Systems pharmacology model describing the kinetics of insulin-like growth factors

Zinnia P Parra-Guillen¹, Alvaro Janda², Ulrike Schmid³, Iñaki F Troconiz¹

¹Pharmaceutometrics & Systems Pharmacology Group, School of Pharmacy and Nutrition, University of Navarra, Spain; ²School of Engineering, University of Edinburgh, United Kingdom; ³Translational Medicine, Boehringer Ingelheim Pharma, Germany

Objectives: Insulin-like growth factors (IGF-I and IGF-II) signalling is involved in growth and survival of different human cancer cells [1]. Therefore, neutralising their activity has been suggested as a potential target in oncology [1]. This work aimed at developing a systems pharmacology model describing the kinetics of both factors together with their main binding protein (IGFBP-3), tightly regulating their fate.

Methods: Total and free IGF-I and/or IGFBP-3 plasma time profiles after administration of recombinant IGF-I to healthy subjects were extracted from [2-4]. Total IGF-II and IGFBP-3 levels at baseline were partly assumed as reported in literature (total IGF-II was set to three times total IGF-I and total IGFBP-3 to the sum of total IGF-I and IGF-II [5]). Ordinary differential equations describing protein synthesis, degradation and binding kinetics were implemented in Matlab. Parameter estimates from literature were explored as initials followed by a fine tuning process.

Results: Initially, protein profiles could be characterised assuming equal binding properties to IGFBP-3 and different synthesis rate constants, but also assuming different dissociation constant (K_D) and same synthesis rate (to fulfill the 3:1 ratio above mentioned). After fine tuning, a lower K_D and an increase IGFBP-3 baseline level (accounting for binding other than IGFBP-3) were needed to describe all scenarios in both cases.

Conclusions: A system pharmacology model characterizing the disposition of IGF-I, IGF-II and IGFBP-3 has been developed using literature data. Additional data are needed to discriminate between both parameterisation. The model provides a quantitative framework to explore the impact of drugs binding to IGFs, that could assist drug development and guide dose optimisation.

References:
6. Vorwerk et al., Endocrinology, 2002