CYP2C9 variant alleles significantly affected on the pharmacokinetics of zafirlukast

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Zafirlukast is an oral leukotriene receptor antagonist (LTRA) for the maintenance treatment of asthma, often used in conjunction with an inhaled steroid and/or long-acting bronchodilator. A previous study showed that cytochrome P450 (CYP) 2C9 and 3A4 are the major enzymes participating in zafirlukast metabolism. We investigated the effects of CYP2C9 genetic variants on the pharmacokinetics of zafirlukast. Twelve subjects with CYP2C9*1/*1 (EM) and thirteen subjects with CYP2C9*1/*3 or *1/*13 (IM) were enrolled in this study. After overnight fasting, each subject received a 20 mg oral dose of zafirlukast. Blood samples were collected up to 12 hr after drug administration, and plasma concentrations of zafirlukast were determined by validated LC-MS/MS method. C_max of zafirlukast in CYP2C9 IM was 1.52-fold higher than that in CYP2C9 EM. AUC_{inf} of zafirlukast in CYP2C9 IM was also 1.90-fold higher than that in CYP2C9 EM. Apparent oral clearance (CL/F) of zafirlukast in CYP2C9 IM was 44.2% lower than that in CYP2C9 EM. Genetic polymorphism of CYP2C9 significantly affected the pharmacokinetics of zafirlukast.