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COMPARISON OF CONVECTIVE TRANSPORT OF DRUG BETWEEN INTRAVITREAL INJECTION AND CONTROLLED RELEASE IMPLANT

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ABSTRACT

It is important to know the drug distribution following administration of drug in order to properly treat with adequate dosage and thus, avoid damage to tissues due to excessive high concentrations. A computer model was developed to determine drug distribution by convective-diffusive transport processes in a rabbit eye. When compared with pure diffusion within vitreous, the ratio of the amount of a model compound, fluorescein, reaching the retina to that cleared by aqueous outflow increased by 93% and 84% for intravitreal injection and implant, respectively, with maximum vitreous outflow (glaucomatous eye). The result shows that the combined "convective" effect due to the vitreous outflow and "wash out" effect by aqueous outflow has significant impact on drug distribution for both intravitreal injection and implant. These two effects should be considered in the design of drug delivery strategies.

INTRODUCTION

Aqueous humor (AH) is actively secreted by the ciliary process and drains through two major pathways; trabecular outflow, and uveoscleral outflow. Most of the AH (70-90%) leaves via the trabecular outflow while the remaining (10-30%) of it exits through uveosclera outflow (Forrester et al. 2002). However, there is a strong evidence that a fraction of fluid from the ciliary process flows through the vitreous in healthy eye (Araie et al. 1991), called vitreous outflow (Fig. 1). Obstruction of aqueous outflow increases intraocular pressure (IOP), which results in the pathogenesis of glaucoma. The vitreous outflow will increase in case of glaucoma because of the increase of the aqueous outflow resistance.

To overcome the blood-retinal barrier, either intravitreal injections or controlled release implants are currently being used to treat retinal and vitreal disease. This study compares drug distribution between intravitreal injection and implant with different vitreous outflow i.e. healthy and glaucomatous eye.

METHOD

The model was based on the rabbit eye (Jack et al. 1960). The twelve-compartments modeled are sclera, retina-choroid, vitreous, lens, posterior and anterior chamber, iris, ciliary processes, hyaloid membrane, Schlemm's canal, cornea, and a drug source by intravitreal injection or implant. Figure 1 shows the cross-section of the 3D eye model. Since drug source was positioned closer to the hyaloid membrane, half of the eye was modeled, with the symmetry plane passing through the middle of drug source as well as all other eye compartments. Fluorescein was selected as a model compound due to available experimental data (Araie et al. 1991) and known physical properties such as diffusion and permeability parameter in different compartments of eye.

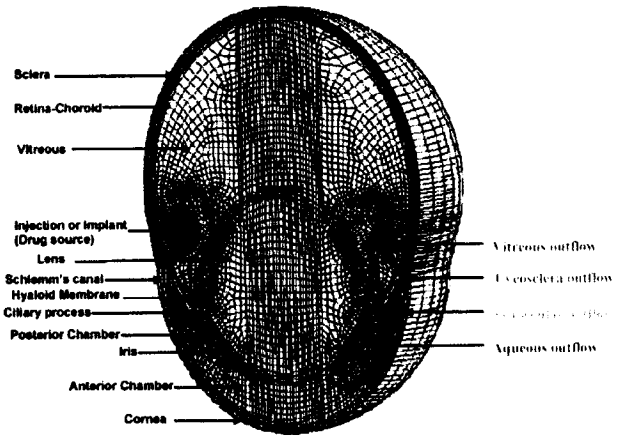

Fig. 1 3D Rabbit eye model and Eye fluid pathways

Using an advection-diffusion approach, the flow field was solved first using the nonlinear Navier-Stokes equation, and then the developed flow was coupled with species (fluorescein) mass balances to calculate the fluorescein distribution within the eye. The AH was modeled as a fluid source with a constant flow rate of 2.2 μL/min generated by the ciliary process and with 4 different vitreous outflow rates: F0, F1, F5, and F10, which were 0, 0.1, 0.5, and 1 μL/min, respectively. The remaining fluid (aqueous outflow) was cleared through Schlemm's canal. The fluorescein mass was 30 μg which was delivered in a spherical drug source of 0.1 cm radius. For intravitreal injection, the initial concentration was specified at the spherical location (Fig. 1) of the injected bolus of fluorescein within the vitreous. In contrast, for the implant, an equivalent amount of fluorescein was delivered at the same location with a constant flux over 15 hours time period. At the surface of the lens and cornea, and at all the symmetry surfaces, a zero species flux boundary condition was used. Species concentration at outer surface of the sclera is a perfect sink and thus, the concentration was set to zero to model complete clearance by the blood. Retinal permeability of fluorescein was kept constant having a value of 2.6×10^{-5}cm/s (Friedrich et al. 1997) and the diffusivity of fluorescein in the vitreous, hyaloid membrane and posterior and anterior chambers was 6×10^{-6}cm^2/s (Araie et al. 1991). The eye compartments were meshed with 8 noded hexahedral elements. To avoid excessive distortion of the elements in the eye compartments, a total of 149,761 elements was used. The Galerkin finite element method was used to solve the equations.

RESULT AND DISCUSSION

Figure 2 shows the time histories of the concentration close to the center location of the retina comparing intravitreal injection and implant for different vitreous outflows. For the intravitreal injection and the implant having the same quantity of drug, the concentration peaked at 6.8 hr and 18.5 hr, respectively. As compared with the intravitreal injection, the peak concentration for implant was reduced about 40% for different vitreous outflows. When compared with pure diffusion case with no flow in vitreous, the peak concentration for the intravitreal injection increased by 4, 22, and 47% for different vitreous outflows of 0.1, 0.5, and 1 μL/min respectively. Similarly, for the implant the peak concentration increased by 5, 27, and 59% for vitreous outflows of 0.1, 0.5, and 1 μL/min, respectively.

Figure 3 shows cumulative amount of fluorescein reaching the retina for intravitreal injection and implant with various vitreous outflows. For no vitreous outflow, at long times (40 hr), 57% and 59% of the fluorescein reached the retina for intravitreal injection and implant, respectively. For maximum vitreous outflow of 1 μL/min, 73% of the fluorescein reached the retina for both intravitreal injection and implant. Remaining drug is washed out by aqueous outflow through Schlemm's canal. Thus, when compared with pure diffusion (no vitreous outflow), the ratio of fluorescein reaching the retina to that cleared by aqueous outflow increased by 93% and 84% for intravitreal injection and implant, respectively, with maximum vitreous outflow.

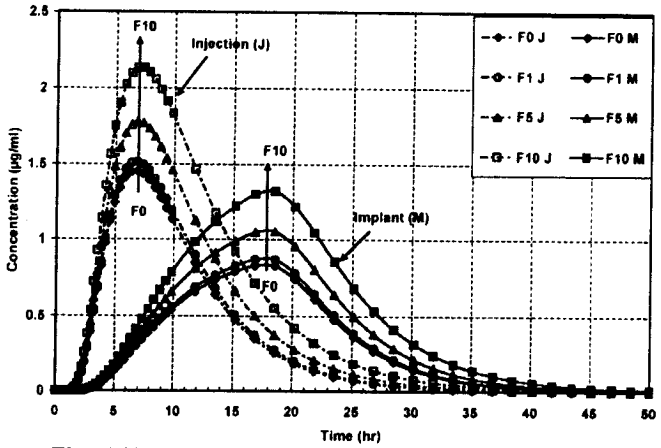

Fig. 2 Time histories of the concentration at the retina comparing intravitreal injection and implant with different vitreous outflows

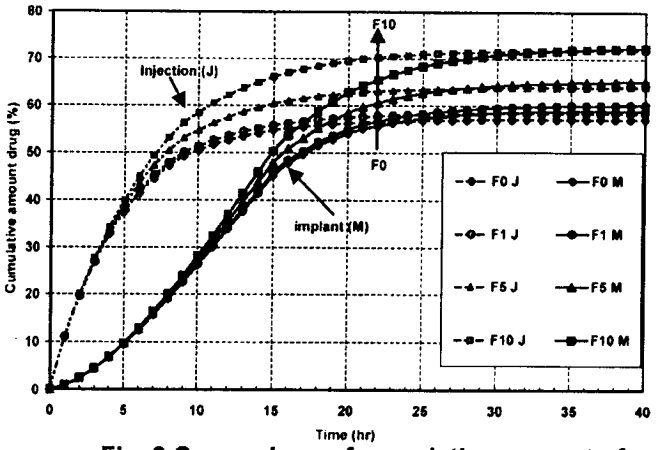

Fig. 3 Comparison of cumulative amount of fluorescein reaching retina between intravitreal injection and implant with different vitreous outflows

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