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Inter-individual Variability of *In Vivo* CYP2D6 Activity in Different Genotypes

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Summary: Cytochrome P450 2D6 (CYP2D6), which has a large number of genetic polymorphisms, is involved in the metabolism of a wide range of substrates. Dextromethorphan (DM) is a well-known probe drug for CYP2D6 and metabolic ratio (MR) is often used to measure the enzyme activity *in vivo*. Using the literature values of DM MR, we estimated the inter-individual variability of CYP2D6 hepatic intrinsic clearance ($CL_{int,h,2D6}$) in each genotype by Monte Carlo simulation and found that the homozygote of *CYP2D6*1* and the heterozygote of *CYP2D6*1* and null alleles had a coefficient of variation (CV) of 43% and 56%, respectively. The variability of homozygotes of *CYP2D6*2* and *CYP2D6*10* was 63% and 66%, while that of the heterozygotes of *CYP2D6*2* and null alleles and *CYP2D6*10* and null alleles was 125% and 109%, respectively. Based on the variability and reported frequency of the *CYP2D6* genotype in Asians and Caucasians, the inter-individual variability of $CL_{int,h,2D6}$ of extensive metabolizers was estimated at 60–70%, which provided comparable variability of AUC with the literature values of DM, tolterodine, risperidone and atomoxetine. It is suggested that the produced inter-individual variability of $CL_{int,h,2D6}$ in each genotype is useful for estimating AUC variability of the CYP2D6 substrates in the regional population.

Keywords: inter-individual variability; CYP2D6; Monte Carlo simulation; physiologically based pharmacokinetics; pharmacogenetics; dextromethorphan; drug discovery

Introduction

During the process of drug development, inter-individual variability is a key factor demanding close attention. For example, variability of exposure is sometimes associated with the variability of pharmacological effects, especially with respect to drug efficacy and safety. SimCYP software, which is commercially available, can predict inter-individual variability using a physiologically based pharmacokinetic (PBPK) model that employs a bottom-up approach. Variability is estimated from *in vitro* information, including expression in the recombinant cytochrome P450 (CYP) system, evaluation of metabolizing enzyme activity in each genotype, and demographic parameters such as body weight and frequency of genotypes in target populations, with some scaling factors.[1,2] Recently, Kato *et al.* proposed a different method to estimate the inter-individual variability of hepatic intrinsic clearance ($CL_{int,h}$).[3] They collected various coefficients of variation (CV) of CYP3A4 content in human liver microsomes (33–99%) from the literature and extracted 33% $CL_{int,h}$ variability of CYP3A4 using a dispersion model based on the *in vivo* variability of the area under the plasma concentration curve (AUC) of CYP3A4 substrates. For CYP2D6, Ito *et al.* reported a CV of 60% for $CL_{int,h}$ of extensive metabolizers (EM) and intermediate metabolizers (IM), using the metabolic ratio (MR) of CYP2D6 probe drugs.[4]

CYP2D6 genotypes have approximately 80 polymorphisms [http://www.cypalleles.ki.se/cyp2d6.htm], and the number of reported genotypes continues to increase, accounting for a wide range of enzyme activities from deficient to ultrarapid metabolism. Among the reported polymorphisms, some alleles cause increased activity by gene multiplication (*CYP2D6*1*×*N*, *CYP2D6*2*×*N*), while others lose their enzyme activity as a result of chromosomal deletion

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(*CYP2D6*5*), splice site mutation (*CYP2D6*4*), or insertion of a stop codon with deletion of a single base pair (*CYP2D6*3* and *CYP2D6*6*). Some polymorphisms lead to decreased enzyme activity (*CYP2D6*10*, *CYP2D6*17*).[5] Thus, *CYP2D6* genotypes are associated with the inter-individual variability of CYP2D6 activity *in vivo*.[6] This may explain the larger variability in $CL_{int,h}$ of CYP2D6 ($CL_{int,h,2D6}$) compared with CYP3A4.

The frequency of the *CYP2D6* allele is influenced by regional population differences and is also responsible for ethnic differences in enzyme activity. The frequency of poor metabolizers (PM) in Caucasian populations is approximately 10%, but among Asian populations it is 0–1.6%.[7] The frequency of the reduced-type allele *CYP2D6*10* is approximately 40% in East Asia, but only 3% in Europe. Consequently, the finding of Caucasian EM having 60% variability by Ito *et al.*[4] may not apply to other ethnicities or regions.

Dextromethorphan (DM) has been appraised as one of the best probe drugs specifically for CYP2D6, from points of *in vivo*/*in vitro* correlation, contribution of CYP2D6 to metabolism, and registration of CYP2D6 as a therapeutic drug.[8] Myrand *et al.* used DM as a probe drug to investigate ethnic differences in pharmacokinetics and pharmacogenetics among Caucasian, Chinese, Korean, and first- and third-generation Japanese populations, with more than 100 volunteers in each population. They concluded that there were no ethnic differences in MR in each genotype of *CYP2D6*.[9]

Extensive evidence on the relationship between MR and *CYP2D6* phenotypes and genotypes has been accumulated using DM. However, there are no reports for estimation of the variability of $CL_{int,h,2D6}$ using DM MR. In this study, we introduced a theory to transfer the MR of DM to $CL_{int,h,2D6}$ and estimate mean values with variability in each *CYP2D6* genotype, which can then be used to estimate the mean population exposure and variability.

Methods

Estimation scheme of mean and standard deviation (SD) of $CL_{int,h,2D6}$ with DM: The mean and SD of $CL_{int,h,2D6}$ with DM in different genotypes were estimated from the mean and SD of MR. The estimation method is described in **Figure 1**. Numerous MR values (mean ± SD) were generated from $CL_{int,h,2D6}$ (mean ± SD) by Monte Carlo simulation and numerous combinations of MR (mean ± SD) and $CL_{int,h,2D6}$ (mean ± SD) were made. Data regarding DM MR (mean ± SD) were extracted from the literature with genotype information, and the $CL_{int,h,2D6}$ (mean ± SD) values corresponding to MR were found from the combinations as mentioned above.

Theory of estimation of $CL_{int,h,2D6}$ from DM MR: MR is expressed as follows:

$$\mathrm{MR} = \frac{\text{amount of unchanged drug collected in urine}}{\text{amount of metabolite(s) collected in urine}} \quad (1)$$

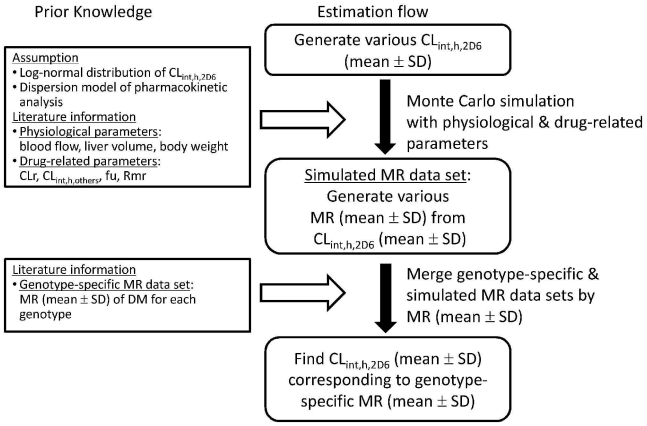

Fig. 1. A scheme for estimation of CYP2D6 intrinsic clearance ($CL_{int,h,2D6}$) of dextromethorphan in each *CYP2D6* genotype using metabolic ratio (MR)

where amount of metabolite(s) includes further metabolites from the target metabolite. Under the condition of linear pharmacokinetics, MR is expressed as follows:

$$\mathrm{MR} = \frac{D \cdot F_a \cdot F_g \cdot F_h \cdot \dfrac{CL_r}{CL_{tot}}}{f_{m2D6} \cdot D \cdot F_a(1 - F_g \cdot F_h) \cdot R_{m,r}} \quad (2)$$

where D represents amount of dose and F_a, F_g, and F_h are the fraction absorbed, intestinal and hepatic availability, respectively. CL_{tot} and CL_r are total clearance and renal clearance, respectively. CL_{tot} is the summation of hepatic clearance (CL_h) and CL_r. f_{m2D6} and $R_{m,r}$ are the contribution of CYP2D6 to the metabolism, expressed as Eqs. (3) and (4), respectively.

$$f_{m2D6} = \frac{CL_{int,h,2D6}}{CL_{int,h,2D6} + CL_{int,h,others}} \quad (3)$$

$$R_{m,r} = \frac{CL_{m,r}}{CL_{m,tot}} \quad (4)$$

where m represents the metabolite of interest and r and tot represent renal and total clearance, respectively. $CL_{int,h,2D6}$ and $CL_{int,h,others}$ represent intrinsic clearance by a metabolic reaction mediated predominantly by CYP2D6 and that mediated by metabolism other than CYP2D6, respectively.

Then, MR is expressed as follows:[4]

$$\mathrm{MR} = \frac{\left(1 - \dfrac{CL_h}{Q_h}\right) \cdot CL_r}{f_{m2D6}\left(CL_{tot} - \left(1 - \dfrac{CL_h}{Q_h}\right) \cdot CL_r\right) \cdot R_{m,r}} \quad (5)$$

where Q_h represents hepatic blood flow rate.

CL_h was determined by Eq. (6) using a dispersion model as the mathematical model for the liver: