USING IN SILICO THROMBOPOIESIS TOOL FOR IDENTIFYING MECHANISMS OF DRUG-INDUCED THROMBOCYTOPENIA AND FOR DEFINING PATIENTS OF HIGHER RISK

Author: H. Harpak, Institute for Medical BioMathematics, Beney Ataroth, Israel
Co-author(s):   I. Cohen, Optimata Ltd., 11 Tuval St. Ramat-gan, Israel
Y. Ginosar, Institute for Medical BioMathematics, Beney Ataroth, Israel
A. Ianovski, Optimata Ltd., 11 Tuval St. Ramat-gan, Israel
Y. Kogan, Institute for Medical BioMathematics, Beney Ataroth, Israel
M. Shani, Optimata Ltd., 11 Tuval St. Ramat-gan, Israel
M. Shoham, Optimata Ltd., 11 Tuval St. Ramat-gan, Israel
K. Skomorovski, Institute for Medical BioMathematics, Beney Ataroth, Israel
V. Selitser, Institute for Medical BioMathematics, Beney Ataroth, Israel
V. Vainstein, Institute for Medical BioMathematics, Beney Ataroth, Israel
Z. Agur, Optimata Ltd., 11 Tuval St. Ramat-gan, Israel
Topic: 27: Platelets
Keywords: drug action mechanism, simian, simulation model, thrombocytopenia

 Background: Thrombocytopenia is an important clinical problem in the management of hematology and oncology patients. It remains a significant contributor to morbidity and mortality in patients with cancer. Moreover, thrombocytopenia can impede cancer therapy by preventing administration of drugs at the optimal doses and schedules. Recently, a detailed mathematical model of thrombopoiesis has been put forward and has been empirically shown to successfully predict the effect of Thrombopoietin (TPO) treatment on mice, as well as suggest an alternative, more efficient, TPO treatment (Skomorovski et al, 2001). Another important application of this model regards the research of drug–induced thrombocytopenia. Aims: To check the suitability of the thrombopoiesis model as a method of i) deciphering the mechanism of a drug's thrombocytopenic toxicity; ii) distinguishing the target cell populations of this toxicity; iii) a-priori identifying individual patients or subpopulations of higher risk for this adverse effect. Materials and Methods: The thrombopoiesis model, previously adjusted to simulate murine thrombopoiesis, was now adjusted to do so in monkeys. This was done by a comprehensive literature search for the kinetic parameters of simian thrombopoiesis. The resulting in silico monkey simulation tool was proven to retrieve empirical simian results (Figure 1). In accordance with biological and medical knowledge of possible mechanisms of thrombocytopenia and chemotherapy in general, putative molecular drug toxicity mechanisms were modeled and implemented as alternative modules of the in silico monkey simulation tool. By analyzing their simulation results, each of these toxicity mechanism models was evaluated for its ability to retrieve real life toxicity. Results: Despite the fact that all other system parameters were kept identical, simulations of the different models of molecular toxicity mechanisms generated significantly different profiles of blood platelets. By comparing different simulation results to the empirical ones, one can evaluate which mechanism assumption best portrays the pathophysiology of the adverse effect. The suggestion of the most probable toxicity mechanism, along with the analysis of its simulation results, enables the quantification of direct drug damage to the different thrombopoiesis compartments. By fitting the results of the suggested toxicity mechanism to various empirical results, we can evaluate kinetic parameters of subjects with different susceptibilities. Conclusions: We showed that different models of drug toxicity mechanism yield different profiles of blood platelets, even when all other medical conditions are similar. Once a mechanism model is at hand, along with empirical results of drug effects, individual kinetic parameters can be evaluated. These parameters serve as a key to a-priori identifying patients or patient subpopulations prone to be more sensitive to the drug. Thus, a tool has been put forward enabling identification of drug action mechanism as well as categorization of subpopulations or individuals by their susceptibility level. Further empirical validation of the tool will support its clinical use in suggesting safer drug protocols, i.e.; of reduced toxicity. Correspondence: hila@imbm.org
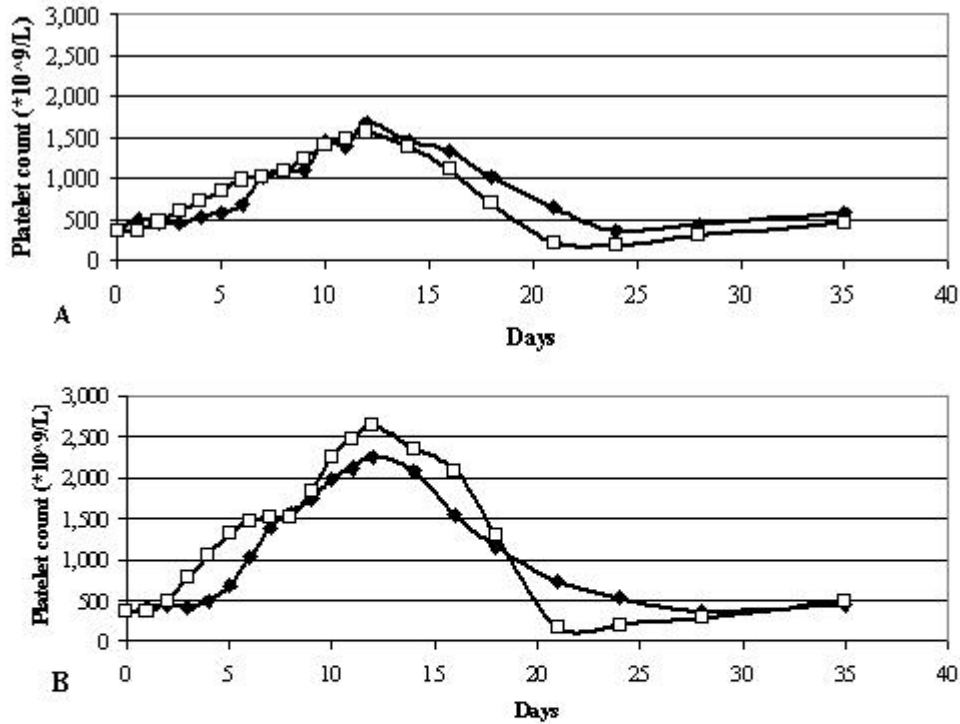
Figure 1. Experimental vs. computer simulated platelet profiles: Black diamonds - empirical platelet counts of two cohorts of Rhesus monkeys (n=3) that were administered recombinant human TPO subcutaneously, once per day, for 10 consecutive days, each cohort receiving a different daily dose (Farese et al 1995); White squares - simulation results of the *in silico* monkey tool responding to the same drug protocols; **A** - daily dose was 2.5μg/Kg. **B** - daily dose was 25μg/Kg.

Experimental vs. simulated platelet profiles