In vivo evaluation of a new extracellular Gd(III) complex endowed with high relaxivity for tumor detection in mice

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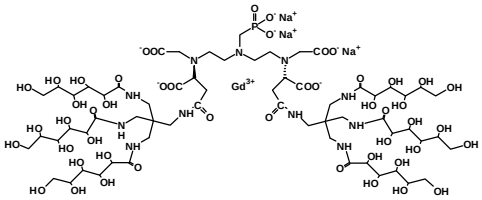
Introduction

The search for high relaxivity continues to be a subject of intense scrutiny because it would allow the use of lower doses also for current indications of MRI contrast agents. High relaxivity can be pursued through the optimization of the three contributions that determine the observed relaxation rates of water protons, namely inner-, second- and outer-coordination sphere. We have takled this task by synthesizing a new Gd(III) complex (B24856/1) that is a DTPA derivative in which the central arm has been replaced by a methyl phosphonate moiety and two outer acetate moieties have been functionalized with highly hydrophilic substituents as depicted in scheme 1.



Scheme 1: B24856/1

Materials and Methods

The synthesis of the ligand has been carried out through the alkylation of the di- ter-butyl aminomethylphosphonic ester with a suitable aspartic acid derivative already containing all the required carboxylic moieties. The introduction of the two hydrophilic substitients has been performed through a selective amidation reaction. The corresponding Gd(III) complex has been obtained by mixing stoichiometric amounts of the ligand and gadolinium chloride. The complex B24856/1 has been characterized by elemental analysis, HPLC, MS and Field Cycling relaxometry. The “in vivo” evaluation of B24856/1 has been carried out on healthy mice and on transgenic mice (HER-2/ neu) that spontaneously develop breast tumors. The MR images were acquired on a 2T scanner equipped with a SMISS console.

Results and discussion

Complex B24856/1 displays a relaxivity of ca. 19 mM-1s-1 in water at 20MHz and 298K (Fig.1). The observed relaxivity is definitively higher than other q=1 systems previously reported and reflects the relevant contribution from water molecules in the second coordination sphere that are associated to the surface of the complex owing to the H-bonding network formed with hydroxyl and phosphonate groups. The complex results to be highly stable and it did not display any detectable transmetallation reaction in blood. The “in vivo” evaluation of B24856/1 was first carried out on healthy mice and compared with ProHance®. The two agents display an analogous biodistribution and excretion patways (Fig. 1). Clearly when administered at the same concentration B24856/1 shows an higher contrast enhancement as expected on the basis of the higher relaxivity. Finally the ability to detect tumor has been assessed on Her-2/neu mice that are well established models for tumor brest.

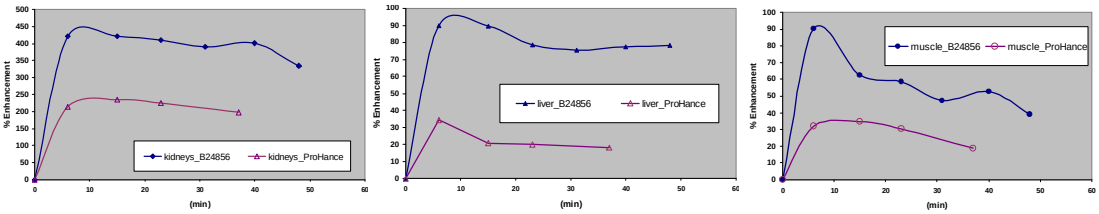


Figure 1. Contrast enhancement % in: a) kidney; b) liver and c) muscle in t a healthy mouse using B24856/1(◆) or ProHance® (▲)

The achieved high relaxivity allows an excellent delineation of the tumor area (Fig. 2) in respect to that obtained upon the administration of ProHance®.

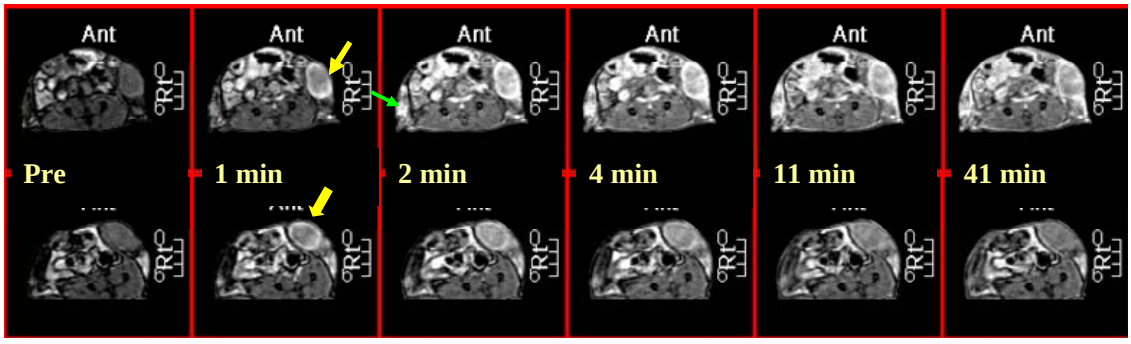


Figure 3. Comparison between B24856/1 (upper time series) and ProHance® (lower time series) with HER-2/neu mice (dose 0.1mmol/kg). The tumor lesions are pointed out by yellow arrows.

Conclusion

The new Gd(III) complex synthesised and characterized in this work has demonstrated to be a good candidate for its use as MRI extracellular contrast agent and thanks to its high relaxivity, it may be used at doses significantly lower than those currently administered in clinical protocols with commercially available Gd-based agents.