A new glycosylated complex of gadolinium, a potential contrast agent for MR angiography

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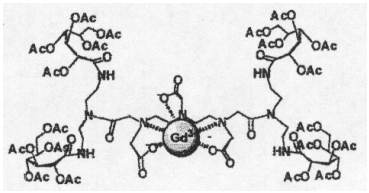
Introduction

Dendrimer-based MRI contrast agents are designed primarily to enhance the blood pool and the sites of abnormal endothelial permeability [1]. They are highly branched polymers with molecular masses larger than 20,000 Da, which allows longer imaging windows without multiple injections. An alternative approach has been explored in the present work by grafting a glycodendrimer on Gd-DTPA (Gd-D1 complex) [2]. The new contrast agent is a low-molecular weight compound (2,270.64 g), which preserves the basic properties (i.e. long rotational correlation time, relatively high r_1) of macromolecular dendrimers, important for the blood-pool MRI. The Gd-D1 complex has been characterized by relaxometry, while its pharmacokinetic parameters and biodistribution pattern were determined on rats.



GdD1

Materials and methods

The complex Gd-D1 was prepared as described by Takahashi [2]. Proton longitudinal relaxation dispersion profiles (NMRD) were recorded on a IBM field cycling relaxometer. The water residence time τ_M of the complex was obtained from the analysis of the temperature dependence of the oxygen-17 transverse relaxation rate [3]. Blood pharmacokinetics were assessed on tracheotomized male Wistar rats. The left carotid artery was catheterized for blood collection. Gd-D1 was injected as a bolus through the femoral vein at a dose of 0.1 mmol/Kg b.w. Blood samples were collected before and at different delays after injection. The gadolinium content of the blood samples was determined by relaxometry at 37°C and 60 MHz on a Bruker Minispec. A two-compartment distribution model was used to calculate the pharmacokinetic parameters. The biodistribution has been determined in rats, 2 h after a single i.v. injection of 0.1 mmol Gd/kg bw. Gd-DTPA has been used as a control. The organs were weighted, dried and subsequently were digested. The gadolinium content was determined by ICP.

Results

Relaxivity and τ_M measurement: The temperature dependence of the relaxivity at 20 MHz shows a clear limitation of the relaxivity by the water exchange. A water residence time in the first coordination sphere of the complex equal to 1494 ns was obtained from the temperature dependence of the transverse paramagnetic relaxation rate of oxygen-17, for comparison, a value of 331 ns is measured for Gd-DTPA. The longer water residence time of Gd-D1 is typical of bisamide derivatives. The NMRD profiles of Gd-D1 and Gd-DTPA have been acquired at 310K and 278 K. The relaxivity, particularly at high field (10-60 MHz) is higher than for the Gd-DTPA complex, the relaxivity (310 K , 20 MHz) is 5.64 s^{-1} mM^{-1} for Gd-D1.

Blood pharmacokinetics and biodistribution: The pharmacokinetic parameters reveal a prolonged blood residence ($T_{e1/2}$ = 85.04 min, Cl_{tot} = 8.72 ml/kg/min) of Gd-D1 as compared to Gd-DTPA ($T_{e1/2}$ = 16.36 min, Cl_{tot} = 15.61 ml/kg/min). The VD_β value (224 ml/kg) reflects a distribution in the interstitial space comparable to that of Gd-DTPA (205 ml/kg). The biodistribution data show significantly higher concentrations of dendritic Gd chelate as compared to Gd-DTPA in different organs, such as kidneys (24% of ID/g), liver (0.36% of ID/g), heart (0.64% of ID/g), lungs (1.7% of ID/g). The high Gd concentration found in kidneys two hours after administration seems to be related to the delayed blood clearance ($T_{e1/2}$ = 85.04 min) as compared to Gd-DTPA ($T_{e1/2}$ = 16.36 min). On the other hand, this result reflects that dendritic Gd chelate has a renal elimination.

Conclusions

Large macromolecular contrast agents are useful for MR angiography (MRA), but their delayed excretion and increased retention in liver, spleen and kidney represent the major limitation for their clinical use. Our new small-molecular dendrimer compound presents advantages as a blood-pool contrast agent not only from the relaxometric point of view but also from the biological one (convenient $T_{e1/2}$ = 85 min and significantly lower accumulation in liver and spleen as compared to other dendrimer compounds).

References

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