St. John’s Wort Enhances the Platelet Inhibitory Effect of Clopidogrel in Clopidogrel “Resistant” Healthy Volunteers

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INTRODUCTION

We previously demonstrated that platelet aggregation inhibition by clopidogrel inversely correlated with the metabolic activity of the hepatic cytochrome P450 (CYP) 3A4 isoenzyme. Rifampin, co-administered with clopidogrel, effectively converted volunteers who were known clopidogrel non- and low-responders (clopidogrel “resistant”) to responders, measured by ex vivo platelet aggregometry.1 Rifampin, an inducer of the hepatic CYP3A4 isoenzyme enhanced the platelet anti-aggregatory effect of clopidogrel.

St John’s Wort (SJW), an herb, with the constituent hyperforin, is a potent ligand for the nuclear steroid pregnane X receptor (PXR) response element that induces hepatic CYP3A4 enzymatic activity and increases the efficacy of drugs that are dependent on CYP3A4 for their metabolic activation.2 We thus hypothesized that SJW would also enhance the platelet inhibitory effect of clopidogrel by induction of CYP3A4.

METHODS

● Six healthy clopidogrel “resistant” subjects were recruited. “Resistance” was defined as a relative decrease in platelet aggregation < 30% measured by Plateletworks™ test (Helena Laboratories, Beaumont, TX) whole blood aggregometry using 20µM ADP at 2, 4, and 6 hours after clopidogrel 450 mg. (Blue bars)

● After a 14 day washout period, subjects were treated with SJW 300 mg (Nature’s Way, standardized to 3% hyperforin), three times daily for 14 days.

● Platelet aggregation was again measured before clopidogrel and 2, 4, and 6 hours after clopidogrel 450 mg. (Yellow bars)

● Erythromycin breath test was subsequently measured in the latter two subjects before, after 14 days of SJW, and 4 hours after SJW + clopidogrel 450 mg.

RESULTS

Figure 1
Conversion of clopidogrel non-responders to responders at 4 and 6 hours after SJW detected by point-of-care whole blood aggregometry.

Figure 2
Hepatic CYP3A4 metabolic activity measured by erythromycin breath test increased greater than 1.5 fold after SJW. Clopidogrel utilizes CYP3A4 for its metabolic activation.

CONCLUSION

1. SJW increases CYP3A4 activity, converting clopidogrel non- and low-responders to clopidogrel responders.
2. Clopidogrel utilizes CYP3A4 for its metabolic activation and is a substrate inhibitor of CYP3A4.
3. Herb-drug interactions are pharmacologically important.

REFERENCES

1. Lau et al., Circulation 2004; 109; 166 - 171.
2. Watkins et al., Biochemistry 2003; 42; 1430 - 1438.