In Silico Prediction of Intravitreal Primary Pharmacokinetic Parameters and Drug Concentrations: Tool for Ocular Drug Development

E. M. del Amo 1, K-S. Vellonen 1, H. Kidron 2, A. Urtti 2
1 University of Eastern Finland, 2 University of Helsinki

Purpose
To build computational QSPR models for prediction of the intravitreal volume of distribution (Vss) and clearance (CL) of drugs and derivative pharmacokinetic models for estimation of vitreal drug concentrations.

Methods
Vss and CL values were determined from a curated database of intravitreal injections of 40 small molecular weight drugs and 12 macromolecules into the rabbit eyes using WinNonlin software. Multivariate analysis was used to build in silico models for intravitreal Vss and CL. Pharmacokinetic simulations with Vss and CL values and drug release rates were used to estimate vitreal drug concentration profiles.

Results
A simple and reliable model for intravitreal CL was obtained with a Q² value of 0.62.

\[ \log CL = -0.25269 - 0.53747 (\log HD) + 0.05189 (\log D_{7.4}) \]

The relevant descriptors were logD7.4 and hydrogen bond donor capacity. The model predicted the internal and external test sets with a mean fold error of 1.33. For 80% of the compounds the intravitreal Vss was 1.18 - 2.28 ml. The implementation of the predicted parameters into pharmacokinetic simulation models yielded good estimates of vitreous drug concentrations. Moreover, predicted CL is useful in the PK design of drug delivery systems.

Conclusion
The present work offers useful in silico tools to investigate a priori the intravitreal PK profiles for intravitreally injected drugs and delivery systems.