First in vivo characterization of a low molecular weight Gd-metallostar – a contrast agent with high relaxivity

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Introduction

Recently, a heterometallic, self-assembled metallostar, $[Fe\{Gd_2L(H_2O)_4\}_3]^{4-}$, was reported which exhibits a particularly high relaxivity at high magnetic fields for its moderate molecular weight of 3.7 kDa (1,2). At 4.7 T (measured in saline at 37°C) its relaxivity is 13.5 $s^{-1}mM^{-1}$ Gd. Small molecular weight contrast agents (CAs) like GdDTPA (0.55 kDa) and GdDOTA (0.56 kDa) have relaxivities in the range of 3 – 4 $s^{-1}mM^{-1}$ Gd. In this study, first in vivo characterization of the metallostar was performed in mice. Its in vivo relaxivity and pharmacokinetics (PK) were compared to GdDOTA.

Methods

In vivo experiments were performed in female, healthy C57/BL6 mice (n=8, 20 - 25 g) at 4.7 T (Bruker Biospec). The metallostar was injected as a bolus via a tail vein catheter with an infusion pump at doses of 0.050 mmol Gd/kg BW (high dose) or 0.0125 mmol Gd/kg BW (low dose). For comparison, the experiments were repeated in the same mice with GdDOTA (Dotarem, Guerbet, France) at the clinical dose of 0.100 mmol Gd/kg BW.

Regional CA uptake in the abdomen and the head was assessed with dynamic contrast enhanced MRI (DCE-MRI) with two different imaging methods: 1. a series of single slice inversion recovery (IR) FLASH images (TE = 3.0 ms, TR = 6.9 ms, matrix = 128 x 96, inversion delay 0.9 s, 256 repetitions with temporal resolution 6 s). Before start of the DCE-MR image series, a reference image was acquired without the inversion pulse. 2. A series of single slice IR TrueFISP images (TE = 1.69 ms, TR = 3.38 ms, matrix 64 x 48, 16 inversion delays from 210 ms to 2480 ms, 80 repetitions, temporal resolution 8 s). CA was injected at repetition 8 for both methods.

T_1 was calculated from the IR FLASH images using the standard IR equation (3). For the IR True FISP data, T_1 was calculated using the method described in (4). Gd concentration C was then calculated with following formula $C=(1/T_1-1/T_{10})/r_1$ using the relaxivities r_1 13.5 $s^{-1}mM^{-1}$ for the metallostar and 3.3 $s^{-1}mM^{-1}$ for GdDOTA. T_{10} was the mean of the first 7 baseline scans.

Results

The metallostar was very well tolerated by the mice. The signal enhancement in the IR FLASH images after high dose metallostar injection was considerably higher than after GdDOTA injection despite its lower dose. The T_1 drop calculated from the IR TrueFISP data in ROIs in various tissues was larger after high dose metallostar injection than after GdDOTA injection or low dose metallostar injection (see Fig 1). The Gd concentrations for GdDOTA were approx. twice as high than for high dose metallostar, whereas they were 2 – 4 times lower for low dose than for high dose metallostar (see Fig. 2).

Fig. 1: T1 time course in muscle and kidney cortex

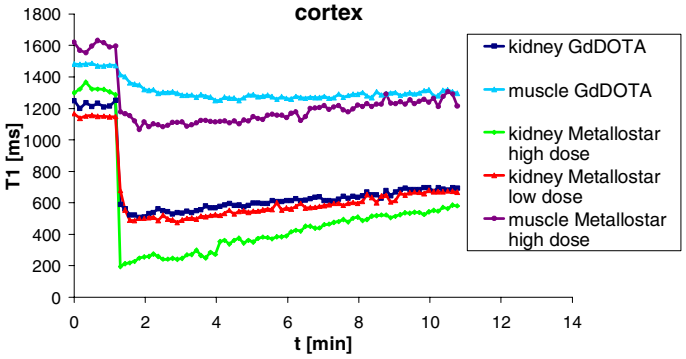
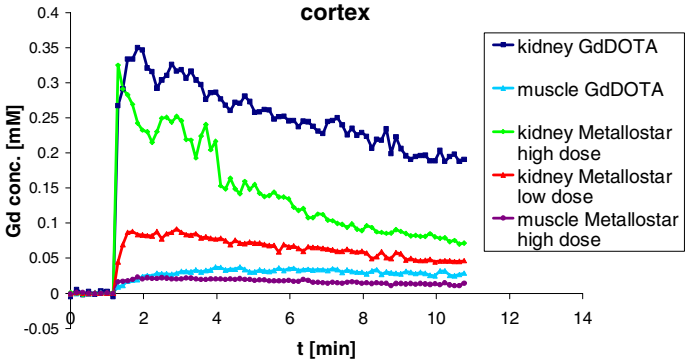


Fig. 2: Gd conc. time course in muscle and kidney cortex



Discussion

The PK for the metallostar and GdDOTA were similar. Both CAs were mainly filtered by the kidneys from the blood stream as evidenced by accumulation in the kidney medulla. The metallostar as well as GdDOTA showed small leakage to muscle and no leakage to brain. Both CAs were not acting as blood pool agent as seen from the PK and due to their small sizes. The differences in the calculated Gd concentration in tissue reflected the different injected doses: factor of 2 was between GdDOTA and high dose metallostar, factor 4 between high and low dose of the metallostar.

The theoretical Gd concentration in blood based on a blood volume of 1.5 ml for a mouse of 20 g is 0.17 mM for 0.0125 mmol Gd/kg BW metallostar. The initial Gd concentration derived in the jugular veins was approx. 0.12 mM. This result was close to the theoretical estimate showing that the in vivo relaxivity of the metallostar is very close to the value of 13.5 $s^{-1}mM^{-1}$ as measured in saline.

In conclusion, the results confirmed the approx. four times higher in vivo relaxivity of the metallostar compared to GdDOTA.

References

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