Individual Variability in Drug Therapy and Drug Safety

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ABSTRACT:

One of the most challenging research areas in pharmacology in the new millennium is to understand why individuals respond differently to drug therapy and to what extent that individual variability in disposition is responsible for the observed differences in therapeutic efficacy and adverse reactions. To answer these complex questions, drug-metabolism research will rely on multidisciplinary approaches more than ever to investigate the many components involved in drug metabolism and disposition. Major research challenges include the following: (1) the genetic variation of drug targets (receptors, enzymes, etc.), drug transporters (multispecific organic anion transporter, P-glycoprotein, alpha-1-acid glycoprotein, etc.), and drug-metabolizing enzymes (cytochrome P450s and other enzymes); (2) the structure and function of all genetic variants of drug receptors, transporters, and metabolizing enzymes; (3) the induction, repression, and inhibition of all components involved in drug disposition; (4) the development of noninvasive in vivo methods to determine the physiological significance of various components in the handling of specific therapeutic agents in humans; (5) the mechanism of idiosyncratic adverse drug reactions; and (6) the pharmacokinetic and pharmacodynamic relationships to explain the individual differences in therapeutic efficacy and drug safety. Thus successful drug-metabolism research in the new millennium must integrate receptor biology, enzymology, recombinant DNA technology, biochemical toxicology, and drug disposition into study design and conduct balanced in vitro and in vivo experiments to allow a full understanding of the mechanisms of individual variability in drug therapy and drug safety.

The ultimate goal in drug-metabolism research is to understand the fate of therapeutic agents in humans, the interaction between drugs and the biological system, and the optimum utilization of such knowledge in the treatment of human diseases. Although impressive progress has been made in many areas of research in clinical pharmacology and drug metabolism, drug therapy, for the most part, is still far from being optimum. The standard dosage regimen of a drug may prove to be therapeutically effective for most patients, but often it is ineffective for some individuals and even toxic for others, particularly for those drugs that have a narrow therapeutic index. Thus one of the challenges in drug-metabolism research in the new millennium is to understand why individuals respond differently to drug therapy and to what extent that individual variability in disposition is responsible for the observed differences in therapeutic efficacy and adverse reactions. Understanding such variations at the molecular level would be very valuable because it would allow drug makers and physicians to tailor a therapy to meet the specific needs of individuals.

1 Abbreviations used are: HMG CoA, β-hydroxy-β-methylglutaryl-CoA; LDL, low-density lipoprotein; HVDRR, 1,25-dihydroxyvitamin D–resistant rickets; 5-HT, 5-hydroxytryptamine; AAG, α1-acid glycoprotein; NAT, N-acetyltransferase; AGT, O6-alkylguanine-DNA alkyltransferase.

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gradually directing their research activities toward the goal of achieving individualized medicine (Cohen, 1997; Persidis, 1998). Pharmacogenomics, which relates genomic function to molecular pharmacology, promises to redefine basic notions in drug discovery and disease management. Some companies are devoting their efforts to establishing the involvement of a specific gene or a group of genes in certain diseases, while others are genotyping patients in clinical trials. With a better understanding of gene variations and the effect of such variations on pharmacodynamics and pharmacokinetics, it is hoped that maximum drug response can be achieved in drug therapy by compensating for individual variability.

**Origins of Individual Variability in Drug Therapy**

The first step in minimizing drug-response variability among individuals is to define the origin of individual variability. Table 1 shows that multiple factors, including both genetic and environmental factors, contribute to the individual variability in drug therapy. Although future research may identify additional factors, the list includes most of the important targets involved in drug-protein interaction and drug handling in humans that are currently known.

Genetic factors represent an important source of individual variations in drug response. Genetic variations refer not only to gene alterations, which lead to protein modifications, but also to gene regulations, which result in the expression of different amounts of proteins. For example, at the level of enzyme function, structurally altered proteins can either exhibit an increased or decreased Michaelis constant or maximum velocity value, or both. In some cases, mutant enzymes are totally nonfunctional. At the enzyme protein level, genetic alterations can cause either the increase, decrease, or absence of proteins, depending on the nature of gene alteration. All of these changes can have profound effects on the capability of receptors and enzymes to interact with drugs.

While genetic factors generally cause permanent changes in an individual’s response to drug therapy, environmental factors are more transient in nature. Some dietary constituents, environmental chemicals, and multiple drug therapies are known to induce or inhibit human drug-metabolizing enzymes, particularly cytochrome P450, resulting in drug levels that are either too low or too high for proper drug response. However, drug response returns to normal once these factors are removed from the environment. Physiological factors such as age and disease are also known to cause pharmacokinetic variability (Breimer, 1983).

**Genetic Variations of Drug Targets**

Receptors (such as the serotonin receptors, \( \beta_2 \)-adrenergic receptor, leukotriene \( \Delta_4 \) receptor, etc.) and enzymes (such as testosterone 5α-reductase, HMG CoA reductase, aromatase, etc.) that play key roles in pathogenesis of certain diseases are potential targets for drug intervention. Receptor agonists and antagonists are designed based on the understanding of how receptors interact with their natural ligands. Enzyme inhibitors are developed based on how enzymes and their physiological substrates interact at the active sites. Any structural changes affecting the physiological functions of the receptors or enzymes because of gene alterations could potentially impact the interaction between drugs and the intended targets and, thus, the drug response.

In contrast to the wealth of information available on the genetic polymorphism of enzymes involved in drug metabolism, the importance of genetic factors in determining pharmacodynamics has yet to be properly defined. However, important progress has already been made in recent years regarding the structure and function of receptors, the role of gene mutation in human diseases, the identification and characterization of naturally occurring mutants and their impact on ligand binding, and the activation and deactivation of receptors (Shenker, 1995). Liggett (1997) reported the identification of several polymorphisms within the coding block of the \( \beta_2 \)-adrenergic receptor gene in the human population. The substitution of three key amino acids can significantly alter receptor function. For example, mutant R16G exhibits enhanced agonist-promoted downregulation, mutant Q27E is resistant to downregulation, and mutant T164I shows altered coupling to adenyl cyclase. Case-control and family studies support the notion that polymorphic forms of the \( \beta_2 \)-adrenergic receptor may play roles in promoting asthmatic phenotypes, establishing bronchial hyperactivity, and influencing the response to acute or chronic \( \beta \)-agonist therapy. Indeed, Green et al. (1993) reported that mutant T164I displays a lower binding affinity for epinephrine (1450 nM), compared with the wild-type receptor (368 nM). This naturally occurring variant of the human \( \beta_2 \)-adrenergic receptor also demonstrates decreased affinity with isoprotanol (295 vs. 68 nM) and norepinephrine (45000 vs. 10395 nM) but not with dobutamine or dopamine.

Mutations in the receptor genes can sometimes cause cellular hyporesponsiveness to the physiological ligands. For example, hereditary 1,25-dihydroxyvitamin D–resistant rickets (HVDRR) is an autosomal recessive disorder that has been shown to be caused by mutations in the vitamin D receptor (Feldman and Malloy, 1990). The disease is characterized by early onset rickets, hypocalcemia, secondary hyperparathyroidism, elevated 1,25(OH)\(_2\)D\(_3\) levels, and resistance to 1,25(OH)\(_2\)D\(_3\) treatment. Malloy et al. (1997) recently reported a single point mutation, H305Q, in the vitamin D receptor of a HVDRR patient. This mutant receptor has an eightfold-lower affinity for 1,25(OH)\(_2\)D\(_3\) than does the normal vitamin D receptor, leading to cellular resistance and decreased responsiveness to hormone. When treated with very high doses of 1,25(OH)\(_2\)D\(_3\) that overcame the affinity defect, the HVDRR patient showed cellular responsiveness to the hormone and improvement in his rickets.

Not all mutations in the receptor genes cause cellular resistance to
the natural ligands. Koper et al. (1997) identified five novel polymorphisms in the gene for the human glucocorticoid receptor but found no association between polymorphisms and those individuals with a reduced sensitivity to glucocorticoids. In addition, mutations in receptor genes can sometimes be beneficial to drug treatment. Sodhi et al. (1995) investigated the possibility of allelic association of 5-HT2c receptor genotype (a substitution of Cys 23 by Ser 23) with schizophrenia or with response to clozapine, an antipsychotic agent. Of the 21 patients with at least one 5-HT2c Ser allele, 90% of the patients demonstrated good clozapine response, while in patients with both Cys alleles, the response was 60%. These results indicate that slight modification of the 5-HT2c receptor enhances the antipsychotic action of clozapine.

Genetic Variations of Drug Transporters

In order to reach the intended targets, an orally administered drug must be absorbed from the intestine and distributed to its targets before it is metabolized and excreted from the body. Physiological factors, such as gastric emptying time, small-intestine motility, and renal and hepatic function, and dietary factors, such as fat content, play important roles in drug absorption, distribution, and excretion. These factors can vary considerably among individuals and could contribute significantly to the pharmacokinetic variability (Lin and Lu, 1997). In addition, a number of proteins are known to be involved in the absorption, distribution, and excretion of drugs. Genetic variations of these drug transporters could also contribute significantly to the pharmacokinetic variations among individuals. Since the total numbers of drug transporters are still unknown and the function of some of these transporters has not been fully defined, information regarding genetic variations of these transporters is still lacking but hopefully will become available soon.

The multidrug-resistant transporter, a group of P-glycoproteins, is an ATP-dependent efflux membrane transporter with broad substrate specificity for a large number of structurally diverse drugs (Endicott and Ling, 1989; Gottesman and Pastan, 1993). In humans, this P-glycoprotein is known as MDR1 and is expressed at high levels in barrier tissues such as the intestinal epithelium, brain capillary endothelium, and placenta. In contrast to humans, mice have two genes encoding P-glycoprotein: mdr1a and mdr1b (Devault and Gros, 1990). MDR1 plays an important role in limiting oral absorption and target-organ accumulation of a number of pharmaceutical agents. Kim et al. (1998) recently examined the transport characteristics of indinavir, nelfinavir, and saquinavir, three human immunodeficiency virus protease inhibitors in the gut, using human Caco-2 cells and in vivo after iv and oral administration of these agents to mdr1a knockout mice. They found that all three protease inhibitors were MDR1 substrates and that the in vitro transport of these compounds was diminished by the addition of the P-glycoprotein inhibitors quinidine and PSC 833. After oral administration of these inhibitors, their plasma concentrations in mdr1a (−/−) mice increased two- to five-fold, suggesting that the presence of P-glycoprotein in the epithelial cells of the gastrointestinal tract limits the oral bioavailability of these compounds. The concentrations of HIV protease inhibitors in the brains of mdr1a (−/−) mice increased 7- to 36-fold after iv administration, indicating that P-glycoprotein limits the penetration of these agents in the brain. Schinkel and coworkers (1995) have shown that absence of the mouse mdr1a P-glycoprotein in mdr1a (−/−) knock-out mice has a profound effect on the tissue distribution, pharmacokinetics, and toxicity of a number of important pharmaceutical agents, including vinblastine, ivermectin, dexamethasone, digoxin, and cyclosporine. Koren et al. (1998) attributed the toxic interaction of digoxin and many other drugs to P-glycoprotein in the renal tubular cells.

Considering the important role of MDR1 in limiting oral absorption and target-organ accumulation of many therapeutic agents, one may expect that variable expression of P-glycoprotein in barrier tissues among individuals may, in part, explain the individual oral bioavailability variations and the resistance of some patients to certain therapeutic agents. To examine the role of intestinal MDR1 to interpatient variability in the oral bioavailability of cyclosporine, Lown et al. (1997) studied the oral pharmacokinetics of cyclosporin in 25 kidney-transplant recipients. They found that intestinal P-glycoprotein expression varied by eightfold, liver CYP3A4 activity varied by threefold, and enterocyte CYP3A4 concentration varied tenfold. On the basis of statistical analysis, the authors concluded that intestinal MDR1 plays a significant role in the first-pass elimination of cyclosporine, presumably by being a rate-limiting step in absorption. Surprisingly, intestinal levels of CYP3A4 did not appear to influence any of the cyclosporine pharmacokinetic parameters.

Structural alterations due to MDR1 genetic polymorphism should, in principle, also contribute significantly to the individual variability in oral bioavailability and drug response to therapeutic agents. Although such information is still very limited in humans, Lankas et al. (1997) recently reported that a subpopulation of CF-1 mice is deficient in mdr1a in the intestinal epithelium and brain capillary endothelium. The exact defect that leads to the loss of functional protein is not known, but a restriction fragment–length polymorphism (RFLP) assay can be used to determine the genotypes of individual mice (Umbenhauer et al., 1997). The +/+ or −/− genotypes each comprise approximately 25% of the population, while 50% are +/−. Animals deficient in mdr1a in their brains and intestines (−/−) are sensitive to the neurotoxicity induced by the avermectins, a class of natural products widely used in veterinary and human medicine as antiparasitic agents. Insensitive CF-1 mice (+/+) show abundant levels of P-glycoprotein in the brain and intestine and tolerate doses of abamectin at least 50-fold greater than the minimum toxic dose in the sensitive group, whereas the +/− animals have less P-glycoprotein and increased central nervous system sensitivity, compared with the +/+ animals. Consistent with the role of P-glycoprotein as a barrier to tissue entry, the plasma and brain levels of abamectin in the sensitive mice are markedly higher than in the insensitive mice. These studies provide powerful evidence that P-glycoprotein can contribute to individual variability in drug response by varying drug levels in plasma and tissues in a heterogeneous population.

In addition to MDR1, a number of other proteins are involved in the transport of drugs and endogenous substances across the hepatocyte canalicular membrane (Keppeler and Arias, 1997; Keppeler et al., 1997; Suchy et al., 1997). For example, human MDR2 P-glycoprotein (also known as MDR3) is responsible for the translocation of phospholipids across the canalicular membrane. Human canalicular multidrug-resistant protein, known as cMrp, cMOAT, or MRP2, can transport glutathione, glucuronide, and sulfate conjugates of certain drugs across the apical membrane, whereas the human bile salt export pump is responsible for the transport of canalicular bile acid. The total number of drug transporters is unknown at the present time, but the intensive research efforts by many investigators in this field will undoubtedly yield more information regarding the structure and function of each transporter. Recently, Sippel et al. (1997) expressed the rat liver canalicular bile acid transporter, a 110-kDa transmembrane phosphoglycoprotein, in COS cells and demonstrated time-, temperature-, and concentration-dependent efflux of taurocholate in this reconstituted system. Expression of various transporters in a heterologous cell or other system will permit the study of the substrate specificity and kinetics of each transporter. Although it is still early to describe the presence of genetic variants of transporters and the
contribution of genetic variations in drug transport among individuals, the Dubin-Johnson Syndrome has already been shown to represent an inherited defect in the secretion of amphophilic anionic conjugates from hepatocytes into bile. Keppler et al. (1997) have demonstrated that the MRP2 protein is only expressed in normal human liver but not in the liver of a patient with Dubin-Johnson syndrome. Genetically determined structure alterations of transporters will undoubtedly impact the disposition of therapeutic agents and contribute to individual variability in drug response and drug safety.

Plasma protein binding, an important determinant for drug disposition and action, varies widely among individuals because of qualitative or quantitative differences in binding proteins, primarily serum albumin and α1-acid glycoprotein (AAG). The pharmacokinetic and pharmacodynamic significance of individual differences in plasma protein binding varies, depending on the use of specific drugs. However, interindividual variability in drug binding is generally less as compared with other pharmacokinetic processes, such as absorption and metabolism.

The level of both serum albumin and AAG is subjected to modulation by various pathological conditions. Serum albumin levels are decreased in a disease state (such as renal failure and liver cirrhosis), whereas AAG levels are elevated in an inflammatory state (such as infection and rheumatic disorders). AAG is also known to be inducible by phenobarbital treatment. In addition, genetic variants of serum albumin and AAG can also contribute to individual variability in drug binding. Kragh-Hansen et al. (1990) reported pronounced reductions in high-affinity binding of warfarin, salicylate, and diazepam to human albumin variants Canterbury (Lys 313→Asn), and Parklands (Asp 365→His). Three main phenotypes are observed for AAG in the human population: F1S/A, F1/A, and S/A. Herve et al. (1993) found that each of the AAG variants has a specific role in drug binding. For example, imipramine can bind to the A variant with high affinity, whereas the F1S variant mixture has been shown to bind to warfarin and mifepristone with high affinity but to imipramine with low affinity. Whereas the F1S variant mixture has been shown to bind to warfarin, salicylate, and diazepam, the F1/A variant mixture has been shown to bind to warfarin with high affinity, whereas the S/A variant mixture has been shown to bind to imipramine with moderate affinity.

Genetic Variations of Cytochrome P450

The genetic polymorphism of cytochrome P450 has been extensively studied in humans, particularly the CYP2D6-mediated debrisoquine hydroxylation (Eichelbaum and Gross, 1990; Tucker, 1994; Bertilsson, 1995; Meyer and Zanger, 1997) and CYP2C19-mediated S-mephenytoin hydroxylation (Goldstein and de Morais, 1994). Dahl et al. (1995) reported that after oral administration of debrisoquine, more than 10,000-fold variations in individual metabolic ratio (defined as the ratio of debrisoquine to 4-hydroxydebrisoquine in the urine) were noted in a Swedish population. As shown in Table 2, phenotyping studies in large populations have allowed the classification of individuals into poor metabolizers, extensive metabolizers, and ultrarapid metabolizers. The poor-metabolizer phenotype is caused by several mutant alleles of the CYP2D6 gene, resulting in the absence of the enzyme or the presence of altered enzyme with little or no enzyme activity. About half of the ultrarapid metabolizers are caused by duplication or amplification of an active CYP2D6 gene (Johansson et al., 1993). Because of the large variations in metabolic ratio, the extensive metabolizer group should not be considered as a uniform population. Extensive metabolizers are often heterozygotes carrying fast or slow mutant alleles or homozygotes carrying alleles with mutations that either increase or decrease enzyme activity moderately.

CYP2D6 catalyzes the oxidation of many clinically used drugs, including antiarrhythmics, antidepressants, and neuroleptics. Individual variability to metabolize these drugs by CYP2D6 has significant therapeutic consequences, ranging from increased risk for adverse reactions at recommended dose for poor metabolizers to therapeutic failure at normal drug dose for ultrarapid metabolizers. Dalen et al. (1997) reported that a 33-year-old woman experienced severe abdominal pain after a normal dose of codeine. This side-effect is typical of that of morphine. Genotyping and phenotyping studies established the patient as an ultrarapid metabolizer with a high capacity to metabolize codeine to morphine by CYP2D6. The quick onset of the symptom and the severity of the pain is presumably caused by rapid formation of morphine in the liver, with high concentrations in the biliary tracts. These results clearly demonstrate the importance of interindividual metabolism variability in drug response and drug safety.

Genetic Variations of Other Drug-Metabolizing Enzymes

In addition to cytochrome P450, genetic variations of other drug-metabolizing enzymes, such as uridine diphosphate-glucuronosyltransferase, glutathione S-transferase, N-acetyltransferase (NAT), methyltransferase, and sulforotransferase, also contribute to individual variability in drug response and drug safety. For example, individuals known as “rapid acetylators” or “slow acetylators” have marked differences in their ability to acetylate isoniazid and other arylamines because of genetic polymorphism of NAT2 (Meyer and Zanger, 1997). The slow-acetylator phenotype is caused by several mutant alleles of the CYP2D6 gene, resulting in the absence of the enzyme or the presence of altered enzyme with little or no enzyme activity. About half of the ultrarapid metabolizers are caused by duplication or amplification of an active CYP2D6 gene (Johansson et al., 1993). Because of the large variations in metabolic ratio, the extensive metabolizer group should not be considered as a uniform population. Extensive metabolizers are often heterozygotes carrying fast or slow mutant alleles or homozygotes carrying alleles with mutations that either increase or decrease enzyme activity moderately.

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**TABLE 2**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Metabolic ratio*</th>
<th>Frequency</th>
<th>Genetic Basis</th>
<th>Possible Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor metabolizer</td>
<td>Greater than 12</td>
<td>5%–10% Caucasian, 1%–2% Oriental</td>
<td>Gene deletion, mutation, frameshift or other defects; no protein or very poor enzyme activity.</td>
<td>Lower drug clearance and higher plasma level; exaggerated pharmacodynamic outcome and increased risk of concentration-dependent side-effects.</td>
</tr>
<tr>
<td>Ultrapid metabolizer</td>
<td>Less than 0.1</td>
<td>From 2% in a Swedish population to 30% in an Ethiopian population</td>
<td>About 40% carrying multiple copies of the CYP2D6 gene; mechanism of other ultrapid metabolizers unknown.</td>
<td>Higher than normal doses required for efficacy; side-effects if metabolites are toxic.</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Between 0.1 and 12</td>
<td>Rest of the population</td>
<td>Large variations in metabolic ratio of this group; genetic basis for such a large variation unclear.</td>
<td>High or low end may need dose adjustment for acceptable efficacy and safety.</td>
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</tbody>
</table>

* Metabolic ratio refers to the ratio of debrisoquine to 4-hydroxydebrisoquine in urine after oral dosing of subjects.
Asian populations to greater than 50% among Caucasians. Thus different human populations are likely to have different drug responses if acetylation does play an important role in the biotransformation of the therapeutic agents.

**Genetic Variations of DNA-Repair Enzymes**

DNA-repair enzymes play a critical role in protecting cells against mutation and toxic response induced by many therapeutic agents. For example, O\(^6\)-alkylguanine-DNA alkyltransferase (AGT) specifically repairs O\(^6\)-alkylguanine in DNA, a major premutagenic lesion produced by many anticancer alkylating agents. There are significant individual variations in human AGT activity levels. In addition, two genetic variants have recently been found, each resulting from a single amino acid alteration (Jun-Yan Hong, Rutgers University, personal communication, 1998). These mutants have a reduced ability to repair drug-induced DNA damage. Furthermore, CHO cells expressing mutant AGT are less resistant to alkylating agent–induced toxicity than do cells expressing wild-type AGT. Thus genetic variations of AGT can contribute to individual variability in the safe use of alkylating anticancer drugs.

**Idiosyncratic Adverse Reactions**

Characterized by rare occurrence and requiring multiple exposure, idiosyncratic adverse drug reactions represent the most extreme case in individual variability in drug safety. Although the underlying mechanisms are still not clear, studies in recent years have suggested that drug-induced idiosyncratic adverse reactions relate to individual variability in metabolic, cytoxic, and immunological components (Lennard, 1993; Spielberg, 1996). In a series of investigations to study the metabolism of sulfonamides in order to search for pharmacogenetic variants predisposing individuals to toxicity, Spielberg (1996) described the following risk factors: slow acetylation, which allows the formation of reactive intermediate via oxidative metabolism; metabolism of sulfonamides to hydroxylamine metabolites by CYP2C9 and other peroxidases; an inherited abnormality in detoxification of the hydroxylamines; and further metabolism of hydroxylamines to reactive metabolites. Thus sulfonamide-induced idiosyncratic adverse reactions are determined by individual differences in multiple metabolic pathways and in immunological responses. Spielberg (1996) concluded that investigations of patients with these rare adverse reactions by using a variety of tools from \textit{in vitro} and conduct balanced in \textit{in vitro} and \textit{in vivo} experiments to allow a full understanding of the mechanisms of individual variability in drug therapy and drug safety.

**Acknowledgments.** I wish to express my sincere thanks to all of the chairmen and speakers who had contributed so much to the ASPET Colloquium “Drug Metabolism in the New Millennium.” Particularly, I would like to thank Gerald Miwa, Jud Coon, Paul Hollenberg, and Christine Carrico for the planning and organizing of the meeting and Jim Halpert for serving as the guest editor for this issue of \textit{Drug Metabolism and Disposition}. I would also like to thank Haiyang Cheng, Gloria Kwei, Jiunn Lin, Mary Vore, and Regina Wang for providing valuable information for my lecture and Ms. Florence Florek for the preparation of this manuscript. Finally, I would like to acknowledge the pharmaceutical companies who contributed funding to support this colloquium.

**The Future**

With the rapid progress in the understanding of genetic polymorphism and the development of genechip technology, it becomes quite feasible for individuals to be genotyped with respect to critical genes targeted for drug intervention and genes essential for drug transport and metabolism. In the future, each individual could carry a “smart card” with vital genetic information on important target enzymes, receptors, cytochrome P450s, and other drug-metabolizing enzymes and drug transporters. The objective is to identify key genetic variations that could impact drug response and drug safety.

Identification of genetic variations is only the first step in understanding individual variability in drug therapy. As shown in Table 3, it will be necessary to relate structural alterations of these genes to functional changes. One of the most challenging areas is the development of noninvasive \textit{in vivo} methods so that the pharmacokinetic, pharmacodynamic, and, most importantly, the clinical significance of genetic variants can be evaluated in humans. Thus successful drug metabolism and pharmacological research in the new millennium must integrate receptor biology, enzymology, recombinant technology, biochemical toxicology, and drug disposition into study design and conduct balanced in \textit{in vitro} and \textit{in vivo} experiments to allow a full understanding of the mechanisms of individual variability in drug therapy and drug safety.

**Table 3**

<table>
<thead>
<tr>
<th>Key steps in understanding individual variability in drug therapy</th>
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<tr>
<td>1. Define origins of variability.</td>
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<tr>
<td>2. Relate structural alterations to functional changes \textit{in vitro}.</td>
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<tr>
<td>3. Develop noninvasive \textit{in vivo} methods to determine the physiological significance of genetic variants of various components in the handling of specific therapeutic agents in humans.</td>
</tr>
<tr>
<td>4. Establish pharmacokinetic and pharmacodynamic relationship, if possible, to explain the individual differences in therapeutic efficacy and drug safety.</td>
</tr>
<tr>
<td>5. Improve drug therapy, based on the understanding of individual variability.</td>
</tr>
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</table>

**References**


Erratum

In the article entitled “Physiologically Based Pharmacokinetics Model of Primidone and Its Metabolites Phenobarbital and Phenylethylmalonamide in Humans, Rats, and Mice” (El-Masri HA and Portier CJ (1998) 26:585–594), Dr. Patrick Poulin noted the following errors in Tables 2 and 3, about which the authors of the article agree. The neutral lipids content of plasma in Table 2 should be 0.639 instead of 0.631. The neutral lipids content of adipose tissue in Table 2 should be 0.997 instead of 0.11. The neutral lipids content of muscle tissue should be 0.459 instead of 0.451. The total lipids content of muscle tissue in Table 2 should be 0.019 instead of 0.011. The neutral lipids content of adipose tissue in Table 3 should be 0.999 instead of 0.111. The reference concerning the phospholipids content of muscle tissue in Table 3 should be (De Krester et al., 1977) instead of (Poulin and Krishnan, 1995a). The complete reference of this item is as follows: De Krester TA, Livett BG (1977) Skeletal-muscle sarclemma from normal and dystrophic mice: isolation, characterization, and lipid composition. Biochem J 168:229–237. In all cases, these were simple typographical errors, and the correct values were used in our analysis.