Drug Metab. Pharmacokinet. 29 (5): 379–386 (2014).

Regular Article

Prediction of Inter-individual Variability in the Pharmacokinetics of CYP2C19 Substrates in Humans

Koji CHIBA[1,2,3,*], Keiko SHIMIZU[4], Motohiro KATO[5], Takaaki NISHIBAYASHI[2], Kazuki TERADA[1], Nobuo IZUMO[1] and Yuichi SUGIYAMA[3]

[1]*Laboratory of Clinical Pharmacology, Yokohama College of Pharmacy, Yokohama, Japan*
[2]*Department of Drug Development Science & Clinical Evaluation, Faculty of Pharmacy, Keio University, Tokyo, Japan*
[3]*Sugiyama Laboratory, RIKEN Innovation Center, Research Cluster for Innovation, RIKEN, Yokohama, Japan*
[4]*Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan*
[5]*Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan*

Full text and Supplementary materials of this paper are available at http://www.jstage.jst.go.jp/browse/dmpk

Summary: Significant inter-individual variability of exposure for CYP2C19 substrates may be only partly due to genetic polymorphism. Therefore, the *in vivo* inter-individual variability in hepatic intrinsic clearance ($CL_{int,h}$) of CYP2C19 substrates was estimated from reported AUC values using Monte Carlo simulations. The coefficient of variation (CV) for $CL_{int,h}$ in poor metabolizers (PM) expected from genotypes *CYP2C19*2/*2*, *CYP2C19*3/*3* or *CYP2C19*2/*3* was estimated as 25.8% from the CV for AUC of omeprazole in PMs. With this, CVs of $CL_{int,h}$ in extensive metabolizers (EM: *CYP2C19*1/*1*), intermediate metabolizers (IM: *CYP2C19*1/*2* or **3*) and ultra-rapid metabolizers (UM), *CYP2C19*17/*17* and **1/*17*, were estimated as 66.0%, 55.8%, 6.8% and 48.0%, respectively. To validate these CVs, variability in the AUC of CYP2C19 substrates lansoprazole and rabeprazole, partially metabolized by CYP3A4 in EMs and IMs, were simulated using the CV in $CL_{int,h}$ for CYP2C19 EMs and IMs and 33% of the CV previously reported for CYP3A4. Published values were within 2.5–97.5 percentile range of simulated CVs for the AUC. Furthermore, simulated CVs for the AUC of omeprazole and lansoprazole in ungenotyped populations were comparable with published values. Thus, estimated $CL_{int,h}$ variability can predict variability in the AUC of drugs metabolized not only by CYP2C19 but also by multiple enzymes.

Keywords: CYP2C19; inter-individual variability; human pharmacokinetics; Monte Carlo simulation; pharmacogenetics; drug development

Introduction

The cytochrome P450 2C19 (CYP2C19) is important for the metabolism of several therapeutic agents, such as proton pump inhibitors (PPIs), anticonvulsants and antidepressant drugs.[1] It is well known that genetic polymorphism exists for this enzyme and affects its activity. In addition to the wild-type *CYP2C19*1* allele, 33 variant CYP2C19 alleles with mutations have been identified (*CYP2C19*2* to **34*) (http://www.cypalleles.ki.se/cyp2c19.htm). Of these mutated alleles, *CYP2C19*2* and *CYP2C19*3* are the most common variants to contain a splice-defective mutation and premature stop codon, respectively, which lead to the creation of truncated nonfunctional proteins.[2] By contrast, the *CYP2C19*17* allelic variant with an 806C > T mutation is associated with an increased, ultra-rapid enzyme activity for CYP2C19.[2] The frequency of the alleles varies across ethnic populations. The *CYP2C19*2* and *CYP2C19*3* alleles are found in 28.6% and 8.8% of individuals in Eastern Asia but only 12.8–16.1% and ~0.1% in Europe, respectively.[2] The frequency of *CYP2C19*17* alleles is 19.0–27.2% in Europe but 1.1% in Eastern Asia.[2] Due to this ethnic difference in the frequency of the alleles, the exposure of CYP2C19 substrates varies among ethnic groups and shows a large inter-individual variability.[3]

The inter-individual variability is an important factor in determining the dosing regimen, because the variability of exposure may be associated with differences in pharmacological effects. Therefore, individual therapy based on testing for the CYP2C19 genotype is recommended in gastroesophageal reflux disease[4] and in *Helico-*

Received December 16, 2013; Accepted March 25, 2014
J-STAGE Advance Published Date: April 15, 2014, doi:10.2133/dmpk.DMPK-13-RG-137
**To whom correspondence should be addressed:* Koji CHIBA, Ph.D., *Laboratory of Clinical Pharmacology, Yokohama College of Pharmacy, 601 Matano-cho, Totsuka-ku, Yokohama 245-0066, Japan. Tel. +81-45-859-1300, Fax. +81-45-859-1301, E-mail: k.chiba@hamayaku.ac.jp*
Software supported in part by KAKENHI (grant no. 24590210) was used in the present analysis.

bacter pylori infection[5] to reduce the variability of exposure of PPIs and for antiplatelet therapy to adjust for clopidogrel exposure.[6]

Recently, we used the metabolic ratio of dextromethorphan to demonstrate that different genotypes showed variability in their intrinsic hepatic clearance ($CL_{int,h}$) of CYP2D6, such that the homozygotes *CYP2D6*1*, *CYP2D6*2* and *CYP2D6*10* demonstrated coefficient of variation (CV) values of 43%, 63% and 66%, respectively. Moreover, the variability of exposure of CYP2D6 substrates was successfully predicted using the estimated CV values for $CL_{int,h}$ and the frequency of the genotypes.[7]

Abundant data for exposure of CYP2C19 substrates for each of the CYP2C19 genotypes have been accumulated, especially for PPIs. The exposure and its variability for a substrate can be converted to those of $CL_{int,h}$ for the substrate based on a mathematical model such as a dispersion model. It is then possible to simulate the variability of exposure with the variability of $CL_{int,h}$ and other physiological parameters, such as blood flow rate, protein content bound to the drug, liver volume and body weight, using Monte Carlo simulations. Conversely, the appropriate $CL_{int,h}$ (mean and CV) can be estimated to determine the mean and CV for the area under the plasma concentration-time curves (AUCs). In our previous paper, a method to estimate the $CL_{int,h}$ and its variability for CYP3A4 substrates was proposed.[8] Various CV values for the CYP3A4 content in human liver microsomes (33–99%) were collected from the published literature. Then, the variability in the $CL_{int,h}$ of CYP3A4 substrates was determined to be 33% using a dispersion model based on the variability in the AUCs for the CYP3A4 substrates *in vivo*; thus the theory could be applied to obtain the variability in $CL_{int,h}$ of CYP2C19 ($CL_{int,h,2C19}$) substrates separately from the variability of other parameters.

In this study, a similar process was applied to transfer the variability in the values for the AUC of CYP2C19 substrates to that for the $CL_{int,h,2C19}$ of CYP2C19 substrates and produce an estimated variability for each CYP2C19 genotype. These values were then used to estimate the mean population exposure and variability in various ethnic groups.

Methods

Data collection: The mean and variability values (standard deviation, SD; standard error, SE; confidence interval, CI) for the AUCs following oral administration of the CYP2C19 substrates lansoprazole, omeprazole, and rabeprazole to healthy volunteers were collected from published data (**Supplemental Table S1**). The published literature was searched *via* PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and the selected references were cited. The AUC values were used from studies that included population data with CYP2C19 genotypes or ethnicity, or from those studies that included the country where the clinical studies were conducted.

Estimation of the mean and CV for $CL_{int,h,2C19}$ and $CL_{int,h}$ of enzymes other than CYP2C19 for omeprazole: The mean and CV values for the AUC of omeprazole in human subjects with CYP2C19 genotypes that are active [denoted extensive metabolizers (EM: *CYP2C19*1/*1*)], are inactive [denoted poor metabolizers (PM: *CYP2C19*2/*2*, *CYP2C19*3/*3*, *CYP2C19*2/*3*)], have intermediate activity [denoted intermediate metabolizers (IM: *CYP2C19*1/*2* and *CYP2C19*1/*3*)], and have *CYP2C19*17* allele which indicates ultra-rapid activity (*CYP2C19*17/*17*, *CYP2C19*1/*17*, *CYP2C19*2/*17* and **3/*17*) were collected separately. If there were multiple sources for AUCs in each group, their respective values were pooled (see Statistical methods). Since the mean and CV values for the omeprazole AUC among *CYP2C19*2/*2*, *CYP2C19*3/*3* and *CYP2C19*2/*3* in the PM group, were theoretically indistinguishable, those were pooled. Similarly those in the IM group, *CYP2C19*1/*2* and *CYP2C19*1/*3*, were also pooled. The AUCs for omeprazole with *CYP2C19*17/*17* and *CYP2C19*1/*17* [ultra-rapid metabolizer (UM) group] were designated separately, but those for *CYP2C19*2/*17* and **3/*17* in that same group were pooled.

The CV values for the AUC of omeprazole were also estimated using Monte Carlo simulations from the mean and CV of the $CL_{int,h}$ (**Fig. 1**). First, numerous values of intrinsic clearance mediated by metabolism other than CYP2C19 ($CL_{int,h,other}$) were generated using Monte Carlo simulations with one log-normal distribution of mean (μ) and variance (σ^2). From each $CL_{int,h,other}$, the AUC was calculated (see Simulation of AUC). Then, numerous combinations of AUC, expressed as an arithmetic mean and CV, and of $CL_{int,h,other}$ with a log-normal distribution [(μ, σ^2) or (mean, CV), see Statistical methods] were made. These AUC values were assumed equivalent to those for the PM group. To find the simulated AUC (mean, CV) with the combinations (simulated AUC – $CL_{int,h,other}$) corresponding to published AUC values, the mean and CV values of the $CL_{int,h,other}$ were changed manually to obtain the same values for the mean and CV as those obtained for the pooled literature AUC values. Similarly, numerous values of $CL_{int,h,2C19}$ (mean, CV) for the EM group ($CL_{int,h,2C19EM}$) and $CL_{int,h,other}$ obtained from the PM group were generated and each $CL_{int,h,2C19EM}$ and $CL_{int,h,other}$ were summed randomly. The AUC for the sum of $CL_{int,h,2C19EM}$ and $CL_{int,h,other}$ were calculated, and this corresponded to the AUC of the EM group (combination of simulated AUC – $CL_{int,h,2C19EM}$). The $CL_{int,h,2C19EM}$ (mean, CV) values corresponding to the published values for the AUC of the EM group were found from the combinations. For the UM and IM groups, the $CL_{int,h,2C19}$ (mean, CV) was estimated from the pooled literature values of the AUCs for these respective groups.

To confirm whether the CV values of $CL_{int,h,2C19EM}$ and $CL_{int,h,2C19IM}$ could be used to predict the variability in the AUCs for other CYP2C19 substrates, those $CL_{int,h,2C19}$ CV values were applied to Monte Carlo simulations for CV values for the AUC of lansoprazole and rabeprazole. The mean values for $CL_{int,h,2C19EM}$ and $CL_{int,h,2C19IM}$ were estimated according to a dispersion model, if necessary, following transfer of the AUC values to the geometric mean.

Simulation of AUC: The fraction of drug excreted unchanged in urine for omeprazole, lansoprazole and rabeprazole was reported as $< 1\%$[9–11] and could be disregarded for the calculation of AUC divided by dose (AUC/D) in the following equation:

$$\mathrm{AUC/D} = \frac{F_a \cdot F_g (1 - CL_h/Qh)}{CL_h} \tag{1}$$

where F_a and F_g are assumed to be 1.0. CL_h was determined with Eq. (2) using a dispersion model as the mathematical model for the liver:

$$CL_h = Qh\left[1 - \frac{4a}{(1+a)^2 \cdot \exp\{(a-1)/2/D_N\} - (1-a)^2 \cdot \exp\{-(a+1)/2/D_N\}}\right]$$
$$a = (1 + 4R_N \cdot D_N)^{1/2},\ R_N = f_B \cdot \frac{CL_{int,h}}{Qh} \tag{2}$$

where f_B and D_N are the unbound fraction in the blood and the dispersion number, respectively, and Qh is the liver blood flow. D_N