

Convection Enhanced Delivery of Drugs to the CNS

P. A. Hardy¹, Z. Zhang¹, D. Gash¹, D. U. Gwost², D. Stiles², B. D. Nelson², P. Ge³, and D. Sah³

¹Anatomy & Neurobiology, University of Kentucky, Lexington, Kentucky, United States, ²Medtronic Neurological, Minneapolis, Minnesota, United States, ³Alnylam Pharmaceuticals, Inc., Cambridge, Massachusetts, United States

Introduction: Convection Enhanced Delivery (CED) uses a catheter implanted in a target tissue in the brain to deliver drugs to the CNS. CED is an effective method of circumventing the blood-brain barrier and chronically delivering a therapeutic dose of a drug to a localized region. The technique is being used clinically to treat intracerebral tumors and neurodegenerative diseases. An important issue for CED to progress is the development of imaging methodologies to measure drug distribution so that its effectiveness can be related to its distribution or so that the flow rate might be adjusted to achieve the desired coverage. This work tested the ability of MR imaging to measure the distribution and the mass of Magnevist present in the brain when it was infused at different flow rates and over different times.

Method: Using stereotaxic procedures, five rhesus monkeys were each implanted with a catheter (Medtronic, Inc.) into the putamen which was connected to a Synchromed pump (Medtronic, Inc.) implanted in the abdomen. The reservoir of the pumps were filled with a 10mM concentration of Magnevist prepared to have physiological osmolality of 300 mOs/Kg. The pumps were programmed to deliver this solution at a flow rate of either 0.1, 0.55 or 1.0 $\mu\text{L}/\text{min}$ over a period of seven days. Two animals were used for each flow rate. One animal was used to monitor a flow rate of 0.1 $\mu\text{L}/\text{min}$ and then reimplanted with a new catheter in the contralateral putamen and used to assess a flow rate of 1.0 $\mu\text{L}/\text{min}$. The animals were imaged on a 3.0 T Siemens Trio MR imager at time points, 1, 4 and 7 days after the initiation of pumping. At each imaging session, multiple MPRAGE and T1-weighted gradient echo images were acquired to image the brain and to estimate the T1 of the region of infusion.

Results: All animals tolerated the surgery well and recovered without incident. No leak-back of the infusate around the catheter was observed on any animal. MR images were acquired using 3D FLASH technique. Multiple series were acquired with different alpha to enable the calculation of T1. The images were analyzed in a custom-written program to estimate the relaxation rate $R1=1/T1$ on a pixel-by-pixel basis. From the MPRAGE images the volume of infusion was estimated by a region-growing technique thresholded to 10% of the maximum image intensity of the region of the brain nearest to the catheter insertion point.

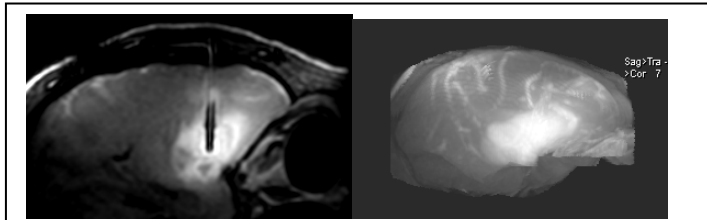


Figure 1. (left) Sagittal MPRAGE image showing the catheter implanted into the putamen of one rhesus monkey and four days after the infusion of 10 mM Magnevist. (right) MIP image of the MPRAGE set.

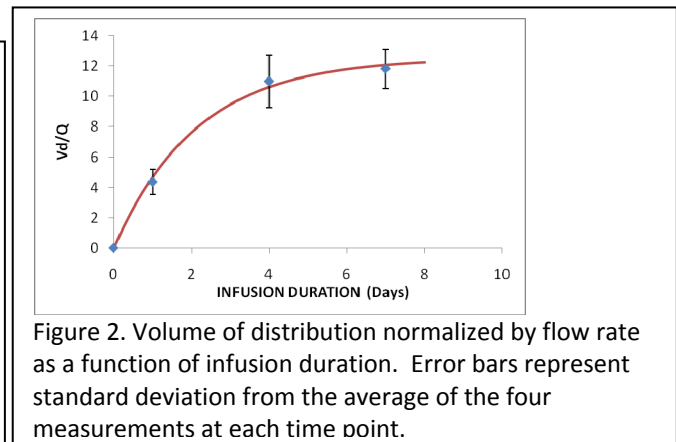


Figure 2. Volume of distribution normalized by flow rate as a function of infusion duration. Error bars represent standard deviation from the average of the four measurements at each time point.

Figure 1 demonstrates the placement of the catheter and the compactness of the resulting infusion. Figure 2 demonstrates the variation of the volume of distribution normalized by the flow rate. The best fit of the data to first order kinetics results in an estimated half life for Magnevist of 36 hours. Extrapolated to $t \rightarrow 0$ the $Vd:Vi$ ratio is 6.

Conclusions: These results demonstrate the ability to place the catheter into the desired target in the center of the putamen. The catheter design was effective in reducing leak-back for all the flow rates investigated. The measured $Vd:Vi$ ratio is in agreement with that measured for other small molecular weight compounds infused into the brain. Imaging was useful to visualize and to measure the distribution of the tracer in the brain.