P-29

Pharmacokinetic and pharmacodynamic modeling of clopidogrel in healthy volunteers.

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Clopidogrel is an oral antiplatelet agent used in the treatment of cerebrovascular disease, peripheral vascular disease and coronary artery disease. This study was designed to develop an analytical method to detect three analyte, clopidogrel, its inactive carboxyl metabolite and active thiol metabolite in human plasma and to model its pharmacokinetics and pharmacodynamics in healthy volunteers. Clopidogrel 300 mg was administered on the first day and followed by 75mg once a day for 5 days. Blood samples were serially collected up to 24 hrs on the first day, and clopidogrel and its metabolites (carboxy-metabolite, active metabolite) in plasma were simultaneously detected using LC/MS/MS. The inhibitory effect of clopidogrel on the ADP-induced platelet aggregation was measured during 12 days. A mechanism based pharmacokinetic and pharmacodynamic model has been developed: plasma concentration-time profiles of three compounds were modeled by compartmental approaches, and the plasma concentration of an active metabolite was linked with drug-receptor interaction for an integrated PK/PD modeling. To best our knowledge, it is for the first time to quantify the relationship between the plasma concentration of an active metabolite and anti-platelet aggregation effect, and the combined kinetic-dynamic model may provide further insight into the action mechanism of clopidogrel.