Population Pharmacokinetics and Food Effect of the Antihypertensive Drug Aranidipine 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 (PK) of AR, the food effect, and the contribution of physiological factors (e.g., body weight, age, gender) were assessed using nonlinear mixed effect modeling (NONMEM).

Methods: The AR plasma-concentration data were collected from a clinical study in healthy Chinese subjects (n=9) receiving a single oral dose of sustained-released AR capsules of 10 mg under fasted or fed conditions with a cross-over design. Population PK modeling was performed using nonlinear mixed effects modeling (NONMEM). The final models were selected based on the likelihood ratio test, goodness-of-fit plots, non-parametric bootstrap analysis and visual predictive check. No significant contribution of physiological factors was observed.

Results: The AR plasma maximum concentration (Cmax) and area under the curve (AUC(0-inf)) at 10 mg were 4.2 ± 0.5 μg/L and 11.4 ± 1.4 μg·hr/L for the fasted group, and 6.8 ± 1.5 μg/L and 15.9 ± 2.0 μg·hr/L for the non-fasted group respectively, suggesting that food increased AR exposure. Plasma AR concentration-time profiles were best described by a two-compartment PK model with 1st-order absorption. The model estimated AR absorption rate constant (Ka), apparent clearance (CL/F), volume of distribution in the central (Vc/F) and peripheral compartments (Vp/F) were 0.59 ± 0.02 hr⁻¹, 714 ± 648 L/hr, 210 ± 112 L, and 2151 ± 33 L for the fasted group; 0.64 ± 0.02 hr⁻¹, 484 ± 58 L/hr, 573 ± 395 L and 2340 ± 35 L for the non-fasted group, respectively.

Conclusions: The absorption and disposition of AR was successfully characterized by population PK models. AR exposure was higher and CL/F was lower in subjects under non-fasted condition. The population PK model developed in this study is useful for dose optimization and study design in Chinese population.