VIRTUAL CLINICAL TRIALS (II): PREDICTING INTER-INDIVIDUAL DIFFERENCES IN EXPOSURE TO DRUGS METABOLIZED BY CYP2D6

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Inter-individual differences in pharmacokinetics of drugs are caused by differences in physiologic and genetic background, as well as environmental influences. These differences are of clinical interest because of their potential to cause or worsen adverse reactions. We have established methodology to predict inter-individual differences in the pharmacokinetics of CYP3A4 substrates using Monte Carlo simulation. This investigation describes the search for the activity of CYP2D6 and its variability to apply this methodology to drugs metabolized by CYP2D6. The results indicate that the urinary metabolic ratio (MR) of probe substrates, which has been commonly used as an index of intrinsic clearance in each person, represents the relative index of metabolic activity only if the probe substrate exhibits intrinsic clearance limited pharmacokinetics. The metabolic activity of CYP2D6 and its variability were estimated in extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs) by analyzing the MR values found in literature for probe substrates. The metabolic activity of IMs and PMs were estimated to be about 15% that of EMs and about 0.5% that of EMs, respectively. The coefficient of variance (CV) for the metabolic activity was estimated to be about 60% for both EMs and IMs, which was larger than the CV value of 33% estimated for CYP3A4. It is thought this information will be useful in predicting inter-individual differences in exposure to drugs metabolized by CYP2D6.

CLASSIFICATION OF CLEARANCE ROUTES OF DRUGS BASED ON PHYSICOCHEMICAL PARAMETERS

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Although the importance of pharmacokinetic screening system at early stage of the drug development is recognized, it is not practical to determine hepatic/renal elimination routes, metabolic enzymes or transporters by in vivo studies at early stage of development, where the candidate compounds are still so many. On the other hand, based on their experiences, researchers specialized in metabolism and/or transporters instinctively predict the clearance route/mechanism (renal or hepatic, CYPs or transporters) based on the physicochemical properties of the compound. If this instinctive prediction can be described objectively, experience by the experts can be shared by all the researchers involved in the drug development. In our study, pharmacokinetic parameters were collected on about 280 drugs and they were classified into the groups such that metabolized mainly by CYP3A4, 2C9, 2D6, or eliminated via renal route, or hepatic uptake via OATP family transporters. Collected physicochemical properties were MW, lipophilicity (log D), ratio of unbound fraction in blood, charge and solubility. When these physicochemical parameters were plotted, it formed clusters corresponding to the pharmacokinetic classification groups. By setting appropriate threshold to each physicochemical parameters, pharmacokinetic groups were almost distinguished by each other. This approach is useful when elaborated further as it will enable us to predict the necessary pharmacokinetic investigations.