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Effects of Genetic Variation of CYP2C19 on the Pharmacokinetics of Zolpidem

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Zolpidem, an imidazopyridine derivate, is widely prescribed for the short-term treatment of insomnia. It is predominantly metabolized by CYP3A4, and to a lesser extent, by CYP1A2 and CYP2C19 (1). Recently, It was reported that CYP2C19*2 is associated with the poor metabolism of zolpidem (2). Thus, we investigated the effects of CYP2C19 genetic polymorphism on the pharmacokinetics of zolpidem in healthy subjects with/without a potent CYP3A4 inhibitor (clarithromycin). Twenty-five healthy subjects were recruited and classified into three different groups according to their CYP2C19 genotypes, CYP2C19EM (*CYP2C19*1/*1*, n=10), CYP2C19IM (*CYP2C19*1/*2* or *CYP2C19*1/*3*, n=9), CYP2C19PM (*CYP2C19*2/*2, *2/*3* or **3/*3*, n=6). In the control phase, each subject ingested 5 mg oral dose of zolpidem after overnight fasting. In the CYP3A4 inhibition phase, 500 mg oral dose of clarithromycin were administered at 8 A.M. and 8 P.M., respectively, for five consecutive days, and 5 mg oral dose of zolpidem and 500 mg clarithromycin were simultaneously administered. Blood samples were collected up to 12 hours after zolpidem administration, and plasma concentrations of zolpidem were determined by using LC-MS/MS analytical system. In CYP2C19EM, IM and PM when zolpidem was administered alone, C_{max} were 51.2 ± 18.4, 45.3 ± 10.0 and 59.6±10.1 ng/ml, respectively (not significant differences, *NS*), and AUC_{inf} were 184.4±91.6, 182.9±62.2 and 204.2±62.1 ng·hr/ml, respectively (*NS*). The clearance was also not significantly differ between three genotype groups. When a potent CYP3A4 inhibitor was pretreated for five days, there is no significant difference in C_{max}, AUC_{inf} and CL/F between CYP2C19EM, IM and PM groups. In conclusion, we did not find any effects of genetic variation of CYP2C19 on the pharmacokinetic parameters of zolpidem.

1. Pichard L *et al.* (1995) *Drug Metab Dispos* **23**: 1253-1262.

2. Shen M *et al.* (2013) *Forensic Sci* **227**: 77-81.