Quantitative Analysis of Distribution and Clearance Rate of Charged and Uncharged Gd-chelates in Rat Brain

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Introduction. In the goal of this study is to quantitatively analyze the distribution characteristics of the Gd-chelates, GdDTPA-BMA, $GdDTPA^{2-}$, or $GdDOTP^{5-}$, in rat brain. The blood brain barrier precludes delivery by vascular routes so agents were infused directly into ventricular cerebrospinal fluid yielding useful quantities of agent throughout the brain parenchyma for many hours after infusion. Identical quantities of each respective agent were delivered by direct infusion at a constant rate over 5 hours into the left lateral ventricle. Qualitative preliminary results were presented previously and we now present quantitative results obtained from fitting the contrast agent clearance curves from regions of interest throughout the entire brain volume.

Materials and Methods. All experiments where performed on male Sprague-Dawley rats weighing between 390 and 420 gms. Isofluorane anesthesia was employed. A stereotaxic frame (Stoelting) was used to position a 26 Gauge infusion cannula to a depth of 3.4 mm from the dural surface at 1 mm posterior and 1.4 mm lateral from bregma through which 30 µL volumes a respective agent was infused at 6 µL/hr over 5 hours. Agents were prepared at 250 mM by diluting Magnevist® (Berlex) for the $GdDTPA^{2-}$, dilution of Omniscan® for the GdDTPA-BMA, or were made up gravimetrically for $GdDOTP^{5-}$ (in powder form from Macrocyclics). Images were acquired at 9.4 T with a Varian imaging spectrometer using a 3.2 cm surface coil. T_1 maps were obtained by inversion recovery gradient echo (Turboflash) MRI from each rat every hour between 4 and 16 hours after infusing a respective agent. Images were acquired in 2 centric-ordered k-space segments with TE=2 ms, TR=5 ms, 128x128 matrix, 3x3 cm FOV, 1 mm slice, 8 ms adiabatic full passage inversion pulse, 1 ms Gaussian 90º pulse, with inversion time delays of 0.01, 0.05, 0.2, 0.4, 0.7, 1, 1.4, 2, 3, 4, and 6 sec. Individual T_1 maps have a spatial resolution of 0.312 x 0.312 x 1 mm^3 and were acquired in 2 minutes per slice. 250 mM agent solutions were delivered in through the infusion cannula placed in the left lateral cerebroventricle.

Results and Discussion. We previously presented qualitative results showing that all 3 agents readily distribute throughout brain regardless of charge-state, that equivalent agent doses resulted in similar decreases in T_1 throughout the brain for $GdDTPA^{2-}$ and GdDTPA-BMA, while the decrease in T_1 was as much as 2 to 3-fold greater with $GdDOTP^{5-}$, that differences in *in vivo* T_1 change cannot be accounted for by differences in measured *in vitro* relaxivities, and that it is possible to deliver Gd-chelates in a dose-dependent manner with a linear response in brain T_1 [1]. In the present study, rate constants of contrast agent clearance from specific regions of interest throughout the brain were obtained from time-course curves for each ROI by NNLS fitting to a 3 parameter exponential model using the Levenberg-Marquardt algorithm. Representative R_1 maps that were used for this analysis are shown in Figure 1; these maps were obtained for the entire brain volume.

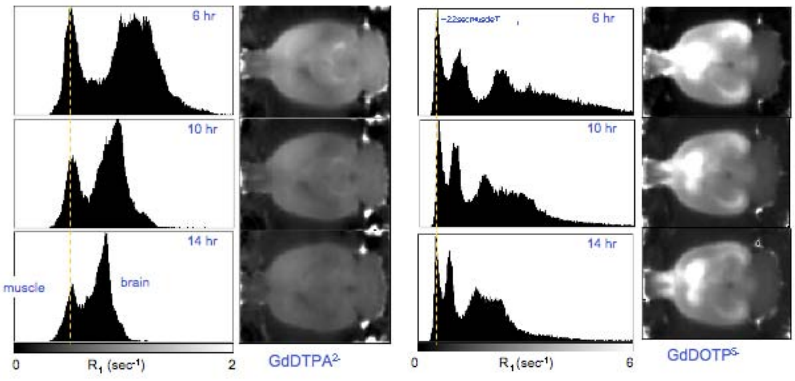
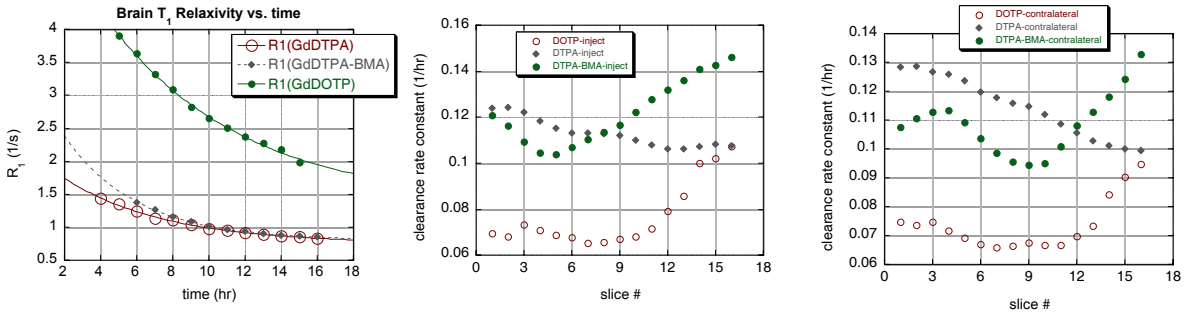


Figure 1. R_1 maps and corresponding whole brain histograms for $GdDTPA^{2-}$ and $GdDOTP^{5-}$ at 6, 10, and 14 hours after infusion. GdDTPA-BMA images were similar to those of GdDTPA.

Representative R_1 time-courses are shown in the left most panel of Figure 2. The Gd-chelates are cleared from the brain with different rate constants depending on ROI. Still the rate constants of agent clearance were remarkably similar for GdDTPA and GdDTPA-BMA and were markedly less for GdDOTP. We have found clearance rates for $GdDTPA^{21}$ that are 3-fold greater than those reported by Quirk and coworkers [2].

Figure 2 (below). R_1 vs. time on left. Plots of the spatial dependence of contrast agent clearance determine from ROI's in the injected side and contralateral side of the brain are on the right.



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References. 1.) Schornack PS *et al. Proc Intl Soc MRM* **13**: 2639, 2005; 2.) Quirk JD *et al.*, *Magn Reson Med* **50**: 493-499, 2003.