**INTRODUCTION**

Clopidogrel is an inactive thienopyridine prodrug which requires in vivo metabolism by the cytochrome P450 (CYP) 3A subfamily of enzymes to form an active metabolite. CYP3A4 is the primary catalytic enzyme for the metabolic activation of clopidogrel, and it is expressed to varying extents in human hepatocytes: polymorphism in its expression is unlikely to interfere with clopidogrel metabolism in vivo. CYP3A5 is primarily expressed in African Americans. Individuals with at least one CYP3A5/*1 allele express large amounts of CYP3A5. Individuals with genetic polymorphism resulting in homozygous expression of CYP3A5/*1, */3, or */7 do not have CYP3A5. Thus, we present preliminary data from three studies that support the hypothesis that differences in CYP3A4 activity largely account for the observed inter-individual variability in platelet aggregation by clopidogrel. CYP3A5 genetic polymorphism leads to variability in the response to clopidogrel.

**METHODS**

**Study 1:** Rifampin is a known inducer of CYP3A4 and would be expected to influence the platelet inhibitory activity of clopidogrel.

- Human volunteers (n=25) received clopidogrel 450 mg.
- Breath test (ERMBT, Metabolic Solutions, Inc., Nashua, NH) was determined at days 0, 6, 20, 24, and 30.
- CYP3A5 genetic polymorphism leads to variability in the response to clopidogrel.
- Linear regression analysis comparing platelet aggregation and ERMBT.

**Study 2:** A preliminary prospective study to determine whether CYP3A5*3, *5, or *7 do not have CYP3A5. Differences in CYP3A4 activity largely account for the observed differences in the platelet inhibition response to clopidogrel.

- Platelet surface P-selectin expression by flow cytometry (Dr. Erin Schuetz, St. Jude Children’s Research Hospital, Memphis, Tennessee).
- Platelet-rich plasma aggregation (Chronolog Corp., Haverton, PA).
- linear regression analysis comparing platelet aggregation and ERMBT.

**Study 3:** Genotypes of CYP3A4 and Platelet Activity Determined by Point-of-Care Platelet Aggregation Testing

- Preliminary data from three studies that support the hypothesis that differences in CYP3A4 activity largely account for the observed differences in the platelet inhibition response to clopidogrel.

**RESULTS**

**Study 1:** Point-of-care platelet aggregation was measured before and four hours after clopidogrel.

- Linear regression analysis comparing platelet aggregation and ERMBT.

**Study 2:** A preliminary prospective study to determine whether CYP3A5 genetic polymorphism leads to variability in the response to clopidogrel.

- African American human volunteers (n=6) received clopidogrel 450 mg.
- Platelet function tests were performed before and four hours after clopidogrel using:
  - Platelet-rich plasma aggregation
  - Platelet-rich plasma aggregation (Chronolog Corp., Haverton, PA).
  - Platelet surface P-selectin expression by flow cytometry (Dr. Alan D. Michelson, Center for Platelet Function Studies, Georgia).

- Isolation of genomic DNA, amplification, and sequencing of CYP3A5 from whole blood component of each subject (Dr. Erin Schuetz, St. Jude Children’s Research Hospital, Memphis, Tennessee).

**CONCLUSION**

- Inter-individual variability exists in the response to clopidogrel.
- Preliminary data strongly support the hypothesis that the mechanism of variability in clopidogrel response is inter-individual differences in the expression of CYP3A4.

- These data warrant the awareness of potential drug-drug interactions with other CYP3A4 substrates.
- These data further support the need to monitor platelet activity during clopidogrel therapy to ensure pharmacologic efficacy.

**REFERENCES**