초청연제

Pharmacokinetic Population Modeling Incorporating CYP2A6 Genotypes following Different Routes of Administration of Nicotine

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Objectives: We developed a comprehensive population pharmacokinetic model to quantify the influence of CYP2A6 genetic polymorphisms and covariates on the pharmacokinetic of nicotine following different routes of administration, and to predict individual subjects' pharmacokinetics.

Methods: Three groups of 278, 64 and 40 subjects received intravenous (iv), oral and patch administration of nicotine and deuterium-labeled nicotine, respectively. A multi-compartment model was developed to assess the kinetic profile of the three studies separately, including a Bayesian model for the oral and patch data. Demographic, environmental variables and genotypes of CYP2A6 *(*1A, *1B, *1×2, *2, *4, *7, *9 and *10)* were included in the analysis as covariates. The influence of the in-vitro ratios of enzyme activity of each CYP2A6 genotypes with respect to the wild-type was also evaluated.

Results: Nicotine pharmacokinetics after iv, oral and patch administration were adequately characterized by a multi-compartment model. Body weight and sex were significant covariates on nicotine clearance. The Asian group had a significantly lower clearance compared to other racial groups, which could be accounted for by incorporating the CYP2A6 genotype as a covariate. Smoking, marital status, education, age and body mass index did not significantly affect nicotine kinetics. A significant relationship between clearance and the *in-vitro* ratios of the enzyme activity of each CYP2A6 genotypes with respect to the wild-type was observed. The assumption that the same ratios would apply for a related *in-vivo* activity need to be further defined.

Conclusions: A significant relationship between CYP2A6 genotypes and clearance was observed and we confirm the influence of sex and body weight on nicotine clearance. *In-vitro* enzyme activity of CYP2A6 may provide significant predictions of nicotine pharmacokinetics.