Population Pharmacokinetics and Dose Proportionality of Aranidipine Sustained-release Capsules in Healthy Subjects

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Objectives: Aranidipine (AR) is a dihydropyridine-type calcium channel blocker used for the treatment of hypertension. In this study, the population pharmacokinetics (POPPK) and dose proportionality of AR was characterized using nonlinear mixed effect modeling (NONMEM) to support the proper dosing and drug monitoring of AR in Chinese patients.

Methods: The AR plasma-concentration data were collected from two Phase I clinical studies (n=47) in healthy subjects receiving a single oral dose of sustained-released AR capsules of 5, 10, or 20 mg in fasted state. POPPK modeling was performed using nonlinear mixed effects modeling (NONMEM) and the contribution of physiological factors (e.g., BW, AGE, and SEX) was assessed. The final models were selected based on the likelihood ratio test, goodness-of-fit plots, and visual predictive check.

Results: The model estimated AR exposure (AUC) at 5 mg, 10 mg and 20 mg were 6.72, 14.8, and 31.2 μg·hr/L respectively, suggesting that AR exposure increased dose-proportionally over the dose range of 5 - 20 mg. Plasma AR concentration-time profiles were best described by a two-compartment PK model with 1st-order absorption, and the model estimated AR absorption rate constant (Ka), apparent clearance (CL/F), volume of distribution in the central (V2/F) and peripheral compartments (V3/F) were 0.670 hr⁻¹, 728 L/hr, 299 L, 792 L respectively. No significant contribution of physiological factors was observed.

Conclusions: The present study demonstrated dose proportionality for sustained-release AR capsules at 5 – 20 mg in healthy subjects in fasted state. The POPPK model developed in the present study could provide valuable information for dose individualization and optimization in Chinese patients.