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Effects of CYP3A5 and CYP2D6 genetic polymorphism on the pharmacokinetics of diltiazem and its metabolites in chinese subjects

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Abstract

To assess the possibility of using CYP2D6*10 + CYP3A5*3 as biomarkers to predict the pharmacokinetics of diltiazem and its

two metabolites among healthy Chinese subjects.

Methods: 41 healthy Chinese were genotyped for CYP3A5*3 and CYP2D6*10, and then received a single oral dose of diltiazem hydrochloride capsules (300mg). Multiple blood samples were collected over 48h, and the plasma concentrations of diltiazem, N-desmethyl diltiazem and desacetyl diltiazem were determined by HPLC-MS/MS. Th e relationships between the genotypes and pharmacokinetics were investigated.

Results: Th e pharmacokinetics of diltiazem, N-desmethyl diltiazem were not signifi cantly aff ected by both CYP3A5*3 and CYP2D6*10 alleles. However, the systemic exposure of the pharmacologically active metabolites, desacetyl diltiazem, was 2-fold higher in CYP2D6*10/*10 genotype carriers than in *1/*10 or *1/*1 ones (AUC(0-inf) of CYP2D6*1/*1, *1/*10 and *10/*10 is 398.2 }162.9, 371.0 }69.2 and 726.2 }468.1 respectively, $p<0.05$).

Conclusions: Two of the most frequent alleles, CYP3A5*3 and CYP2D6*10, among Chinese do not have major impacts on the disposition of diltiazem and N-desmethyl diltiazem. However, the desacetyl diltiazem showed 2-fold accumulation in individuals with CYP2D6*10/*10 genotype. Despite this, the eff ect of genotype of CYP2D6 on clinical outcome of diltiazem treatment isexpected to be limited.

Biography

Shengjun Zhang received his MD from Zhengzhou University in 1984 and his MBA in Health Management from Johns Hopkins University in 2010. He participated in clinical fellowship training at Stanford University Sleep Research Center; fi ve years of cardiology postdoctoral training at NIA/NIH; two years of research experience at UMDNJ/RWJMS. In addition to research experiences, Shengjun worked two years in clinical research project management at Johns Hopkins School of Medicine Department of Oncology and two years of international clinical study in infectious diseases (HIV/AIDS) at Johns Hopkins Hospital (HPTN China study project coordinator). Shengjun also has two years of projects management and business development experience at Westat, Inc. and four years of executive-level project director experience at Frontage lab, Inc. Prior to entering the clinical research and trial, he practiced internal medicine and pulmonary in China for twelve years. Currently, Shengjun serves as director of Clinical Research Center-China for Frontage and a Special-Appointed Professor at Zhengzhou University and Adjunct Professor of Drexel University.