EXPLORING THE IMPACT OF SMOKING ON THE RESPONSE TO CLOPIDOGREL: A PBPK-PD STUDY.

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Background

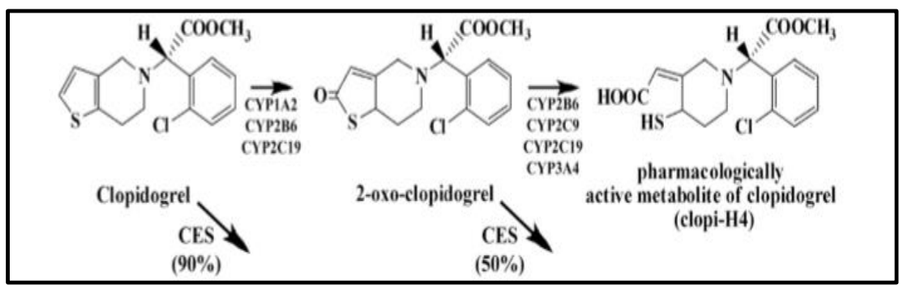
The antiplatelet response to clopidogrel is dependent on conversion of this prodrug to Clopi-H4, the active metabolite. Clopidogrel is metabolized by two major metabolic pathways. An esterase-dependent pathway leads to hydrolysis of clopidogrel into an inactive carboxylic acid derivative (85–92%) while a cytochrome P450 (CYP) dependent pathway leads to the formation of its active metabolite (clopi-H4)[1,2,3]. 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 CYP1A2, CYP2B6, CYP2C19, and CYP3A4[2]. 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[4].

Inhibition of platelet aggregation (IPA) by Clopi-H4 was reported to be lower in non-smokers than in smokers. Induction of CYP1A2 by cigarette smoke was postulated as one of the possible reasons for the increased response in smokers[5].

The aim of this study was to explore the impact of CYP1A2 induction on IPA during clopidogrel therapy.

Methods

PBPK Model: A previously described model[6] that accounted for clopidogrel, its 2-oxo intermediate and the active metabolite Clopi-H4, as shown below, was constructed in the Simcyp population-based simulator (Version 15).



Concentration-time profiles in virtual healthy volunteer (HV) non-smokers (10 trials of 10 subjects aged between 20 and 50 years) were predicted. Subjects were given a loading dose of 300mg clopidogrel, followed by 75mg QD. Similar dosing was used in a population of heavy smokers. Heavy smokers were simulated by increasing the abundance of CYP1A2 by 1.73-fold[7].

PBPK-PD Model: A modified indirect response turnover model [8], with maximum platelet aggregation (MPA%) as the PD marker was used to simulate the response to Clopi-H4. IPA was calculated as

$IPA = [MPA_{predose} - MPA_{postdose} / MPA_{predose}] * 100\%$

Clopi-H4 concentrations from the PBPK model were used as the input to the PD model. Lua scripting was used within the Simcyp simulator for the PBPK-PD model.

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

IPA was compared between the smoker and non-smoker cohorts.

Results

The simulated profiles of clopidogrel and clopi-H4 are shown in Figure 1 and Figure 2, respectively.

Ratios of the predicted (Pred) and observed (Obs) PK AUCs in HV are shown in Table 1.

Ratios of Pred and Obs response AUC ratios in HV are also shown in Table 1.

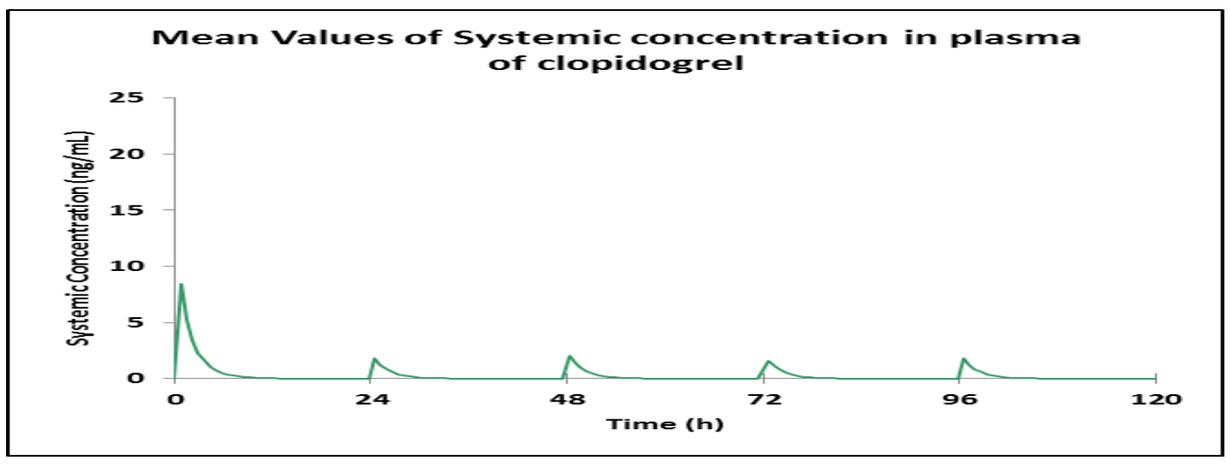


Figure 1: Simulation of clopidogrel concentrations in HV

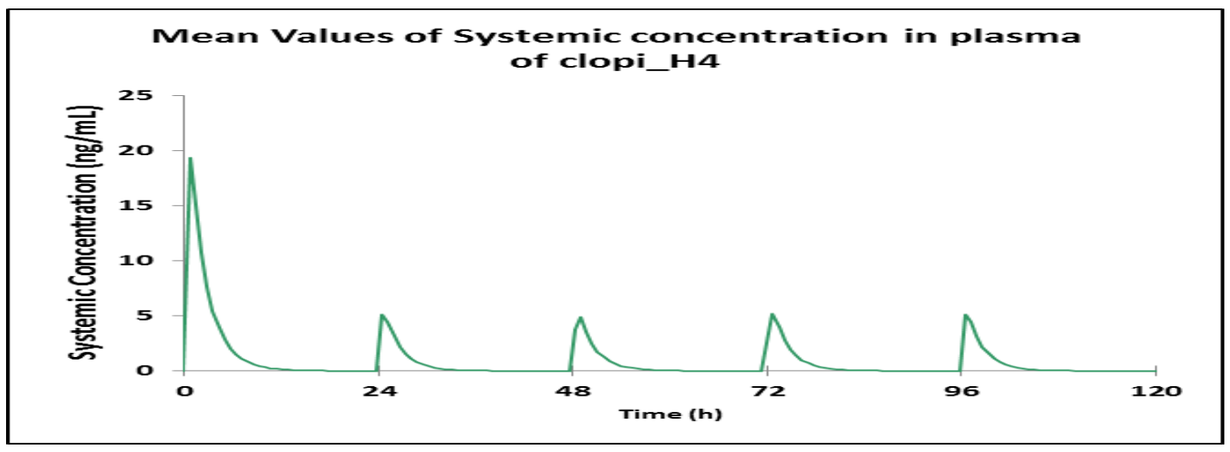


Figure 2: Simulation of clopi-H4 concentrations in HV

Table 1: Pred vs Obs AUC ratios for PK and response

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
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

IPA was predicted as 32.28% (20.53% – 39.53%) in non-smokers and 41.42% (27.07% – 50.52%) in smokers. The predicted IPA is within the clinically observed IPA of 31% (24.5%- 37.5%) in non-smokers and 38% (35.7%-40.3%) in smokers.

Conclusions

Comparison of the predicted and observed PK and response ratios indicate that the PBPK-PD model recovers the clinical data adequately.

The predicted IPA in heavy smokers is similar to the observed IPA in smokers. Since the higher CYP1A2 activity accounts for difference in the predictions between smokers and non-smokers, it can be concluded that CYP1A2 induction is the likely cause of the observed higher response to clopidogrel in smokers.

References

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