Application of a PBPK/PD model to describe the impact of CYP2C19 polymorphisms on the pharmacokinetics and response to clopidogrel

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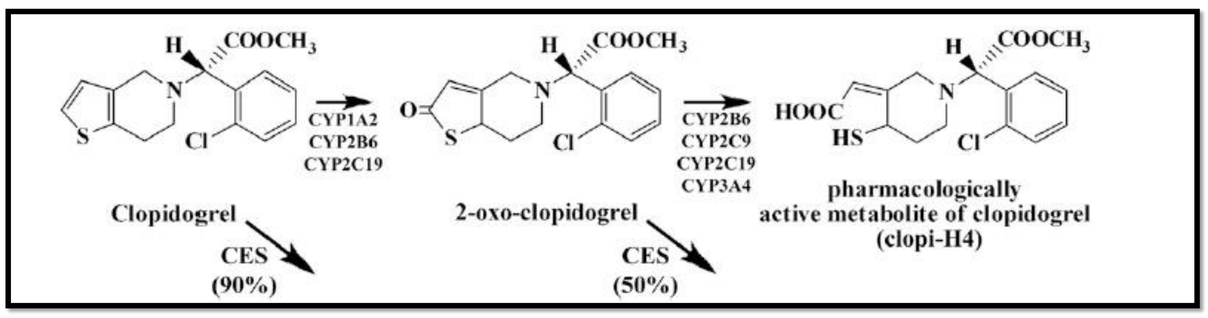
Introduction

CYP2C19 is a key enzyme that converts the prodrug clopidogrel (Clopi) to its active metabolite (Clopi-H4), while esterases hydrolyse Clopi to an inactive carboxylic acid metabolite. Significant differences in PK and response to Clopi have been observed in patient groups with differing CYP2C19 activity.

The aim of this study was to develop a PBPK/PD model to simulate the impact of CYP2C19 polymorphisms on the pharmacokinetics (PK) and pharmacodynamics (PD) of Clopi. A PBPK/PD model will be useful to explore the impact of various scenarios that may influence CYP2C19 activity and Clopi response, such as different population groups, comedications and disease states.

Methods

PBPK model: The model described by Djebli et al[1] was constructed. The model accounted for Clopi, its intermediate metabolite and its active metabolite (Clopi-H4), as shown below.



Differences in PK profiles and PK parameters of Clopi and Clopi-H4 with extensive (EM), intermediate (IM) and poor (PM) metabolizers of CYP2C19 were simulated and verified against clinical data.

PD model - modification of the indirect response turnover model[2,3], with maximum platelet aggregation (MPA%) as the response marker, was used with the Simcyp custom lua scripting feature. Input from PBPK model was unbound plasma concentrations of clopi-H4.

Study design: Based on the clinical trial [1] . Simulations of 10 trials of 10 virtual Caucasian healthy volunteers, aged between 20 and 50 years (50% female) was performed using Simcyp Simulator V15 R1. A Clopi loading dose of 300mg was followed by 75mg QD for 5 days.

Simulation of PK/PD profiles & parameters and verification with clinical data.

Prediction of PD differences in EM, IM and PM of CYP2C19.

Results

The simulated concentration-time profiles of Clopi and Clopi-H4 in the 3 CYP2C19 phenotypes are shown in Figure 1 & Figure 2. Ratios of the predicted (Pred):observed (Obs) PK AUCs are shown in Table 1. Pred:Obs response ratios also appear in Table 1.

Table 1 : AUC ratios in EM, IM and PM

Phenotype	Day 1 Clopi AUC pred/obs	Day 1 Clopi-H4 AUC pred/obs	Day 5 Clopi AUC pred/obs	Day 5 Clopi-H4 AUC pred/obs	Response AUC pred/obs
EM	13.4/8.7 = 1.5	54.3/34.8 = 1.6	2.9/1.5 = 1.9	14.2/11.3 = 1.3	64.9/51.9 = 1.3
IM	17.7/5.5 = 3.2	50.2/26.3 = 1.9	4/1.3 = 3.1	13/9.5 = 1.4	56.6/44.2 = 1.3
PM	29.4/9.3 = 3.2	31.8/15.3 = 2.1	5.5/2 = 2.8	8.8/4.2 = 2.1	40.5/25.6 = 1.6

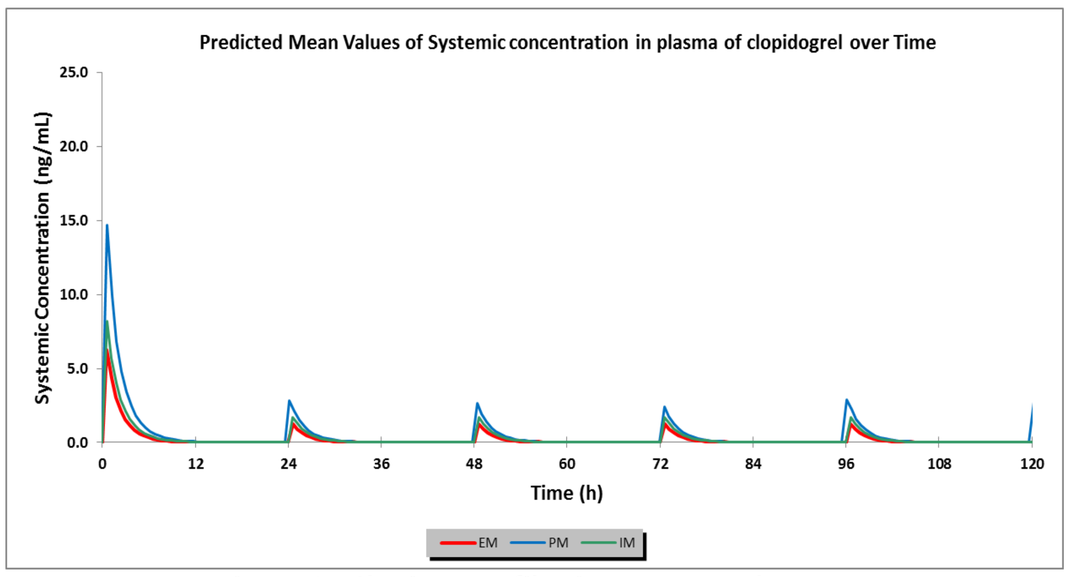


Figure 1 : Clopi PK profiles in EM, IM and PM

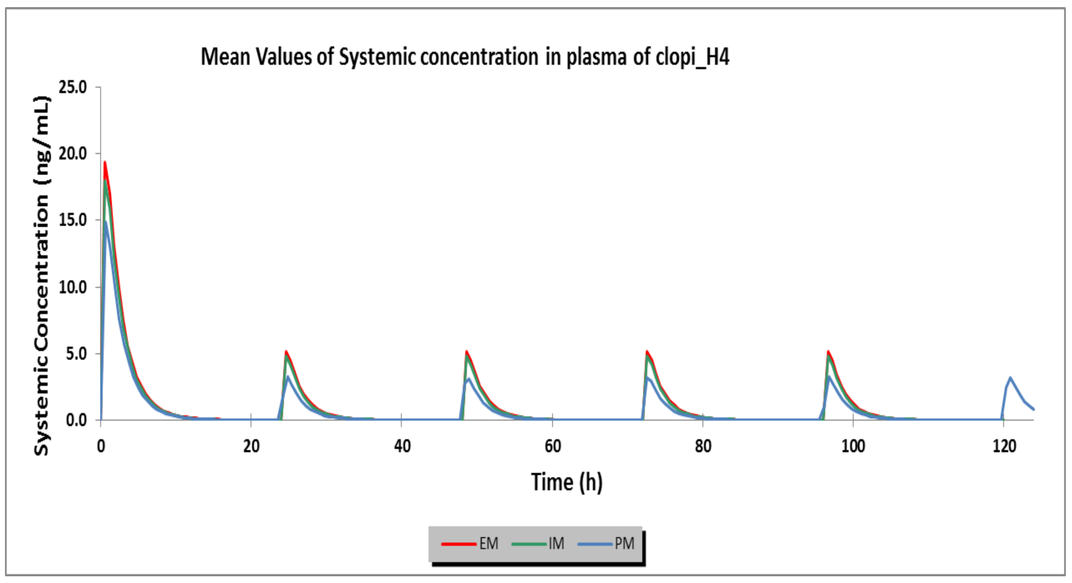


Figure 2: Clopi-H4 profiles in EM, IM and PM

Conclusions

The PBPK/PD model for clopidogrel recovered the clinically observed differences in PK and response acceptably. This model will be useful to explore PK changes and potential dosage adjustments for clopidogrel when used in the presence of variables that may impact on CYP2C19 activity.

References

1. Djebli N. et al (2015) DMD; 2. Dyneka NI. et al (1998) PK Biopharm; 3. Jiang XL.et al (2016) Eur J Pharm Sc