Longer in vivo Retention and Accumulation Improves Detection of PARACEST MRI Contrast Agents

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Abstract: PARACEST MRI contrast agents suffer from poor temporal resolution and limited detection sensitivity. Agents with longer *in vivo* retention times may compensate for poor temporal resolution, and agents that accumulate at high concentrations within *in vivo* tissues may compensate for limited sensitivity. The PARACEST agent EuDOTA-OBnS_2-Gly$_2$-COOH has both of these advantages relative to EuDOTAMGly, due to the addition of two o-benzyl moieties. This was demonstrated by the detection of the PARACEST effect of EuDOTA-OBnS_2-Gly$_2$-COOH in the in the inferior vena cava, kidney, and liver of a normal mouse. and no detection of the PARACEST effect of EuDOTAMGly in the inferior vena cava and liver and only brief detection in the kidney.

Introduction: PARACEST MRI contrast agents can be selectively detected, which provides opportunity to detect multiple agents during one scan session.[1] PARACEST MRI contrast agents have been developed that are responsive to enzyme activity,[2] metabolites,[3,4] metal ions,[5] pH[1] and temperature.[6] However, *in vivo* imaging of PARACEST agents has been limited by poor temporal resolution[7] and limited detection sensitivity.[8] These problems may be addressed by lengthening the *in vivo* retention time and improving the accumulation of the agent within *in vivo* tissues, which can be accomplished by introducing a hydrophobic organic o-benzyl moiety within the PARACEST agent.[9] To investigate this potential solution, *in vivo* PARACEST MRI was conducted to detect EuDOTA-OBnS_2-Gly$_2$-COOH (**Eu(1)**, containing two o-benzyl moieties)[10] relative to EuDOTAMGly (**Eu(2)**, without o-Bzl moieties)[1] in the inferior vena cava, kidney, and liver of a normal mouse.

Methods: To prepare for the MRI exam, a normal female Balb/C mouse was anesthetized with 1.5-2.0% isoflurane delivered in 2 L/min oxygen gas ventilation. A 26g dental catheter was inserted in the tail vein to facilitate the administration of a contrast agent. The mouse was then secured to a customized MRI-compatible cradle, probes for monitoring rectal temperature and respiration were connected to the mouse, and core body temperature was regulated using an automated feedback loop between the temperature probe and an air heater (SA Instruments, Inc). A series of RARE MRI experiments were conducted with presaturation applied at +50ppm, 20 μT and 2.2 sec to generate the PARACEST effect (4 sec TR, 40 sec/image). After acquiring pre-injection images, 100 mM **Eu(1)** in 100 μL was injected via the tail vein catheter, and a series of images were acquired to monitor the dynamic pharmacokinetics of the agent. Post-injection images were subtracted from pre-injection images to measure the PARACEST effect. This procedure did not require an image acquired with presaturaiton applied at -50 ppm as a control, and therefore avoided problems with magnetic susceptibilities. At the conclusion of the MRI scan, the mouse was euthanized with CO_2 asphyxiation prior to recovery from anesthesia. A similar study was conducted with **Eu(2)** in a different mouse. Each contrast agent was well tolerated by each mouse, and no side effects during injection and after the experiment were observed.

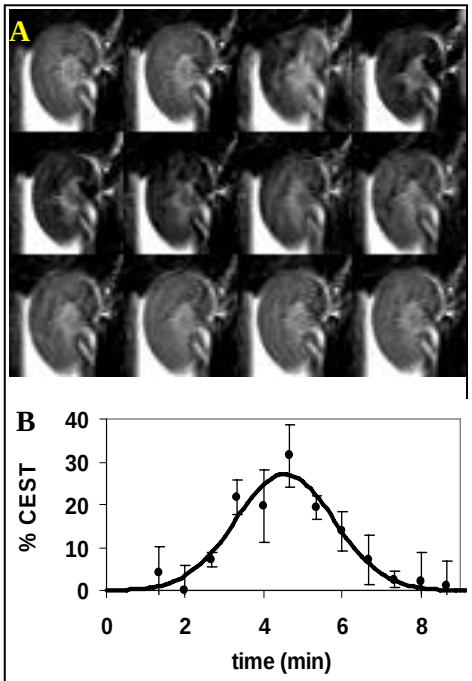

Figure 1. (A) PARACEST DCE MR images and (B) the dynamic PARACEST contrast change of the kidney.

Results: The pharmacokinetics of **Eu(1)** was visualized in the inferior vena cava, liver, and kidneys. A PARACEST effect was observed in the kidney cortex within 40 seconds post-injection, reached a maximum effect in the cortex and medulla at 4.6 min post-injection, and the initial image contrast and disappeared by 8.6 minutes post-injection (Figure 1). This dynamic PARACEST contrast change represented the arrival, and washout of **Eu(1)** in the kidney. A PARACEST effect was also detected in the inferior vena cava at 4.6 min post-injection (Figure 2). A strong 6-8% PARACEST effect was observed in the liver after 30 min post-injection, followed by a PARACEST effect that was observed in the biliary and GI tracts (data not shown). These dynamic PARACEST changes indicated preferential accumulation in the liver, uptake into hepatocytes, and excretion through the biliary and GI tracts. The PARACEST effect of **Eu(2)** was not observed in the vena cava or liver, and showed much faster wash-in and wash-out in the kidney (data not shown).

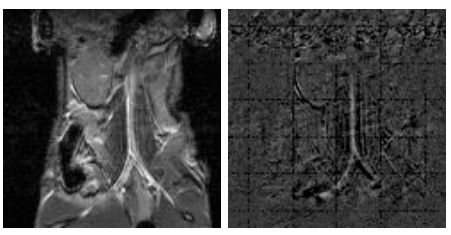

Figure 2. (A) The pre-contrast image and (B) the post-contrast PARACEST image of the inferior vena cava.

Conclusion: Hydrophobic o-benzyl moieties can be incorporated within PARACEST MRI contrast agents to lengthen *in vivo* retention times in the inferior vena cava and kidney, and to improve accumulation of the agent in the liver, which facilitates *in vivo* detection of the PARACEST agent relative to agents without o-benzyl moieties.

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