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

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ABSTRACT

Patients on a prolonged antiplatelet therapy, such as clopidogrel, are at a high risk for severe gastrointestinal hemorrhage.[1] It has been shown that proton pump inhibitors (PPIs), such as omeprazole, can reduce this risk. However, in patients with a decreased function of cytochrome P450 2C19 (CYP2C19) due to a single-nucleotide polymorphism (SNP), it is less likely that clopidogrel will convert to its active metabolite. It is also proposed that omeprazole can reduce the clinical effectiveness of clopidogrel.

It is thought that this interaction is not severe in patients with normal function of CYP2C19. Before starting both medications, patients should be tested for CYP2C19 function to determine if this is an appropriate therapy.

INTRODUCTION

Clopidogrel is a thienopyridine $P2Y_{12}$ inhibitor of platelet function and is a cornerstone of cardiovascular pharmacotherapy, with aspirin, in the prevention of:[2]

- Myocardial infarction (MI)
- Stent thrombosis after acute coronary syndromes (ACS)
- Percutaneous coronary intervention (PCI)

Clopidogrel inhibits the $P2Y_{12}$ receptor by irreversibly binding onto the platelet surface, preventing adenosine diphosphate (ADP) from binding to the receptor; therefore, inhibiting ADP from inducing platelet activation.[2]

This is achieved by clopidogrel going through a two-step oxidation process by CYP2C19 to reach its active thiol metabolite that forms a sulfide bridge with the $P2Y_{12}$ receptor.[3]

Like clopidogrel, PPIs have an irreversible mechanism that occurs through a sulfide bridge. PPIs are a special class of medications that work to irreversibly inhibit proton pumps in the stomach. The primary clinical use for PPIs is for the management of gasteroesophageal reflux disease (GERD).

Omeprazole is a PPI which is metabolized by CYP2C19. Also, omeprazole is a substrate with a stronger affinity for CYP2C19 compared to other PPIs and clopidogrel. This leads to a potential drug-drug interaction when omeprazole and clopidogrel are taken together, as seen in Figure 1.

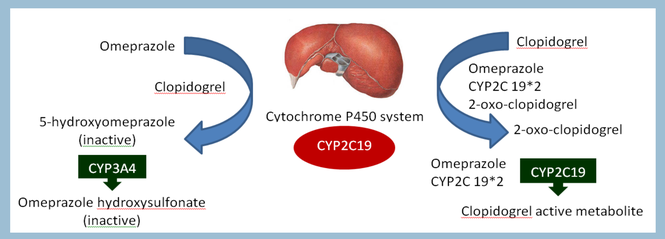

Fig.1 Metabolism of both omeprazole and clopidogrel by CYP2C19 and the potential for inhibition during both metabolic stages.[1,4]

For example, a patient presents to the pharmacy with a prescription for clopidogrel. The pharmacist fills the prescription and proceeds to educate the patient. During the education the pharmacist notices the patient had picked up a box of omeprazole and educates the patient on the following potential drug-drug interaction between the two medications.

If the patient has a deficiency in their CYP2C19 SNP, they will have lower levels of the clopidogrel active metabolite, thus causing less platelet inhibition and higher rates of major adverse cardiovascular events.[1]

However, if the patient has an overactive function of CYP2C19 SNP, they will have a greater bioavailability of proton pump inhibitors (PPI), where an interaction could be more evident clinically.[1]

This is evident because clopidogrel and omeprazole both require CYP2C19 for their metabolism. If the patient has an overactive CYP2C19 SNP, omeprazole will block clopidogrel from binding to the enzyme. It is also the same for the patient having a deficient CYP2C19 SNP due to omeprazole's strong binding affinity to the enzyme.

MOLECULAR STORY

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 $P2Y_{12}$ receptor, used for its specific anti-platelet activity.[3]

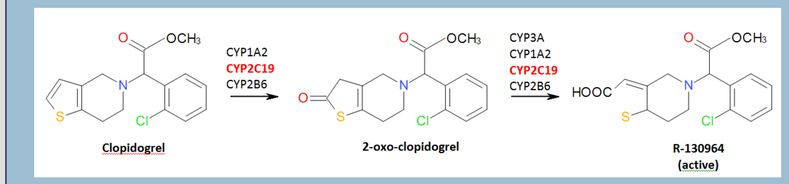

Fig 2 The metabolism of clopidogrel[5]

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 thiophene ring to free the sulfur so it can form the sulfide bridge to the $P2Y_{12}$ receptor.[6]

Currently there is no crystal structure of clopidogrel bound to human CYP2C19; however, there is a crystal structure of the homologous rabbit enzyme, CYP2B4, bound to clopidogrel. The rabbit enzyme CYP2B4 shares 78% sequence identity with human CYP2B6.[6] CYP2B6 produces the same thiolactone intermediate during clopidogrel metabolism as CYP2C19 and it has been assumed that both enzymes are inactivated by a related mechanism.[6] Because of these similarities, the rabbit enzyme CYP2B4 can be used to infer the mechanistic relationship in the human enzyme CYP2B6, which can then be used to estimate the action of the human CYP2C19.

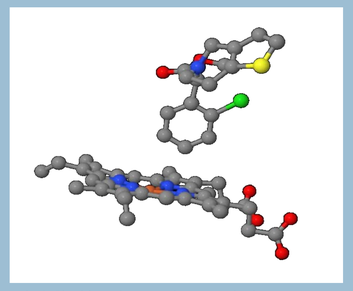

Fig 3 Clopidogrel group closest to the heme ring structure. Orange is iron, blue is nitrogen, green is chlorine, red is oxygen, and yellow is sulfur. 3ME6.pdb[7]

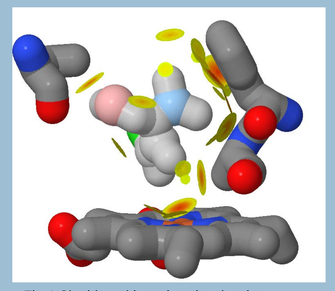

Fig 4 Clopidogrel in active site showing phenylalanine, valine, and alanine. Yellow-orange discs represent bonding sites. Orange is iron, dark blue is nitrogen, green is chlorine, red is oxygen, yellow is sulfur, light blue is nitrogen, pink is oxygen. 3ME6.pdb[7]

Clopidogrel was found to occupy a trilobe of electron density above the heme plane with the chlorophenyl group most closely approaching the heme ring that lays beneath.[6] Due to clopidogrel's stereocenter (Figure 5), it is easier to fit in the electron density and exhibit a single orientation, which points the chlorophenyl ring towards the heme, shown in Figure 3.[6]

There is no coordination between the thiol structure and the heme ring. With the lack of tight binding from the clopidogrel thiol ring, the drug has more rotational freedom in the binding cleft.

With no hydrogen bonding occurring with the molecule, it must rely primarily on multiple van der waals forces and pi-pi bonds of the hydrophobic phenylalanine side chains, shown in Figure 4.[6] Clopidogrel floats around within the active site and where its large benzyl ring bumps against the phenylalanine amino acids, is where it will have a pi-pi bond to hold the molecule in place.

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.

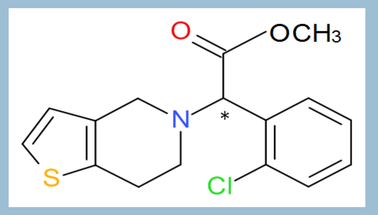

Fig 5 Clopidogrel structure, * marks stereocenter.[8]

As seen in figure 5, the chlorine (Cl) group on the benzyl ring is the best choice to modify due to Cl being a good leaving group. Cl and oxygen (O) have similar leaving group properties; thus, Cl can be replaced with an OH group. Theoretically the H can be donated, which leaves O free to react with the surrounding amino acids, phenylalanine, alanine, or valine of CYP2C19 and form a hydrogen bond. Because the interaction is only known from the rabbit, we have to make an assumption on which amino acids in the human the O would bind.

Therefore, clopidogrel will have a greater binding affinity to the CYP2C19 enzyme and will prevent omeprazole from getting to the binding site.

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.[5] 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.

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