Effects of the Concurrent Use of Clopidogrel & Omeprazole Due to CYP2C19

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ABSTRACT
Clopidogrel is a thienopyridine prodrug that requires activation to its thiol by CYP450 enzymes within the liver, in particular CYP2C19. Thienopyridine compounds are classified as inhibitors of the P2Y12 receptor, used for its specific anti-platelet activity.2

MOLECULAR STORY

Shown above in Figure 2 is the molecular structure of clopidogrel and its stepwise metabolism. The oxidation step from clopidogrel to 2-oxo-clopidogrel is completed by multiple CYP450 enzymes including CYP2C19. Next, between 2-oxo-clopidogrel and the thiol metabolite there is an equilibrium between constitutional isomeric states of the clopidogrel compound, also known as tautomers. The final hydrolysis step opens the thiopeptide ring to free the sulfur so it can form the sulfide bridge to the P2Y12 receptor.6

PROPOSED DRUG MODIFICATIONS
Clopidogrel currently does not form any hydrogen (H) bonds within the active site of CYP2C19; therefore, it has a lower binding affinity to the enzyme compared to omeprazole. Keeping this in mind, a way to modify the chemical structure of clopidogrel is to find a way for it to bind to the receptor with an H-bond. This may potentially increase the drug’s binding affinity and prevent it from being blocked from the active site by omeprazole.

SUMMARY
Patients on a prolonged antiplatelet therapy are at a high risk of developing severe gastrointestinal hemorrhage. PPIs have been shown to reduce this risk. However, in certain patient populations, those with a reduced CYP2C19 SNP, PPIs can reduce the clinical effect of clopidogrel. With the new technology available today, patients can be tested to see if they have a normal functioning CYP2C19 or not. This will allow providers and pharmacists the ability to prescribe the right therapy for the patient. In the future, this technology could be used in other patient populations or disease states to tailor medications to the patient. By doing this, drug-drug interactions and drug-disease interactions could be avoided.

REFERENCES
7. 3MeS pdb