X-RAY CRYSTALLOGRAPHIC STUDY OF HUMAN ALPHA1-ACID GLYCOPROTEIN AND DRUG COMPLEX

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[Purpose] Human alpha1-acid glycoprotein (AGP) is a glycoprotein that functions as a carrier of basic drugs. In most individuals, AGP exists as a mixture of mainly two genetic variants, F1*S and A variant, which have selectivity on drug binding. However, little has not been understood on its selectivity. We determined the crystal structures of AGP and its complexes with drugs to elucidate the topology of drug binding site and the mechanism of drug binding selectivity for two variants. [Methods] E. coli expression system of unglycosylated AGP was established and homogeneous A variant was prepared for crystallization. A variant and its complexes with drugs (disopyramide and amitriptyline, specific drugs for A variant; chlorpromazine, nonspecific drug for two variants) were crystallized by the hanging-drop vapor diffusion method. [Results and Discussion] Compared with F1*S variant, similar structural properties were obtained for A variant. However, the entrance size of the binding pocket was narrow for A variant, due to the differences of amino acid residues at the position of 112-117 and 156, especially 112 and 114 between two variants. The orientation of aromatic ring was different between drugs selectively bound to A variant and nonspecific for both variants. [Conclusions] Phe112 and Ser114 may play an important role for the drug binding selectivity for A variant.

VIRTUAL CLINICAL TRIAL - PREDICTION OF INTERINDIVIDUAL VARIABILITY IN PHARMACOKINETICS FOR SUBSTRATES METABOLIZED BY CYP2C19 AND CYP3A4

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[Purpose] We have developed and previously reported on methodology using Monte Carlo simulation to predict interindividually variability in pharmacokinetics of P450 substrates. The prediction premises the variability of metabolic activity. We demonstrate that the variability of CYP2C19 activity is evaluated from the variability of pharmacokinetics for the 2C19 substrates, which are also metabolized by CYP3A4, in extensive 2C19 metabolizer (EM).

[Methods] The pharmacokinetic parameters of 2C19 substrates with complementary metabolized pathway by 3A4 were collected in literature. The contribution of 2C19 (fm) to metabolism was determined from the intrinsic metabolic clearance (CLint) in each genotype. The coefficients of variance (CV) of AUC for the substrate with a high fm in EM were used to set at CV of CLint for 2C19 (CLint,2C19). The CV of AUC in intermediate metabolizers (IM) were predicted from the CV of CLint,2C19 obtained in EM and compared with reported CV of AUC in IM.

[Results and Discussion] The fm in IM could be estimated from CLint in EM and in poor metabolizer (PM). The CV of AUC from simulation using 35 and 40% for the CV of CLint,2C19 were confirmed to correspond with the medians of reported CV of AUC from Lansoprazole and Omeprazole in EM. Then, use of the mean CV of CLint,2C19 (38%, the mean of 35 and 40%), CV of CLint,3A4 (33%, a value reported previously) and fm was able to predict the reported values in IM.

[Conclusions] This methodology could apply to predict the CV of AUC from substrates of 2C19 and 3A4 in EM and IM.