VIRTUAL CLINICAL TRIAL (I) – ASSOCIATION OF INTERINDIVIDUAL VARIABILITY IN PHARMACOKINETICS WITH CYP2D6 GENOTYPES

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[Purpose] We have demonstrated from variability of metabolic ratio (MR) in Caucasians that the coefficient of variance (CV) of intrinsic clearance (CLint) of CYP2D6 in extensive metabolizer (EM) is approximately 60%. With the CLint variability, the interindividual variability of AUC was successfully predicted using Monte-Carlo simulation, in which all of the variability of body weight, liver weight, blood flow rate, and albumin concentration in plasma were also incorporated in the pharmacokinetic liver model (23rd JSSX). In the present study, to apply the method to intermediate metabolizer and other ethnic groups, we tried to estimate the CV of CLint for each CYP2D6 genotype. [Methods] Mean MR and its variability for each genotype were collected from literature. CV of AUC for each genotype was also gathered from literature. Contribution of CYP2D6 of each genotype to the total CLint (fm2D6) was estimated using CLint for genotype that had only null alleles. [Results and Discussion] CLint of *1/*1 (CV: 40%-50%) was less variable than EM (60%). The variability of AUC for *1/*1 obtained from literature was consistent with values estimated by the Monte-Carlo simulation of relationships between AUC/Dose and CV (%) of AUC/Dose (AUC/D-CV (%)). Reduced genotypes showed lower fm2D6 than *1/*1. When fm2D6 was low, it was difficult to determine the influence of CLint variability in AUC/D-CV (%). [Conclusions] The variability of AUC was successfully predicted for *1/*1. The possibility of prediction for other genotypes will also be discussed in this presentation.

VIRTUAL CLINICAL TRIAL (II) - PREDICTION OF INTERINDIVIDUAL VARIABILITY IN PHARMACOKINETICS OF CYP2C9 SUBSTRATES IN POPULATION OF EACH GENOTYPE

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[Purpose] Following our report on the successful prediction of the interindividual variability in pharmacokinetics of CYP2C9 (2C9) substrates in extensive metabolizers (EMs) (23th JSSX), this study applied the same Monte Carlo simulation to predict the interindividual variability of each substrate in a population of each 2C9 genotype. [Methods] The contribution of 2C9 (fm) to the entire intrinsic metabolic clearance (CLint) of each substrate was estimated from in vitro 2C9 inhibition assay data. The CLint values from 2C9 (CLint,2C9) and another pathway (CLint,other) were calculated using fm and CLint from 2C9 EMs. The CLint,2C9 for each genotype was predicted based on the relative activity of the mutant to the wild type in vitro. The coefficients of variance (CV) of CLint,2C9 in all genotypes were set at 22%, as done previously for EMs, while the CV of CLint,other at a much higher value. The distributions of the mean and CV of AUC in each genotype were estimated by 200 repeats of simulation using the mean and CV of the predicted CLint,2C9 to compare with the actual values in genotyped population from the literature. [Results] Simulation about tolbutamide with an fm of 0.9 showed that the distribution of the predicted CV of AUC in each genotype population was similar to that on EMs and consistent with the actual value from each genotype. Similar results were obtained with other 2C9 substrates tested. [Conclusion] The study indicates that this method can predict the interindividual variability in pharmacokinetics of 2C9 substrates in each genotype population and that interindividual variability in the pharmacokinetics of any 2C9 substrate is similar in both populations of individuals with a decreased 2C9 activity and of EMs.