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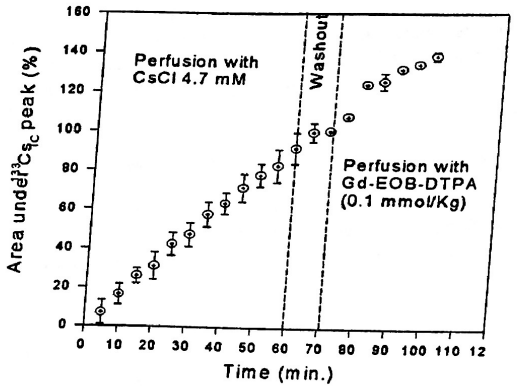

Figure 1

At the end of perfusion with the contrast agent, liver Gd concentrations of 1.12 ± 0.2 mM and 0.94 ± 0.16 mM were obtained by ICP indirectly from perfusate samples and directly from digested tissues, respectively. For the same time, a cytoplasmic Cs concentration of 25 mM was also determined from digested tissues, respectively. For the same time, a cytoplasmic Cs concentration of 25 mM was also determined from digested tissue samples.
Conclusion: With a 100% visibility, a high stability in the IC space and relatively long intrinsic relaxation times, ^{133}Cs is a promising candidate as a probe for monitoring the internalization of hepatotropic contrast agents in the context of preclinical studies. Our results indicate that the amount of ingested Cs^+ is large enough to acquire well-resolved peaks over short periods of time. Under the paramagnetic influence of Gd. the longitudinal relaxation rate is significantly increased, in a dose-related way. The results of this study seem to prove that a direct *in situ* dosage of Gd-EOB-DTPA or any other specific paramagnetic agent in liver cells is a feasible through the study of the ^{133}Cs peak evolution.

References

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211 Noninvasive evaluation of the pharmacokinetic and relaxivity of new MR contrast agents for MR angiography

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Introduction: Ideally, contrast agents for MR angiography should fulfill the following criteria: a high T1 efficiency, a low interstitial diffusion during first-pass but yet a relative rapid clearance. The purpose of this study was to evaluate in-vivo two contrast agents of a new class of blood pool agents, compared to gadolinium chelates.
Methods: *Contrast agents* Two products of a new class of contrast agent (P760 and P775, Guerbet, France) with a 7 time higher in vitro relaxivity than Gd-DOTA (DOTAREM, Guerbet, France) were evaluated. Equivalent doses in term of R1 relaxation efficiency were injected in rabbits.
Animal preparation New Zealand rabbits of 3 kg were anesthetized with a mixture of ketamine and xylazine (i.m. injection). A catheter was placed in the ear vein for contrast agent bolus injection. The animals were then positioned supine in the magnet (Vision 1.5 T, Siemens, Germany) with a surface coil, centered on the kidneys. An oil phantom was used as reference signal intensity (SI).
MR imaging protocol
MR Angiography study. A 3D MRA sequence was performed with the following parameters: TR/TE = 5/2 msec, flip angle 20°, coronal volume = 40 mm, pixel size = 1.54 × 0.98, acquisition time <11 sec.
MR pharmacokinetic study. First-pass imaging was performed with an ultrafast T1-weighted sequence (TR/TE = 3.3/1.4 msec, flip angle = 8°, FOV = 250 mm, 3 transverse slices of 8 mm thickness, matrix = 64 × 128, acquisition time <1 sec, 60 measures), with the bolus injected after the third measure. To evaluate delayed enhancement, the sequence was repeated (10 measures) every 5 minutes over 30 minutes. Each product was injected to the same animal, with a one week delay.
Image analysis
MR Angiography study. Qualitative assessment was done on MIP and native images.
MR pharmacokinetic study. Normalized SI was measured on regions of interest positioned in the descending aorta, inferior vena cava, cortex and medulla of kidneys. ΔSI was calculated in the different regions.
Result: MR Angiography study. With the new agent injected at a 7 time lower dose than Gd-DOTA, aorta enhancement was similar on both MIP and native images (n = 5). In the kidney, diffusion of the contrast agent was delayed compared to Gd-DOTA.
MR pharmacokinetic study. On first-pass images, enhancement in the aorta was similar with new agents at a 7 time lower dose than Gd-DOTA (n = 9). Time at which the cortical and medullary curves cross (C-M crossing time) is inversely correlated with kidney clearance. The mean C-M was 29 sec for P775, 28 sec or P760 and 39 sec for Gd-DOTA, confirming a lower rate of diffusion in the kidney in the early phase. On delayed, images, the elimination half time in the aorta was comprised between 6 and 12 minutes for all agents.
Conclusion: High relaxivity contrast agents injected at 7 time lower dose demonstrated similar enhancement of vessels compared to Gd chelate. Their early diffusion in kidneys was less than Gd chelate. However, their rapid elimination rate found on delayed images differentiate this new class of contrast agent from remanent intravascular contrast agents.

212 Comparative study of some C-substituted Gd-DTPA exhibiting non-covalent binding to blood proteins

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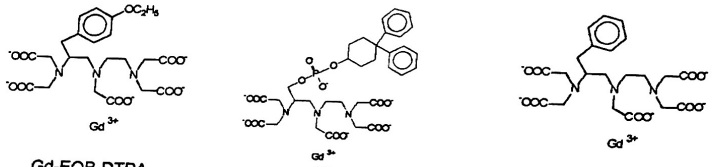
Introduction: Small gadolinium complexes covalently- or non covalently-bound to proteins or other high molecular weight molecules are potential intravascular MRI contrast agents. Non covalent binding to endogenous proteins like serum albumin is preferable since biocompatibility and excretion problems can be minimized. Gd-DTPA derivatives carrying lipophilic groups linked to a carbon of the ethylene bridges seem to exhibit good binding properties towards human serum albumin (HSA). In this work, proton relaxivity and association ability of some C-substituted complexes ((S) Gd-EOB-DTPA, MS-325 and Gd-C_4BzDTPA) are reported.



Gd-EOB-DTPA **1** | MS-325 **2** | Gd-C_4BzDTPA **3**

Materials and Methods: Compounds 1 and 2 were kindly provided by Schering AG (Berlin, Germany). Compound 3 was synthesized as described earlier (1). Proton Nuclear Resonance Dispersion profiles were recorded at 310 K on a Field Cycling System relaxometer. Relaxivity at 300 MHz and ^{17}O NMR data needed for the calculation of the water residence time (τM) were measured on a Bruker AMX-300 spectrometer (Bruker, Karlsruhe, Germany). Association with HSA was studied by proton relaxometry at 20 MHz and 310 K (Minispec PC-20, Bruker, Karlsruhe, Germany) on solutions containing 4% of HSA and increasing amounts of gadolinium complexes using the following equation:

$$R_1^{p^{obs}} = 1000\left\{r_1^f s^\circ + \frac{1}{2}(r_1^c - r_1^f)\left(Np^\circ + s^\circ + Ka^{-1} - \sqrt{(Np^\circ)+s^\circ+Ka^{-1})^2 - 4Ns^\circ p^\circ}\right)\right\}$$

where p° is the protein concentration, s° is the paramagnetic complex concentration, N is the number of independent sites (usually set to 1), r_{1c} and r_{1f} are the relaxivities of the complex HSA-contrast agent and free contrast agent respectively, and Ka is the association constant.
Results: *Water solutions:* The proton relaxivities at 310 K and 20 MHz are 5.5, 5.5 and 4.8 s^{-1} mM^{-1} for compounds 1, 2 and 3 respectively. These relaxivities are higher than that of Gd-DTPA (r_1 = 3.8 s^{-1} mM^{-1}). At 310 K, the residence time τM (1: 83 ± 21 ns, 2: 83 ± 13 ns, 3: 87 ± 25 ns) is shorter than for Gd-DTPA (142 ± 26 ns).
HSA Solutions: The association constants obtained by proton relaxometry are 887 ± 79, 6100 ± 2130 and 330 ± 24 M^{-1} for compounds 1, 2 and 3 respectively.
Conclusion: DTPA complexes carrying hydrophobic substituents on the ethylene bridge are characterized by: i) higher proton relaxivities than the parent compound in water, ii) good binding capabilities to HSA, and iii) shorter residence time of the coordinated water molecule. This type of

derivatives is thus preferable to bisamides since the high values of τM reported for the latter (2, 3) can limit the relaxivity of the HSA complex and therefore reduce their efficiency as blood pool contrast agents.

References

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213 Assessment of a weakly binding Gd-chelate (Gd-BOPTA) for MR-angiography: Results of phase I studies

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Introduction: Two different Phase I studies with 10 volunteers in each study have been performed with Gadobenate dimeglumine (Gd-BOPTA, MultiHance, Bracco, Milan) a weakly protein binding gadolinium chelate [1]. One study evaluated the influence of dose and flow rate on the intravascular signal intensity for 3D-MR-Angiography [2], the other compared the intravascular signal intensity for 3D-MR-Angiography of Gd-BOPTA and Gadopenate dimeglumine (Gd-DTPA, Magnetvist®, Schering, Berlin), a non binding chelate.

Subjects and Methods: 10 healthy volunteers were examined in both studies. An intraindividual comparison of three doses (0.025; 0.1; 0.4 ml/kg BW) and two flow rates (0.5; 2.0 ml/s) was performed in the dose finding study. The efficacy of Gd-BOPTA compared to Gd-DTPA was performed in a double blinded, randomized, intraindividual crossover comparison. A standard dose of 0.2 ml/kg BW and constant flow rate of 2 ml/s were given for both chelates. In both studies the contrast media was administered by an automated infusion system CAI 626 (Doltron AG, Uster, Switzerland). All measurements were performed using a phased array body coil on a 1.5 T MRI system (SIEMENS Vision, Erlangen, Germany) with a maximum gradient strength of 25 mT/m and 300 µs minimum rise time. In order to allow quantitative assessment of the temporal vascular enhancement characteristics comparable to 3D MR-Angiography, a fast 3D FLASH (TR = 5 ms, TE = 2 ms, BW = 488 Hz/pixel) sequence was modified by removing the partition encoding gradient table. This sequence enables a dynamic acquisition of a 20 mm coronal slab (matrix: 200 × 256) within 1 s and 128 repetitive measurements. Quantitative assessment of vascular enhancement in the suprarenal abdominal aorta was carried out by ROI analysis of relative signal difference (S-So). The obtained time-signal curves were analysed in terms of intensity and duration of peak-enhancement.

Results: The dose finding study exhibited a clear dose dependency for the signal intensities. Signal peaks were higher and lasted longer for the higher doses (Fig. 1). Regarding flow rates, the peaks occurred earlier, were higher but shorter for the faster flow rate (2 ml/s). Low flow contrast administration led to higher plateau periods following the peaks than high flow administration. The comparison of peak duration at three different signal intensity levels (15, 20, 25) showed significant longer duration ($p < 0.01$, $p < 0.01$, $p < 0.05$) for Gd-BOPTA than for Gd-DTPA (Fig. 2).

The average maximum signal intensity after Gd-BOPTA was 29% higher compared to Gd-DTPA. The area under the average enhancement curve was nearly twice as high after Gd-BOPTA than after Gd-DTPA application, due to the higher and wider peak as well as the higher plateau level following the peak (Fig. 3).

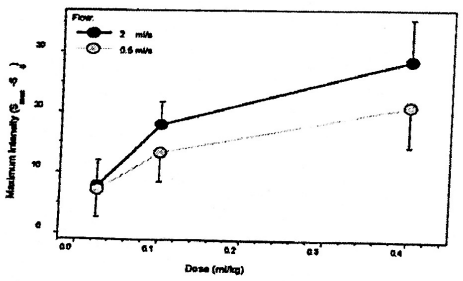

Figure 1: Averaged peak signal intensity difference (S-So) in relation to dose and flow of Gd-BOPTA in the 10 volunteers.

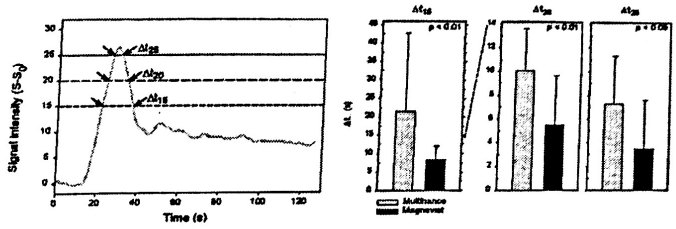

Figure 2: Comparison of the peak duration in the averaged time-signal curves for three signal intensity levels (15, 20, 25) reveal longer duration for Gd-BOPTA (Multihance) at al levels than Gd-DTPA (Magnevist®).

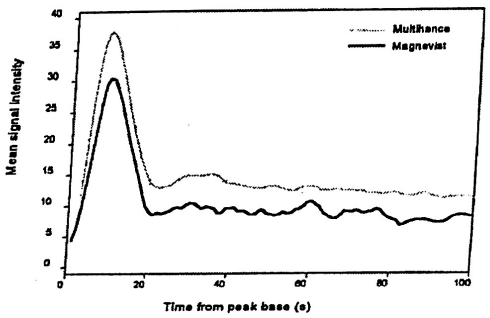

Figure 3: Averaged time-signal curves for Gd-BOPTA (Multihance) and Gd-DTPA (Magnevist®) show the higher and longer peak followed by a higher plateau level for Gd-BOPTA.

Discussion: The efficacy of Gd-BOPTA for MR-Angiography was determined to be higher than Gd-DTPA. These phase I studies exhibit that Gd-BOPTA suggests further improvements for MR-Angiography compared to the non-binding Gd-DTPA. These benefits seem to be due to the weak binding to serum proteins of Gd-Bopta.

References

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214 Detection of iron-oxide labeled rat T-cells using the background gradient MRI

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Purpose and Introduction: Previous study has verified the cell labeling of rat T-cells using the superparamagnetic iron-oxide particles without perturbing the surface nature and function of T-cells (1). But the *in vivo* detectability of the labeled cells was limited by the minimal cell concentration as 1×10^6 cells/ml for ordinary MRI techniques (1, 2). For improving the MR imaging detection of iron-oxide labelled T-cells, the background gradient image was applied with comparison to other imaging methods, such as spin-echo, gradient-echo, and diffusion measurement.

Subjects & Methods: 1. Labeling of rat T-cells

Cell labeling with detran-coated iron-oxide particles (BMS, Squibb Diagnostics, Plainsboro, NJ) was obtained as previously described (1, 2). Three cell samples were utilized in this study, (a) 1×10^7 intact BMS-labeled T-cell/ml 2% gelatin, (b) 1×10^7 ultrasound-broken BMS-labeled T-cell/ml 2% gelatin, and (c) 1×10^7 intact unlabeled T-cell/ml 2% gelatin.

2. NMR methods

All experiments were performed on a 4.7 T NMR system (Bruker Biospec). A co-axial double-sphere glass phantom (outer sphere diameter = 3.5 cm, and inner sphere diameter = 2.5 cm with separated outlets) was utilized to create a two-compartment model with an optimal condition for magnetic field homogeneity. As outer sphere was filled with 2% gelatin, and various cell samples were loaded to the inner sphere. The *in vitro* imaging studies of the cell phantom included the following; (a) gradient-echo images: TR (Repetition time)/TE (Echo time) = 100 ms/10.5 ms with a flip angle of 30 degree; (b) spin-echo images: TR/TE = 2000 ms/30 ms; (c) T_2-map was genertaed from the single-slice multiple-echo image; (d) T_1map was generated from the saturation recovery; (e) T_2 (delta)-map was generated from a three-pulse weighted sequence (90x-τ-180y-τ-90-x); (f) DC (diffusion coefficient) map