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Effects of radiation on the NMR relaxation effects of aqueous solutions of gadolinium contrast agents

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Abstract

We investigate the effects of radiation on aqueous solutions of two common MRI contrast agents based on paramagnetic gadolinium chelates. Aqueous solutions of Gd–DTPA (gadolinium diethylenetriaminepentaacetic acid) and Gd–HP–DO3A (gadoteridol), as well as Gd–DTPA in the presence of concentrations of several common metabolites (*N*-acetylaspartate, Choline, Creatine and myo-inositol) typical of conditions *in vivo*, were irradiated at dose levels up to 30 Gy using a 6 MV linear accelerator and imaged using a 1.5 T MRI system. In addition, the effects of radiation dose on solution relaxation rates were compared with the effects of temperature by subjecting the same samples to varying temperatures over a range of 4 K using the same experimental conditions and imaging sequences. Radiation caused small increases (1% or less at a dose of 20 Gy) in the relaxivity of solutions. The effects of radiation on relaxivities were orders of magnitude smaller than the effects of temperature over the range in this study.

Keywords

contrast agents; relaxivity; temperature; radiation dose

1. INTRODUCTION

Magnetic resonance imaging (MRI) and spectroscopy (MRS) are in widespread use in the diagnosis and management of patients with cancer, and a majority of studies involve the administration of a paramagnetic contrast agent, which is usually a form of chelated gadolinium (Gd). Cancer patients may also undergo other procedures, including irradiation and thermotherapy. The mean half-lives for distribution and elimination of commonly used contrast agents are typically 0.2 and 1.6 h, respectively, in patients with normal renal function, while in patients with severe renal insufficiency, the mean half-life of elimination can be 30 h or more (1,2). There is then a potential interaction of radiation treatment on the stability, safety and relaxivity of contrast agents *in vivo*, and this may in turn affect the quantification of metabolites by MRS. To evaluate such possibilities, we studied the effects of radiation dose and temperature on the relaxivities of aqueous solutions of two widely used extracellular Gd contrast agents, Gd–DTPA (gadolinium diethylenetriaminepentaacetic acid, Magnevist, Berlex Labs) and Gd–HP–DO3A (gadoteridol, ProHance, Bracco Inc.) as well as Gd–DTPA

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in the presence of metabolites [*N*-acetylaspartate (NAA), creatine (Cr), choline (Ch) and *myo*-inositol (mI)] at typical concentrations found in the brain (3,4). Gd-DTPA is an ionic linear molecule (molecular weight (MW) 938) (5) and Gd-HP-DO3A is a nonionic macrocyclic molecule (MW 558.7) (6). Both agents are usually administered in doses of 0.1 mmol/kg weight when used clinically.

2. EXPERIMENTAL METHOD

Aqueous solutions of 0.5 mM of Gd-DTPA, Gd-HP-DO3A and Gd-DTPA + metabolites were irradiated using a 6 MV Varian Clinac 21EX linear accelerator and their relaxation rates were assessed using a 1.5 T GE Excite MRI/S System. The relaxivities were obtained by subtracting the relaxation rates of water from the relaxation rates of solutions and dividing them by the concentration of the contrast agents. The composition of the aqueous solution of metabolites is given in Table 1.

The solutions of Gd-DTPA and Gd-HP-DO3A in cylindrical phantoms (radius = 2.5 cm, height = 6 cm) were immersed in water evenly and irradiated together while solutions of Gd-DTPA + metabolites in spherical phantoms ($r = 5$ cm) were immersed in water evenly and irradiated individually at radiation dose levels of 10, 20 and 30 Gy over multiple fractionations with a fractional dose of 5 Gy, a dose rate of 4 Gy/min, a source to surface distance (SSD) of 97 and 94 cm, depth of 3 and 6 cm (cylinder and sphere), a beam size of 15×15 cm and a beam energy of 6 MV photon. A single beam was used and the dose variation was estimated to be $\pm 10\%$ for spherical and $\pm 7\%$ for cylindrical phantoms. The irradiated aqueous solutions of Gd complexes and metabolites were examined the same day by MRI. An inversion recovery fast spin echo (IR-FSE) sequence [echo time (T_E): 7.8 ms; inversion time (T_I): 50, 100, 200, 500, 1000, 2000, 3000 ms; repetition time (T_R): 6 s; FOV: 14×14 cm; matrix size: 128×128 ; echo train length: 16; imaging plane: axial; slice thickness: 5 mm; bandwidth (BW): 15.6 kHz] was used to measure R_1 (7–9). A multi-echo spin echo (MESE) sequence (T_E : 20, 40, 60, 80 ms; T_R : 6 s; FOV: 14×14 cm; 128×128 ; thickness: 5 mm; BW: 15.6 kHz) was used to measure R_2 (7,8). A single voxel point resolved spectroscopy (PRESS) sequence (T_E : 35, 70, 105, 140, 300, 500 and 1000 ms; T_R : 2 s; BW: 2500 Hz; 2048 points; eight phase-cycle; voxel size: $2 \times 2 \times 2$ cm³) was used to measure R_2 (variable T_E) and to acquire high-resolution spectra (10). Measurements were also made of solutions of Gd contrast agents and metabolites receiving no radiation over a temperature range of 4 K near room temperature (291–295 K). The thermal experiments were carried out by allowing the temperature of the sample in a thermally insulated polystyrene container to increase very slowly from the storage temperature (291 K) to the scanner's room temperature (295 K) through thermodynamic equilibrium. The temperature course of the sample was verified through measurement of the thermally induced spin phase shift or proton resonance frequency (11,12). The temperature accuracy in this experiment was estimated to be ± 0.1 K. The imaging and spectroscopic data were analyzed using Matlab (Mathworks, USA) and SAGE/Probe-P (GE Medical Systems, USA). The experimental R_1 was obtained by fitting a least squares curve to inversion recovery data; R_2 was obtained by fitting a straight line to the logarithm of the magnitude of half echo (PRESS) and echo (MESE) over variable echo times; metabolite quantification was done using Probe/SVQ method (13). The fitting was made for a region of interest (ROI) or PRESS voxel placed in the center of the phantom.

3. RESULTS

The effects of contrast agents are usually expressed in terms of the spin-lattice and spin-spin relaxivities, r_1 and r_2 , which denote the increase in relaxation rate per concentration of the agent (14). Figure 1 shows the values of these relaxivities (r_1 and r_2) for each solution as a function of radiation dose (D). The relationships of relaxivity vs radiation dose and temperature

were fit to straight lines, and these are summarized (along with standard errors) in Table 2 and Table 3. The effects of radiation dose and temperature on the quantification of metabolites in aqueous solution using a single voxel PRESS sequence (T_E : 35 ms) are given in Table 4.

The effects of radiation dose were much smaller and could easily be masked by the effects of temperature variation during the measurements. To improve the accuracy, all the samples were stored at the scanner's room temperature and the measurements were performed on all the samples sequentially in the same imaging plane to detect the effects of radiation dose.

4. DISCUSSION

Small effects of irradiation on the relaxivity of commonly used MRI contrast agents were measurable at 1.5 T. The relaxivities for the two agents were considered to have changed to different degrees after irradiation. For Gd-DTPA a 20 Gy dose changes the relaxivity by only 0.5%, whereas for Gd-HP-DO3A the change is roughly 1%.

An increase in relaxivity upon radiation may indicate the release of Gd^{3+} ions from DTPA and HP-DO3A chelates. Free Gd^{3+} ions relax more efficiently than chelated ions as long as they remain soluble. The reduced effect of radiation in solutions containing metabolites may indicate reduced solubility of the Gd^{3+} , non-specific binding of the Gd^{3+} without relaxivity enhancement, or possible reductions of the effects of radiation on the complexes, e.g. by free-radical scavenging or non-uniform dose distribution.

Assuming that the spin-lattice relaxivity (r_1) of aqueous solutions of free Gd^{3+} is $r_1 \approx 8 \text{ s}^{-1}\text{mM}^{-1}$, and given the radiation dependent spin-lattice relaxivity coefficients of the contrast agents, an estimate of the concentration of free Gd^{3+} ion needed to explain these effects can be made as $0.58 \mu\text{M Gy}^{-1}$ for Gd-DTPA and $0.97 \mu\text{M Gy}^{-1}$ for Gd-HP-DO3A.

The estimates of metabolite concentrations from MRS, acquired by a single-voxel PRESS sequence (T_E : 35 ms), appeared to decrease slightly (although comparable to standard errors except for Ch) with increasing radiation dose but increase with increasing temperature. This may largely be due to the effects of radiation dose and temperature on the relaxivities and the line width of the spectra, which may affect the quantification of metabolites (15).

The effects of radiation dose on the relaxivities were positive while the effects of temperature on the relaxivities were negative. The radiation dose effects were orders of magnitude smaller than the temperature effects in aqueous solutions of Gd contrast agents and metabolites over the range in this study. A radiation dose of 30 Gy had an effect on relaxivity equivalent to a temperature depression of -0.46 K for Gd-DTPA and -0.97 K for Gd-HP-DO3A.

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Figure 1.

Experimental r_1 and r_2 vs D for aqueous solution of Gd-DTPA + metabolites (Δ), Gd-DTPA ($\circ$) and Gd-HP-DO3A ($\diamond$) contrast agents. Open legends are r_1 and closed legends are r_2 ; solid, dashed and dotted lines are least square lines fitted to the experimental data. Slope and intercept along with standard errors are given in Table 2. This figure is available in colour online at <http://www.interscience.wiley.com/journal/cmmi>

Table 1

The composition of aqueous solution of metabolites in MRS phantoms

Concentration	Symbol	Chemical name
50 mM	KH_2PO_4	Potassium phosphate monobasic
56 mM	NaOH	Sodium hydroxide
12.5 mM	NAA	<i>N</i> -acetyl-L-aspartic acid
10.0 mM	Cr	Creatine hydrate
3.0 mM	Ch	Choline chloride
7.5 mM	mI	<i>myo</i> -Inositol
12.5 mM	Glu	L-Glutamic acid (monosodium salt)
5 mM	Lac	DL-Lactic acid (lithium salt)
15.4 mM	NaN_3	Sodium azide
0.5 mM	Gd-DTPA	Gd diethylenetriaminepantateic acid

Table 2

Radiation dose dependence of relaxivity for aqueous solutions of Gd-DTPA, Gd-HP-DO3A and Gd-DTPA + metabolites at room temperature at 1.5 T magnet

Substance	r_1 ($s^{-1} \text{ mm}^{-1}$)	r_2 ($s^{-1} \text{ mm}^{-1}$) ^a
Gd-DTPA	$0.0015 \pm 0.0003 \cdot D + 5.5058 \pm 0.0062$	$0.0038 \pm 0.0006 \cdot D + 5.5481 \pm 0.0113$ $0.0048 \pm 0.0007 \cdot D + 6.4080 \pm 0.0130$
Gd-HP-DO3A	$0.0029 \pm 0.0002 \cdot D + 4.9805 \pm 0.0033$	$0.0082 \pm 0.0003 \cdot D + 5.1452 \pm 0.0050$ $0.0062 \pm 0.0010 \cdot D + 6.0220 \pm 0.0190$
Gd-DTPA + metabolites	$0.0006 \pm 0.0001 \cdot D + 5.9373 \pm 0.0012$	$0.0021 \pm 0.0002 \cdot D + 6.0825 \pm 0.0029$ $0.0028 \pm 0.0003 \cdot D + 6.8780 \pm 0.0050$

^aMeasurements were made by single-voxel PRESS (first row) and MESE (second row) sequences.

Table 3

Temperature dependence of relaxivity for aqueous solutions of Gd-DTPA, Gd-HP-DO3A and Gd-DTPA + metabolites receiving no radiation at 1.5 T magnet

Substance	r_1 (s ⁻¹ mm ⁻¹)	r_2 (s ⁻¹ mm ⁻¹)
Gd-DTPA	$-0.099 \pm 0.009 \cdot T + 34.930 \pm 2.694$	$-0.108 \pm 0.012 \cdot T + 37.323 \pm 3.654$
Gd-HP-DO3A	$-0.090 \pm 0.005 \cdot T + 31.733 \pm 1.527$	$-0.097 \pm 0.006 \cdot T + 33.785 \pm 1.916$
Gd-DTPA + metabolites	$-0.119 \pm 0.009 \cdot T + 41.053 \pm 2.774$	$-0.126 \pm 0.016 \cdot T + 43.292 \pm 4.960$

Table 4

Effects of radiation dose and temperature on the quantification of metabolites, acquired by a PRESS sequence (T_E : 35 ms) at 1.5 T magnet

Substance	Amount (relative) vs dose D^a	Amount (relative) vs temperature T
NAA	$-0.005 \pm 0.027 \cdot D + 121.867 \pm 0.500$	$3.3 \pm 1.4 \cdot T - 837.6 \pm 408.7$
Ch	$-0.015 \pm 0.008 \cdot D + 71.600 \pm 0.162$	$2.2 \pm 0.8 \cdot T - 580.3 \pm 251.5$
Cr	$-0.012 \pm 0.029 \cdot D + 84.925 \pm 0.549$	$2.2 \pm 1.2 \cdot T - 551.1 \pm 348.0$
mI	$0.002 \pm 0.027 \cdot D + 38.266 \pm 0.509$	$0.8 \pm 0.7 \cdot T - 182.3 \pm 213.2$

^aBased on multiple measurements at room temperature (n = 12).