INTRA-INDIVIDUAL IN-VIVO COMPARISON OF GD-CONTRAST AGENTS FOR QUANTITATIVE PHARMACOKINETIC ANALYSIS USING DYNAMIC CONTRAST ENHANCED MR IMAGING

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Introduction

The usefulness of magnetic resonance (MR) imaging contrast agents to improve visualization of brain imaging is firmly established. Total six gadolinium–based MR contrast agents have been approved by the US FDA for MR imaging procedures[1]. Numerous intraindividual comparative studies within different Gd agents at equivalent dose and equivalent magnetic field strength, from 1.5T to 3T, have been investigated[2, 3]. This study compared the intra-individual crossover dynamic signal characteristics of three different Gadolinium chelates: gadopentetate dimeglumine (Gd-DTPA), gadodiamide (Gd-DTPA-BMA) and Gadobenate dimeglumine (Gd-BOPTA) in a clinical ultra-high field (7T) system using dynamic contrast enhanced MR imaging (DCE-MRI) in a pre-clinical beagle model.

Materials and Methods

7 beagles with mean age of 2 years and a mean weight of 9.2±2.1 kg (range 7-12 kg) underwent DCE-MRI seven times with 7 days interval in an ultra-high 7T MR system (Achieva, Philips, OH). One of three different Gd contrast agents, including gadopentetate dimeglumine (Magnevist, Gd-DTPA; Berlex Inc., Montville, NJ), gadodiamide (Omniscan, Gd-DTPA-BMA; GE Healthcare, Princeton, NJ) and Gadobenate dimeglumine (MultiHance, Gd-BOPTA; Bracco Diagnostics Inc., Princeton, NJ) were injected in each dog at every scan in a randomized order. A power injector (Spectris®, MedRad, Indianola, PA) was used during the contrast agent injection with body weight dosage of 0.1mmol/kg BW and flow rates of 0.06ml/sec. 20 ml saline was subsequently injected with 0.3 ml/sec flushing rate following after contrast agent injection. Everyone except the drug dispensing person was blinded regarding the use of the contrast agents for the individual subject. The power injector was placed outside of the 10 Gauss line of the ultra-high field scanner and was used connected the dogs via extended tubing sets through a dedicated waveguide. A 3D RF-spoiled fast field echo sequence was used (TR/TE:6.8/3.3ms; FA:20º; FoV:120mm; voxel=0.47x0.47x4.0mm^3; 16 conti-guous slices; temporal resolution: 9.5s with 60 time points) for dynamic scans. Regions of interest (ROIs) were drawn in the dynamic images on within both carotid arteries and temporalis muscle tissue on both sides of the head. The signal intensity data was used for pharmacokinetic analysis by fitting the time-SI curves according to the three different two-compartment models: the Tofts model[4], the Brix model[5] and the AIF decomposed refined Brix model[6]. Data analysis was performed using in-house developed software based on IDL environment.

Results

In Tofts's model, K^{trans} from the Gd-BOPTA group (0.12±0.04 min^{-1}) was significantly higher than the Gd-DTPA and Gd-DTPA-BMA groups. In the Brix's model, Amp and k_{el} were significantly higher in the Gd-BOPTA group. In the refined Brix's model, the difference of k_{ep}^{RB} between Gd-BOPTA and the other two contrast agents were not statistically significant. Further, none of the three k_{ep}'s (k_{ep}^{T}, k_{ep}^{B}, k_{ep}^{RB}) were determined to be significantly different between Gd-BOPTA and the other two Gd chelates.

Table 1 Summary of pharmacokinetic parameters in muscle from three different DCE-MRI models (Bonferroni method, with an overall significance level of 0.05)

	Gd-BOPTA	Gd-DTPA		Gd-DTPA-BMA	
	Mean±SD	Mean±SD	p-value	Mean±SD	p-value
K^{trans} [min^{-1}]	0.12±0.04	0.08±0.02*	0.002	0.07±0.03*	6×10^{-4}
k_{ep}^{T} [min^{-1}]	0.62±0.19	0.55±0.10	0.21	0.49±0.14	0.08
Amp [a.u.]	0.56±0.10	0.40±0.07*	1×10^{-5}	0.37±0.09*	1×10^{-7}
k_{ep}^{B} [min^{-1}]	1.11±0.25	1.06±0.24	0.37	1.20±0.25	0.26
k_{el}^{B} [min^{-1}]	0.06±0.02	0.02±0.01*	0.001	0.02±0.03*	2×10^{-5}
k_{ep}^{RB}[min^{-1}]	0.58±0.17	0.52±0.11	0.20	0.46±0.15	0.02

* observed difference is statistically significant after Bonferroni correction.

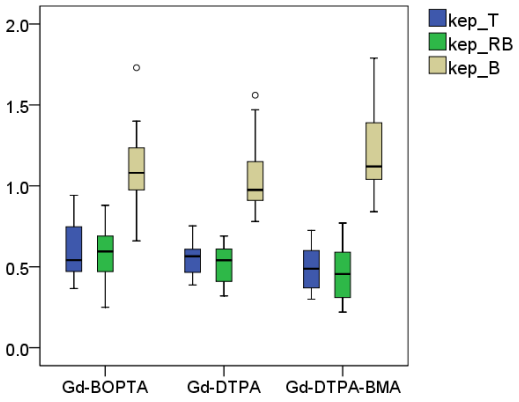

Fig. 1 The comparisons of clustered box plots for all three k_{ep}'s from muscle time-SI curves between Gd-BOPTA, Gd-DTPA and Gd-DTPA-BMA injections. The plots showed that AIF decomposed exchange rate constant k_{ep}^{RB} from the refined Brix's model obtained close results compared with k_{ep}^{T} from Tofts model.

Discussion and Conclusion

Gd chelate containing MR contrast agents can be used at ultra-high field for DCE-MRI and revealed similar enhancement characteristics compared to 1.5T and 3T. Contrast-agent-dependent differences were observed in the pharmacokinetic parameters K^{trans} from Tofts's model, and Amp and k_{el}^{B} from Brix's model. All the k_{ep} values derived from three different pharmacokinetic models (Toft's k_{ep}^{T}, Brix's k_{ep}^{B} and the redefined Brix's k_{ep}^{RB}) are more independent from the choice of contrast agent, which might be an advantage in multi-site clinical trials and long-term clinical studies. Moreover, our data reveals the equivalency between exchange rate constants derived from the Toft's model and the refined Brix's model.

References

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