Gd-labelled Polylysine as a Tracer for Convective Enhanced Delivery

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Introduction: Convection Enhanced Delivery (CED) is a powerful method of circumventing the blood-brain barrier to deliver therapeutic compounds directly to the CNS. A limiting factor in the wider use of the technology is the inability to visualize the distribution of the compound so that its efficacy can be correlated with dosing and distribution. This project developed Gd-DTPA tagged polylysine compounds with various molecular weights (MW) to use as MR tracers for therapeutics with a range of MW. The compounds were tested in vitro and in vivo using a novel implantable pump and catheter system.

Method: Gd compounds of various MW including Gd-DTPA alone were infused through a multiport catheter into 0.6% agarose gels. The gels were imaged on a 3.0 T Siemens Symphony imager using 3D gradient echo techniques. Initial experiments tested the accuracy of estimating the Gd concentration from the MR images. Multiple gradient echo images acquired with different flip angles were combined to estimate T1. The Gd concentration at various points in the gel was independently measured using ICP-OES. A correlation between T1 and Gd concentration was established from which an accurate measurement of Gd concentration at any point in the image could be made. Multiple gels were infused with varying volumes of Magnevist to determine the correlation between the volume of infusion and the volume of distribution for the four compounds studied. Images of the gels were acquired immediately at the end of the infusion and again several hours later to estimate the separate contribution to the distribution arising from convection and diffusion. Finally, each of the four compounds was infused through a multiport catheter implanted into the putamen of a rhesus monkey and connected to a MedStream programmable pump. Each pump was programmed to deliver a predetermined volume of fluid with alternating on-off periods to take advantage of the convective and diffusive contributions to the volume of distribution. The animals were maintained for over thirty days during which multiple infusion and imaging sessions were conducted. From the images the volume of distribution of the various compounds was determined from T1 and T2 weighted images.

Results: The estimate of T1 from SPGR imaging of gels infused with various Gd concentrations demonstrated a linear relationship between 1/T1 and [Gd]. The imaging – ICP correlation showed good agreement between the two methods of estimating the concentration of Gd. The coefficients describing the convective and diffusive contributions to the CED volume of distribution for the four compounds are shown in figure 1 as a function of their MW. The slopes of these lines of best fit to the data are -0.34±0.03 and -0.81±0.24 for convective and diffusive components respectively. For the diffusive component this is in modest agreement with the value of -0.5 which would be expected for passive, unobstructed diffusion. T1-weighted images acquired in each rhesus monkey demonstrated a region of enhancement surrounding the implanted catheter. The region was the largest for the Magnevist infusion (Fig. 2). The polylysine infusions did not move far from the catheter in contrast to their behavior in the gels.

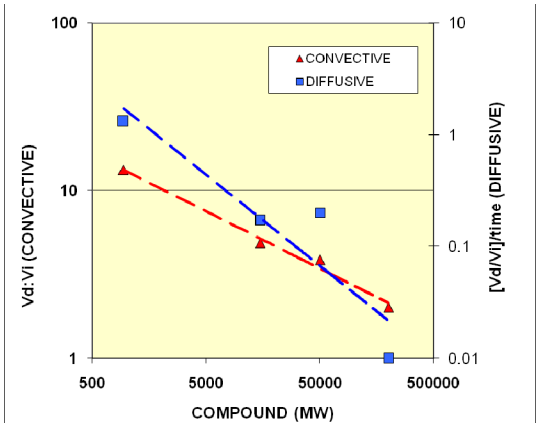

Figure 1. Variation of the convective and diffusive contributions to CED for compounds of different MW.

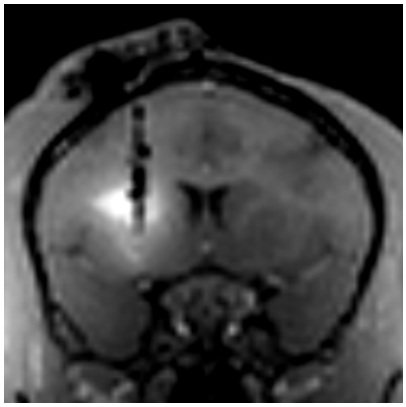

Figure 2. T1-weighted image of a monkey receiving Magnevist infusion through a catheter implanted in its putamen.

Conclusions: The compounds tested had a strong relaxivity and profoundly increased the image intensity on T1-weighted images. The compounds distributed in the agarose gels inversely proportional to their MW in a manner consistent with convection and diffusion through a porous media. When infused into animals the Magnevist distributed in the putamen in a manner predicted by the gel results. On the other hand the polylysine compounds did not move far from the catheter and may have been digested by endogenous enzymes. Thus polylysine may not be useful as a tracer for therapeutics with large MW.