SIMULATING THE IMPACT OF THE INTERPLAY BETWEEN CYP2C19 POLYMORPHISMS AND ETHNICITY ON RESPONSE TO CLOPIDOGREL, USING PBPK-PD MODELS.

Manoranjenni Chetty, Khaled Abduljalil.

Certara UK, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, United Kingdom.

Background

Clopidogrel is a prodrug that produces its anticoagulant effect after conversion to Clopi-H4, the active metabolite. Clopi-H4 binds irreversibly to the platelet $P2Y_{12}$ adenosine diphosphate (ADP) receptor, which inhibits platelet aggregation and reduces platelet reactivity for the platelet's life span[1].

Clopidogrel is metabolized by two major metabolic pathways. An esterase-dependent pathway leads to hydrolysis of clopidogrel into an inactive carboxylic acid derivative (85–92%) while a cytochrome P450 (CYP) dependent pathway leads to the formation of its active metabolite (clopi-H4)[2,3,4]. CYP2C19, CYP2B6, and CYP1A2 first convert clopidogrel to the 2-oxo-clopidogrel intermediate, which is then metabolised by esterases (about 50%) or converted to Clopi-H4 by CYP2C19, CYP2B6, CYP1A2, and CYP3A4[3], as shown in the figure below.

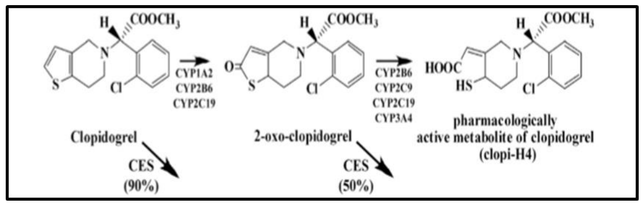

Figure 1: Metabolism of clopidogrel

CYP2C19 is the key enzyme in the activation of this prodrug. Variability in CYP2C19 activity is expected to result in variability in response to clopidogrel. The aim of this study was to simulate and compare the combined impact of CYP2C19 polymorphisms and ethnicity on response to clopidogrel in Caucasian and Chinese subjects.

Methods

PBPK Model: The Simcyp population-based simulator (Version 15) was used to construct a PBPK model that accounted for clopidogrel, its 2-oxo intermediate and the active metabolite Clopi-H4[5], as shown in the figure above.

Concentration-time profiles in virtual healthy Caucasian extensive metabolisers of CYP2C19 (EM) and healthy Chinese EM (10 trials of 10 subjects aged between 20 and 50 years – 50% females) were predicted. Subjects were given a loading dose of 300mg clopidogrel, followed by 75mg QD.

These PBPK models were linked to the PD model.

PBPK-PD Model: Lua scripting was used within the Simcyp simulator for the PBPK-PD model. A modified indirect response turnover model[6], with maximum platelet aggregation (MPA%) as the PD marker was used to simulate the response to Clopi-H4. % IPA was calculated as:

$$\% \text{ IPA} = [\text{MPA}_{\text{predose}} - \text{MPA}_{\text{postdose}} / \text{MPA}_{\text{predose}}] * 100\%$$

Clopi-H4 concentrations from the PBPK model were used as the input to the PD model.

Model Performance Verification: The PBPK model was verified by comparison of the predicted and clinically observed pharmacokinetic parameters.

Following the verification of the performance of the PBPK-PD model, simulations were repeated using healthy Chinese PM and Caucasian PM populations. The change in % IPA was compared in the 4 groups to determine the need for dosage adjustments.

Results

The PBPK-PD model recovered the clinical data acceptably, as seen in Table 1, where ratios of the predicted (Pred) and observed (Obs) PK and PD AUCs in Caucasian and Chinese subjects are within 1.5-fold.

Mean response for each of the ten trials in each population group are shown in Figure 2. <20% %IPA is indicative of inadequate response to clopidogrel.

Table 1: Predicted vs Observed [5,6,7] AUC ratios for Clopi-H4 PK and response

Phenotype	300 mg SD Clopi-H4 AUC Pred/obs	75 mg QD Clopi-H4 AUC Pred/obs	Response AUC Pred/Obs
Caucasian			
EM	49.88/39.8 = 1.25	13.08/11.3 = 1.16	53.47/44 = 1.22
PM	20.88/15.3 = 1.36	5.67/4.2 = 1.35	17.2/16 = 1.30
Chinese			
EM	21.21/18.9 = 1.12	13.94/16.7 = 0.83	60.88/59.7 = 1.02
PM	16.44/11.8 = 1.39	11.23/10.5 = 1.07	33.7/36.8 = 0.92

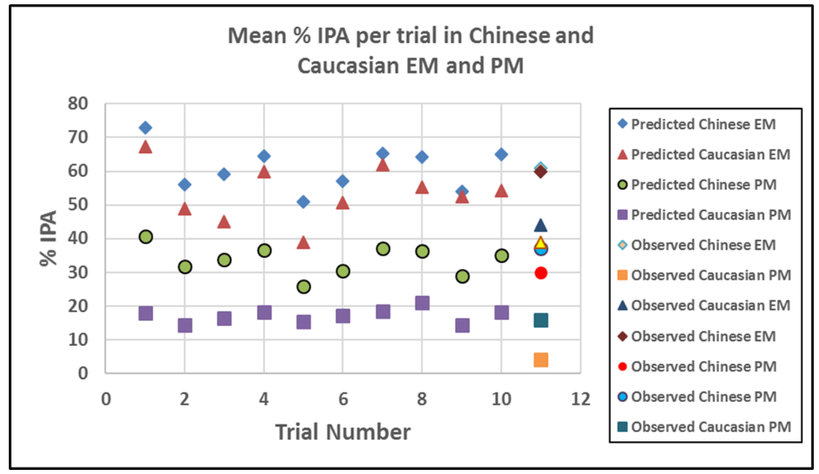

Figure 2: Simulation of clopi-H4 concentrations in HV

Conclusions

PM subjects show a lower response than EMs due to lower concentrations of clopi-H4. The response in Caucasian PM is significantly lower than that in Chinese PMs. The majority of the response values in Caucasian PMs were < 20% IPA, indicating that a dosage adjustment may be required in this group. Predictions for all the other population groups suggest that adequate clinical response will be achieved and no dosage adjustment is necessary.

References

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