Quantitative MRI to Study Ocular Drug Distribution from Sub-Tenons' Injection

S. S. Lee[1,2], D. Z. D'Argenio[1], G. Karapetyan[2], I. Harutyunyan[2], H. Kim[2], and R. A. Moats[2]

[1]Dept of Biomedical Engineering, University of Southern California, Los Angeles, CA, United States, [2]Childrens Hospital Los Angeles, Los Angeles, CA, United States

Introduction

A major goal in ocular drug delivery is minimally invasive sustained drug release over an extended period of time. Sub-Tenons' injections of a drug depot have been shown to deliver steady anterior segment drug concentrations up to 6 hours[1,2]. Standard preclinical methods of assessing ocular drug distribution, which require euthanasia of several animals at variable time points and subsequent tissue dissection, offer limited information on real-time drug delivery characteristics. Therefore, magnetic resonance imaging was used in our experiments to capture diffusion gradients from the source using drug surrogate formulations in live animals.

Materials and Methods

0.05 M Gd-DTPA (Magnevist, Berlex, Inc.) was prepared in 4% HPMC, hyaluronic acid and PBS. Sprague-Dawley rats (Harlan, Inc.) were anesthetized under 2% isoflurane gas, and 10 uL sub-Tenons' injections of each formulation were performed either superiorly or inferiorly and 1 mm from the limbus of one eye. Serial 3-D magnetic resonance images were acquired on a 7-T magnet (Bruker). A calibration curve was derived from phantom scans and pharmacokinetics of each injection was assessed (Fig. 1). T2 relaxometry maps were computed with a multi-spin multi-echo sequence to assess the residency time of each formulation.

Results and Discussion

Drug depots composed of 0.05M Gd-DTPA and 4% HPMC remained in the sub-Tenons' space longer than drug depots composed of PBS, demonstrating that the increased viscosity of a drug formulation provides a longer drug residence time. Pharmacokinetic analysis demonstrates that as drug depot concentrations decrease over time, aqueous humor concentrations increase (Fig. 2). Drug distribution of both formulations spread down a concentration gradient from the depot, to the ciliary body region, and into the anterior chamber. This experiment suggests superior sub-Tenons' injection of viscous formulations is a potential method to achieve sustained drug release to the anterior chamber.

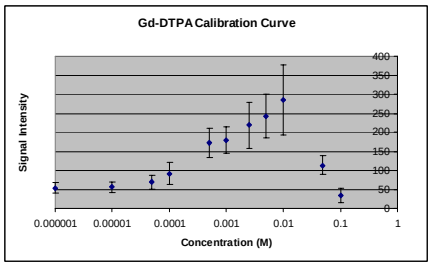

Fig. 1 – Gd-DTPA calibration curve was computed from scans of varying concentrations of Gd-DTPA-saline phantoms

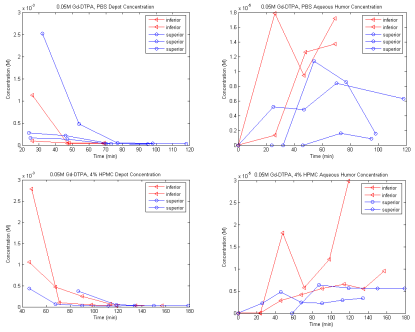

Fig. 2 – Top left shows Gd-DTPA-PBS depot concentration changes over time. Top right is the Gd-DTPA-PBS aqueous humor concentration over time. Bottom left is Gd-DTPA-4% HPMC depot concentration changes over time. Bottom right is Gd-DTPA-4% HPMC aqueous humor concentration changes over time.

[1]Ghate D, Brooks W, McCarey BE, et al. Pharmacokinetics of intraocular drug delivery by periocular injections using ocular fluorophotometry. Invest Ophthalmol Vis Sci 2007; 48:2230-7

[2]Tsuji A, Tamai I, Sasaki K. Intraocular penetration kinetics of prednisolone after subconjunctival injection in rabbits. Ophthalmic Res 1998;20:31-43