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Effect of Ketoconazole on Clopidogrel Pharmacokinetics and Pharmacodynamics in Healthy Subjects

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Background: Clopidogrel is a prodrug converted to an active metabolite mainly by the cytochrome P450 3A, and also metabolized to an inactive metabolite by carboxylesterase. The active metabolite of clopidogrel irreversibly inhibits platelet aggregation by acting on the adenosine diphosphate (ADP) receptor. We investigated the effect of ketoconazole on clopidogrel pharmacokinetics (PK) and pharmacodynamics (PD).

Methods: An open, crossover study with a five-day washout period in between was conducted in 22 healthy male volunteers. A single oral dose of 300 mg clopidogrel was administered alone (Period I) and after pretreatment with a 400 mg ketoconazole for 3 days daily (Period II). Serial PK blood samples were collected for a period of 24 h after dosing and plasma concentrations of the inactive carboxyl metabolite was analyzed by LC-MS/MS. The platelet aggregation responses were measured by Chronolog Lumi-Aggregometer.

Results: The geometric mean ratios (90% CI) for Period II to Period I were 1.44 (1.26±1.64) for AUCinf and 1.05 (0.90±1.22) for Cmax of the carboxyl metabolite of clopidogrel. The half-lives were 8.9±1.9 h for clopidogrel alone and 8.7±1.7 h for pretreatment with ketoconazole. The least square mean values of changes from baseline in platelet aggregation were 24.1% for Period I and 16.8% for Period II, showing a significant difference ($P < .001$).

Conclusions: The extent to be metabolized from clopidogrel to the inactive metabolite was increased after pretreatment with ketoconazole, thus attenuating the clopidogrel action measured by optical platelet aggregation in healthy subjects.