Poster

[P26-3] P26-3: Central nervous system drugs (2)

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[P26-3-8] Influence of the cytochrome P450 2D6 polymorphisms on the pharmacokinetics of paroxetine in Japanese patients with major depressive disorder: a population pharmacokinetic analysis

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Background

Paroxetine is a selective serotonin reuptake inhibitor that is used widely in the treatment of mental disorders, including major depressive disorder, panic disorder, obsessive-compulsive disorder, social anxiety disorder, generalized anxiety disorder, and post-traumatic stress disorder. Paroxetine undergoes significant first-pass metabolism and it is catalyzed largely, but not exclusively, by cytochrome P450 (CYP) 2D6. Although the reduced function of the CYP2D6*10 allele is common among Asian populations, existing evidence does not support paroxetine therapy adjustments for patients who have the CYP2D6*10 allele. In this study, we attempted to evaluate the degree of the impact of different CYP2D6 genotypes on the pharmacokinetic (PK) variability of paroxetine in a Japanese population using a population PK approach.

Methods

This retrospective study included 179 Japanese patients with major depressive disorder who were being treated with paroxetine. CYP2D6*1, *2, *5, *10, and *41 polymorphisms were observed. A total of 306 steady-state concentrations for paroxetine were collected from the patients. A population PK analysis of paroxetine was carried out using nonlinear mixed-effect modeling (NONMEM, version 7.2.0; ICON Dev Soln, Ellicott City, MD). A nonlinear mixed-effects model identified the apparent Michaelis–Menten constant (Km) and the maximum velocity (Vmax) of paroxetine; the covariates included CYP2D6 genotypes, patient age, body weight, sex, and daily paroxetine dose.

Results

The allele frequencies of CYP2D6*1, *2, *5, *10, and *41 were 39.4, 14.5, 4.5, 41.1, and 0.6%, respectively. There was no poor metabolizer who had two nonfunctional CYP2D6*5 alleles. A one-compartment model showed that the apparent Km value was decreased by 20.6% in patients with the CYP2D6*10/*10 genotype in comparison with the other CYP2D6 genotypes. Female sex also influenced the apparent Km values. No PK parameters were affected by the presence of one CYP2D6*5 allele.

Conclusions

The presence of one CYP2D6 null allele or one CYP2D6*10 allele had no quantifiable effect on paroxetine PKs, whereas elimination was unexpectedly accelerated in individuals with the CYP2D6*10/*10 genotype.

Our results show that the presence of one CYP2D6*5 allele or any CYP2D6*10 allele may have no major effects on paroxetine PKs in the steady state.