일반연제

Effect of *UGT2B15* Genotype on the Pharmacokinetics, Pharmacodynamics, and Drug Interactions of Lorazepam

Jae-Yong Chung, Joo-Youn Cho, Kyung-Sang Yu, Jung-Ryul Kim, Hye-Ryung Jung, In-Jin Jang, Sang-Goo Shin

Department of Pharmacology and Clinical Pharmacology Unit, Seoul National University College of Medicine and Hospital, Seoul, Korea

Objective: To investigate the effect of the *UGT2B15* genetic polymorphism on the pharmacokinetics and pharmacodynamics of lorazepam in basal, inhibited, and induced metabolic states in healthy normal volunteers.

Methods: Twenty four healthy subjects were enrolled and grouped into *UGT2B15*1/*1* or *UGT2B15*2/*2* genotype groups. The pharmacokinetic and pharmacodynamic profiles of intravenous lorazepam were characterized before and after valproate administration (600 mg once daily for 4 days), and also following rifampin pretreatment (600 mg once daily for 10 days), with a washout period of 10 days between. The plasma concentrations of lorazepam and lorazepam-glucuronide were analyzed before and 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, and 48 hours after lorazepam administration by LC-MS/MS. Visual analog scale assessments and psychomotor coordination tests (Vienna) were done before and up to 12 hours after drug administration.

Results: The *UGT2B15*2/*2* group showed less systemic clearance by 42% ($p<0.0001$) during the basal state, and a greater area under the visual analog scale-time curve by 37% ($p=0.037$) during the induced state than the *UGT2B15*2/*2* group. The average systemic clearance of lorazepam reduced by 20% in the inhibited state, and increased by 140% in the induced state. Metabolic inhibition or induction effects on pharmacokinetic or pharmacodynamic parameters were no different by genotype.

Conclusions: Our results suggest that the *UGT2B15* genotype is a major determinant of interindividual variability with respect to the pharmacokinetics and pharmacodynamics of lorazepam.