구연 15

Genetic Variants of SLC22A2 (Organic Cation Transporter 2, OCT2) Significantly Influence on the Disposition of Metformin

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The genetic variants of SLC22A2 (OCT2) were evaluated for their contribution to the pharmacokinetic variation of metformin, a substrate of OCT2, especially on its renal elimination in vitro and in vivo. The intrinsic clearance of metformin was decreased by 68.6%, 60.1%, and 39.6% in HEK293 cells overexpressing SLC22A2 variants, SLC22A2-T199I, -T201M, and -A270S, respectively, compared with that of wild-type OCT2. After administration of single oral dose of 500mg metformin to 26 healthy subjects whose SLC22A2 genotypes were predetermined, plasma and urine concentrations were measured for 12h. The SLC22A2 variant genotypes showed significant difference of metformin pharmacokinetics compared to the subjects with wild genotype, with higher Cmax and AUC ($P<0.01$) and lower CL/F, Vd/F ($P<0.05$), and renal clearance ($P < 0.01$), suggesting that decreased transport function of OCT2 variants resulted in reduced renal clearance, and consequently increased plasma concentrations of metformin. In conclusion, SLC22A2 genetic variants of SLC22A2 seem to be responsible for the inter-individual variation of metformin disposition and should be considered for the prediction of metformin dose.