Development of an Ocular PBPK-PD model to predict drug-mediated intraocular pressure reduction in preclinical species

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PURPOSE

- Glaucoma, caused by an elevation of the intra-ocular pressure (IOP), leads to vision loss
- Modification of the aqueous humor (AH) dynamic using drugs can slow or prevent vision loss
- Development of new or generic ophthalmic drug products designed to reduce IOP is based on preclinical pharmacokinetic (PK) & pharmacodynamic (PD) studies
- Rabbits are the typical preclinical model to study drugs' ocular PK but may not be sensitive to a drug (depending on drug's mechanism of action), limiting pharmacodynamic (PD) clinical extrapolation
- An alternative methodology to scale both PK and PD of ophthalmic drug products across multiple species is mandatory to support new and generic ophthalmic drugs development
- The purpose of this study is to demonstrate the utility of an ocular PBPK (O-PBPK) model to describe drug-mediated IOP reduction in preclinical species

OBJECTIVES

- Develop and validate an O-PBPK model for betaxolol (BET) and latanoprost (LAT) administered as ophthalmic solutions in rabbits and monkeys, respectively
- Predict BET and LAT IOP reduction effects in rabbits and monkeys, respectively

METHODS

- All simulations were performed using GastroPlus® version 9.8.3 (Simulations Plus Inc., USA)
- The Ocular Compartmental Absorption and Transit (OCAT™) model was used to build O-PBPK models for BET and LAT ophthalmic solution. The OCAT accounts for tear drainage, ocular absorption, and distribution (Figure 1)

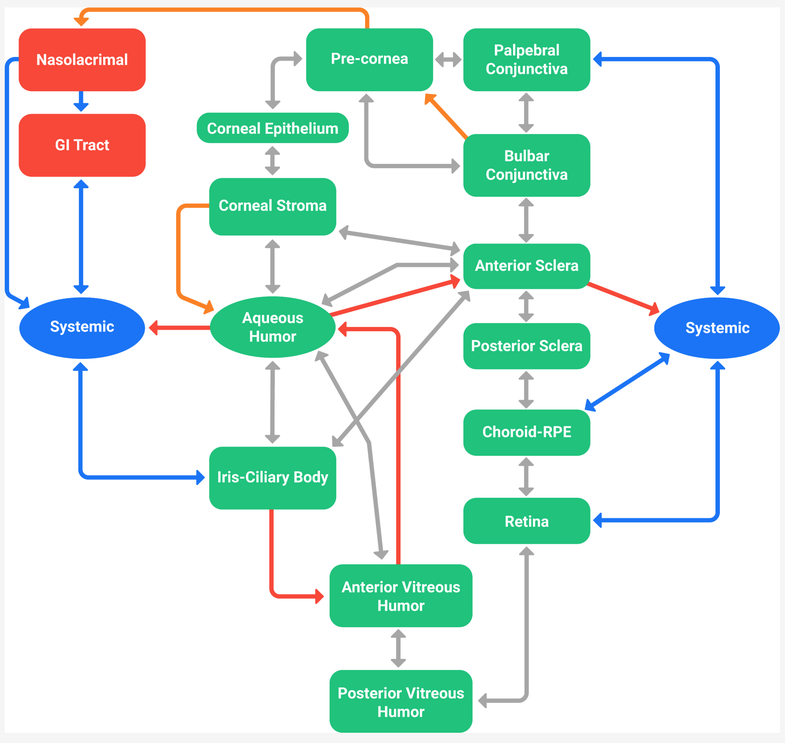

Figure 1: OCAT model version 3 schematic

- Permeabilities and systemic absorption rates for ocular tissue compartments were fitted against ocular tissue concentrations in rabbits.
- For LAT, the model was extrapolated to predict ocular PK in monkeys
- PDPlus™ module was then used to develop drug-specific PD models describing IOP reduction
- Based on the mechanism of action, the simulated Iris-Ciliary Body (ICB) and AH concentrations were used as input into the PD IOP model for BET and LAT, respectively

RESULTS

BETAXOLOL

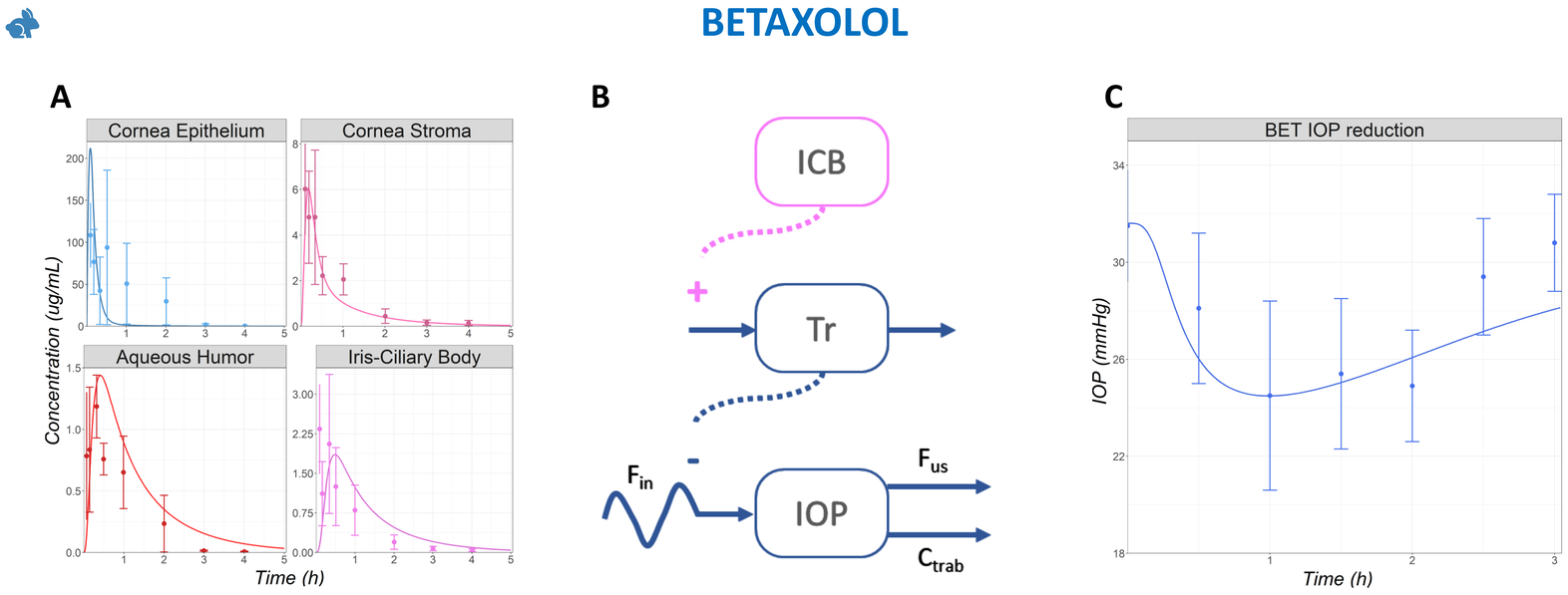

Figure 2: A) BET ocular disposition in New Zealand rabbits: cornea epithelium (blue), stroma (green), AH (red), and ICB (pink) concentration-time courses following a single administration of BET topical solution (dose = 250 nmol)[1]; B) Representative structure of the BET IOP reduction PD model; C) Observed and simulated IOP reduction in New Zealand rabbits following a single administration of BET topical solution (0.5%)[2].

LATANOPROST

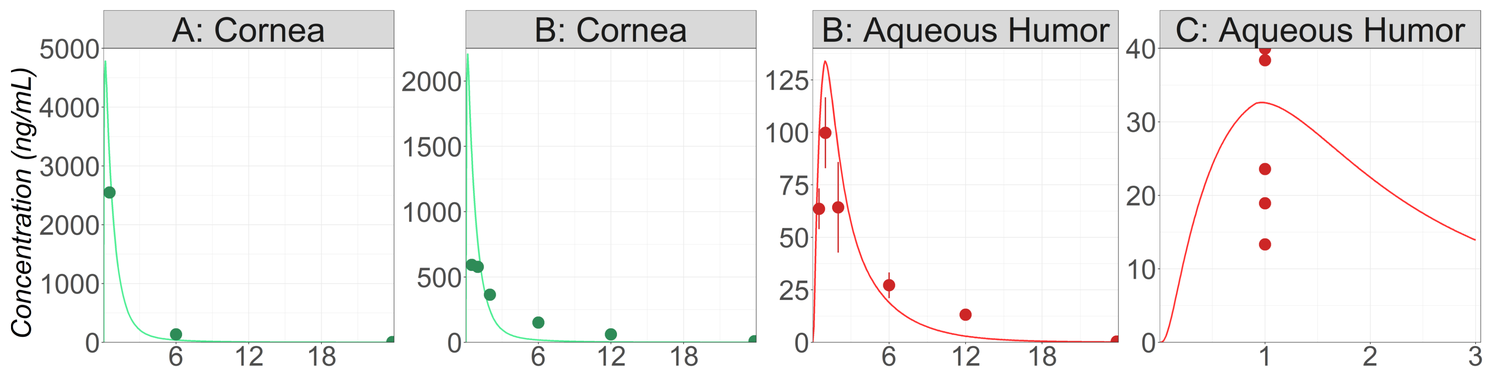

Figure 3: LAT OCAT model development and validation in monkeys: cornea (green) and AH (red) concentration-time courses following a single administration of Lat[3-5] (doses: study A: 0.06%, study B: 0.02%, study C: 0.005%).

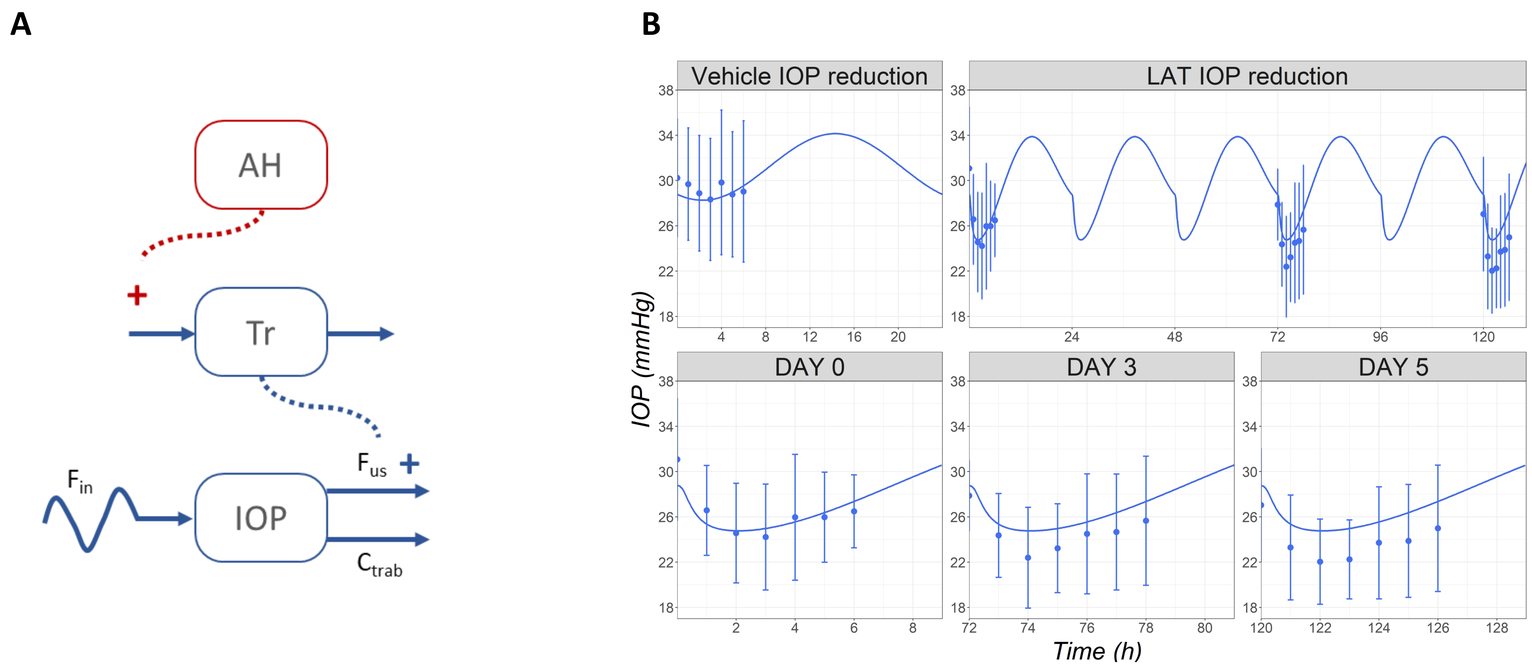

Figure 4: A) Representative structure of the LAT IOP reduction PD model; B) Observed and simulated IOP reduction in monkeys following a multiple administration of LAT topical solution (0.005%)[6].

CONCLUSIONS

- The presented case studies demonstrate the ocular PBPK-PD model's ability to describe IOP reduction following the administration of drugs either limiting AH production (BET) or inducing its outflow (LAT)
- This successful study represents an important step in establishing an extrapolation method for the prediction of human ocular PK and PD using ocular PBPK-PD models
- This method could have a significant impact on new and generic ophthalmic drug product development.

REFERENCES

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1. Fayyaz A, Vellonen KS, Ranta VP, Toropainen E, Reinisalo M, Valtari A, et al. Ocular pharmacokinetics of atenolol, timolol and betaxolol cocktail: Tissue exposures in the rabbit eye. European Journal of Pharmaceutics and Biopharmaceutics. 2021 Sep 1;166:155–62.
2. Hussain SA, Mohammed HM, Jwaied AH, Abdulrazzaq MH. Effect of Silibinin in Lowering the Intraocular Pressure in Normotensive Rabbits: Interaction with Betaxolol. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683 - 3597 E-ISSN 2521 - 3512). 2007;16(2):39–44.
3. Sjöquist B, Uhlin A, Byding P, Stjernschantz J. Pharmacokinetics of latanoprost in the cynomolgus monkey. 2nd communication: repeated topical administration on the eye. Arzneimittelforschung. 1999 Mar;49(3):234–9.
4. Sjöquist B, Johansson A, Stjernschantz J. Pharmacokinetics of latanoprost in the cynomolgus monkey. 3rd communication: tissue distribution after topical administration on the eye studied by whole body autoradiography. Glaucoma Research Laboratories. Arzneimittelforschung. 1999 Mar;49(3):240–9.
5. Kasai H, Aoyama Y, Kurasawa T, Imamura T, Tsuruma K, Hara H, et al. Comparison of Efficacy and Safety Evaluation of Latanoprost Formulations with and without Benzalkonium Chloride. Pharmacology & Pharmacy. 2013 Jul 1;4(4):377–84.
6. Daull P, Buggage R, Lambert G, Faure MO, Serle J, Wang RF, et al. A comparative study of a preservative-free latanoprost cationic emulsion (Catioprost) and a BAK-preserved latanoprost solution in animal models. J Ocul Pharmacol Ther. 2012 Oct;28(5):515–23.