

## CYP2D6 Genotype Affects Aripiprazole Clearance in Korean Patients: Population Pharmacokinetic Analysis

Ji-Young Jeon

Seoul National University College of Medicine and Hospital

**Background:** The aim of this study was to determine the population pharmacokinetics (PK) and to evaluate clinical covariates that influence PK of aripiprazole and its metabolite, dehydroaripiprazole, in Korean patients.

**Methods:** In 80 Korean patients (34 men and 46 women) with schizophrenia or schizoaffective disorder, blood concentrations of aripiprazole and dehydroaripiprazole were collected before dosing and/or at 6 h after dosing at steady state. Population PK parameters for both aripiprazole and dehydroaripiprazole were estimated simultaneously using nonlinear mixed-effect modeling assuming a one compartment model with first order absorption and elimination. The effects of age, weight and genotype were explored as covariates for PK of aripiprazole and dehydroaripiprazole.

**Results:** The typical values for apparent clearance (CL/F) and apparent volume of distribution (V/F) of aripiprazole were  $2.36 \pm 0.1$  L/h (mean  $\pm$  SE) and  $191 \pm 12.1$  L, respectively. The population mean elimination half-lives were 63 h for aripiprazole and 80 h for dehydroaripiprazole. Only CYP2D6 genotype was identified as a significant covariate for CL/F of aripiprazole. The CYP2D6 alleles were classified into functional (CYP2D6 \*1 or \*2), non-functional (CYP2D6 \*4, \*5, \*14 or \*36), and reduced functional alleles (CYP2D6 \*10 or \*41). The CL/F estimates according to allele function were as follows; 3.17 L/h for patients with homozygous for functional alleles, 2.55 L/h for heterozygous for one functional allele and one reduced functional or non-functional allele, 1.85 L/h for homozygous for reduced functional alleles, and 1.54 L/h for heterozygous for one reduced functional allele and one non-functional allele.

**Conclusions:** This population PK model adequately described PK of aripiprazole and dehydroaripiprazole in Korean patients. Our results indicate that CYP2D6 genotype influenced the apparent clearance of aripiprazole, and therefore implies that patients may need to be dosed differently based on genotype.