Characterization of a novel gadolinium-based high molecular weight polymer as an intravascular MR contrast agent

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Objectives: Blood pool contrast agents used in magnetic resonance imaging (MRI) are characterized by intravascular distribution and prolonged persistence in the blood compared with conventional contrast agents in clinical use such as Gd-DTPA (Magnevist, Bayer Pharma AG, Germany) and Gd-DOTA (Dotarem, Guerbet, France). Since the size of the contrast agent molecule is a main factor determining the distribution and elimination of the agent *in vivo*, macromolecules are excellent candidates as blood pool contrast agents. Due to their larger size, macromolecular agents can potentially overcome the limitations of small molecules such as the rapid elimination from the blood pool, nonspecific extravasation into surrounding tissue, and poor relaxation enhancement efficiency [1]. In addition, due to the enhanced permeation and retention (EPR) effect, macromolecular contrast agents can extravasate from fenestrated blood vessels into surrounding tissue of inflamed or tumorous areas. Thus, besides assisting contrast-enhanced magnetic resonance angiography (MRA), blood pool agents can also be used to target e.g. necrotic myocardium [2, 3], or to detect various tumors [4, 5].

Methods: In the present work, a novel blood pool contrast agent composed of Gd-DTPA conjugated to a biodegradable polymer of high molecular weight (M_r ~200,000) was synthesized, formulated and characterized *in vitro* as well as *in vivo*. Relaxivity measurements were performed at 1.41 T on a Bruker MiniSpec spectrometer (Bruker BioSpin, Ettlingen, Germany). *In vivo* experiments were performed in C57BL/6 mice after intravenous injection of 100 µL of the polymer solution per 25 g mouse, corresponding to a dose of 100 µmol Gd/kg body weight. T1-weighted images were acquired on a 4.7 T Biospec 47/40 scanner (Bruker BioSpin, Ettlingen, Germany) using a FLASH sequence.

Results: The longitudinal and transverse relaxivities, r_1 and r_2, of the gadolinium-based polymer in water at 37 °C and 1.41 T were found to be 10.2 $mM^{-1} s^{-1}$ and 12.2 $mM^{-1} s^{-1}$, respectively. These values are 2 - 3 times higher than those of conventional contrast agents in clinical use indicating a high contrast enhancement. *In vivo* imaging in mice demonstrated that on intravenous injection, the gadolinium-based polymer remained within the vascular system for a prolonged period of time compared to Gd-DTPA. The macromolecular agent was cleared from the blood through renal excretion with a half-life of 1.9 h.

Conclusion: In this study we report on a novel gadolinium-based polymer that acts as an intravascular MR contrast agent (blood pool contrast agent) having a high contrast efficiency as well as optimal biocompatibility and clearance properties. The agent enables higher resolution through a longer steady state period and a wide acquisition timeframe in magnetic resonance angiography (MRA) and can also be of use in studies of renal structure and function.

References:

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