Field dependence of relaxivity of Gd chelates as a function of macromolecular content

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Introduction

Target Audience: Researchers interested in the factors that affect the relaxivity of Gd chelates at high B_0 and in vivo for a variety of applications.

Purpose: To measure the T_1 relaxivity of Gd-DTPA as a function of macromolecular content and different high B_0 strengths (up to 15.2T).

Gd-DTPA is a common MRI contrast agent widely used in tumor imaging[1], MR angiography[2], modeling hemodynamic behavior[3], and myocardial perfusion[4]. T_1 relaxivity (r_1) is a fundamental property of contrast agents that is important for modeling and quantitative analyses. Measurements of Gd-DTPA r_1 have previously been extensively reported[5,6,7], including field-cycling measurements over a range of frequencies. However, previous studies did not address the behavior of r_1 at very high fields or how r_1 may be modified in the presence of realistic media to different extents at different fields. The Solomon-Bloembergen-Morgan equations predict a frequency effect that depends on the relevant correlation time(s) of the paramagnetic interaction, which were investigated by simulation studies[8]. Here, we report Gd-DTPA r_1 measurements using the same samples and analysis over a range of high B_0. We also investigate the r_1 dependence on macromolecular content at different fields, which is known to modulate r_1[6].

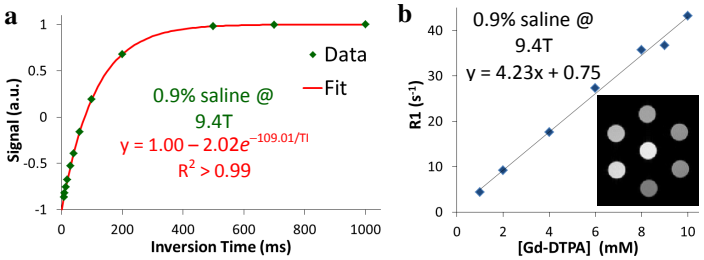

Fig 1. (a) Sample IR three parameter fit ($y(TI) = a+b*e^{-TI/TI}$) for single pixel. Note fitted a and b were close to the expected values 1 and -2, respectively. (b) Sample linear fit to measure r_1 ($R1=1/T_1= r_1[Gd\text{-}DTPA]+1/T_1^0$) where T_1^0 is the T_1 in the absence of Gd-DTPA. Inset: sample IR-SE image of NMR tube phantom.

Methods

Four sets of solutions were prepared with seven concentrations (0.6–10 mM) of Gd-DTPA (Magnevist, Schering): saline, 3% w/v milk powder in saline, 12% w/v milk powder in saline, 30% w/v milk powder in saline, and 24% w/v homogenized rat brain tissue in saline. All saline solutions had a concentration of 0.9%. The milk powder was fat-free. The brain tissues were harvested from healthy adult Sprague-Dawley rats. The 12% milk powder solution was chosen to approximate the reported protein content in rat brain[9], while the 3% milk powder solution was chosen to approximate the expected protein content in the 24% homogenized rat brain tissue solution. Each set of solutions were transferred into 5mm NMR tubes and bundled together for MRI experiments.

MRI experiments were run on both Varian (4.7, 7, and 9.4T) and Bruker (15.2T) systems at room temperature (20°C). A single-slice 2D inversion-recovery spin-echo (IR-SE) imaging sequence was used to measure T_1 of each Gd-DTPA concentration simultaneously with the following parameters: 128×128, FOV/THK=30/3mm, TR = 1.5s, TE=8ms, and TI=8.5-1400ms. An adiabatic RF pulse was used for inversion. Magnitude images were generated and a phase-based polarity correction was used[10]. Pixel-wise inversion curves were fit to the standard three-parameter model (Fig.1) to generate a T_1 map (Matlab, Mathworks). ROIs were drawn in each NMR tube to measure mean T_1 values and r_1 could be determined by a linear fit (Fig.1).

To estimate the error in r_1 measurements, it was assumed that the dominant error was from volume measurements while preparing the solutions. With our protocol, an error of 0.1ml is reasonable and can be propagated through the various dilutions to calculate the maximum and minimum expected Gd-DTPA concentrations. These values, in turn, can be used to calculate the maximum and minimum expected r_1 values.

Results and Discussion

Fig. 1 shows example T_1 and r_1 fits. All fits had R^2>0.99. Note that fitted T_1 in absence of Gd-DTPA (T_1^0) for 0.9% saline at 9.4T was 1.34s. Fig. 2 shows plots of measured r_1 vs B_0 strength for various solutions. Error bars for saline r_1 are smallest as saline solutions were prepared first and subsequently used to prepare the other solutions. The r_1 of saline falls between 4–5 $mM^{-1}s^{-1}$ at all B_0 which agrees with literature values[5,6]. All solutions show a trend of decreasing r_1 with increasing B_0 matching previous simulation results[8] and consistent with theory.

It is known that increasing macromolecular content increases r_1 presumable due to the increased correlation times of the dipolar interaction of Gd-DTPA with water. At 4.7T, r_1 increased 20% and 50% for 12% and 30% milk powder solutions similar to reported values[6]. Simulation studies have investigated the effect of correlation times on r_1 of Gd-DTPA as a function of B_0[8]. Under saline solution conditions, r_1 did not show a strong B_0 dependence, while under conditions mimicking large macromolecular content there was a strong B_0 dependence – r_1 increased significantly at lower fields, but not at higher fields. The results in Fig. 2 agree well with the simulation studies and provide experimental confirmation.

The r_1 for 24% rat brain solution and saline were observed to be almost the same at all B_0. This observation was repeated with 3% milk powder solution, which approximates the protein content in the rat brain solution, suggesting that it was the dilution of the rat brain homogenate that removed any macromolecular effect. 12% milk powder solution, which approximates the protein content in intact rat brain[9], shows increased r_1 at lower B_0 but not at higher B_0. In fact, at 15.2T, there was no observed difference in r_1 among all solutions. These results suggest that Gd-DTPA r_1 in rat brain approaches that of Gd-DTPA in saline at higher B_0.

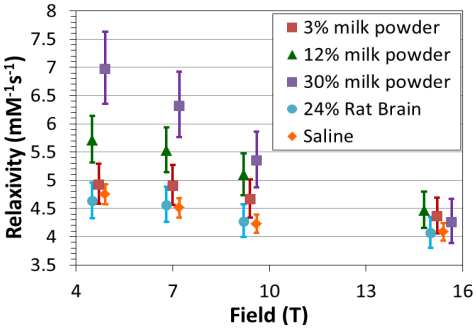

Fig 2. Plots of r_1 vs B_0 strength for various solutions. Markers at a given B_0 are offset to make error bars clearly visible. Error bars represent the minimum and maximum expected r_1 assuming dominant errors are from volume measurements in solution preparation.

Conclusion

This work is a study of Gd-DTPA r_1 as a function of macromolecular content across a range of high B_0. The results suggest that modification of correlation times by viscosity and binding effects do not increase r_1 at very high fields confirming simulation studies.

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