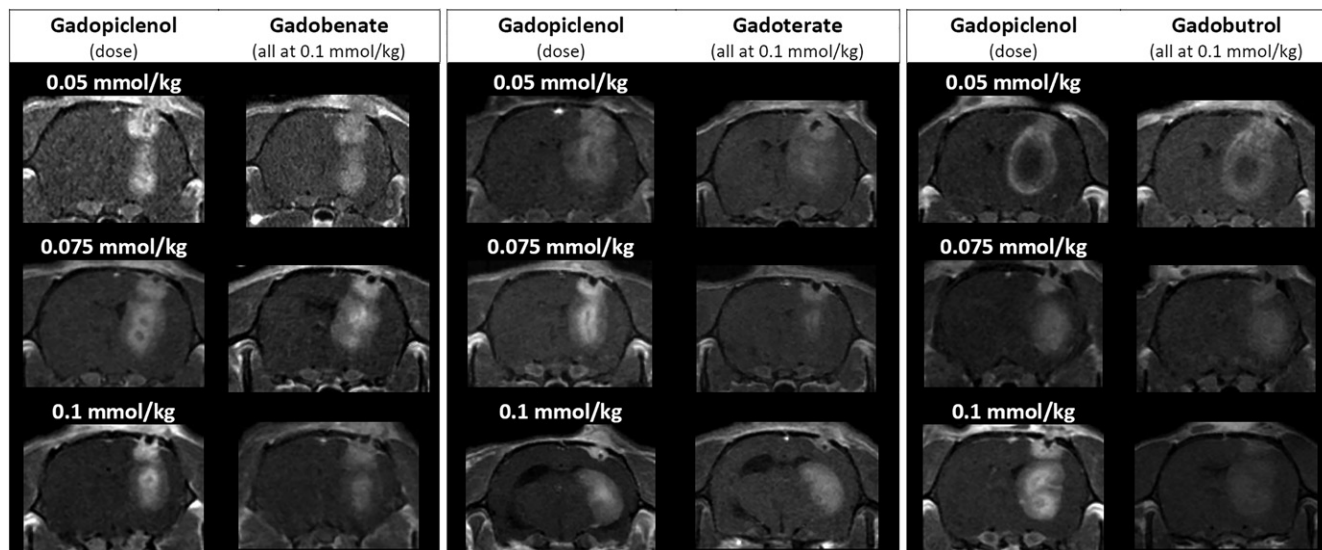


Figure 2: Example crossover images from T1-weighted MRI (repetition time msec/echo time msec, 500/10) of the brain tumors of nine rats 5 minutes after contrast agent injection.

Dose (mmol/kg)	0.025			0.05			0.075			0.1			0.2		
	BD	IM	CE	BD	IM	CE	BD	IM	CE	BD	IM	CE	BD	IM	CE
Reader 1	1	1	1	3	4	4	4	4	4	3	3	3	4	4	4
Reader 2	1	1	2	2	2	3	3	4	3	4	4	4	4	4	4

Figure 3: Relationship of dose of gadopichlenol to visual assessment of contrast enhancement at T1-weighted MRI (repetition time msec/echo time msec, 500/10). Images obtained 5 minutes after contrast agent injection are shown with examples of the scores from the two independent radiologists. Reader 1 was S.K., and reader 2 was G.B. BD = border delineation, CE = contrast enhancement (with the rating scale 1 = none or poor, 2 = moderate, 3 = good, 4 = excellent [see details of the rating scale in Table 2]), IM = internal morphology.

(Fig 5). Statistics comparing the mean Δ CNR at 5 minutes are reported in Table 4. No difference in preinjection Δ CNR was demonstrated between the first and the second injection with a 24-hour delay (preinjection Δ CNR was 0.00 ± 0.22 and 0.04 ± 0.24 for the first and second injections, respectively). Peak enhancement was observed at approximately 5 minutes after injection for gadobutrol, gadoterate, and gadobenate, whereas maximum contrast enhancement occurred at approximately 10–15 minutes after injection for gadopichlenol. For gadopichlenol, tumor enhancement improved with a higher dose. The reference GBCAs were in the range of 0.05 mmol/kg gadopichlenol during the 30 minutes of follow-up.

The mean contrast enhancement 5 minutes after injection was extracted from the data and compared between the groups (Fig 6). A linear relationship was found between the improved contrast in the tumor and a dose of gadopichlenol of between 0.025 and 0.1 mmol/kg: Δ CNR = $126 \cdot \text{dose}$ ($R^2 = 0.99$). The linearity was lost between 0.1 and 0.2 mmol/kg; at 0.2 mmol/kg, the mean Δ CNR was 17 ± 5 compared with the linear regression,

which predicted 25. The gain in enhancement with gadopichlenol is summarized in Table 4. At 5 minutes after injection, no difference was demonstrated between the three reference GBCAs (5.3 ± 1.5 , 7.1 ± 3.0 , and 6.6 ± 2.3 for gadobutrol, gadobenate, and gadoterate, respectively; $P \geq .55$). The lower dose resulted in twofold lower contrast compared with the three reference compounds (mean gain, 0.5 ± 0.1 ; $P \geq .06$). The protocol did not demonstrate any difference between gadopichlenol at 0.05 mmol/kg and the reference GBCAs at 0.1 mmol/kg (mean gain, 1.1 ± 0.2 , $P = .44$). Gadopichlenol at a dose of 0.1 mmol/kg provided double CNR enhancement compared with marketed contrast agents at the same dose (mean gain, 2.1 ± 0.3 ; $P \leq .002$). If gadopichlenol was injected at 0.2 mmol/kg, the Δ CNR improved by a factor of 2.6 ± 0.4 ($P < .001$).

Additional Evaluation of the Long-Term Presence of Gadolinium in the Cerebellum after Gadopichlenol

Additionally (see details in Appendix E1 [online]), an animal study performed between April and November 2018 evalu-

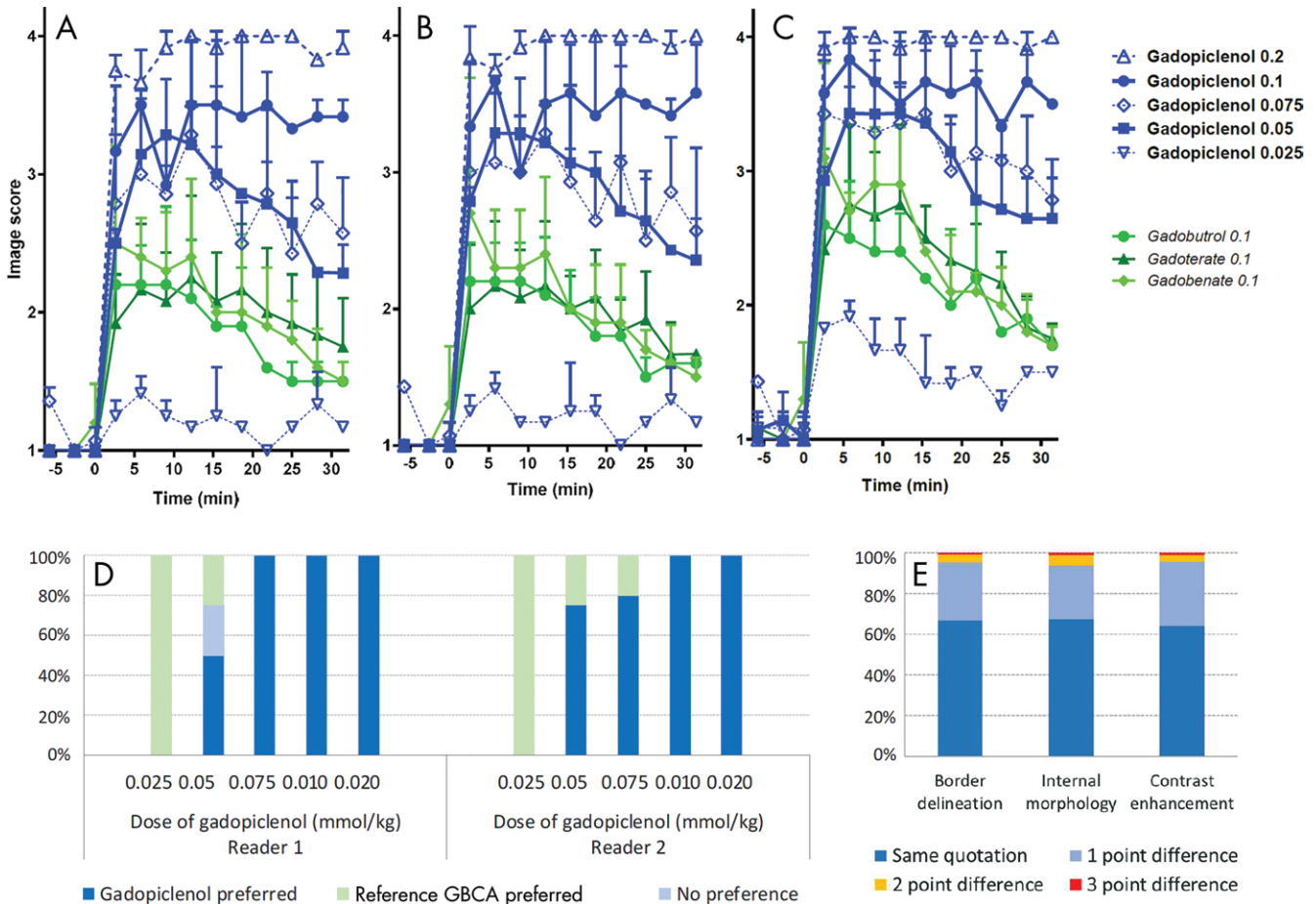


Figure 4: Graphs show results of qualitative analysis by two independent radiologists blinded to gadolinium dose of enhancement of brain tumor lesions at MRI. A, Time-dependent border delineation performance for the tumor. B, Time-dependent capacity to see the internal morphology. C, Time-dependent level of contrast enhancement. D, Diagnostic preference on paired images obtained 5 minutes after injection for each reader. E, Interreader variability (determined by counting the occurrence for having an identical image rating score by the two readers for the same image [same score = 0% difference] or having 1, 2, or 3 points of difference for the same image).

Table 3: Mean Scores of the Two Readers for Images Obtained 5 Minutes after Injection

Contrast Agent and Dose (mmol/kg)	Border Delineation	Internal Morphology	Contrast Enhancement
Gadoplicenol 0.025	1.4 ± 0.1	1.4 ± 0.1	1.9 ± 0.1
Gadoplicenol 0.05	3.1 ± 0.4	3.3 ± 0.4	3.4 ± 0.2
Gadoplicenol 0.075	3.0 ± 0.6	3.1 ± 0.5	3.4 ± 0.7
Gadoplicenol 0.1	3.5 ± 0.0	3.7 ± 0.0	3.8 ± 0.0
Gadoplicenol 0.2	3.7 ± 0.2	3.8 ± 0.1	4.0 ± 0.0
Gadobenate 0.1	2.4 ± 0.3	2.3 ± 0.4	2.7 ± 0.1
Gadoterate 0.1	2.2 ± 0.5	2.2 ± 0.5	2.8 ± 0.6
Gadobutrol 0.1	2.2 ± 0.3	2.2 ± 0.3	2.5 ± 0.4

Note.—Data are means ± standard deviations. Details of the rating scale are provided in Table 2 (briefly, a score of 1 = none or poor, and a score of 4 = excellent).

ated the long-term gadolinium presence in the cerebellum of healthy rats 5 months after injections of gadoplicenol, gadobutrol, gadodiamide (repeated administrations; total gadolinium dose, 12 mmol/kg), or saline, according to the protocol published by Robert et al (19). This analysis showed that gadoplicenol has a similar level of gadolinium in the cer-

ebellum as the macrocyclic gadobutrol (at 5 months: 0.07 nmol/g ± 0.02 and 0.09 nmol/g ± 0.08, respectively; $P > .99$) and 29-fold lower as compared with linear gadodiamide (2.02 nmol/g ± 0.21, $P < .05$ and $P < .02$, respectively). Results are in accordance with previous published results comparing gadoterate and gadodiamide in the same protocol at the same delay time after injection (0.08 nmol/g ± 0.04 and 2.29 nmol/g ± 0.30, respectively) (19).

Discussion

Contrast-enhanced MRI is the first-line diagnostic approach for the detection and characterization of brain lesions with suspected abnormal vascularity or disrupted blood-brain barrier, such as primary CNS tumors (1), brain metastases (20), or active inflammatory lesions of multiple sclerosis (21). Gadoplicenol is a new macrocyclic GBCA characterized by a longitudinal relaxivity of 12.8 mM⁻¹ · sec⁻¹ at 1.5 T and 11.6 mM⁻¹ · sec⁻¹ at 3.0 T, 2-to-3.6-fold higher than that of currently marketed GBCAs (10). Our study demonstrated that 5 minutes after injection, gadoplicenol provides similar contrast enhancement at 0.05 mmol/kg as three reference extracellular GBCAs at 0.1 mmol/kg ($\Delta\text{CNR} = 6.6 \pm 2.5$ for gadoplicenol vs 5.3 ± 1.5 [$P =$

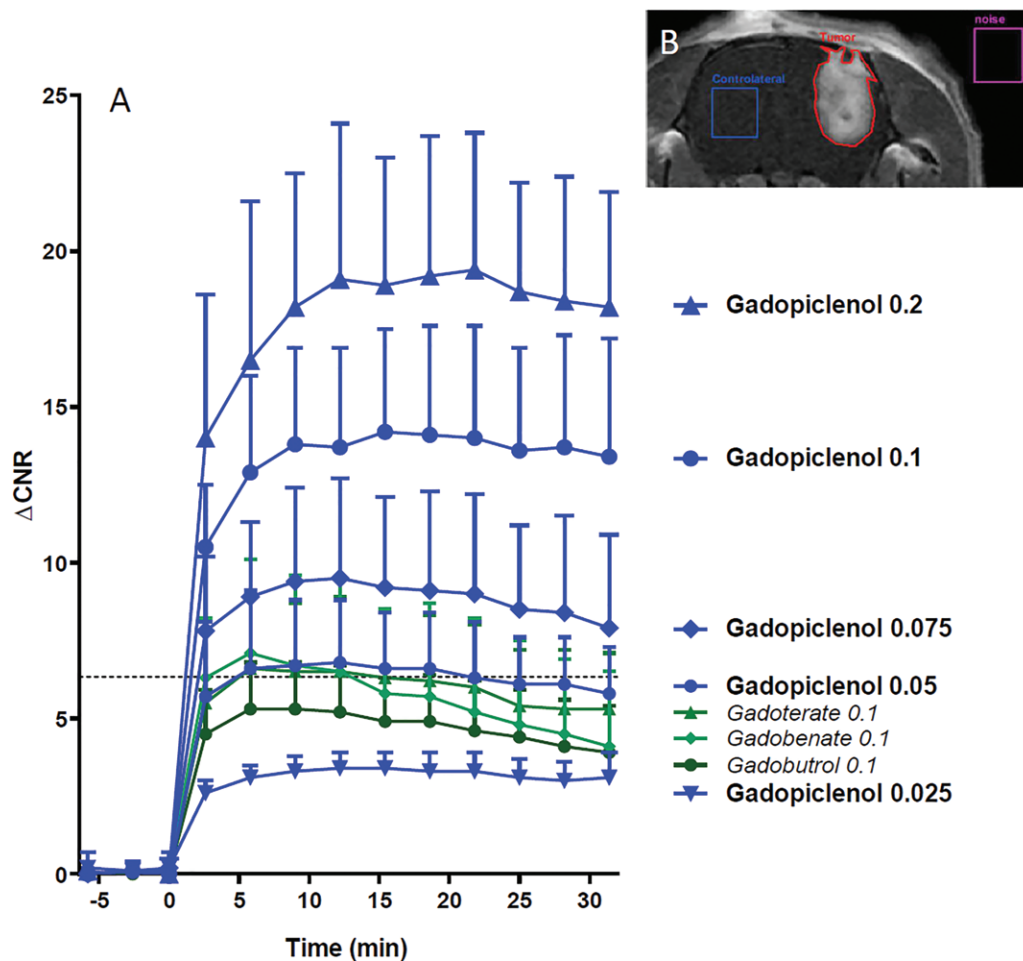


Figure 5: A, Graph shows evolution of change in contrast-to-noise ratio (ΔCNR) between 0 and 30 minutes after gadolinium injection. Dashed line = mean ΔCNR (6.3) at 5 minutes of reference contrast agents (0.1 mmol/kg gadoterate, gadobenate, gadobutrol). Error bars = standard deviations (only positive values are shown so as not to obscure the curve). B, Region of interest positioning on the tumor, the contralateral brain, and adjacent background air. ΔCNR comparisons at 5 minutes are reported in Table 4.

.35] for gadobutrol, 7.1 ± 3.0 [$P > .99$] for gadobenate, and 6.6 ± 2.3 [$P = .44$] for gadoterate). Blinded qualitative analysis suggested that overall image quality was higher with gadopixelenol at a half dose (qualitative scores ≥ 3.1 for all criteria), as compared with full doses of reference GBCAs (qualitative scores ≤ 2.8 for all criteria of the reference GBCAs at 0.1 mmol/kg). In addition, gadopixelenol provided 1.8-to-2.4-fold higher contrast enhancement at 0.1 mmol/kg ($\Delta\text{CNR} = 12.9 \pm 3.1$ for gadopixelenol vs 5.3 ± 1.5 [$P < .001$] for gadobutrol, 7.1 ± 3.0 [$P = .002$] for gadobenate, and 6.6 ± 2.3 [$P < .001$] for gadoterate). Furthermore, our study demonstrates the linearity of the contrast-to-dose relationship from 0.025 to at least 0.1 mmol/kg.

Contrast-enhanced MRI is frequently used during follow-up to evaluate the individual patient's response to treatment (22,23). With the continuous advances made in therapeutic strategies (24) such as stereotactic radiosurgery (25) and immunotherapies (26), the better imaging performance of gadopixelenol may improve patient follow-up in clinical practice (22,23). This greater imaging performance than that of marketed contrast agents was previously shown with a prototype of a high-relaxivity nonspecific GBCA, which was

studied for liver tumor imaging at very high field strength in a rat model (9.4 T) (27) and for MR angiography in a rabbit model at 1.5 T and 3.0 T (28).

High Longitudinal Relaxivity Applied to Improvement in the Diagnostic Efficacy

The CNR, spatial resolution, and acquisition time are interdependent parameters when optimizing an MRI protocol. The use of a contrast agent improves the CNR without impacting any of these parameters. The increase in contrast at 0.1 mmol/kg can also be used to improve the spatial resolution or reduce the acquisition time. Reduced MRI duration without affecting the diagnostic performance may be of interest to optimize the imaging session (29). Greater spatial resolution can improve tumor assessment and allow better detection of brain metastasis (30). At the standard clinical dose of 0.1 mmol/kg, higher relaxivity may improve brain lesion depiction (4), as shown by crossover preclinical (31,32) and clinical (33,34) studies comparing GBCAs and the linear GBCA gadobenate characterized by a higher relaxivity than conventional GBCAs because of protein binding. Finally, because contrast-enhanced MRI is the standard

Table 4: Δ CNR 5 Minutes after Gadopiclenol Injection as a Function of Dose

Contrast Agent	Dose (mmol/kg)	Mean Δ CNR at 5 Minutes	Increase vs Reference GBCAs	P Values
Gadobutrol	0.1	5.3 \pm 1.5	\times 0.7 vs gadobenate; \times 0.8 vs gadoterate	NS vs gadobenate ($P = .67$); NS vs gadoterate ($P = .99$)
Gadobenate	0.1	7.1 \pm 3.0	\times 1.3 vs gadobutrol; \times 1.1 vs gadoterate	NS vs gadobutrol ($P = .67$); NS vs gadoterate ($P = .55$)
Gadoterate	0.1	6.6 \pm 2.3	\times 1.2 vs gadobutrol; \times 0.9 vs gadobenate	NS vs gadobutrol ($P = .99$); NS vs gadobenate ($P = .55$)
Gadopiclenol	0.025	3.1 \pm 0.4	\times 0.6 vs gadobutrol; \times 0.4 vs gadobenate; \times 0.5 vs gadoterate (mean, 0.5 \pm 0.1)	NS vs gadobutrol ($P = .35$); NS vs gadobenate ($P = .06$); NS vs gadoterate ($P = .45$)
Gadopiclenol	0.05	6.6 \pm 2.5	\times 1.2 vs gadobutrol; \times 0.9 vs gadobenate; \times 1.0 vs gadoterate (mean, 1.1 \pm 0.2)	NS vs gadobutrol ($P = .56$); NS vs gadobenate ($P > .99$); NS vs gadoterate ($P = .44$)
Gadopiclenol	0.075	8.9 \pm 2.4	\times 1.7 vs gadobutrol; \times 1.3 vs gadobenate; \times 1.3 vs gadoterate (mean, 1.4 \pm 0.2)	$P = .02$ vs gadobutrol; NS vs gadobenate ($P = .29$); $P = .02$ vs gadoterate
Gadopiclenol	0.1	12.9 \pm 3.1	\times 2.4 vs gadobutrol; \times 1.8 vs gadobenate; \times 2.0 vs gadoterate (mean, 2.1 \pm 0.3)	$P < .001$ vs gadobutrol; $P = .002$ vs gadobenate; $P < .001$ vs gadoterate
Gadopiclenol	0.2	16.5 \pm 5.1	\times 3.1 vs gadobutrol; \times 2.3 vs gadobenate; \times 2.5 vs gadoterate (mean, 2.6 \pm 0.4)	$P < .001$ vs gadobutrol; $P < .001$ vs gadobenate; gadoterate ($P < .001$ vs gadoterate)

Note.—Unless otherwise specified, data are means \pm standard deviations. Δ CNR = change in contrast-to-noise ratio, NS = nonsignificant.

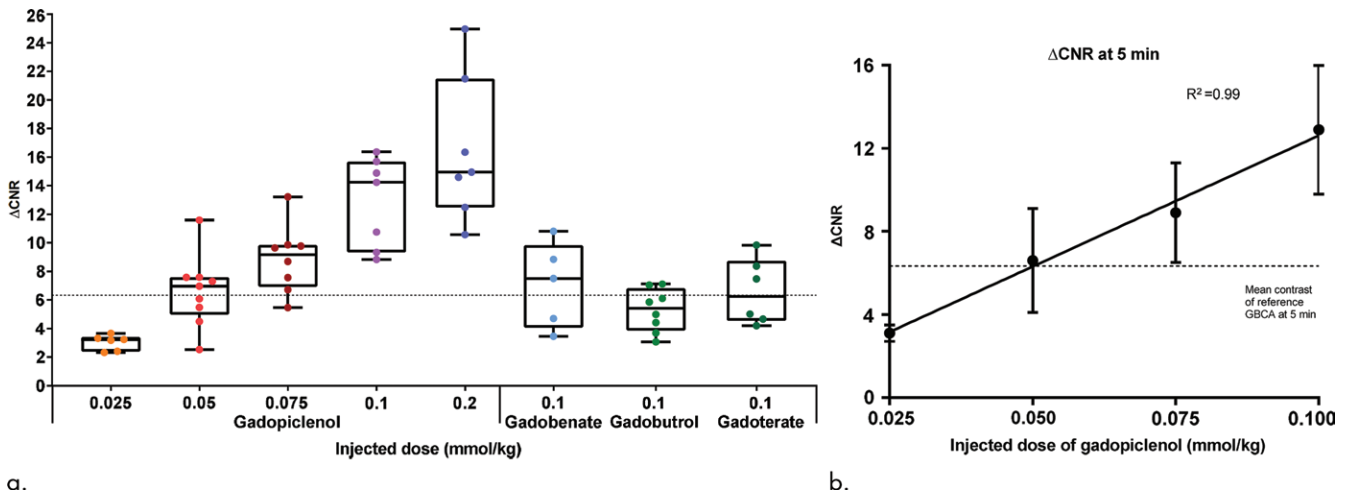


Figure 6: (a) Graph shows comparison of contrast-to-noise ratio (Δ CNR) at 5 minutes in relationship to gadolinium dose (as means \pm standard deviations [SDs]). (b) Graph shows comparison of gadopiclenol Δ CNR between doses of 0.025 and 0.1 mmol/kg.

approach to monitor low-grade glioma malignant transformation (35), high contrast enhancement may help in many clinical applications: In detection of smaller lesions or metastasis, which may help for gamma-knife surgery (36), early recognition and diagnosis of brain tumors, identifying early low-grade glioma malignant transformation, and more efficient CNS tumor follow-up.

High Longitudinal Relaxivity Applied to Reduce the Dose

A dose of 0.1 mmol/kg is usually applied according the recommendations for use in the summary of product characteristics. Because a causal relationship has been established

between linear contrast agents and the gadolinium deposition in tissues (bone, skin, brain) (37), there is growing interest in applying a low-dose MRI protocol while maintaining diagnostic accuracy to maintain an optimal benefit-to-risk ratio. In parallel, this study shows that gadopiclenol limits the long-term presence of gadolinium in the cerebellum as compared with linear GBCAs, comparably to gadobutrol (this study) and gadoterate in the same conditions (19), and as expected for a macrocyclic GBCA (37). We did not evaluate the dose dependence of gadolinium presence after gadopiclenol, but considering that residual long-term gadolinium presence is known to depend on the injected

dose (38), these results suggest that a 0.05-mmol/kg dose of gadopiclesol will lead to lower residual gadolinium than a 0.1-mmol/kg dose of gadobutrol. This study demonstrates that the use of a high-relaxivity GBCA allows this dose reduction while maintaining at least the same efficacy (19,37).

Our study had some limitations. First, because of the low number of animals, the preference in terms of glioma lesion detection was evaluated on only a few paired images (24 rats). Second, our study was applied in orthotopic xenografts that are not a perfect translational model of late-stage human glioma. In practice, comparison of the GBCAs took into account only large and highly vascularized tumor lesions with massive leakage of contrast agent, which could easily be observed with any of the tested agents. It would have been interesting to evaluate the detection of smaller lesions associated with low blood-brain barrier permeability that could hardly be seen with current, lower-relaxivity agents. Finally, it would have been interesting to perform our study in an multiple sclerosis model, because contrast material uptake plays a central role in evaluating the inflammatory status of plaques (39).

In conclusion, with more than twofold higher relaxivity than currently marketed gadolinium-based contrast agent (GBCAs), gadopiclesol provides at least 2.5 times greater enhancement of the tumor at the same dose (0.1 mmol per kilogram of body weight). In addition, at 0.05 mmol/kg, gadopiclesol provided the same contrast enhancement as marketed GBCAs at 0.1 mmol/kg.

Acknowledgments: We thank Robin Santus, BS, Martine Nain dit Ducret, BS, Claire Hollenbeck, BS, Marjorie Lemaître, BS, Miguel Soares, BS, Xavier Violas, BS, Jean-Sébastien Raynaud, PhD, Jean-Philippe Roquecave, BS, Anne Dencausse, PharmD, PhD, and Cécile Factor, PhD, at Guerbet Research for their experimental help; Atlantic Bone Screen (Nantes, France) for histologic analysis; and Jean-Marc Idée, PharmD, and Aymeric Seron, PhD, at Guerbet Research for their help in the manuscript.

Author contributions: Guarantors of integrity of entire study, P.R., G.L., S.B., C.C.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, P.R., V.V., A.L.G., S.K., G.B., G.L., C.C.; clinical studies, G.L.; experimental studies, all authors; statistical analysis, P.R., V.V., A.L.G., G.L.; and manuscript editing, P.R., V.V., A.L.G., S.K., G.L., S.B., C.C.

Disclosures of Conflicts of Interest: P.R. Activities related to the present article: is an employee of Guerbet; has stock or stock options in Guerbet. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. V.V. Activities related to the present article: is an employee of Guerbet; has stock or stock options in Guerbet. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. A.L.G. Activities related to the present article: is an employee of Guerbet. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. S.K. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a member of the board of Bayer; is on the speakers bureaus of Biogen, Roche, Sanofi, Novartis, and GE; has been paid for travel by Biogen, Guerbet, Bayer, and Bracco. Other relationships: disclosed no relevant relationships. G.B. disclosed no relevant relationships. G.L. disclosed no relevant relationships. S.B. Activities related to the present article: is an employee of Guerbet; has stock or stock options in Guerbet. Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships. C.C. Activities related to the present article: is an employee of Guerbet.

Activities not related to the present article: disclosed no relevant relationships. Other relationships: disclosed no relevant relationships.

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