

PK-PD-VK modeling for hepatitis C treatment with the CI and Generalized multiscale model.

Objectives:

PK-PD models are used to describe the behaviour of drugs and combinations of drugs in patients with chronic viral diseases like HCV. They play an important role in drug development and optimizing effectiveness ($\epsilon(t)$) of antiviral therapy. New models (VK-models) were developed in order to describe the viral kinetics under treatment with direct-acting antivirals (DAAs). Clinical data with such new drugs showed a triphasic decay with a rapid first phase, a moderate second phase decay and a relatively slow third phase decay during the first few weeks. Therefore, classical biphasic models may not be suitable. The viral kinetic modeling will be based on PK-PD models.

Methods:

Pharmacokinetics of the serum drug level of Sofosbuvir as well as its metabolite was modelled by Bateman function. For the pharmacodynamic model we assumed that the effect of blocking viral production does not depend directly on the serum drug level but on an intermediate compartment. Here we compare the generalized multiscale model that describes both, intracellular and cellular dynamics, with the classic biphasic model (CI). We evaluate the two models with the design of the SPARE study [1], by using a fully PK-PD model. In order to estimate the pharmacokinetic parameters, the efficacy of treatment and viral kinetic curves, data from 25 patients were fitted by maximum likelihood method individually in each patient.

Results:

All patients were fitted well by both models. The estimated viral kinetic parameters (viral clearance rate, infected cells loss rate and the total treatment effect) were significantly different between the two models. In contrast to the other multiscale models that use approximation solutions, the generalized multiscale model can be easily adapted for modelling full PK-PD.

Conclusions:

The new variant of a multiscale model presented here is able to describe the viral kinetics of HCV in a combination with PK-PD, under these new treatments without a computational effort.

References:

[1] Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013 Aug;310(8):804-811. Available from: <http://dx.doi.org/10.1001/jama.2013.109309>.