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Numerical simulation of aqueous humor flow: From healthy to pathologic situations

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ABSTRACT

A mathematical model which simulates drug delivery through the cornea, from a therapeutic lens to the anterior chamber of the eye, is proposed. The model consists of three coupled systems of partial differential equations linked by interface conditions: drug diffusion in the therapeutic lens; diffusion and metabolic consumption in the cornea; diffusion, convection and metabolic consumption in the anterior chamber of the eye. The dependence of intraocular pressure on the obstruction of the trabecular mesh and the production rate of aqueous humor by the ciliary body is modeled. The therapeutic effects of drugs that act on the trabecular mesh or on the ciliary body are analysed. Comparisons between topical administration and drug delivery from a therapeutic lens are included.

1. Introduction

The anterior segment of eye is filled with a clear fluid called aqueous humor (AH) that is composed predominantly of water. It has two main roles: to deliver oxygen and nutrition to tissues within the eye; and to maintain a correct balance and regulation of intraocular pressure (IOP), which is important in early ocular development as well as maintaining integrity throughout life. The fluid is continuously produced in the ciliary body. It leaves the eye through the trabecular meshwork (TM) sievelike structure, and convects into a tube called the Schlemm's canal, located in the angle of the anterior chamber. The aqueous humor flows through this drainage structure and mixes with venous blood (Fig. 1). Consequently, the two main structures related to the dynamics of AH are the ciliary body – the site where AH is produced – and the limbal region, which includes the trabecular meshwork – that regulates its outflow [1,2]. Clinical research points out that "the combined resistance of the TM and the Schlemm's canal are the primary source of resistance in outflow". This pathway accounts for about 70% – 90% of aqueous outflow.

Intraocular pressure (IOP) is the result of a complex interplay of the components of aqueous humor dynamics. When an obstruction of the TM or the Schlemm's canal occur an increase of the IOP is then observed. Several studies have shown evidence that IOP can be controlled by decreasing the production of AH and/or decreasing the grade of obstruction of such structures [3,4].

Glaucoma is a progressive optic nerve neuropathy where the direct mechanical effect of an increase of IOP is the most common risk factor for its progression (Fig. 2). It can result in vision loss and it is one of the leading causes of blindness. Glaucoma is the 3rd most common cause of blindness worldwide and the 2nd most common cause of blindness in the

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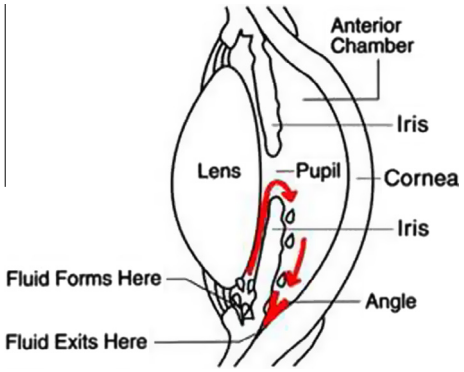

Fig. 1. Anatomy of the eye (http://www.theeyecenter.com/educational/005.htm).

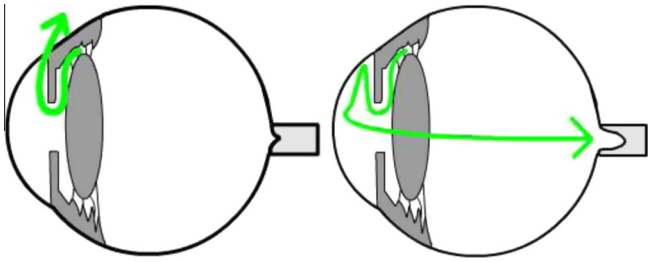

Fig. 2. Increase of IOP and damage of the optic nerve represented by the rectangle shaped structure on the right side of the schemes (http://www.thecontactlenspractice.co.uk/page/glaucoma/).

US and Europe and the disease is expected to affect more and more people as elderly population grows. With early treatment it can be controlled and therefore its diagnosis is crucial.

Open angle glaucoma is characterized by an obstruction of the drainage structures and an increase in the IOP is a major risk factor. Lowering this pressure is the principal option of treatment in this clinical situation. In closed angle glaucoma the iris moves forward from its normal position and reduces drastically or completely eliminates the camerular angle (space between the iris and the cornea). It causes a total obstruction of AH outflow and consequently a sudden increase of IOP. In this study we only consider open angle glaucoma and its treatment with beta-blockers (which decrease the AH production rate) and prostaglandin derivatives (that increase the uveal-scleral outflow).

As the behaviour of IOP is mainly related with the dynamics of AH in the anterior chamber of the eye, computational simulations in healthy and pathologic conditions can be a very useful tool for clinicians and pharmaceuticals. Several studies have addressed recently the dynamics of AH [5–9]. However at the best of our knowledge the interaction of drug flow with the dynamics of AH and the effects on IOP decrease of different families of drugs have not been modelled and simulated so far. Also the effects on IOP of the production rate of AH and the obstruction of TM as well as the coupling of AH flow with drug delivery mechanisms and transport mechanisms through the cornea have not yet been described in the literature. The findings of these studies clarify the mechanisms of IOP variations and they can give indications on how to tailor a treatment in order to fit specific patient's needs.

To simulate a treatment the type of drug and the release mechanism must be specified. Several families of drugs are used to lower the intraocular pressure (IOP) and consequently to prevent optic nerve damage. We mention without being exhaustive: beta-blockers that reduce AH production; prostaglandin derivatives which increase the outflow of AH; alpha agonists and combined medications that decrease the production of AH and simultaneously increase its outflow [10–12,3,13]. In the present paper we simulate the therapeutic effect of beta-blockers and prostaglandin derivatives. As far as drug release mechanisms are concerned two procedures are clinically used: ophthalmic drops and therapeutic lens. Ophthalmic drops are by far the most used route of drug delivery to the eye. However it is estimated that when a drop is instilled into the eye it is diluted by the lachrymal secretion and 95% is cleared by the tear fluid. To improve the efficiency of drug delivery avoiding drug loss and also deleterious side effects many researchers have proposed the use of therapeutic contact lenses as a vehicle to deliver ophthalmic drugs [4,14–18]. The method is particularly important in the case of severe diseases of the eye, as for example glaucoma, accompanying population ageing for which long periods of drug delivery are needed [21]. The main advantage of this route is the possibility of controlling drug delivery by means of the use of polymeric lens designed to achieve pre-defined performances with a high degree of comfort and biocompatibility.