Interplay of Pharmacogenetic Variations in ABCB1 Transporters and Cytochrome P450 Enzymes

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Interindividual variability in oral drug efficacy and toxicity is commonly observed in all therapeutic areas. Importantly, interindividual variability in drug uptake and metabolism can result in poor drug response, adverse drug reactions, or unfavorable drug-drug interaction. One of the common causes of individual variations in drug response is genetic variation of drug transporters and metabolizing enzymes. Pharmacogenetics are rapidly elucidating the inherited nature of these differences in drug disposition and effects, thereby providing a stronger scientific basis for optimizing drug therapy on the basis of each patient’s genetic constitution. Knowledge of the genotype-phenotype correlation and frequency distribution of functional single nucleotide polymorphisms may be a valuable tool for individualizing drug therapy. This information can also be useful for explaining inter-individual and inter-ethnic variations in drug response and/or adverse effects. In this review, we focus on the interplay between efflux transporter (ATP-binding cassette, sub-family B (MDR/TAP), member 1/ABCB1) and cytochrome P450s according to genetic polymorphism.

Key words: ABCB1 transporter, Cytochrome P450 enzyme, Genetic polymorphism, Interplay, Pharmacokinetics

INTRODUCTION

Most drug responses are determined by the interplay of several gene products that influence pharmacokinetics and pharmacodynamics, i.e., drug metabolizing enzymes, drug transporters and drug targets (Sakaeda et al., 2004). The field of pharmacogenetics began with a focus on drug metabolizing enzymes (Weinshilboum, 2003; Meyer, 2004), but has been extended to membrane transporters that influence drug absorption, distribution and excretion (Kim, 2002b; Evans and McLeod, 2003; Kerb, 2006). One important factor that can alter the function of drug transporters and metabolizing enzymes is the genetic polymorphism of drug transporters and metabolizing enzymes whose clinical significance has been gradually disclosed by many clinical and in vitro studies (Maeda and Sugiyama, 2008). As the importance of drug transporters in the clinical pharmacokinetics of drugs has recently been recognized, genetic polymorphisms of drug transporters have emerged as one of the determinant factors that produce the inter-individual variability in pharmacokinetics (Maeda and Sugiyama, 2008).

Drug transporters are located in several absorptive and excretory tissues, including the intestinal epithelia, the liver, and the tubular epithelial cells of kidneys (Lee, 2000; Ayrton and Morgan, 2001; Gerloff, 2004), and have an important role in regulating the absorption, distribution and excretion of many drugs. In many organs, several kinds of drug transporters are expressed on both sides of the plasma membrane, and coordination of the function of uptake and efflux transporters determines the efficient transcellular transport of drugs (Maeda and Sugiyama, 2008). Drug transporters mediate the transfer of most hydrophilic drugs and many hydrophobic drugs across plasma membranes, and they bind their substrates at one side of the plasma membrane, undergo a conformational change,
and release them on the other side.

Cytochrome P450s (CYPs) are the major Phase I biotransformation enzymes and are responsible for maintaining homeostasis in metabolizing both endogenous substances and exogenous xenobiotics (Ramamoorthy et al., 2001). Furthermore, CYP enzymes are the major catalysts involved in drug metabolism. These enzymes are most predominant in the liver but can also be found in the intestine, lung and other organs. A range of CYP enzymes have been identified in human intestine: CYP3A4, CYP3A5, CYP1A1, CYP2C9, CYP2C19 and CYP2D6. The expression of metabolic enzymes varies within the small intestinal villus, with the highest levels found in mature enterocytes lining the villus tips (Galetin and Houston, 2006).

In drug therapies, one reason for individual differences in drug effect, such as reduced therapeutic effect or unwanted side effects, is the variation of bioavailability. Drugs administered by oral route are dissolved in small intestine, pass through enterocytes, and finally reach the liver. In these processes, the rate and extent of drug absorbed into the systemic circulation cause the variations in bioavailability. The biopharmaceutics classification system (BCS) (Amidon et al., 1995) is a guide for pharmaceutical tests and evaluations by the U.S. Food and Drug Administration (Chen et al., 2001) because the solubility and intestinal permeability are regarded as the most important factors in the variation of bioavailability. However, the BCS is classified by drug solubility and intestinal permeability only, and it does not consider the function and influence of drug metabolizing enzymes and efflux transporters in the intestinal cell. To complement these limitations, Benet et al. suggested the biopharmaceutics drug disposition classification system (BDDCS), which reflects the function and influence of drug metabolizing enzymes and transporters in the intestinal cell (Wu and Benet, 2005). Confirmation of the function and influence of drug transporters and metabolizing enzymes during drug absorption from intestine to systemic circulation is very important. Previous studies have mostly focused on the pharmacokinetics of the target drug with respect to individual transporters or metabolizing enzymes, that is, whether the drug is a substrate for a particular transporter or metabolizing enzyme, or the relationship between pharmacokinetics and individual genetic types of transporter and metabolic enzyme. However, because drug transporter and metabolizing enzyme do not work separately but together in pharmacokinetics with respect genetic polymorphisms, previous studies could not entirely predict the pharmacokinetics of drugs.

In this article we review recent clinical studies to evaluate the influence of genetic polymorphisms in CYP enzymes and/or ABCB1 (ATP-binding cassette, sub-family B (MDR/TAP), member 1) transporter on the pharmacokinetics of drugs and address the interplay of drug metabolizing enzymes and transporters according to genetic polymorphisms.

**ABCB1 TRANSPORTERS**

Drug transporters have been classified into two main categories: (1) ATP-binding cassette (ABC) family transporters, which actively pump out substrates from the intracellular compartment by directly utilizing the energy of ATP hydrolysis, and (2) solute carrier (SLC) family transporters, which can generally transport substrates bidirectionally by utilizing the electrochemical potential gradient that is generated primarily by active transporters (Maeda and Sugiyama, 2008). In the ABC transporter superfamily, drug transport has primarily been associated with P-glycoprotein (P-gp, ABCB1), breast cancer resistance protein (BCRP/ABCG2), and several members of the multidrug resistance associated protein (MRP/ABCC) family. These transporters act to limit the access of drugs to protected tissue compartments and to eliminate drugs and metabolites via bile and urine (Schinkel et al., 1996; Leslie et al., 2005; Hesselson et al., 2009).

P-gp is a member of the adenosine triphosphate-binding cassette superfamily of transporters (Higgins, 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992). The ABCB1 transporter affects the efflux of a wide variety of drugs, such as immune-suppressants (Kuypers et al., 2008), antiviral agents (Lee et al., 1998), antipsychotics and antidepressants (Shinkai et al., 1992).