EVAULATION OF PHAMARCOKINETICS AND RETINAL PERMEABILITY FOR GANCICLOVIR IN A RABBIT AND HUMAN EYE

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ABSTRACT

Cytomegalovirus (CMV) is the most common cause of viral retinitis in patients with AIDS. Ganciclovir (GCV) has been widely used in the treatment of CMV retinitis. The GCV distribution in the vitreous is obviously influenced by the rate of elimination through the retina. The retinal permeability of GCV was calculated to be 9.25×10^{-5} cm/s for both rabbit and human. The half-life of GCV in the vitreous was 6.8 hr and 13.2 hr for rabbit and human respectively. The difference of half-life between rabbit and human was only caused by the difference in the volume of vitreous humor. The numerical analyses provide a useful tool for identifying animal model and relevant parameter for developing drug delivery strategies to treat vitreoretinal diseases.

INTRODUCTION

Intravenous GCV is effective, but requires frequent and long-term intravenous dosing. Also, low permeability of the blood-retinal barrier may necessitate higher dosage during intravenous GCV administration to achieve therapeutic levels near the retina. The long term treatment and high dosage of GCV increases the risk of systemic adverse effects such as bone marrow suppression and neutropenia. To avoid the systemic adverse effect and overcome the blood-retinal barrier, intravitreal therapy such as intravitreal injection and controlled release implants are currently being used to treat CMV retinitis.

The 50% effective dose (ED_{50}) of GCV for human CMV has a narrow concentration range (0.1-2.75 µg/ml). Therefore, to maximize the therapeutic benefits, it is critical to know GCV distribution within the eye following intravitreal administration. The GCV distribution in the vitreous is obviously influenced by the rate of elimination through the retina. In this study, retinal permeabilities and pharmacokinetics of GCV are evaluated in the rabbit and human eye.

METHOD

The model twelve-compartments of the eye are sclera, retina-choroid, vitreous, lens, posterior and anterior chamber, iris, Ciliary processes, hyaloid membrane, Schlemm's canal, cornea, and a drug source. Figure 1 shows the cross-section of the 3D eye model for a rabbit (Fig. 1A) and human (Fig. 1B). The most significant differences between a rabbit and human eye are the size of the lens and the volume of the vitreous. In a human eye, the lens is smaller than that in the rabbit eye. The volume of the vitreous is 4 mL for the human eye, whereas 1.5 mL for the rabbit eye.

When the drug source (red zone in Fig. 1) was positioned closer to the hyaloid membrane, half of the eye was modeled. For this model the symmetry plane passed through the middle of the drug source as well as through all other eye compartments. When the drug source was positioned in the center of the vitreous, a quarter of the eye was modeled.

To compare with the in vivo studies, the delivered location and amount of GCV in the model corresponded with in vivo studies (Table 1). Since the in vivo data measured by Luis et al (196 µg injection) [1] mostly eliminated by first order process, it was chosen to calculate retinal permeability using numerical computation.
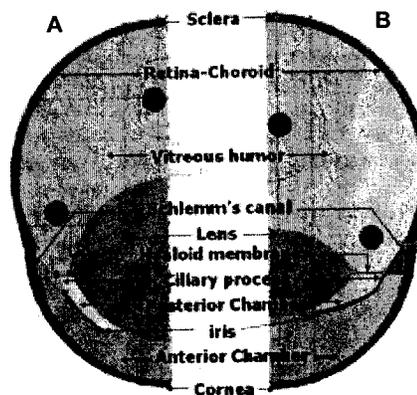

Figure 1. Eye model for rabbit (A) and human (B)

Model	GCV source (location)	Delivered amount	Ref
Pigmented Rabbit	Injection (center)	196 and 800 μg (in 40 μl)	[1]
Pigmented Rabbit	Injection (center)	200 μg (in 100 μl)	[2]
Albino Rabbit	Implant *	6 mg (5.2 and 1.9 μg/h)	[3]
Human	Injection (center)	200 μg (in 100 μl)	[4]

* GCV location is closer to hyaloid membrane

Table 1. *In vivo* studies for intravitreal GCV transport

In order to evaluate the convection-diffusion drug transport within the eye, the flows of the aqueous and vitreous humors were first solved using the nonlinear Navier-Stokes equation (Eq. 1). To calculate the GCV distribution by the convective-diffusive drug transport, the species mass conservation equation (Eq. 2) was coupled with the flow field.

$$\rho U \cdot \nabla U = -\nabla P + \mu \nabla^2 U \qquad (1)$$

$$\frac{\partial C}{\partial t} + U \cdot \nabla C = D \nabla^2 C \qquad (2)$$

The aqueous humor generated by the Ciliary process was modeled as a fluid source with a constant flow rate of 2.2 μL/min for rabbit and 2.5 μL/min for human. Vitreous outflow was modeled 0.1 [5] and 0.14 μL/min [6] for a healthy rabbit and human respectively. The balance of the aqueous humor (aqueous outflow) was cleared through Schlemm's canal. Since the fluid properties of the aqueous and vitreous humors are nearly identical to that of water, a viscosity of 6.9×10^{-3} g·cm^{-1}·s^{-1} and a density of 1 g·cm^{-3} were used.

The GCV entering the retina from the vitreous was assumed to be cleared through the blood capillaries of the retina. So, the retina was treated as a perfect sink for the drug passing through the retina. Thus, the drug concentration at the outer surface of the retina was set to zero. Because the iris, lens, cornea, and symmetrical surfaces were assumed to be impermeable to the GCV, a zero species gradient boundary condition was imposed. The diffusivity of GCV was 9.89×10^{-6} cm^2/s in the vitreous and 1×10^{-5} cm^2/s in the posterior and anterior chambers [7]. The eye compartments were meshed with 8 noded hexahedral elements. The Galerkin finite element method was used to solve the equations.

RESULT AND DISCUSSION

The retinal permeability of GCV was calculated to be 9.25×10^{-5} cm/s by comparing the *in vivo* data measured by Luis et al (196μg injection) [1]. The difference between regressed data of Luis's *in vivo* concentration and the present numerical result was less than 0.1%. Using the retinal permeability of 9.25×10^{-5} cm/s, the additional numerical calculations were conducted to compare with other *in vivo* studies for the injection (Fig. 2) and for the implant (Fig. 3). The difference between the comparisons was less than 1%. Thus, these comparisons support the calculated value of retinal permeability.

Half-life for intravitreal injection (0.693/K$_{el}$) was calculated from the slopes (K$_{el}$) in Fig. 2. The half-life of GCV in the vitreous was 6.8 hr for both albino and pigmented rabbit. In general, there were differences in the drug distribution between albino and pigmented rabbits. However the GCV showed no significant difference in the pharmacokinetics between the two types of rabbits. For the human, the half-life was 13.2 hr. The difference of half-life between rabbit and human was only caused by the difference in the volume of vitreous.

The *in vivo* experiments were conducted in albino rabbit [3], pigmented rabbit [1, 2], and human eye [4]. The predicted retinal permeability in this study, however, was found to be same in albino and pigmented rabbit and human. In summary, the numerical analyses provide a useful tool for identifying animal model and relevant

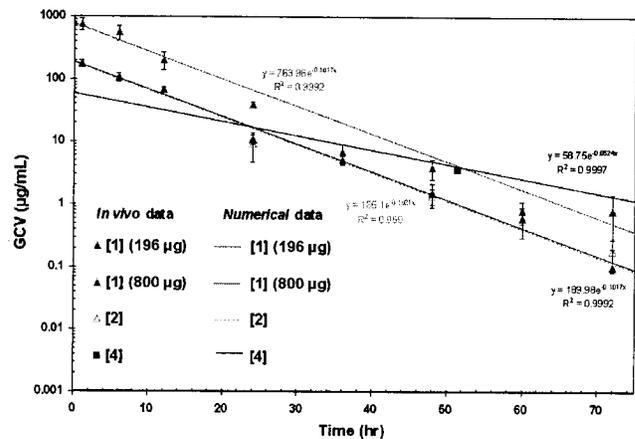parameter for developing drug delivery strategies to treat vitreoretinal diseases.

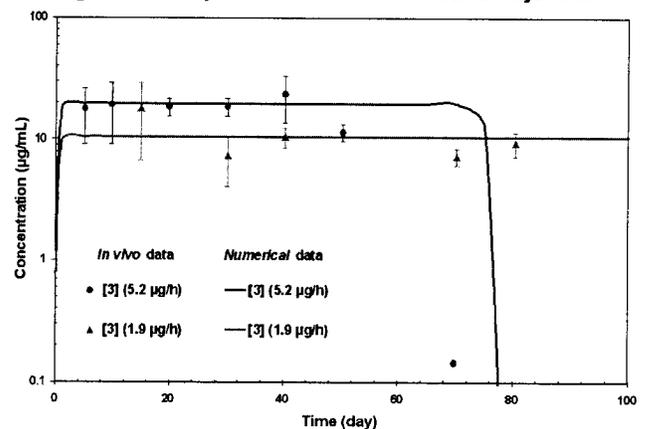**Figure 2. Comparison with *in vivo* data of injection**

Figure 3. Comparison with *in vivo* data of implant

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