Biodistribution of lanthanide-based MRI contrast agents assessed by BIRDS

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TARGET AUDIENCE – Scientists and clinicians interested in development and biodistribution of MRI contrast agents.

PURPOSE – Paramagnetic (i.e., lanthanide or transition metal ions) macrocyclic complexes are widely used as MRI contrast agents. Recent advances in design of contrast agents for molecular imaging have expanded to include paramagnetic probes for chemical exchange saturation transfer (CEST) and biosensor imaging of redundant deviation in shifts (BIRDS). In CEST the exchangeable protons on the paramagnetic complex are detected (i.e., paraCEST probes), whereas in BIRDS the detection focus is on the non-exchangeable protons on the paramagnetic complex (i.e., paraBIRDS probes). Although paraCEST and paraBIRDS probes are known for thermodynamic stability and kinetic inertness, the utility of these agents in vivo requires understanding of their biodistribution. The norm for biodistribution studies is to replace the paramagnetic metal ions with radioisotopes[1,2]. Complexes chelated with paramagnetic metal ions other than gadolinium can be detected with BIRDS and the resonance intensities of non-exchangeable protons on the complexes can be measured. The aim of this study was to demonstrate feasibility of BIRDS to evaluate tissue biodistribution of thulium-based contrast agents. $TmDOTP^{5-}$ was selected as a model molecule because it has been used widely as MRS shift agent[3] for sodium imaging as well as paraBIRDS probes[4] for pH and temperature mapping.

METHODS – To assess the biodistribution of $TmDOTP^{5-}$ using BIRDS under different infusion protocols, nine Sprague-Dawley rats (200-250 g) were separated into three groups: (i) intravenous infusion of 1 mmol/kg $TmDOTP^{5-}$, (ii) intravenous infusion of 100 mg/kg probenecid solution followed by 1 mmol/kg $TmDOTP^{5-}$, (iii) renal ligation followed by intravenous infusion of 1 mmol/kg $TmDOTP^{5-}$. Additional nine rats were infused with 0.1 mmol/kg $TmDOTP^{5-}$. After infusion, rats were euthanized with focused microwave irradiation and organs of interest (brain cortex, brain subcortex, liver, lung, spleen, heart, thigh muscle, and kidney) were removed, weighed, and homogenized for later BIRDS analysis. Blood plasma samples were also collected to measure the agent in the plasma for correction of agent concentration in the tissue using tissue-plasma volumes.[5] NMR solutions of each organ suspensions were prepared and 0.1 mM $TmDOTMA^{-}$ was used as internal reference. NMR spectra were acquired using standard pulse-acquire experiments with vertical bore magnet operating at 11.7 T using short TRs (~50 ms) and resonance intensities of H6 proton of $TmDOTP^{5-}$ were measured. Final tissue concentrations of $TmDOTP^{5-}$ were calculated after reference and plasma corrections.

RESULTS – Two $TmDOTP^{5-}$ doses (i.e., 0.1 mmol/kg and 1 mmol/kg) were assessed to evaluate the biodistribution profiles in various organs (**Figure 1**). Most low molecular weight MRI contrast agents are cleared out of the body through renal system within hours after injection. Three infusion conditions were tested. Renal ligation allows the agents to accumulate in various organs without renal clearance. For example, agent concentrations in brain regions were much higher in renal ligated rats to facilitate the BIRDS applications for in vivo pH and temperature mapping in brains.[4] Probenecid, a uricosuric drug that inhibits renal excretion of the agent, can be used to increase plasma and tissue concentration for BIRDS imaging. The results show that probenecid is effective in improving the tissue concentration in various organs, though its effect is not as noticeable as renal ligation. However probenecid infusion requires much less intervention compared to renal ligation. At high dose, the differential agent distributions in tissues across different infusion protocols are obvious, but at low dose, the agent distributions are similar in most organs. At both doses, the agent concentrations in kidney are higher when probenecid is used before the agent is administered.

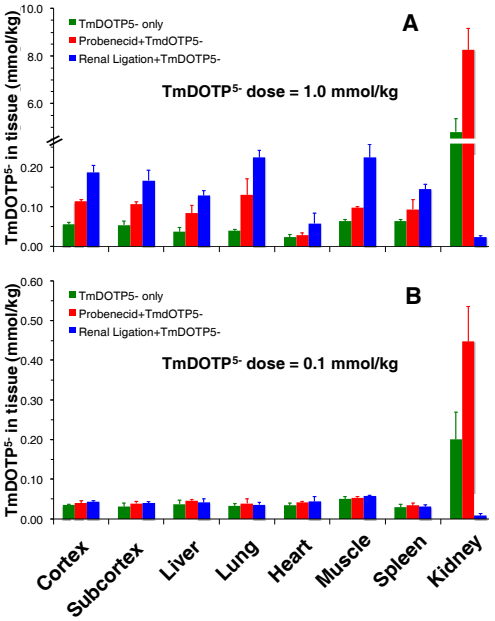

Figure 1. Biodistribution for $TmDOTP^{5-}$ infusion doses of (A) 1.0 mmol/kg and (B) 0.1 mmol/kg.

DISCUSSION – Biodistribution studies of lanthanide (except for gadolinium) complexes are possible with BIRDS even at low doses. The advantages of biodistribution studies using BIRDS include the ability to use original contrast agents without radioisotopic metal replacements and radiation exposure, fast averaging to obtain high SNR of proton resonances, unambiguous measurements because of non-overlapping resonances with other metabolites. Probenecid can improve agent circulation time and increase tissue concentration for MRI studies, especially in conditions when higher doses are required. Furthermore, at low dose, probenecid can enhance agent concentrations in kidney as much as two fold compared to infusion of agent only. Thus future in vivo BIRDS studies of kidney are feasible when probenecid is used together with the contrast agents.

CONCLUSION – We have shown the potential to use BIRDS to assess the biodistribution of lanthanide-based MRI contrast agents without using radioisotopes in vivo. We anticipate in vivo BIRDS can be used for future biodistribution of other MRI contrast agents with appropriate experimental setup (e.g., body coils). In addition, probenecid can be used together with contrast agents to facilitate MRI detection.

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