PHYSIOLOGICALLY-BASED PHARMACOKINETIC AND PHARMACODYNAMIC MODELLING OF THE ANTIPLATELET EFFECT OF ASPIRIN TO CHARACTERIZE VARIABLES AFFECTING DRUG RESPONSE

Alberto Giaretta[1], Carlo Patrono[2], Bianca Rocca[2], Gianna Toffolo[1]

[1]Department of Information Engineering, University of Padua, Padua - Italy, [2]Istituto Farmacologia, Università Cattolica, Rome - Italy

A physiologically-based mathematical model of aspirin pharmacokinetics (PK) and pharmacodynamics (PD) in regenerating platelets and megakaryocytes was recently developed by our group (Giaretta et al, Clin Pharmacol Ther, 2017), that predicted the main features of low-dose aspirin inhibition on cyclooxygenase (COX)-1activity both in healthy subjects and in clinical conditions of increased platelet turnover. Moreover, this model was successfully used for in silico experiments where COX-1inhibition was monitored in accessible (circulating platelets) and non-accessible (bone marrow progenitors) pools, in response to different aspirin regimens. We simulated healthy conditions, as well as conditions characterized by accelerated platelet turnover or reduced aspirin bioavailability.

The major aims of this study are: i) better refine the role of key PK/PD parameters on the COX-1dynamics (i.e. circulating platelets, bone marrow megakaryocytes and pro-platelets); ii) perform in silico experiments to further investigate COX-1in accessible and non-accessible pools; iii) simulate in silico personalized antiplatelet regimens in health and disease.

To this purpose, a sensitivity analysis of the model was performed to characterize the influence of the main processes influencing COX-1dynamics. In addition to the consolidated sensitivity metric related to the overall pattern (integrated local sensitivity analysis over the total interval of aspirin administration), five indices (plateau value related to COX-1steady state, the COX-1decline due the first aspirin dose, the overall COX-1reduction, the peak-to-peak COX-1abundance in the periodic phase of daily aspirin administration and the COX-1recovery time after aspirin withdrawal) were defined to reflect the influence of each model parameter on the main features of the COX-1activity before, during and after 3weeks of daily low-dose aspirin.

Model sensitivity analysis indicated a major influence of parameters related to megakaryocyte and platelet turnover on the steady-state COX-1level (e.g., a 1% perturbation of the parameters induces an increment of ~1% on the COX-1steady state level) and on the degree and duration of platelet COX-1inhibition following the last aspirin dose (i.e., a 1% perturbation of platelets count and lifetime produces a perturbation of ~0.7% and ~0.4% on COX-1inhibition, respectively), while the nadir value reached after a few doses and the daily oscillations are influenced, to a different extent, by parameters related to all the involved processes. In silico experiments also suggested personalized antiplatelet regimens in thrombocythemic patients and obese subjects, based on multiple daily administration and/or dose adjustments.

In conclusion, our in silico physiologically-based PKPD model adequately elucidated the dynamic features of aspirin PK and PD, and thus it is potentially useful to design personalized dosing regimens to guide clinical trials in specific clinical conditions associated with reduced responsiveness to standard aspirin dosing.