Comparison of biodegradable macromolecular MRI contrast agents with Gd-(DTPA-BMA) and albumin-(Gd-DTPA) in tumor characterization with DCE MRI

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Introduction

DCE MRI with macromolecular MRI contrast agents is effective in the characterization of tumor vascularity or tumor vascular permeability. However, no macromolecular MRI contrast agents are available for clinical applications because they excrete slowly from the body. We have recently developed a novel class of biodegradable macromolecular MRI contrast agents that can readily excrete from the body. We report the evaluation of the effectiveness of the biodegradable macromolecular MRI contrast agents, Gd-DTPA cystamine copolymers (GDCC) and Gd-DTPA cystine copolymers (GDCP), in the characterization of tumor vascular permeability with DCE MRI in an animal tumor model and in comparison with a clinical agent, Gd(DTPA-BMA), and a prototype macromolecular agent, albumin-(Gd-DTPA).

Materials and Methods

GDCC and GDCP with molecular weights of 20 and 70 KDa and narrow molecular weight distribution were prepared by the fractionation with size exclusion chromatography. Animal tumor model was developed by subcutaneous inoculation of Pca-2b prostate adenocarcinoma cells in male nude mice. DCE MRI was performed when tumor size reached 1 cm in diameter. Mice were anesthetized with an intraperitoneal injection of a mixture of ketamine (90 mg/kg) and xylazine (10 mg/kg). A tail vein was catheterized using 30-gauge needle connected with heparinized saline filled 2-meter long tube. 120 μL of contrast agent was injected via the tubing and 250 μL saline was used to flush the tubing after contrast agent injection. The dose for all contrast agents is 0.1 mmol-Gd/kg except for albumin-Gd-DTPA at 0.03 mmol-Gd/kg. All images were acquired on a Siemens Trio 3T scanner using the system body coil for RF excitation and a human wrist coil for RF reception. Fractional tumor plasma volume (f^{PV}), flow leakage rate (FLR) and permeability surface product (K^{PS}) were calculated with a modified compartment model[1] and a homemade MATLAB program.

Results and Discussion

Figure 1 shows the dynamic MRI signal intensity in tumor tissue up to 30 minutes after injection of the contrast agents. The fractional plasma volume (f^{PV}), flow leakage rate (FLR) and permeability surface product (K^{PS}) were calculated from the DCE MRI signal data with a two-compartmental model[1]. These parameters are listed in Table 1. The biodegradable macromolecular contrast agents showed various tumor uptake kinetics in between those of Gd(DTPA-BMA) and albumin-(Gd-DTPA) corresponding to their sizes and structures. The f^{PV} determined by GDCC and GDCP with 20 KDa was close to that by Gd(DTPA-BMA), due to their relatively small size. The f^{PV} determined by GDCC and GDCP with 70 KDa was higher than but close to that by albumin-(Gd-DTPA).

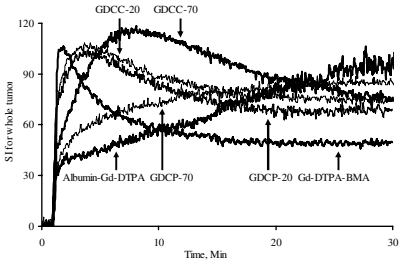

Figure 1. DCE MRI signal intensity of different agents

K^{PS} is the product of f^{PV} and FLR and is a measure of tumor vascular permeability. The low molecular weight agent Gd(DTPA-BMA) had much high tumor vascular permeability. The tumor vascular permeability of GDCC and GDCP with 20 KDa was lower than Gd(DTPA-BMA) but higher than other tested macromolecular agents. The permeability measured by GDCC and GDCP with higher molecular weight (70 KDa) was lower than that by lower molecular weight agents, but higher than that by albumin-(Gd-DTPA). GDCC degraded faster than GDCP and GDCC-70 showed higher tumor permeability than GDCP-70.

Table 1. The DCE MRI parameters of different agents in the Pca-2b tumor xenografts

	Gd(DTPA-BMA)	GDCC-20	GDCP-20	GDCC-70	GDCP-70	Albumin-(Gd-DTPA)
f^{PV}	0.16±0.04	0.12±0.01	0.11±0.03	0.089±0.006	0.075±0.021	0.044±0.007
FLR (1/hr)	17.5±7.4	5.99±1.05	6.65±3.38	3.43±1.25	1.26±0.30	0.86±0.39
K^{PS} (1/hr)	2.9±1.5	0.70±0.13	0.81±0.6	0.30±0.10	0.096±0.042	0.038±0.017

Conclusions.

The biodegradable macromolecular MRI contrast agents had lower tumor vascular permeability than the Gd(DTPA-BMA) and higher permeability than the non-degradable albumin-(Gd-DTPA). The tumor vascular permeability of the biodegradable macromolecular agents decreased with increasing molecular weight. Biodegradable macromolecular MRI contrast agents with a large molecular weight and slow degradation rate would be suitable for accurate evaluation of tumor vascularity with DCE-MRI.

1. Shames DM, Kuwatsuru R, Vexler V, Muhler A, Brasch RC. Measurement of capillary permeability to macromolecules by dynamic magnetic resonance imaging: a quantitative noninvasive technique. Magn Reson Med 1993; 29:616-622.