Study of Ocular Drug Delivery Using Contrast-Enhanced Magnetic Resonance Imaging

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Introduction: Ocular drug delivery to the retina and posterior segment via the transscleral route is being recognized as an attractive method to achieve therapeutic drug levels in the eye [1]. However, drugs encounter several transport barriers and clearance streams following their administration in the sclera [2]. The development of efficient transscleral drug delivery systems requires an accurate understanding of the factors that affect the transport of drugs in ocular tissues. The contributions of various barriers and clearances in ocular tissues that limit the transscleral delivery of drugs (sclera, choroid, retina) have not been studied in depth due to the difficulties in obtaining data *in vivo*. This study utilizes contrast enhanced (CE)-MRI to determine the effects of various barriers and clearances *in vivo* on the spatial and temporal distribution of infused Gd-DTPA in the rabbit eye.

Methods and Materials: *Gd-DTPA Infusion:* A conjunctival flap was made in the right eye of New Zealand White rabbits and a 24 G angiocath tube was inserted into the sclera. Five millimeters of the angiocath tubing was advanced nasally into the sclera at a distance of 5 mm from the limbus in the superonasal quadrant. The angiocath was connected to a syringe pump located outside the scan room using a PE-10 tubing prefilled with 0.005 M Gd-DTPA. The infusion rate was set to 1 μl/min until steady state was obtained; the flow rate was then increased to 10 μl/min. Separate experiments, which involved halting the infusion once at steady state, were performed to examine the clearance mechanisms within the retina and sclera. MRI scans were performed over a period of three hours.
MRI Experiment: MR images were acquired using a 4.7 T magnet and Bruker Avance spectrometer. Following placement of the angiocath, a 4 cm passively decoupled surface coil was placed over the rabbit's eye. The rabbit was placed on a home-built cradle and inserted in a volume coil. T_1-weighted images were acquired using a 2D spin echo sequence. The sequence parameters were: TR/TE = 400/16 ms, FOV = 4.7 cm^2, matrix = 256x256, and averages = 2. Each scan lasted 3.5 minutes. Three contiguous slices, slice thickness 1.5 mm, were acquired with coronal and sagittal orientations.

Results: In T_1-weighted images the sclera (yellow arrow) and retina (red arrow) appear light and choroid (between arrows) dark. Figure 1 shows the effect of infusion rate on Gd-DTPA distribution after 17.5 minutes of infusion at 1 μl/min (A) and 10 μl/min (B). Higher infusion rates allow more posterior delivery as Gd-DTPA is seen to reach the optic nerve in the retina during infusion at 10 μl/min. At the lower infusion rate, Gd-DTPA only traveled about half the distance to the optic nerve. Figure 2 shows the effect of clearance mechanisms on signal intensity in the retina when the infusion is halted. Figures 2B and 2C show a considerable reduction in signal intensity in the retina compared to Figure 2A.

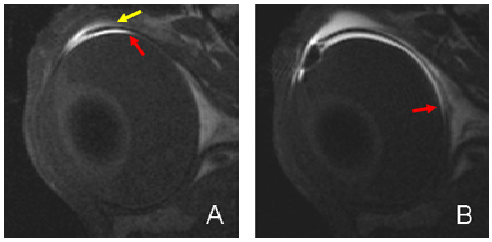

Figure 1. A) infusion rate at 1 μl/min; B) infusion rate at 10 μl/min

Discussion: The spatial and temporal distribution of Gd-DTPA delivered *in vivo* showed the effects of infusion rate on posterior delivery and the clearance mechanisms in the retina. Greater convective flow provided by higher infusion rates seems to enhance the posterior distribution of Gd-DTPA in the sclera and retina. Retinal clearance of Gd-DTPA appears to be very fast as signal intensity diminishes within minutes of halting infusion. Scans acquired with CE-MRI show that effective transscleral drug delivery requires high infusion rates of drug to achieve delivery to the posterior regions of the eye and sustained infusion to minimize loss through rapid retinal clearance.

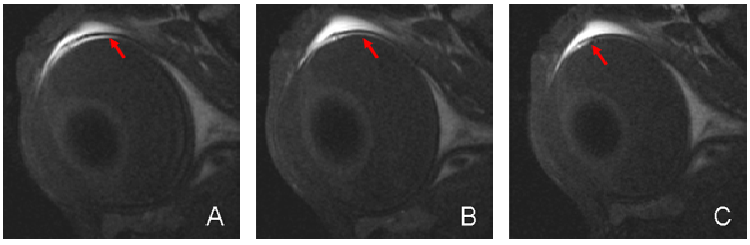

Figure 2. A) 1 μl/min infusion at steady state; B) 3.5 minutes after halting infusion; C) 17.5 minutes after halting infusion

References:

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