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Effects of metabolizing enzyme gene polymorphisms on Sulindac pharmacokinetics in pregnant women with preterm labor

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Sulindac which inhibits prostaglandin synthetase is used as a tocolytic agent. It is well-known that gene polymorphisms could result in inter-individual differences in drug concentrations and activities. However, studies have rarely conducted on the effects of gene polymorphisms on sulindac pharmacokinetics in clinical settings. The objective of this study was to determine the impact of the polymorphisms of sulindac-related metabolizing enzyme genes, including *FMO3* and *CYP2C9*, on sulindac pharmacokinetics in pregnant women with preterm labor. 68 patients diagnosed with preterm labor between 16 and 37 weeks' gestation were enrolled in the study cohort and given 200 mg sulindac orally twice a day. Blood samples were collected at 1.5, 4 and 10 hours after the first dose. Plasma concentrations of sulindac and its active metabolite of sulindac sulfide were determined using HPLC method and pharmacokinetic analysis was carried out using the WinNonlin program. 9 single nucleotide polymorphisms (SNPs) of *FMO3* and *CYP2C9* were analyzed by the SNaPshot and Taqman genotyping assays. The mean maternal age and gestational age at dosing were 32.6±4.3 years old and 26.4±4.7 weeks, respectively. In *FMO3* SNPs, no significant difference was found in the $AUC_{0\rightarrow10hr}$ for both sulindac and sulindac sulfide. *FMO3* rs2266782 showed marked trend in $AUC_{0\rightarrow10hr}$ of sulindac between homozygote variant type and homozygote wild/heterozygote type (P=0.07). Among *CYP2C9* SNPs, the homozygote wild type group of rs1057910 had a higher $AUC_{0\rightarrow10hr}$ for sulindac sulfide compared to heterozygote group (p=0.04). In rs2253635 SNP, homozygote variant type showed a reduced $AUC_{0\rightarrow10hr}$ for sulindac than homozygote wild type and heterozygote group (p=0.027). The present study demonstrates the effect of genetic polymorphisms on the pharmacokinetics of sulindac and it is expected that the results could help clinicians predict efficacies of sulindac in the development of individualized treatment plans for patients with preterm labor.

Biography

Jin Won Seong is currently a Masters student of Clinical Pharmacy at College of Pharmacy, Ewha Womans University. She has completed her PharmD at Ewha Womans University in 2015. Her research concentrates on the effect of gene mutation on pharmacokinetic characteristics of drugs.

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