In silico modelling of aspirin action on platelet and megakaryocyte Cyclooxygenase-1

A.Giaretta[1], B. Rocca[2], B. Di Camillo[1], G.M. Toffolo[1], C. Patrono[2]

[1]Dept. of Information Engineering, University of Padova, Padova, Italy
[2]Dept. of Pharmacology, Catholic University School of Medicine, Rome, Italy

Background and Aims Low-dose aspirin is a cornerstone in preventing and treating cardiovascular diseases. We have recently reported that aspirin inhibition of platelet cyclooxygenase (COX-1) is impaired under conditions of accelerated platelet formation such as essential thrombocythemia (ET) (Pascale et al., Blood 2012). Aiming to elucidate the dynamic features of aspirin action in normal and pathological conditions, we developed an *in silico* model of aspirin pharmacodynamics.

Model development To account for the presence of a population of bone marrow megakaryocytes (MK), heterogeneous with respect to their stage of differentiation, the model consists of a set of nonlinear two compartment systems, each system representing the COX-1 amount in the MKs at a given stage of maturation and in the pro-platelets and platelets generated from them. COX-1 acetylation, occurring both in the bone marrow and peripheral blood, is assumed to follow a sigmoidal kinetics and to be controlled by the time course of aspirin levels in these two pools, predicted according to a linear compartmental model of its kinetics. Model equations were implemented in a MATLAB software tool, and their parameters were inferred from the literature and/or calibrated using data of serum thromboxane TXB_2 recovery, considered as proxy of COX-1 activity, measured in healthy controls (N=7) or ET patients (N=2) after withdrawal of once-daily low-dose aspirin. The model can be used to predict COX-1 dynamics in normal and pathological conditions and with different aspirin regimens. Moreover, as a first step to assess model reliability, we tested the ability to qualitatively reproduce the effect on COX-1 acetylation, as assessed by serum TXB_2, in 21 ET patients administered, with a crossover design 100 mg once daily (standard regimen), 100 mg twice daily (bid), and 200 mg once daily (Pascale et al., Blood 2012).

Results The model shows a good ability to reproduce TXB_2 data in healthy subjects since, as evident in Fig 1, model predictions are within the mean ±SD range of the experimental data. Model accuracy, quantified in terms of weighted absolute percentage error, is 18%. The model is also able to fit the reduced inhibition observed in 2 ET patients (6 vs. 10 days recovery) provided that three key parameters, identified by sensitivity analysis as the most influent on TXB_2 behavior, are adjusted: platelet count (twofold increase), MK lifetime (from 3 to 1 day) and platelet lifetime (from 7 to 5-6 days). Finally, irrespective of the set of parameter values, the time course of model prediction shows a more pronounced suppression and delayed recovery of serum TXB_2 in ET patients following the bid aspirin administration, in keeping with the experimental findings.

Conclusions The developed model suitably describes COX-1 inactivation in platelets and MKs, in response to low-dose aspirin, both in normal and pathologic (ET) conditions. It appears an useful tool to design personalized aspirin regimens in clinical conditions characterized by altered MK and/or platelet kinetics.