The biodistribution of [153Gd]Gd-labeled DTPA-BMA and DOTA in a transgenic mouse model of renal failure differs greatly from wild-type mice

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Introduction: Nephrogenic Systemic Fibrosis (NSF) is characterized by the thickening, induration and tightening of the skin with subcutaneous edema and can lead to joint contracture and severe limitation of motion in the extremities while also affecting internal organs, such as the lungs, liver, heart and kidney. This condition is observed exclusively in patients with renal insufficiency and is strongly associated with previous exposure to intravenous gadolinium-based contrast materials. There may be additional risk factors for NSF such as a recent or concurrent major inflammatory event. While a direct cause of this condition has not been elucidated, evidence suggests that free gadolinium, which has dissociated from the injected contrast agent may help induce the fibrotic changes associated with this disease. The goal of this work was to examine the biodistribution of radiolabeled contrast agents having different chelate stabilities (Gd-DTPA-BMA vs Gd-DOTA) in the context of renal insufficiency using a transgenic mouse model of progressive renal failure. This transgenic Alport (AL) mouse model is characterized by mutations in any one of the three genes encoding specialized chains of type IV collagen causing loss of kidney function and represents a good model for human Alport Syndrome.

Methods: Radiolabeled analogues of MR contrast agents were prepared by incubating carrier added gadolinium-153 (half-life: 242 d) with the chelators DOTA and DTPA-BMA to a final metal:chelator ratio of 0.4-0.8:1. Radiotracer purity was analyzed by radio-TLC and determined to be greater than 95% at the time of injection. Biodistribution studies were performed in AL mice and aged matched wild-type (WT) control animals by injecting each animal with either 0.13 MBq (3.5 µCi) of Gd-153-DOTA or Gd-153-DTPA-BMA, sacrificing each animal at selected time points post-injection (p.i.) and removing tissues of interest. Radiotracer content in the blood and selected tissues were counted in a gamma counter, compared to a weighed, counted standard, and the %ID/g and %ID/organ for the blood and selected tissues were determined.

Results: After Gd-153-DOTA was injected, activity was effectively cleared from the blood in both AL and WT mice by 7 days p.i. However, AL mice were observed to have 4.5 fold more activity remaining in the kidney (%ID/g±SD, AL vs. WT; p value: 0.32± vs. 0.072±; p = 0.019) after 7 days, which is attributed to the reduced renal function in the AL mouse model. In addition, significantly more activity was observed in the liver of AL mice (%ID/g±SD, AL vs. WT; p value: 0.029±0.006 vs. 0.013±0.004; p = 0.012) and in the bone (%ID/g±SD, AL vs. WT; p value: 0.011±0.002 vs. 0.006±0.0007; p = 0.0043) when compared to age matched WT litter mates. The clearance of Gd-153-DTPA-BMA from the blood was also efficient and was not statistically different between WT and AL mice at 7 d; however, there was higher uptake in the liver and kidney, suggesting this radiopharmaceutical is also being excreted through the hepatobiliary system. Similar to Gd-153-DOTA, three-fold more activity was observed in the AL mouse kidney when compared to the kidneys of WT mice (%ID/g±SD, AL vs. WT; p value: 1.00±0.19 vs. 0.34±0.03; p = 0.0014). Localized activity in the bone and bone marrow was also significantly higher in AL mice when compared to WT mice (Bone %ID/g±SD, AL vs. WT; p value: 1.44±0.10 vs. 0.38±0.02; p =0.0001) (Marrow %ID/g±SD, AL vs. WT; p value: 0.47±0.12 vs. 0.15±0.03; p = 0.02). Additionally, when the clearance properties of both complexes are compared in tissues that are involved with NSF development, significantly more activity was observed in AL mice that received Gd-153-DTPA-BMA than those receiving Gd-153-DOTA at 7 d post-injection. For example, significantly more activity was observed in the skin and bone marrow of AL mice that received Gd-153-DTPA-BMA than those receiving Gd-153-DOTA (AL skin %ID/g±SD, DTPA-BMA vs. DOTA; p value: 0.07±0.008 vs. 0.018±0.004; p = 0.002) (AL Bone Marrow %ID/g±SD, DTPA-BMA vs. DOTA; p value: 0.47±0.12 vs. 0.009±0.015; p = 0.004). This is likely due to the decreased stability of the Gd-153-DTPA-BMA relative to that of the macrocyclic complex, Gd-153-DOTA, and illustrates how MR contrast agent instability combined with poor renal function contributes to the retention of residual gadolinium species that are believed to facilitate the development of NSF.

Conclusion: Using radiolabeled MR contrast agents and a transgenic mouse model of Alport syndrome, this study demonstrates that significantly more radioactivity is localized in several tissues of renally impaired mice than in mice which do not suffer from renal insufficiency. This effect is enhanced when radiolabeled, linear chain MR contrast agents are administered suggesting that they are less stable than their macrocyclic counterparts and further lends support to the hypothesis that dissociated gadolinium and renal impairment work in a synergistic fashion to stimulate the onset of NSF.

No Reveiewer Comments Exist..