DOTAlaP: Single amino acid Gd complex with accelerated water exchange rate leads to increased relaxivity at higher fields

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Target audience: Gd-based T1 agent development for high fields, basic science studies, pre-clinical imaging.

Purpose: Magnetic resonance imaging (MRI) at high magnetic fields benefits from an increased signal to noise ratio, however T_1 based MR contrast agents show decreasing relaxivity (r_1) at higher fields. For this purpose, we have successfully explored the Gd(DOTAla) complex and its derivatives (1-2). It was our aim to design new Gd(DOTAla)-like agents with a shorter water residency time ($_M$), higher relaxivities at high magnetic fields, and subsequently test them in vivo.

Methods: We synthesized a new analogue of Gd(DOTAla), Gd(DOTAlaP), as well as a derivative with the ability to bind to human serum albumin (HSA): Gd(Ibu-DOTAlaP-OH). Water exchange kinetics for the inner-sphere water of Gd(DOTAlaP) were determined by measurement of the temperature dependence of the transverse relaxation time T_2 of $H_2{}^{17}O$ in the presence and absence of Gd(DOTAlaP). Relaxivity of Gd(Ibu-DOTAlaP-OH) in PBS and 4.5 % w/v HSA solution was determined through measurement of T_1 using inversion recovery at different field strengths ranging from 0.47 T to 9.4T, at 10, 25, 37 and 50 °C. T_1-weighted images were acquired of phantoms of Gd(Ibu-DOTAlaP-OH) and gadofosveset with and without presence of HSA at 4.7T (25 °C). T1-weighted images using a 3D Fast Low Angle Shot (FLASH) sequence of healthy, female nu/nu mice were injected with a 100 µmol/kg dose of Gd(Ibu-DOTAlaP-OH) or gadofosveset.

Results: The mean water residency time of Gd(DOTAlaP) at 37 °C in PBS was found to be optimal (τ_M = 8 ± 0.3 ns) for obtaining high relaxivity at intermediate and high magnetic fields. The relaxivity measured for Gd(Ibu-DOTAlaP-OH) in PBS was found to be typical for a Gd complex with no inner-sphere water (q=0; r_1=3.8 $mM^{-1}s^{-1}$ at 1.47T, 37 °C). Fitting of the field- and temperature-dependent relaxivities measured in 4.5% w/v HSA of Gd(Ibu-DOTAlaP-OH) according to the Solomon-Blombergen-Morgan equations revealed a greatly accelerated water exchange rate (τ_M = 1.6 ns) compared to previously investigated Gd(DOTAla) derivatives, as well as an increased inner-sphere hydration (q>0). The relaxivity of Gd(Ibu-DOTAlaP-OH) was found to be greater than gadofosveset in presence of HSA at 4.7T (37 °C) while the observed relaxivity of Gd(Ibu-DOTAlaP-OH) in PBS was lower compared to gadofosveset. Both gadofosveset and Gd(Ibu-DOTAlaP-OH) are 88% bound to HSA under these conditions. This also led to a greater observed contrast between blood vessels and muscle 2 min p.i. in nu/nu mice with Gd(Ibu-DOTAlaP-OH) when compared to gadofosveset at 4.7T.

Discussion and Conclusion: We have successfully expanded the DOTAla-ligand family by adding a new derivative displaying a highly accelerated water exchange rate. The corresponding HSA-binding derivative Gd(Ibu-DOTAlaP-OH) is found to have higher relaxivity at higher magnetic fields than clinically used gadofosveset in presence of HSA. This new compound represents a Gd-based agent with improved properties for high field imaging compared to the currently clinically used agent.

References: (1) Boros, E.; Polasek, M.; Zhang, Z.; Caravan, P. Gd(DOTAla) – A Single Amino Acid Gd-complex as a Modular Tool for High Relaxivity MR Contrast Agent Development. *J. Am. Chem. Soc.* **2012,** *134*, (48), 19858–19868. (2) Boros, E.; Caravan, P. Structure–Relaxivity Relationships of Serum Albumin Targeted MRI Probes Based on a Single Amino Acid Gd Complex. *J. Med. Chem.* **2013,** *56*, (4), 1782-1786.

Figure.

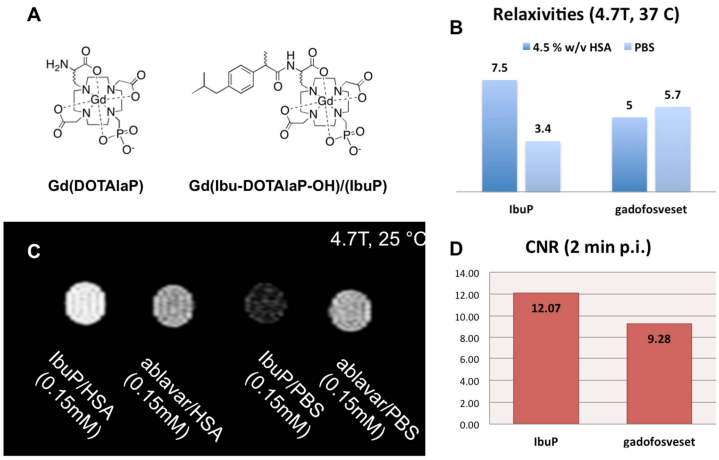

Figure. Chemical structures of derivatives Gd(DOTAlaP) and Gd(Ibu-DOTAlaP-OH) described in this abstract (A). Relaxivities [$mM^{-1}s^{-1}$] at 4.7T of gadofosveset and Gd(Ibu-DOTAlaP-OH) (B). T1 weighted phantom images of gadofosveset and Gd(Ibu-DOTAlaP-OH) in PBS and 4.5% w/v HSA CNR in the vena cava 2 min p.i. obtained from a pilot imaging study in nu/nu mouse with Gd(Ibu-DOTAlaP-OH) and gadofosveset (D).