366 Simulation of tobramycin pharmacokinetics after topical ophthalmic administration

Viera Lukacova, Siladitya Ray Chaudhuri, Michael Bolger, Walter Woltosz
Simulations Plus, Inc., Lancaster, CA 93534

INTRODUCTION

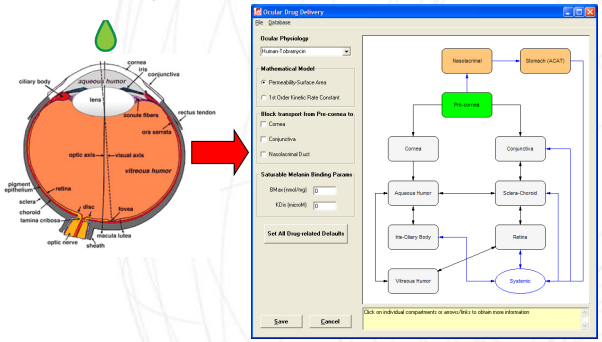
Tobramycin belongs to the class of aminoglycoside antibiotics. It does not bind to serum proteins [1], is eliminated mainly by renal secretion [2] and is poorly absorbed from the gastrointestinal tract [3]. Traditionally, intravenous (*i.v.*) administration is used to treat bacterial infections. Topical ophthalmic suspension is frequently used to treat ocular conditions with risk of bacterial ocular infections [4].

The current work describes simulations of tobramycin ocular PK after topical administration in rabbit and human using a new ocular drug delivery module, which has been developed as a part of the Additional Dosage Routes Module in GastroPlus™ (Simulations Plus, Inc.).

METHODS – Basic Model Description

The new ocular model describes the eye as a collection of 8 compartments, including a pre-corneal area (tear film and the conjunctival sac), cornea, conjunctiva, aqueous humor, iris-ciliary body/lens, vitreous humor, retina and choroid/sclera. The passive diffusion of drug between different compartments is dependent on physiological (e.g. surface area) and drug-dependent physicochemical properties (e.g. permeability) for each compartment.

Mechanisms such as nasolacrimal drainage, ocular metabolism, melanin binding, etc., have also been incorporated into this model. The ocular model is connected to the systemic pharmacokinetic model in GastroPlus to simulate drug appearance in plasma after ocular administration, as well as drug uptake by eye tissues from plasma after oral or systemic administration.



REFERENCES

1. Gordon R.C., Antimicrob Agents Chemother 1972, 2: 214-216.
2. Aronoff G.R., Antimicrob Agents Chemother 1990, 34: 1139-1142.
3. Touw D.J., Antimicrob Agents Chemother 1997, 41: 184-187.
4. Scoper S.V., Adv Ther 2008, 25: 77-88.
5. Gilbert M.L., Invest Ophthalmol Vis Sci 1987, 28: 881-885.
6. Desai S., Int Ophthalmol 1993, 17: 201-210.

ACKNOWLEDGEMENTS

The development of the GastroPlus ocular model was a collaborative effort between Simulations Plus, Inc. and Pfizer.

METHODS – Parameter Optimization (Rabbit)

Experimental tobramycin concentration-time profiles in several ocular tissues (tear film, cornea, aqueous humor and vitreous humor) after topical [5] and intravitreal [6] administration in rabbit were used to fit tobramycin permeabilities for several ocular tissues.

Only the permeabilities showing the highest sensitivity with respect to experimental tissue concentrations were fitted. Estimated permeability values for other tissues were based on default calculations from drug and compartment properties. Retinal permeability and systemic rate constant were fitted to match the observed 'clearance' of tobramycin from vitreous humor after intravitreal injection [Figure 1].

Permeabilities for cornea, aqueous humor and iris-ciliary body and iris-ciliary body systemic rate constant were then fitted to mach experimental tissue concentration profiles in tear film, cornea and aqueous humor after topical administration of solutions of varying strengths [Figure 2]. Tear flow rate was adjusted to match the drug concentration profile in tear film.

METHODS – Prediction of Disposition in Human

The permeability values as fitted against experimental concentration profiles in rabbit tissues were used to predict the tobramycin concentration vs. time profile in aqueous humor [Figure 3] after topical administration in human [6]. The tear flow rate was adjusted by the same factor as optimized for rabbit simulations. Default parameters were used for the remaining human physiological parameters.

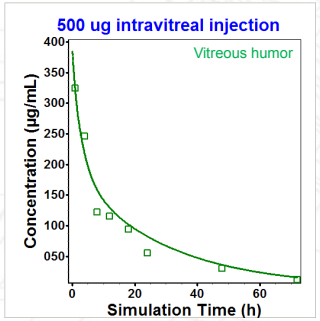


Figure 1. Comparison of simulated (line) and in vivo (squares) concentration vs. time profile in rabbit vitreous humor after intravitreal injection of tobramycin solution (500 ug dose).

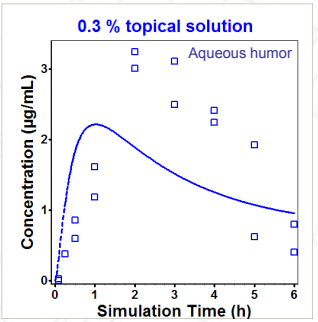


Figure 3. Comparison of concentration-time profile in aqueous humor after topical administration of 0.3% tobramycin solution in human predicted from model developed in rabbit (line) and measured in vivo (squares).

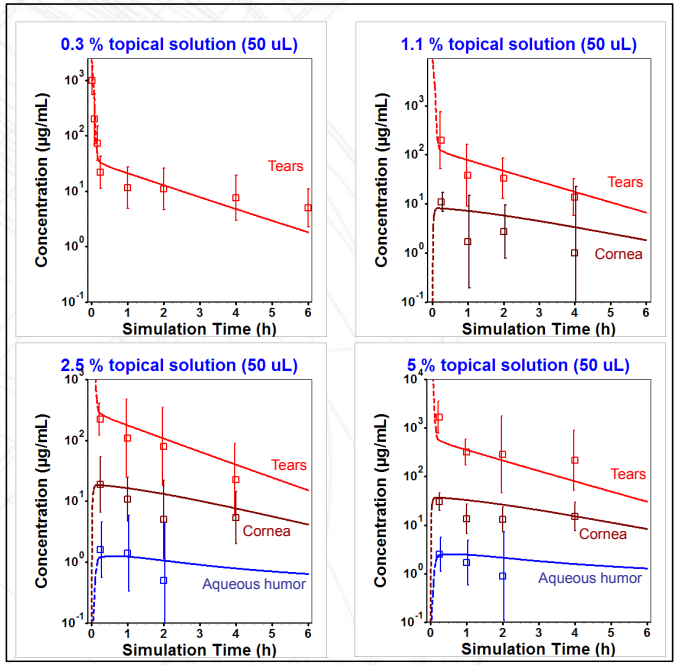


Figure 2. Comparison of simulated (lines) and in vivo (squares) concentration vs. time profiles in rabbit ocular tissues after topical (drops) administration of 50uL of tobramycin solutions of varying strengths. red – tears, brown – cornea, blue – aqueous humor.

RESULTS AND DISCUSSION

A total of seven (7) parameters were fitted to match 46 data points across ten (10) experimental concentration vs. time profiles in different tissues after topical and intravitreal administration of tobramycin in rabbit. Without further changes, these parameters were used to predict the drug disposition in the eye after topical administration in human. The permeabilities of tobramycin between several ocular tissues fitted against experimental profiles in rabbit resulted in good prediction of tobramycin concentration vs. time profile in aqueous humor in human. The prediction error was within ~30% for both C_{max} and AUC in aqueous humor.

CONCLUSION

The new GastroPlus ocular model provided reasonable predictions of tobramycin uptake and distribution in human eye based on preclinical studies (rabbit). This capability provides an important tool for development of ophthalmic drugs by helping to predict absorption and pharmacokinetics from different doses. Drug concentrations in eye tissues rather than in plasma should be more relevant for description of the pharmacodynamic effects of ophthalmic drugs. However, the direct measurement of these concentrations in human is rarely possible; so a model that allows for estimation of these concentrations based on concentrations measured in preclinical species provides a valuable help for the design of dosage forms that will result in safe and effective treatment for humans.

simulationsplus, inc.