Population Pharmacokinetics and Pharmacodynamics of Bivalirudin in Chinese Subjects

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Objectives: Bivalirudin is used as an anticoagulant agent for the treatment of thrombosis associated with heparin-induced thrombocytopenia (HIT) and for patients at risk of HIT undergoing percutaneous coronary intervention (PCI). In this study, bivalirudin population pharmacokinetics and the correlation between bivalirudin plasma concentration and the activated clotting time (ACT) in Chinese subjects was characterized to support the proper dosing and drug monitoring in Chinese patients.

Methods: Twenty healthy male Chinese subjects were enrolled and randomly assigned to two groups. Individuals in the group 1 received a bolus intravenous (IV) dose of 0.75 mg/kg bivalirudin, and in the group 2 received the same bolus IV dose of 0.75 mg/kg followed by a one hour IV infusion of 1.75 mg/kg/hr of bivalirudin. Population pharmacokinetic (PK) and pharmacodynamic (PD) modeling were performed using nonlinear mixed effects modeling (NONMEM). The final models were selected based on the likelihood ratio test, goodness-of-fit plots, and visual predictive check.

Results: Plasma bivalirudin concentration-time profiles in both groups were best described by a two-compartment PK model, and the model estimated systemic plasma clearance (CL±SE), volume of distribution in the central (V1±SE) and peripheral compartments (V2±SE), were 11.2 (±1.5) L/hr, 3.17 (±0.31) and 1.99 (±0.25) L, respectively. The relationship between bivalirudin plasma concentration and ACT was best characterized by a sigmoid E\textsubscript{max} model. Model estimated maximum increase of ACT (E\textsubscript{max}±SE), the plasma concentration associated with 50% of E\textsubscript{max} (EC\textsubscript{50}±SE), and the sigmoidicity factor (γ±SE, steepness of the curve) were 269% (± 63%), 5040 (±2810) μg/L, and 0.824 (±0.096), respectively.

Conclusions: There was a strong direct correlation between the plasma bivalirudin concentrations and the ACT prolongation. The POPPK and PK/PD models developed in the present study could provide very useful information for dose optimization and individualization in Chinese patients.