

Modeling Drug Disposition of Timolol in Ocular Tissues of Rabbit following Topical Eye Drops

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INTRODUCTION

Recently, we reported the successful application of a novel mathematical model describing drug disposition in eye compartments to simulate disposition of clonidine after topical (eye drop) administration [1]. This example extends the methodology to describe the disposition of timolol in different eye tissues and plasma after topical administration. Timolol is a nonselective beta-adrenoceptor antagonist used to lower intraocular pressure (IOP) [2]. A serious disadvantage of ocular timolol therapy is the amount of drug getting into systemic circulation that adversely affects vital organ functions in elderly patients [2].

METHODOLOGY

The ocular model used in this study is identical to the internally-developed model used earlier in Ray Chaudhuri et al. [1]. It describes the eye as a collection of multiple compartments with transport of drugs between compartments modeled by concentration-gradient driven passive diffusion with rates dependent on physiological (e.g. surface area) and drug-dependent physicochemical properties (e.g. permeability) for each compartment. Mechanisms critical to topical delivery such as nasolacrimal drainage (through tear flow and volumetric drainage) have also been incorporated into this model. The ocular model is connected to the pharmacokinetic model in GastroPlus™ (Simulations Plus, Inc.) [3] to allow for simulation of drug appearance in plasma after ocular administration as well as drug uptake by the eye tissues after oral or systemic administration.

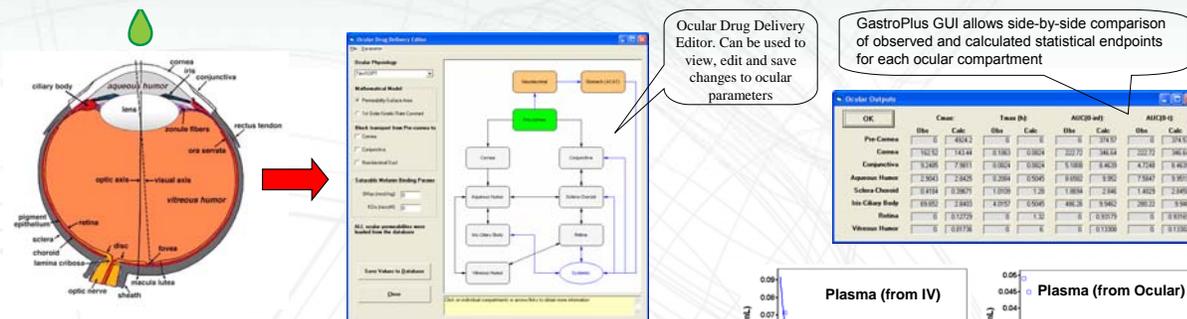
The formulation studied was topical timolol solution, across two distinct research groups [4-5]. The PKPlus™ module of GastroPlus was used to fit systemic PK parameters from observed plasma profiles after intravenous (IV) administration in rabbits [4] and was used to simulate plasma profiles from ocular administration. Lee et al. [4] also reported concentration-time profiles in different ocular tissues from a topical dose, which were used to optimize selected ocular parameters (relevant ocular permeabilities and tear flow rate). The fitted set of parameters was then used to predict the observed concentration-time profiles in three ocular tissues, as reported in Francoeur et al., with a formulation and dose identical to that used in [4].

RESULTS

Figure 1 represents plasma concentration profiles from IV and ocular administrations. Figures 2 & 3 represent the concentration vs. time profiles in individual eye compartments from a topical timolol eye-drop, where the observed data correspond to those reported in Lee et al. (2002) and Francoeur et al. (1985), respectively. The dose (0.1625 mg) and dose volume (25 µL of 0.65% solution) was same in both cases. In all of these figures, squares (with error bars) represent experimental data points while solid lines represent the simulated profiles. All figures were obtained directly from the GastroPlus graphic user-interface

REFERENCES

- [1] Ray Chaudhuri S et al., Modeling Drug Disposition in Ocular Tissues following Topical Eye Drops and Intravitreal Injection, 2009 ARVO Annual Meeting, 2009, May 3-7, Ft. Lauderdale.
- [2] Korte, J-M et al., "Systemic bioavailability and cardiopulmonary effects of 0.5% timolol eye-drops" Graefes Arch Clin Exp Ophthalmol, 2002; 240:430-435
- [3] www.simulations-plus.com
- [4] Lee VHL et al., Pharmacokinetic Basis for Nonadditivity of Intraocular Pressure Lowering in Timolol Combinations, Invest Ophthalmol Vis Sci, 1991; 32:2948-2957
- [5] Francoeur, ML et al., Kinetic disposition and distribution of timolol in the rabbit eye. A physiologically based ocular model, Int J Pharmaceut, 1985; 25, 275-292



Timolol (Lee et al.) - Used for Fitting

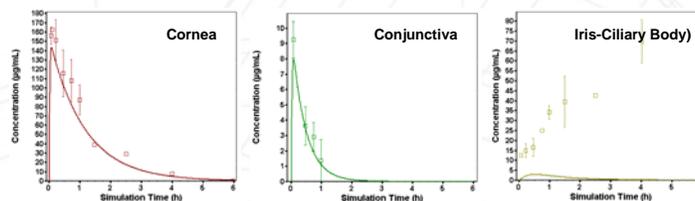


Figure 2. Concentration vs. time profiles in different eye compartments from a 0.1625 mg topical eye-drop of timolol in rabbits. Data obtained from Lee et al. (2002)

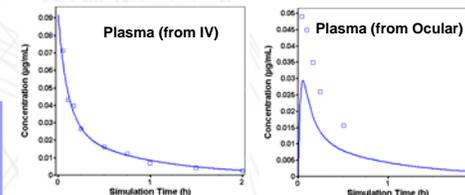


Figure 1. Plasma concentration profile from an IV administration (left) and a topical solution (right). Systemic PK parameters obtained from observed IV plasma profile (using PKPlus) was used unchanged in predicting the plasma profile from a topical ocular dosing (Lee et al.)

Timolol (Francoeur et al.) - Used for Prediction

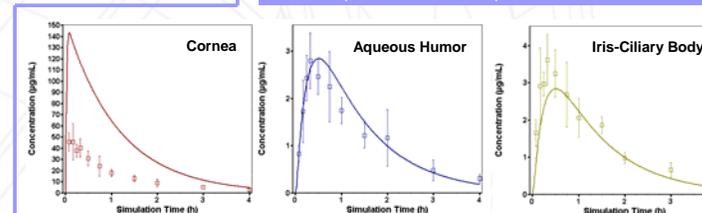


Figure 3. Predicted concentration vs. time profiles in different eye compartments from a 0.1625 mg topical eye-drop of timolol in rabbits. Data obtained from Francoeur et al. (1985) and parameters are identical to those used in simulations shown in Figure 2.

CONCLUSIONS

In both studies, the simulated concentrations of timolol were in agreement with the observed concentrations in the eye compartments (and plasma in one case) for which the *in vivo* data were available. The exceptions were the concentration profiles in the Iris-Ciliary body (for Lee et al) and Cornea (for Francoeur et al.). A similar mismatch for Iris-Ciliary body was also observed for Clonidine [1], indicating a trend that requires further investigation. The observed data in this case for both compartments vary widely and such variations can be attributed to a variety of reasons, in this case, most notably, the presence of melanin binding that affect the disposition characteristics in pigmented (Dutch belted) rabbits [4] versus albino (New Zealand White) rabbits [5]. Other differences, such as body weight, ocular physiology etc. may also be responsible. Finally, errors or differences in measurement techniques in the two research groups may also play a significant role. Overall, such mechanistic models will be a useful tool for scientists in development of new drug candidates, novel dosage forms and devices with specific release rates, new sites of administration, as well as assessment of eye tissue distribution of drugs administered via ocular and other routes.

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