Unravelling the pharmacokinetic interaction of ticagrelor and MEDI2452 (ticagrelor antidote) by mathematical modeling

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Introduction

Antiplatelet therapy for the prevention of atherothrombotic events in patients with *acute coronary syndrome* or *prior myocardial infarction* is known to increase the risk of bleeding complications. The unique reversible binding-mode of the oral antiplatelet agent ticagrelor has enabled the development of MEDI2542, a ticagrelor-specific antidote for rare emergency situations [1].

This study seeks to unravel the pharmaco-kinetic (PK) interaction between ticagrelor, the ticagrelor active metabolite (TAM) and MEDI2452 through the use of mathematical modeling, aiming for both qualitative under-standing as well as detailed quantitative predictions.

A mathematical model describing the simul-taneous PK of ticagrelor and MEDI2452 in the mouse is presented. The model offers a mechanistic explanation for the complex kinetics and can predict the unobserved free ticagrelor and TAM plasma concentration that drives the platelet aggregation pharmaco-dynamics (PD).

The combined ticagrelor-MEDI2452 model can contribute to development of MEDI2452 by assisting in interpretation of observed data, by prediction of free ticagrelor and TAM plasma concentrations, and by simulation of experimental designs.

The full work will appear in a publication [2].

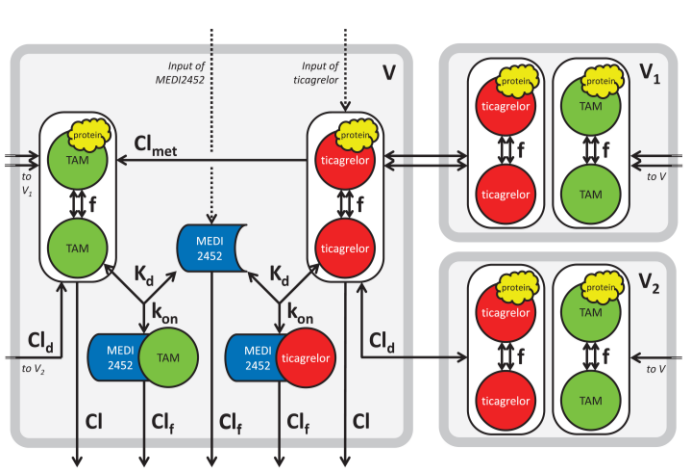

Figure 1. The combined ticagrelor-MEDI2452 PK-model. Double arrows: Reactions assumed to equilibrate instantaneously. Dashed arrows: Input to the system (ticagrelor and MEDI2452). The rapid equilibriums of free and protein-bound ticagrelor and TAM are depicted by encapsulated entities. The fractions of free ticagrelor and TAM within these entities are determined by the parameter f. The total contents of free and protein-bound ticagrelor and TAM in the plasma compartment (V) are cleared at the rate Cl, and ticagrelor is additionally being metabolized to TAM at the rate Cl_{met}. The total content of the encapsulated ticagrelor entity may furthermore distribute instantaneously to one peripheral compartment (V_1), and more slowly, with the intercompartmental clearance Cl_d, to another (V_2). Free ticagrelor and TAM in the plasma compartment can reversibly bind to free MEDI2452 with the rate k_{on}, forming complexes with dissociation constant K_d. Both the complexes and free MEDI2452 are cleared at the rate Cl_f.

Methods

The modeling process consisted of three main steps: i) set-up a mathematical model of the combined ticagrelor-MEDI2452 PK in the mouse based on data of separately administered tica-grelor and MEDI2452, and on assumptions supported by literature; ii) validated and refined the model on several different combined ticagrelor-MEDI2452 PK data sets not used for setting up the model; and iii) used the model to understand the complex PK resulting from the ticagrelor-MEDI2452 interaction, and to predict free levels of ticagrelor and TAM and let these predictions drive a PD turn-over model under different experimental designs.

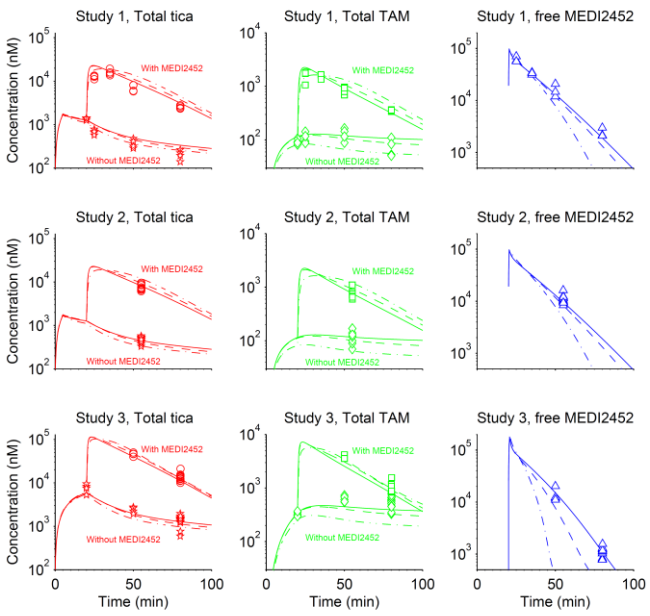

Figure 2. Model validation and refinement. Observed total and free ticagrelor in plasma are shown as red circles (when MEDI2452 has been co-administrated) or red stars (without MEDI2452), observed total and free TAM in plasma as green squares (with MEDI2452) or green diamonds (without MEDI2452), and observed free MEDI2452 in plasma as blue triangles. Model simulations of ticagrelor, TAM, and MEDI2452 are shown in red, green, and blue lines, respectively. Solid lines correspond to simulations of the final model with 0% recycling. The model's ability to describe the observations decreases as the fraction of recycling increases (dashed lines 25% recycling; dashed-dotted lines 100% recycling).

Results

We propose a mechanistic PK model (Fig. 1), including a special observation model for post-sampling equilibration, which is validated and refined using four different combined ticagrelor-MEDI2452 mouse in vivo treatment data sets (Fig. 2, solid lines). A comparison against alternative models (Fig 2, dashed lines) strengthen our *a priori* belief that MEDI2452-bound ticagrelor is primarily eliminated together with MEDI2452 in the kidney, and not recycled to the plasma, thereby providing a key assumption for the extra-polation to humans. The model predicts free tica-grelor and TAM plasma concentrations, which, in turn, drive a PD model that successfully predicts platelet inhibition level (Fig. 3).

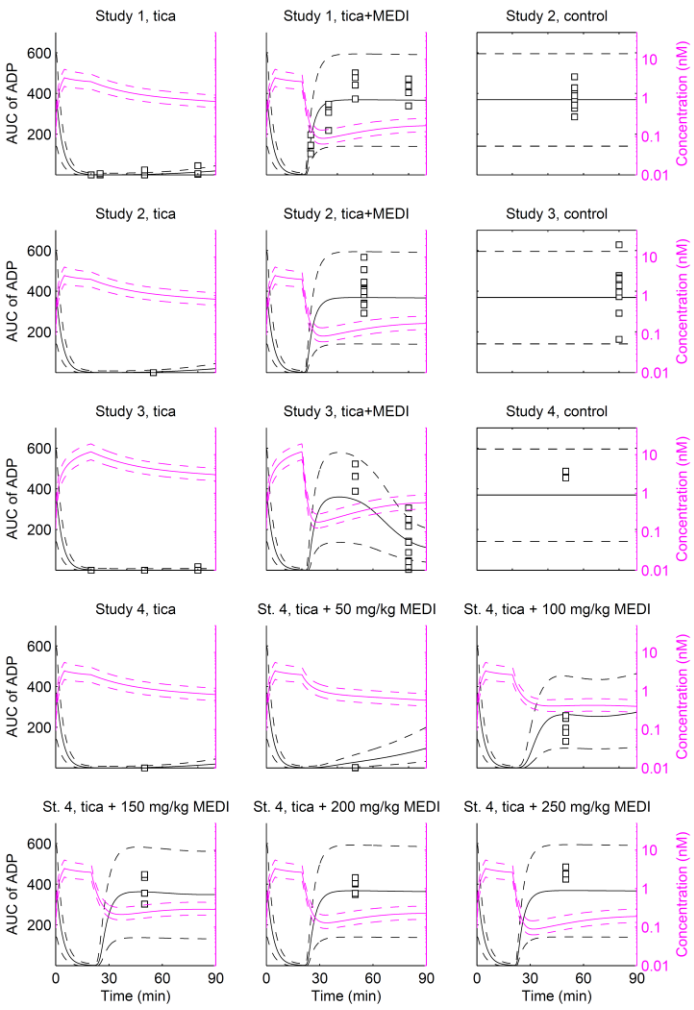

Figure 3. PK/PD model performance. The left axis shows simulated (solid black lines) and observed (squares) areas under the curve (AUCs) of ADP-induced platelet aggregation response in whole blood ex vivo (arbitrary units). The right axis displays (solid magenta lines) corresponding simula-tions of the sum of free ticagrelor and TAM in plasma (V), which drive the PD effect. The impact of both parameter uncertainty and residual variability is considered in the prediction. Solid curves represent the median and dotted curves represent the simulated 5th and 95th percentiles.

Conclusions

The proposed PK model of ticagrelor, TAM, and MEDI2452 has been validated on several mouse data sets and is useful for predicting free plasma concentrations of ticagrelor and TAM. The proposed model is a good starting point for scaling to model the PK of other species, including human, and for expansion to a population model. Hence, we anticipate it to be valuable in the future clinical development of MEDI2452.

References

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2. Almquist J, Penney M, Pehrsson S, Sandinge A-S, Janefeldt A, Maqbool S, Madalli S, Goodman J, Nylander S, Gennemark P. Unravelling the pharmacokinetic interaction of ticagrelor and MEDI2452 (ticagrelor-antidote) by mathematical modeling. Accepted May 2016 by CPT: Pharmacometrics & Systems Pharmacology.

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