Cyclosporine Reduces the Platelet Inhibitory Effect of Clopidogrel in Cardiac Transplant Patients

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Introduction:

The in vivo metabolic activation of clopidogrel occurs via cytochrome P450 (CYP) 3A4. Atorvastatin, a CYP3A4 substrate, has previously been shown to competitively inhibit clopidogrel activation. Cyclosporine is extensively metabolized by CYP3A4 and is also susceptible to interactions with substrate inhibitors and inducers of the CYP3A4 isoenzyme. This ex vivo study was designed to determine whether there is a drug-drug interaction between cyclosporine and clopidogrel.

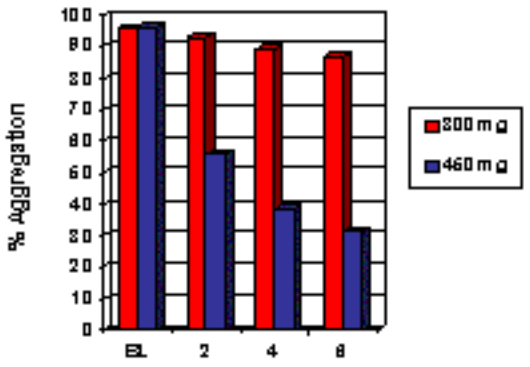
Methods:

We identified 8 heart transplant patients on cyclosporine who were not on other known CYP3A4 substrates. Patients were administered 300 mg (n=4) or 450 mg (n=4) of clopidogrel. Platelet aggregation was determined using Plateletworks™ aggregometry and 20 uM ADP at baseline, 2, 4, and 6 hours after clopidogrel administration.

Results:

The mean percent platelet aggregations at baseline, 2, 4, and 6 hours after clopidogrel administration were: 95.8% ± 4.7%, 93.0% ± 3.7%, 89.0% ± 5.7%, and 87.0% ± 5.5% with 300 mg; and 96.3% ± 2.6%, 55.8% ± 23.4%, 38.3% ± 25.5%, and 31.7% ± 33.5% with 450 mg. Comparisons between groups at 2, 4, and 6 hours were statistically significant ($p<0.05$). Similar results were obtained with light transmission aggregometry (Figure 1).

Figure 1:



Time (hours) Post Loading Dose of Clopidogrel

Conclusions:

In long-term survivors of heart transplantation on cyclosporine therapy, clopidogrel 450 mg, but not 300 mg (or presumably 75 mg), inhibits platelet aggregation. When thienopyridine therapy is required for patients taking cyclosporine, ticlopidine should be considered in place of clopidogrel because of this drug-drug interaction.