A self-assembling heteropolymetallic chelate, potential contrast agent for MR angiography

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Introduction

Desreux et al have proposed a new approach towards enhancement of relaxivity based on the formation of a supramolecular entity by self-assembly of gadolinium(III) complexes around iron(II) ions.[1] In the present study, a Gd-DTPA moiety has been linked to an iron(II) binding 1,10-phenanthroline unit, resulting in a heteropolymetallic species with increased relaxivity. The imaging potential of this system was evaluated *in vivo* on Wistar rats by MR angiography (MRA).

Material and methods

Coronal and sagittal images of the abdominal blood vessels of Wistar rats were obtained at 4.7 T on a Bruker AVANCE-200 imaging system (3D TOF, TR/TE = 13.58/5.2 ms, flip angle = 20°, RF spoiling, matrix = 256 x 128 x 64, FOV = 8 x 5.7 x 3 cm, 64 contiguous slices). The contrast agent was administered as a bolus via the femoral vein at a dose of 0.04 mmol / kg.; Magnevist®, used as a control, was administered at a dose of 0.1 mmol/kg. Images, acquired sequentially up to 90 min post-contrast, were reconstructed by Maximum Intensity Projection (MIP), and analyzed with Osiris software. The SI of blood vessels was measured and the evolution of post-contrast vs. pre-contrast SI as a function of time was calculated (ΔSI%).

Results and discussion

Synthesis and characterization

The Gd-DTPA-5-amido-1,10-phenanthroline was synthesized by reaction of 5-amino-1,10-phenan – throline with DTPA-tetraester[2], hydrolysis of the esters and finally complexation with $GdCl_3$. Upon addition of $FeCl_2$ to an aqueous solution of the Gd complex, the colour of the mixture immediately changed to deep red indicating the formation of a supramolecular structure [(Gd-DTPA-phen)$_3$Fe] (figure 1). Typically, one Fe^{2+}ions complexed with three gadolinium chelates.

The relaxation rate of a 0.2 mM solution of [Gd-(DTPA-phen)$_3$Fe] complex is 6.1 s^{-1} at 20 MHz and 310 K, indicating a significantly higher relaxivity than that of the Gd-DTPA (3.9 s^{-1} for 1 mM solution).

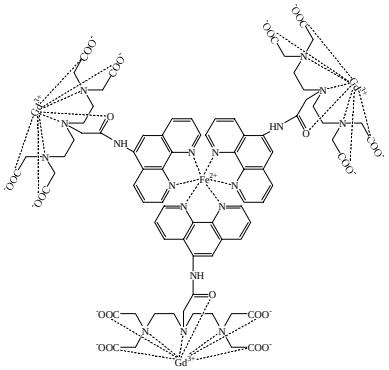

Figure 1: Structure of the heteropolymetallic iron-gadolinium complex [(Gd-DTPA-phen)$_3$Fe].

In vivo evaluation

The images show an enhancement of the arterial system, where SI reaches a maximum (45%) 7 min post-contrast and remains around 25% till the end of the imaging period (90 min); the SI enhancement produced by Magnevist® was less than 5% during the same imaging period (figure 2).

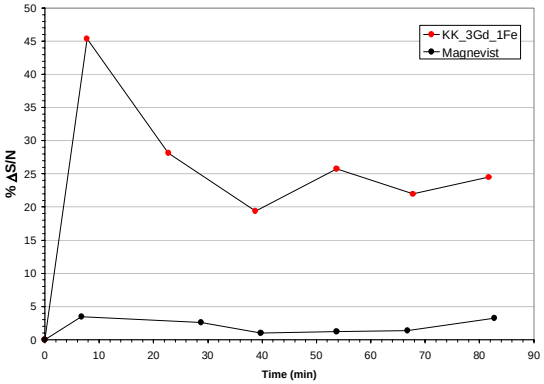

Figure 2: Relative evolution of post-contrast SI as a function of time

Conclusions

We have shown that, by coupling a 1,10 phenantroline unit to Gd-DTPA moieties, the formation of a highly paramagnetic supramolecular structure is possible and is indeed easily obtained mixing an aqueous solutions of the gadolinium complex and of Fe^{2+} ions. The molecular relaxivity of the [(Gd-DTPA-phen)$_3$Fe] complex is much higher than the one of Gd-DTPA and its blood half-life is longer than the one of this reference compound. The [(Gd-DTPA-phen)$_3$Fe] therefore appears as an interesting potential contrast agent for MRA.

References

[1] J. F. Desreux, et al, US Patent 6,056,939 (2000) ; [2] P.L. Anelli et al, Bioconjugate Chem., 10, 137 (1999)