TOLTERODINE PHARMACOKINETICS IN JAPANESE, KOREAN AND CAUCASIAN HEALTHY VOLUNTEERS.

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[Purpose] This study was conducted to investigate the ethnic difference in pharmacokinetics of tolterodine and its active metabolite among Japanese, Koreans and Caucasians with considering the effect of CYP2D6 genotype.

[Methods] Japanese, Korean and Caucasian healthy volunteers (n=36 in each ethnic group) were received once daily multiple doses of tolterodine in this study. After the administrations, serum concentrations of tolterodine and 5-HM were measured. Tolterodine is mainly metabolized to active 5-hydroxymethyl metabolite (5-HM) by CYP2D6 and 5-HM is also metabolized by CYP2D6. All subjects were genotyped for CYP2D6. Intrinsic clearances of CYP2D6 (CL\text{intCYP2D6}) for tolterodine and 5-HM were estimated from the exposures in this study.

[Results and Discussion] The exposures (AUC) of tolterodine and 5-HM in Koreans were 1.9- and 1.4-fold higher than Japanese and those in Caucasians were 1.3- and 1.3-fold higher, respectively. The allele frequency of CYP2D6*10, which is one of the reduced function allele and major in Asian, in Japanese and Korean subjects were approximately 30% and 50%, whereas was only 1.4% in Caucasian. On the other hand, there were no Asian subjects who had CYP2D6*4 allele which is a deficient allele, but the allele frequency of CYP2D6*4 in Caucasians was 16.7%. The estimated CL\text{intCYP2D6} for tolterodine and 5-HM tended to decrease in subjects with these reduced and deficient alleles.

[Conclusions] The apparent differences in exposure among ethnic groups could be explained by the different genotype frequency in each ethnic group.

DEVELOPMENT OF THE WORLD’S FASTEST SNP-TYPING METHOD “SmartAmp” AND ITS CLINICAL APPLICATION

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[Purpose] A key requirement for the development of genotyping-based individualized medicine or personalized therapy is the ability to rapidly and conveniently test patients’ genetic polymorphisms and/or mutations. We aimed to develop a rapid and cost-effective method, named Smart Amplification Process (SmartAmp), which enables us to detect genetic polymorphisms in drug metabolizing enzymes and drug transporters within 30 to 45 min under isothermal conditions.

[Methods] In order to apply the SmartAmp method for clinical research, we have designed SmartAmp primers genotyping of drug metabolizing enzymes and transporters that are critically involved in drug-induced adverse reactions or disease risk.

[Results and Discussion] In the present study, we have developed specific primers for the SmartAmp2 method to clinically genotype human ABCB1, ABCG2, ABCC4, and ABCC11 genes. We have examined whether these SmartAmp primers could detect SNPs in those ABC transporter genes. Genotyping of ABCC11 gene by the SmartAmp method was further examined in the clinical study of axillary osmidrosis. All the SmartAmp primers developed have been proven to accurately detect and discriminate all possible homozygotes and heterozygotes of the SNPs we tested. Thus, the SmartAmp method is expected to provide a practical tool for pharmacogenomics-based personalized medicine.