CLINICAL MICROBIOLOGY REVIEWS, Oct. 2006, p. 763–787 Vol. 19, No. 4
0893-8512/06/$08.00+0 doi:10.1128/CMR.00059-05

Human Pharmacogenomic Variations and Their Implications for Antifungal Efficacy

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INTRODUCTION

For decades, amphotericin B was the only choice for treating invasive fungal infections. The introduction of fluconazole and itraconazole offered alternative options for antifungal chemotherapy, which broadened further with the development of new, more potent azoles, such as voriconazole and posaconazole, as well as the discovery of the new class of echinocandins (123). Despite these advances, mortality rates for invasive fungal infections can approach 90%, particularly in the immunocompromised host (64, 104, 190). Moreover, a significant number of patients experience adverse effects, necessitating the termination of treatment (101). Progression of infection despite antifungal chemotherapy is often observed, and therefore, alternative therapeutic approaches are employed in order to reverse the clinical outcome. The clinical outcome is dependent on factors that include host defenses, the virulence of the fungal pathogen, and drug efficacy/toxicity, as well as drug interactions (148, 277). Pharmacokinetic studies of antifungal agents have shown variability of at least 50% between individuals (45, 49, 101, 103, 192, 206). For instance, interindividual variability in voriconazole plasma levels ranges from 74% to 100% (121). These differences certainly can contribute to a lack of efficacy and adverse side effects. Additional factors, such as age, gender, underlying disease status, and concomitant therapies, can account for these differences, but host genetics probably play important roles in both drug efficacy and toxicity (75).

Pharmacogenomics is defined as the study of the impact of heritable traits on pharmacology and toxicology (213). The association of genetic variations with drug response has been documented for many diseases and drugs (75, 273), leading to impressive progress in this field. While initially the term "pharmacogenetics" was used, it is limited to studies in which single genes are associated with variations in drug metabolism. In contrast, pharmacogenomic studies integrate with genomewide strategies to elucidate the relationship between sets of genetic variation and drug response (181). Furthermore, pharmacogenomics can also refer to the science that focuses on how the genome as a whole influences the actions of drugs (37). When genetic polymorphisms are linked to toxicity rather than to efficacy, the term toxicogenomics is frequently used.

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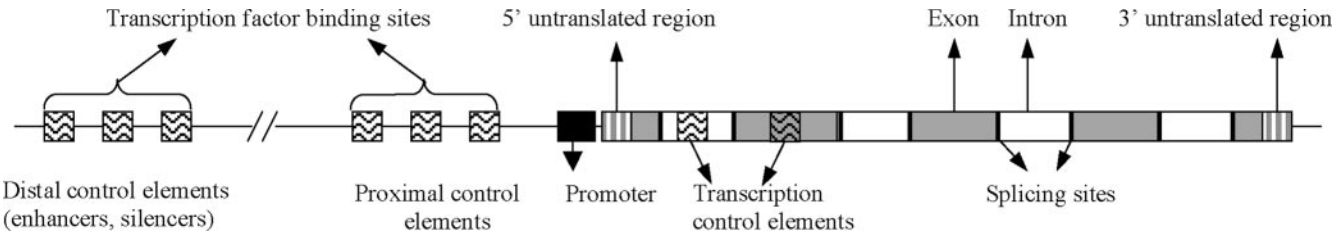

FIG. 1. Components of eukaryotic genes in which functional SNPs may reside and alter the expression levels and form of the encoded protein.

Germ line genetic variation manifests in the genome in different forms, such as structural abnormalities, like chromosomal deletions, insertions, duplications, inversions, and translocations, and by changes in the sequence of DNA, such as single-nucleotide insertions, deletions, substitutions (transition or transversion), or dinucleotide and tandem-repeat deletions/insertions (213). Variations with a prevalence of the minor allele (gene variant) of at least 1% in at least one population are called common polymorphisms. The most abundant source of genetic variation is the single-nucleotide polymorphism (SNP), which accounts for more than 90% of genetic variants and is distributed roughly every 400 bp throughout the genome; there are over 10 million distinct SNPs currently deposited in db-SNP (http://www.ncbi.nlm.nih.gov/SNP) (219). The total number of common SNPs in the human genome is estimated to be more than 10 million (28), and the number of SNPs with minor-allele frequencies of over 10% is estimated to be perhaps as many as 5 million (152).

Most SNPs are distributed throughout the intergenic regions, which comprise over 95% of the genome, yet attention has focused on SNPs in gene-regulatory regions (e.g., promoters, enhancers, silencers, and transcription factor binding sites), coding regions (e.g., exons), noncoding regions (e.g., introns), and untranslated regions (e.g., the 5′ end and 3′ end of mRNA) (Fig. 1) (40, 214). Only a small subset of SNPs actually alter the function of the translated protein (functional SNPs) by affecting the processes of transcription (e.g., no RNA production, wrong splicing, or unstable RNA) and translation (e.g., no protein production, different amino acids, or truncated amino acid chains) (246). It is estimated that there are between 50,000 and 250,000 functional SNPs (40). Studies of genes involved in drug response have shown that the majority of SNPs in coding regions are silent, also known as synonymous (specifying the same amino acid). For the category of nonsynonymous SNPs (i.e., those that alter the amino acid sequence), the majority are conservative, in which there is a replacement of an amino acid by a chemically similar one, but for roughly one-quarter of nonsynonymous SNPs, a radical or nonconservative substitution arises, namely, they are more likely to disrupt the structure/function of the protein. Overall, it is estimated that <1% represent nonsense insertions or deletions, resulting in a premature stop codon (221). SNPs residing in critical *cis*-acting elements and locus control regions can also be important, particularly if they map to a functional binding domain for a transcription binding factor. Recent studies of the dopamine receptor D2 gene have revealed that a noncoding SNP can alter the expression of a gene, in this case by affecting the stability of the mRNA species (70). Seventy-five percent of nonsynonymous SNPs have minor allele frequencies of less than 15% (180). Recent surveys of SNPs suggest that selective pressure has decreased two classes of SNPS that can be most disruptive, radical nonsynonymous changes and insertions/deletions (126).

SNPs are passed from one generation to the next in sets, or blocks. In other words, SNPs are not inherited randomly but in association with one another. This correlation between SNPs is measured as linkage disequilibrium. Linkage disequilibrium across a region of a chromosome is defined on the basis of two or more SNPs cosegregating in a nonrandom manner (89). The challenge of associating common SNPs with outcomes lies in the fact that a single SNP rarely determines an outcome. Thus, the complexity of multigenic factors has to be analyzed carefully and by population parameters. Because SNPs are neither necessary nor sufficient for an outcome, the effect of an SNP is measured as a change in risk. Consequently, sets of SNPs probably act together, usually in a complex pattern. It is possible that the effect of an SNP can follow a dominant or recessive model, but a gene dosage effect is also possible, especially in the context of examining gene-environment or gene-drug interactions (34, 213).

Epigenetic factors, such as DNA methylation and histone modification (79), can also contribute to measured pharmacologic outcomes (15). A phenotype may also be altered in the absence of any structural SNP due to *trans*-acting elements, which are factors usually considered to be proteins that bind to *cis*-acting sequences (DNA sequences in the vicinity of the structural portion of a gene that are required for gene expression) and that control gene expression in a specific tissue (spatial regulation) at a specific time (temporal regulation) after modification (phosphorylation), ligand binding, or an appropriate environmental signal. While these factors should be targeted for the study of pharmacogenomics, for the foreseeable future, the emphasis will be on pursuing germ line genetic polymorphisms and drug pharmacokinetics.

GENETIC ASSOCIATION STUDIES

Genetic association studies are conducted to determine if one or more alleles have a nonrandom distribution with a defined outcome (251). Traditionally, there are two types of association studies: one searches with linked markers across the entire genome, and the second analyzes annotated variants in candidate genes, chosen because of their plausibility in influencing pharmacokinetics. In the indirect method, which is used in a whole-genome approach, the search is intended to identify a region or locus, which in turn is further analyzed.

The follow-up analysis employs the same method as the classical candidate gene approach, in which known genetic variants are analyzed. The whole-genome approach has been successful for mapping rare, highly penetrant diseases in family pedigrees, but due to technical and analytical challenges, it has been less successful in unrelated subjects. Moreover, although this approach has been successful in identifying genes for monogenic traits, its application might be limited for polygenic traits, which by definition have more complex inheritance patterns (13). As an alternative to family-based linkage analysis, preliminary studies have attempted to detect novel genes associated with complex traits by population-based genomewide approaches (180) using anonymous genetic markers (microsatellites and SNPs) spanning the entire genome (52). Although this approach does not require a priori knowledge of the target gene, the identification and mapping of the thousands of SNPs that would be used as genetic markers is needed (35, 214). It is estimated that a minimum of 300,000 to 500,000 evenly spaced SNP markers would be needed to have a marker within the range of linkage disequilibrium (LD) (35). Whereas this density may be useful for uncovering SNPs in genomic regions with extensive LD genes, in regions with less extensive LD, disease-related variants that are rare will be missed.

Currently, the most commonly employed approach for genetic association studies is based on the choice of candidate genes, in other words, those that have high prior likelihood based on a plausible hypothesis (50). Known variants are analyzed in unrelated subjects in a case control study. In contrast to single gene traits, in the complex-disease paradigm, a particular allele does not determine the characteristic but instead alters risk. Population-based studies can provide adequate power to detect relative risks as low as 1.5, which is usually not possible in family studies (214).

Population-based candidate gene association studies are the most commonly employed approach to explore common genetic polymorphisms and drug response. In designing such studies, there are several important issues to be considered. The choice of SNPs in candidate genes requires a good knowledge of the molecular pharmacology of antifungal agents, as well as the physiological processes involved in drug disposition. Data from knockout animal studies for determining the pharmacokinetics of antifungal drugs in the absence of a gene, from the in vivo effects on antifungal pharmacokinetics of inhibitors of physiological processes involved in drug disposition, from in vitro studies for the interaction of antifungal compounds with human biomolecules, and from microarrays and proteomics can be helpful in deciding which genes are important for the disposition of antifungal agents.

Because of the rapid expansion in genotype databases and the falling costs of genotype analysis, it is now possible to conduct candidate gene association studies with sets of genes within a pathway or process. Thus, it is possible to interrogate sets of genes that differentially confer risk. For example, the study of the metabolism of a specific drug compound is ideally suited to this approach, because it is possible to define the critical genes in the activation and elimination of an antifungal compound.

Another important issue in association studies is the number of cases and controls that need to be recruited to achieve sufficient statistical power to detect differences in frequencies among different phenotypic groups. The sample size of an association study influences the level of significance (the probability of finding a difference by chance, or false positive) based on the power of the study (the probability of detecting a real difference, or true positive) and the frequency of the SNP. The literature has been marked by a plethora of findings that could not be replicated in subsequent studies. These false-positive results can be a consequence of inadequately powered studies (i.e., study sets that are too small), errors in genotyping, faulty selection of cases and controls, and population stratification. The last issue is not significant in Caucasian populations (with rare exceptions in isolated groups) but may be more problematic in populations with more admixture, such as individuals of Hispanic or African ancestry in the United States (84, 176, 264). Recently, a new strategy that is based on the prediction of a false-positive report has been advanced for determining whether a finding is notable (263). This approach looks at the prior probability that a finding could be real, as well as the power of the sample size and the allele frequency.

Another important issue, particularly in population-based genetic association studies, is population stratification. The study populations (cases versus controls) should be homogenous with regard to age, gender, ethnicity, and other socioeconomic factors (283). In order to overcome these problems, a method known as genomic control is used, in which the frequency of polymorphisms in other genes unlikely to be associated with the studied phenotype are compared between subjects in addition to the polymorphisms in the candidate gene of interest; appropriate adjustment is then made for population stratification (12) or association tests are performed within the identified subpopulations (205). Spurious associations may also be obtained in population-based studies due to gene-environment interactions, issues in case/control recruitment, and other biases (50). It has been argued that these pitfalls can be avoided in performing family-based association studies, but this approach is often practically challenging (241).

Finally, the correct assessment of outcome characteristics in cases and control is crucial in order to avoid having undetected individuals who bear the phenotypic characteristic in the control group. In the case of pharmacogenomics studies, the phenotype can be any pharmacokinetic parameter, such as the bioavailability, area under the curve (AUC), maximum plasma concentration (C_{max}), time of C_{max}, half-life, volume of distribution, clearance, and drug concentrations in serum and tissues, many of which can be derived after pharmacokinetic modeling. Lastly, pharmacogenomics has successfully identified markers that confer a shift in risk for the outcome or toxicity (180).

PHARMACOGENOMICS IN ANTIFUNGAL DRUG DISPOSITION

The relationship between genetics and pharmacokinetics has been apparent in the literature since the 1950s (253). For instance, it was noted that the half-lives of selected drugs were markedly similar in monozygotic twins but, when measured in dizygotic twins, varied widely. This same trend has been extended to studies of unrelated subjects, especially from different populations. A classic example is atypical cholinesterase

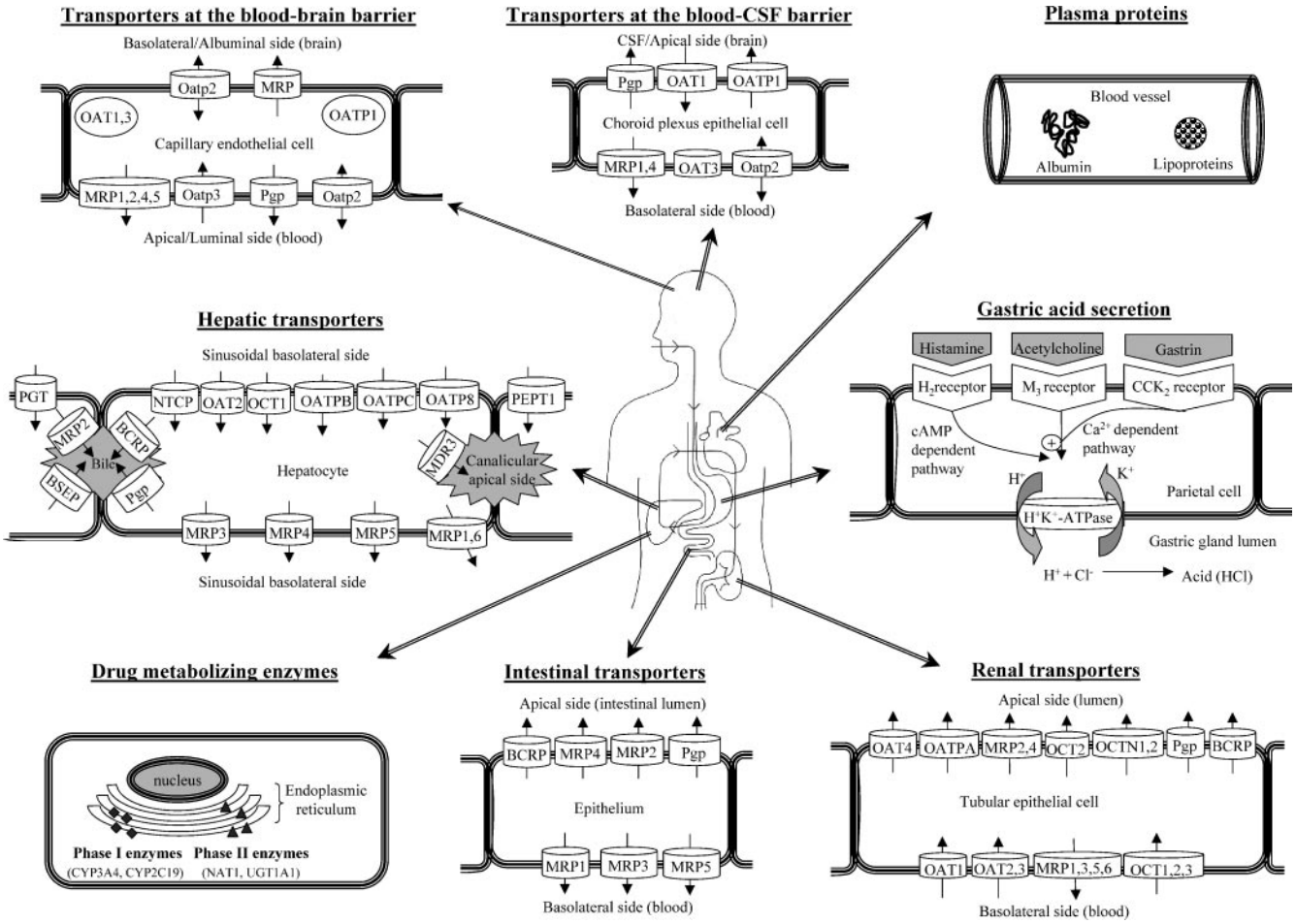

FIG. 2. A schematic diagram of drug disposition and the physiological factors that play roles in drug pharmacokinetics, such as transporters, metabolizing enzymes, protein binding, and gastric acid excretion (data from references 39, 143, 153, 164, 199, and 248). Any variation in genes encoding proteins involved in the disposition of drugs may have an impact on drug pharmacokinetics. NTCP, sodium-dependent taurocholate transporting polypeptide; BSEP, bile salt export pump; PGT, prostagladin transporter; cAMP, cyclic AMP; NAT, *N*-acetyltransferase; UGT, UDP-glucuronosyl transferase. The exact localizations and efflux directions of some of these transporters are still under investigation.

activity, which can extend the half-life of succinylcholine, the neurotransmitter-blocking agent, and thus result in prolonged muscle paralysis and consequent apnea. The *CYP2D6* genetic polymorphisms were originally described in an effort to explain differences in pharmacokinetics of select drugs, such as codeine and debrisoquin (273). Another well-described example has been validated in numerous studies, namely, variation in the thiopurine *S*-methyltransferase gene (*TPMT*); variants in the gene decrease enzymatic activity, thus yielding elevated concentrations of active metabolites. In turn, the extended half-lives of metabolites can induce life-threatening myelosuppression, even with standard doses of thiopurines used for treatment of leukemia and autoimmune disorders (183).

Genetic polymorphisms in drug transporters alter drug pharmacokinetics substantially, but to date, only a few examples have been well described (75). Since only a small percentage of the genes in the genome (roughly 30,000) have been analyzed, it is expected that additional genes will be identified. For example, genetic polymorphisms in the P-glycoprotein (P-gp, encoded by *ABCB1*), an ATP-binding cassette transporter, have been associated with variable expression in the duodenum, resulting in altered bioavailability of drugs such as digoxin. Finally, drug response can be influenced by genetic variation in key genes; for instance, sequence variants in the gene for the b2 adrenoreceptor (*BDKRB2*), which modulates response to b2 agonists, has been associated with efficacy in pulmonary disease. In some circumstances, a gene, such as the apolipoprotein E gene (*APOE*), which has been associated with risk for Alzheimer's disease, can also account for differences in therapeutic response (75). Thus, SNPs in fungal targets (e.g., lanosterol 14a-demethylase, 1,3-β-glucan synthase, and fungal drug transporters) may alter antifungal drug response by altering antifungal pharmacodynamics. These SNPs will not be reviewed here.

The analysis of the pharmacokinetics of antifungal compounds includes the administration, absorption, distribution, metabolism, and excretion of the drug, while pharmacodynamics refers to functional effects, namely, growth inhibition and fungicidal activity. Before a drug or its prodrug reaches the site of action, it has to pass through one or more membranes and frequently undergoes alteration. Each of the steps of the processes can be affected by one or more common genetic varia-

TABLE 1. Pharmacokinetic characteristics of antifungal drugs in humans

Antifungal agent	GI absorption (%)	Distribution (vol, % binding)	Metabolism (%)	Excretion (%)	
				Renal	Hepatobiliary
Amphotericin B	<10	4 liters/kg, 91–95	Minimal	20.6 (parent drug)	42.5 (parent drug)
Itraconazole	55–92	11 liters/kg, >99	>80 (oxidation, deakylation)	<0.03 (parent drug) 35 (metabolites)	3–18 (parent drug) 54 (metabolites)
Fluconazole	>80	0.7 liter/kg, 11–12	<20	80 (parent drug) 11 (metabolites)	Minimal
Voriconazole	>90	4.6 liters/kg, 58	>98 (N-oxidation)	<2 (unchanged) 80 (metabolites)	20 (metabolites)
Posaconazole	8–48	5 liters/kg, 98–99	Minimal (oxidation, glucuronidation)	14 (mostly metabolites)	77 (mostly parent drug)
Terbinafine	70–80	11 liters/kg, >99	>99 (N-demethylation, alkyl oxidation, aryl oxidation, hydrolysis)	80 (metabolites)	20 (metabolites)
Caspofungin	<0.2	0.2 liter/kg, 96	>98.6 (hydrolysis, acetylation)	1.4 (parent drug) 41 (metabolites)	35 (metabolites)
Micafungin	Poor	0.2 liter/kg, 99.8	>99 (arylsulfation, catechol O-methylation)	0.7 (unchanged) 7.4 (mostly metabolites)	>90 (mostly metabolites)
Anidulafungin	Poor	0.6 liter/kg, 84	>90 (not metabolized enzymatically)	<10 (unchanged) >90 (degradation products)	Minimal
Flucytosine	76–89	0.6 liter/kg, <5	<1	>90 (parent drug) 1 (metabolites)	Minimal

tions in one or more genes of the critical pathways (Fig. 2). This review discusses notable examples of common genetic variants that affect drug absorption, distribution, metabolism, and excretion. We review selected issues in pharmacokinetics, many of which are suitable targets for subsequent studies aimed at dissecting the contribution of genetic variation to the pharmacologic outcomes related to antifungal compounds. The principles of pharmacogenomics can be applied to the analysis of drug disposition, which in turn can influence the pharmacokinetics and pharmacodynamics of antifungal agents.

Absorption

The oral absorption of drugs is affected by factors such as gastrointestinal motility, splanchnic blood flow, particle size, formulation of the agent, and physiochemical factors (e.g., binding to gastric contents) (232). Bacterial and gastrointestinal (GI) tract enzyme metabolism can reduce the availability of drugs, and extensive metabolism in the intestine and liver (the first-pass effect) may limit the amount of drug entering the systemic circulation. However, a drug must cross the GI mucosal surface before entering the systemic circulation. Although the carrier-mediated transport system may be responsible for transferring large (>500-molecular-weight) lipid-insoluble drug molecules, which resemble natural physiological metabolites (e.g., 5-fluorouracil) (254), efflux of xenobiotics out of the GI epithelial cells also occurs. In this regard, the location of drug transporters in the cell membrane also defines their contribution to the absorption process (Fig. 2).

Among antifungal agents, terbinafine, flucytosine, and most of the azoles can be administered orally (120, 171). Amphotericin B and echinocandins are administered only intravenously, due to their poor absorption when given orally. Absorption rates vary from >80% for flucytosine, fluconazole, and voriconazole and 70 to 80% for terbinafine to 55% for itraconazole (capsule), 8 to 48% for posaconazole (in animals), and 48 to 74% for ravuconazole (in animals), <10% for amphotericin B, and <0.2% for caspofungin and the other echinocandins (Table 1) (54, 60, 62, 74, 101, 102). The absorption of antifungal agents may be strongly affected by conditions such as overall immunosuppression, hypochlorhydria, and concomitant chemotherapy (58, 60). Absorption may also vary among healthy individuals even under the same dietary conditions (93, 281). Patients with similar underlying conditions and treatment regimens also have demonstrated variable (up to 50% coefficient of variation) pharmacokinetic profiles of orally administered drugs, again underscoring the significance of possible genetic variation in key genes (204). However, there are no studies exploring the role of genetic variation in antifungal absorption.

Gastrointestinal pH. Because the optimum site for drug absorption is the upper portion of the small intestine (the duodenum region), intestinal pH is very critical for absorption (232). Gastric pH is also important for drug absorption, because it influences drug solubility (227). Intestinal pH may vary from 6 to 6.5, while gastric pH varies from 1 to 6. In one study, there was a 10-fold difference in gastric pH between individual subjects for the 24-h area under the curve (282). The low pH in the gastric lumen is produced by a unique hydrogen-potassium ATPase located on the apical membranes of the parietal cells of the walls of the secretory unit of the gastric mucosa (Fig. 2) (199).

The pH of the gastrointestinal tract significantly affects the absorption of weakly acidic or basic drugs, such as itraconazole and ketoconazole. Both drugs are ionized at very low pH, while at high pH, they are insoluble, resulting in poor penetration of the gastric epithelium (57, 258). This effect is increased by concomitant administration of drugs that raise the gastric pH, such as H2 receptor antagonists (cimetidine, ranitidine, and famotidine), proton pump inhibitors, sucralfate (a weak-base aluminum salt), and didanosine (a buffer that contains magnesium and aluminum) (2). In contrast, the absorption of compounds such as fluconazole, voriconazole, posaconazole, terbi-

nafine, and flucytosine is barely perturbed by the gastric pH (45, 101, 137, 159); caspofungin and amphotericin B are poorly absorbed from the GI epithelium, possibly due to insolubility problems, but absorption can be improved when lipid-bile salts mixed micelles are used as a vehicle (55). Thus, genetic polymorphisms in key genes which are involved in gastric acid secretion may affect itraconazole and ketoconazole absorption but not the absorption of the other antifungal drugs.

Efflux drug transporters. Even when a drug crosses the apical membrane of the GI epithelium, efflux drug transporters can pump a compound back out (153). Among the well-known efflux drug transporters located at the apical membrane of the gastrointestinal epithelium are P-gp (*ABCB1*); multidrug resistance protein 2 (MRP2; *ABCC2*) and MRP4 (*ABCC4*); and the breast cancer resistance protein (BCRP; *ABCG2*) (27). However, efflux drug transporters, such as MRP1 (*ABCC1*), MRP3 (*ABCC3*), and MRP5 (*ABCC5*), are located at the basal membrane and are responsible for pumping substrate drugs into the body, thereby enhancing the ability of drugs to enter the systemic circulation (226) (Fig. 2).

The intestinal P-gp transports a wide spectrum of agents, such as etoposide, cyclosporine, vinblastine, taxol, loperamide, domperidone, ondansteron, indinavir, saquinavir, and nelfinavir (85, 167, 235). The same transporter can limit the absorption of a range of other dugs, such as digoxin, tacrolimus, talinol, and fexofenadine (11). The functions of the MRPs and their pharmacological impacts have been shown in both in vitro and in vivo studies (27, 226), although their roles in drug absorption are not well defined.

Genetic variability, which alters the functions of these drug transporters, may have an impact on the absorption of the substrate drugs. In particular, variable expression on P-gp mRNA and protein levels in the gut have been demonstrated, with an estimated 8- to 10-fold variation (11). Thirty percent of the variability in C_{max} and 17% of the variability in oral clearance of cyclosporine in humans can be ascribed to interindividual variation in intestinal P-gp levels (170). The multidrug resistance 1 (MDR1; *ABCB1*) gene, which encodes P-gp, is located on chromosome 7q21.1. It has been suggested that it acts as a "hydrophobic vacuum cleaner," or flippase, which removes its substrates from the lipid bilayer before they reach the cytoplasm. A correlation has been observed between MDR1 (*ABCB1*) T3435C SNP in exon 26 and duodenal P-gp oral-digoxin plasma levels (122).

The transport of antifungal agents by P-gp (*ABCB1*) is well established (267). Itraconazole (4) and ketoconazole, but not fluconazole, miconazole, and amphotericin B, inhibit P-gp function; in fact, this approach has been undertaken to reverse the anticancer resistance of human leukemia cells in vitro (129). However, antifungal agents could also work as substrates of P-gp, given that P-gp mediates the transport of itraconazole across the blood-brain barrier (BBB) and the similarities between P-gp substrates and CYP3A4 substrates/inhibitors, such as itraconazole, fluconazole, and ketoconazole (130, 187, 195). Furthermore, fluconazole resistance in *Candida albicans* has been associated with overexpression of *C. albicans MDR1*, an ortholog of the human *ABCB1* gene (276). Additional ABC transporters are involved in the efflux of antifungal agents, including terbinafine, azoles (223), and possibly caspofungin (228).

Thus, P-gp genotypes and expression levels may influence the absorption of antifungal drugs, and particularly that of azoles. However, the roles of P-gp expression and genotype in posaconazole pharmacokinetics were recently explored in 28 healthy black and Caucasian volunteers (R. Courtney, A. Sansone, D. Devlin, P. Soni, and M. Laughlin, Abstr. 44th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-40, 2004). No association was observed between any MDR1 SNPs, including the C3435T and posaconazole AUCs. Furthermore, no correlation was noted between MDR1 mRNA levels and exposure to posaconazole.

Distribution

Once a drug enters the bloodstream, the drug molecules are distributed throughout the body by systemic circulation and reach the tissues mainly via capillaries (232). Because only free drug diffuses between capillaries and tissue sites, protein binding in plasma has a major impact on distribution, as well as metabolism and elimination, particularly of highly bound drugs (169, 232). Binding to macromolecule components in the blood is also critical for transport; well-defined proteins include albumin, A_1-acid glycoprotein (AAG), lipoproteins, immunoglobulins, and erythrocytes (Fig. 2). Thus, genetic variation in one or more these could be critical for differences in antifungal pharmacokinetics.

Plasma protein binding rates for antifungal drugs range from 4% for flucytosine and 11% for fluconazole to 58% for voriconazole and >95% for amphotericin B, itraconazole, posaconazole, terbinafine, caspofungin, and micafungin; moreover, anidulafungin protein binding is as high as 84%, mainly to albumin (Table 1) (45, 58, 60, 63, 102, 244). However, A_1-acid glycoprotein and lipoproteins can also contribute to drug binding (20, 30, 174, 218). To a lesser degree, antifungal agents can bind to hemoglobin A1 and free fatty acids (10, 225), as well as on red blood cells (171). For instance, extensive uptake by red blood cells was noted for micafungin (63), while coadministration of caspofungin with tacrolimus reduces whole-blood tacrolimus levels by 20%, possibly due to decreased red blood cell binding of the latter (65). In addition, less than 8% of terbinafine is taken up into blood cells (60). Although substantial variation in plasma proteins can occur in pathological situations, such as diabetes (106), levels of proteins can vary up to 10% among healthy individuals (136). Interindividual variation (5%) in drug-protein binding rates for itraconazole and fluconazole has been observed, with a significant association between the binding of drugs and serum protein levels (8). Plasma protein binding of terbinafine had a major effect on brain uptake in rats, varying from 6% to 45% in the presence of plasma, albumin, and very low- (VLDL) and low-density lipoproteins (LDL), A_1-acid glycoprotein, and high-density lipoproteins (HDL) (174). Although several studies have investigated the interaction of antifungals with plasma proteins and the roles of drug transporters in antifungal efflux, the importance of pharmacogenomic issues in the distribution of antifungal agents remains to be explored.

Albumin. Albumin is able to bind, covalently or reversibly, a large number of both endogenous and exogenous compounds, such as metals, fatty acids, amino acids, and metabolites, such

as bilirubin, and drugs (232). Albumin interacts reversibly with a broad spectrum of drugs, primarily anionic drugs, by electrostatic and hydrophobic bonds. It has two high-affinity drug binding sites: site I binds dicarboxylic acid drugs and/or bulky heterocyclic negatively charged molecules, such as warfarin and salicylate, and site II (also called the indol-benzodiazepine site) binds aromatic carboxylic drugs, such as ibuprofen and diazepam (150).

Of the common antifungal agents, ketoconazole (177), itraconazole (8), amphotericin B (20, 109), caspofungin (244), and terbinafine (174, 218) bind to albumin, while fluconazole does not (9, 10). Site II is involved in the binding of both amphotericin B and nystatin, while amphotericin B also binds to site I and nystatin binds to the fatty acid binding sites in albumin (216). However, amphotericin B may also interact with lysine residues 199 and 525 (217). Both polyenes can displace bilirubin, probably at a site shared with site I of albumin. Furthermore, ketoconazole displaces valproic acid, which also binds site I of albumin (56), and itraconazole seems to have a minor effect on the pharmacokinetics of diazepam, which binds to site II of albumin (1). Micafungin has not been demonstrated to exhibit drug interactions with other highly protein bound compounds, such as warfarin, diazepam, salicylic acid, and methotrexate (63). Low serum albumin was associated with a modestly reduced concentration 1 h after dosing, possibly due to reduced protein binding of caspofungin in plasma (J. Stone, G. Winchell, S. Bi, P. Wickersham, M. Schartz, N. Kartsonis, and C. Sable, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1571, 2003).

The albumin gene (*ALB*) is located on chromosome 4q11-q13. More than 50 functional SNPs in the albumin gene have been characterized (83, 175). Functional SNPs that affect the affinity of albumin for drugs have been previously described (149, 260). Conformational changes in the 313-to-365 region of albumin are thought to account for diminished binding, whereas an increase in affinity for binding of warfarin has been found for in vitro recombinant mutants of albumin, such as His242Glu and Lys199Ala, while for Try214Ala and Arg218His a small decrease in affinity was observed (272). The last substitution may also alter the pharmacokinetics of warfarin, since the free-drug concentration in individuals homozygous for Arg218His is expected to be elevated, resulting in a reduction in the serum half-life (201). As most of the antifungal agents are highly protein bound, albumin SNPs may affect antifungal-drug disposition.

A_1-acid glycoprotein. AAG (orosomucoid) is a globulin with a molecular mass of 44 kDa consisting of 59% protein and 41% carbohydrate (133). It is synthesized mainly in the hepatocytes and parenchymal cells and then distributed in body fluids, including plasma (232). The plasma concentration is low (0.4 to 1%) and ranges from 55 to 140 mg/dl among healthy adults. It binds steroids and basic (cationic) drugs, such as propranolol and lidocaine. However, both basic and acidic drugs bind to AAG, although recent studies suggest two separate drug binding sites (133). The binding of drugs may be altered, particularly in pathological states, because of altered sialylation and fucosylation, as well as changes in the glycosylation pattern, increased branching of oligosaccharide chains, and a reduced number of bindings sites.

Although the binding of ketoconazole (177) and itraconazole (10) might not be directly related to circulating AAG levels, an increase in binding of fluconazole is associated with higher levels of AAG (8); some have interpreted this to mean that fluconazole has a higher affinity for AAG than for albumin (9). AAG has been found to contribute to amphotericin B (20) and terbinafine (174) binding. Intracarotid injection of terbinafine together with AAG increased brain uptake in rats eightfold compared to injections of the drug together with plasma (174), indicating that AAG might play a major role in the disposition of the drug.

AAG in human plasma is a heterodimer derived from two separate loci, *ORM1* and *ORM2* (present in 3:1 molar ratio, respectively), mapped to chromosomal region 9q31-34.3. A total of 74 alleles (27 assigned to *ORM1* and the others to *ORM2*) have been identified (287), using immunoblotting and isoelectric focusing. Genetic variants of AAG have different specificities for binding to particular drugs. For example, dysopyramide, imipramine, and methadone bind selectively to the *ORM1**A variant, whereas dypiridamole, quinidine, and mifepristone bind preferentially to the *ORM1**F1 variant (133). Particularly for quinidine, the unbound fraction of drug in subjects with the *ORM1**F1 phenotype is twice as high as that with the *ORM1**S phenotype (166). Furthermore, for drugs that bind to variant A, transport into the brain is significantly lower than for those that bind to both variant A and variant F1/S (138). The effects of SNPs within the AAG gene on the distribution of antifungal agents is not well understood.

Lipoproteins. Lipoproteins are macromolecular complexes in which hydrophobic molecules of triacylglyceride and cholesteryl ester are enveloped within a monolayer of amphipathic molecules of phospholipids, free cholesterol, and apoproteins (95). Lipoproteins are classified according to their densities as chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

Although plasma proteins can contribute substantially to binding to antifungal drugs, there is increasing evidence that lipoproteins play a significant role in drug binding (268), particularly to highly lipophilic antifungal drugs, such as terbinafine and amphotericin B. More than 60% of terbinafine is associated with human plasma lipoproteins, particularly LDL (28 to 31%) and HDL (25 to 27%), and less with VLDL (8 to 16%) (286). Binding to lipoproteins affects the brain uptake of terbinafine in rats, where a high in vivo affinity of terbinafine for LDL has been found (174). In the case of amphotericin B, although less than 40% of the drug in plasma is associated with lipoproteins, particularly HDL (142), patients with higher serum LDL-cholesterol levels are more susceptible to amphotericin B-induced kidney toxicity (269), and amphotericin B pharmacokinetics is significantly altered in hypercholesterolemic rabbits (208, 255, 270). The same pattern of lipoprotein binding is observed for nystatin, with 17 to 28% and 3 to 7% of the drug associated with HDL and LDL, respectively (36, 271). However, when the liposomal formulations of the latter drug are used, more than 50% of the drug is recovered in HDL fractions while small or undetectable amounts are in LDL and VLDL (36, 142). Finally, nonesterified fatty acids appear to have joint responsibility for ketoconazole protein binding (177).

Differences in lipoprotein-drug interactions have been observed in select studies (142, 286); these differences appear

TABLE 2. SNPs affecting lipoprotein metabolism[a]

Gene[b]	SNP name	Position	Nucleotide exchange	Frequency (%)	Effect[c]
CETP	1405V	Exon 14	G+16A	32.9	↑ HDL
	Taq1B	Intron 1	G+279A	41.3	↑ HDL
LPL	S477X	Exon 9	C/G	11	↓ TG, ↑ HDL
	HindIII	Intron 8			↓ TG
APOA-I	M1 site	Promoter (−76)	A/G		
	M2 site	Promoter (−83)	C/T	55.6	↓ LDL
	M2 site	Promoter (−83)	G/A		
APOA-IV	His306Glu		G/T	7–9	↓ HDL
APOB	Arg3611Gln	Exon 26		11–46	↑ LDL
	Glu4154Lys	Exon 29		11–46	↑ LDL
	Thr→Ileu	Exon 4		11–46	↑ LDL
APOC3		Promoter (−455)	T/C		↓ TG
		Nucleotide 1100	C/T		↑ TG
	SstI	3′ untranslated region	C/G	14	↑ TG
APOE	Cys112Arg	Exon 3	T/C	15	↑ LDL
	Arg158Cys	Exon 3	C/T	2	↓ LDL
HL		Promoter (−480)	C/T		↑ HDL
FABP-2	Ala54Thr	Exon 2	G/A	27–29	↑ FA
LDLr	PvuII	Intron 16	A/G		↑ LDL

[a] Data from references 53 and 262.
[b] CETP, cholesteryl ester transfer protein; LPL, lipoprotein lipase; APO, apolipoprotein; HL, hepatic lipase; LDLr, low-density lipoprotein receptor; FABP-2, fatty acid binding protein 2.
[c] ↑, increased; ↓, decreased; TG, triglycerides; FA, fatty acids.

to be attributable to differences in the lipoprotein lipid and protein concentration/composition plasma profile (268), which can vary by up to 310% (142, 269). In particular, increases in HDL coat lipid content resulted in less amphotericin B recovered in this fraction following incubation with liposomal amphotericin B, whereas an increase in the triglyceride/total-protein ratio resulted in more amphotericin B recovered in the fraction following incubation with free amphotericin B (142). In addition, with decreasing HDL protein, nystatin and liposomal nystatin recovered within the fraction decreased (36). The effect of the lipoprotein concentration on drug pharmacokinetics is indicated by the decreased plasma clearance, kidney concentration, and nephrotoxic effects of amphotericin B when plasma HDL/cholesterol levels are elevated following intravenous administration of triglyceride/fatty acid emulsion to rats. The effect of the lipoprotein composition on drug pharmacokinetics is indicated by the increase in the association of nystatin with plasma lipoproteins when nystatin is incubated in plasma treated with dithionitrobenzoate (an enzyme that inhibits the conversion of free cholesterol to cholesteryl ester, resulting in a decrease of the esterified-cholesterol content within HDL and LDL/VLDL) (268). Lipoproteins can also influence the pharmacodynamics of drugs, such as psychotropic drugs, for which lipoprotein levels have been associated with increased clinical response and remission in psychiatric disorders (67, 71). Therefore, genetic polymorphisms that alter lipid metabolism, such as in dyslipidemias (hypo- and hypercholesterolemia and hypertriglyceridemia), may have a great impact on the pharmacokinetics and toxicity of antifungal drugs.

There are four categories of gene products that contribute to the wide spectrum of interindividual variation in plasma lipoproteins (53). These are the apolipoproteins, namely, apo A-I, A-II, A-IV, B, C-I, C-II, C-III, and E and apo (a); the receptors, namely, LDL receptor (*LDLR*), LDL receptor-related protein (*LRP1*), macrophage scavenger receptor (*MSR1*), VLDL receptor (*VLDLR*), and SR-B1 receptor (*SCARB1*) for HDL; modifying proteins, namely, lipoprotein lipase (LP; *LPL*), hepatic lipase (HL; *LIPC*), lecithin-cholesterol acyltransferase (LCAT; *LCAT*), and cholesteryl ester transfer protein (CETP; *CETP*); and factors involved in lipoprotein synthesis or secretion, namely, microsomal triglyceride transfer protein (MTTP; *MTP*) and the apo B-editing protein (*ACF*) (113). Several common functional SNPs in these genes that affect lipoprotein metabolism have been described (Table 2) (91, 113, 146, 262, 283).

Each of these genes may affect the binding of antifungal drugs to lipoproteins, such as the interaction between CETP and amphotericin B (156). Although the majority of lipoprotein-associated amphotericin B is recovered in the HDL fraction, the percentage of amphotericin B recovered in the LDL fraction is increased when the CETP concentration is increased (268). It has been suggested that the ability of CETP to transfer amphotericin B between HDL and LDL is due to its ability to transfer cholesteryl ester between HDL and LDL, because amphotericin B interacts with free cholesterol and cholesteryl ester (26). It will be interesting to study the roles of SNPs in CETP in amphotericin B pharmacokinetics and toxicity (discussed in "Excretion" below).

Drug transporters. Although the impacts of intestinal transporters on drug absorption have been discussed above, drug transporters located in the liver and kidney contribute to intestinal, hepatobiliary, and renal excretion and therefore play significant roles in drug elimination (see "Excretion" below). Drug transporters in tissues may also be important in drug distribution. The passage of drugs from the systemic blood into the central nervous system is limited by the presence of the BBB and the blood–cerebrospinal-fluid (CSF) barrier; several transport families are critical for this process, including P-gp (*ABCB1*), MRPs, organic anion transporting proteins (OATPs), and organic anion transporters (OATs) (248). P-gp (*ABCB1*) is localized to the apical-luminal side of brain capillary endothelial cells and the apical-CSF side of choroid epithelial cells pumping substrates

from inside the cells back into the blood or the CSF, respectively (Fig. 2). The localization of MRP1 (*ABCC1*) is controversial, because it seems to be expressed in astrocytes rather than in capillary endothelial cells (279). MRP5 (*ABCC5*) and MRP2 (*ABCC2*) could play significant roles in the brain and possibly at the BBB (155). However, MRP1, -4, -5, and -6 are expressed in freshly isolated bovine brain capillary endothelial cells, and MRP2 (*ABCC2*) is localized to the luminal membrane of rat brain capillary endothelial cells (Fig. 2). Rat *oatp2*, which is expressed on both the luminal and abluminal membranes of brain capillary endothelial cells, is involved in efflux transport from the brain and can account for 40% of the total efflux in rats (155). OAT1 (*SLC22A6*) and OATP-1 (*SLCO1A2*) have been demonstrated to be on the brush border apical-CSF side membrane, while rat Oatp2, OAT-3 (*SLC22A8*), and MRP-1 (*ABCC1*) are found in the blood-basolateral membrane of choroid epithelial cells. In addition, many drugs are substrates of OAT1 (*SLC22A6*) and OAT3 (*SLC22A3*) (248).

Although the impacts of most transporters on drug distribution in the brain are not clearly known, the role of P-gp in the brain distribution of various substrates, including antifungals, has been shown in P-gp knockout mice (11). Accumulation of itraconazole in the brain tissue of P-gp knockout mice is significantly increased compared to that in control mice (187). Furthermore, the brain/plasma itraconazole ratio is significantly increased in the presence of the P-gp inhibitors verapamil and ketoconazole, suggesting that P-gp in the brain capillary endothelial cells participates in a process of active efflux of itraconazole from the brain to the blood at the BBB. In addition, GF-120918 (a P-gp inhibitor) in pretreated mice significantly increased the cerebral itraconazole AUC compared to that of untreated mice infected with *Cryptococcus neoformans* (130). Preclinical studies indicated that caspofungin is not a substrate of P-gp, although the caspofungin AUC is reduced by 20% with coadministration of rifampin, efavirenz, phenytoin, nevirapine, dexamethasone, and carbamazepamine and increased by 35% with coadministration of cyclosporine (65), compounds which are transported by P-gp and MRPs (226). Penetration of antifungal drugs into the brain is poor for amphotericin B (<4% serum concentration [SC]), itraconazole (<10% SC), ketoconazole (<10% SC), caspofungin (6% SC), and micafungin (<10% SC), but not for flucytosine (74% SC), fluconazole (>60% SC), voriconazole (50% plasma concentration), and terbinafine (6 to 43% plasma concentration; undetectable in CSF) (7, 32, 99, 100, 108, 124, 137, 171). Like itraconazole, drug transporters may be responsible for the poor penetration of antifungal drugs despite their high lipophilicity.

SNPs within the P-gp (*ABCB1*) gene influence drug distribution in the central nervous system (168) (Fig. 3). Higher maximal digoxin plasma concentrations during steady state are found in the 3435TT group in comparison to subjects with the CC genotype (122), while Sakaeda et al. reported higher AUC from 0 to 4 h (AUC_{0-4}) values in Japanese subjects with the 3435CC genotype compared to CT and TT, in accordance with their own data on *ABCB1* mRNA expression (220). Furthermore, the reduced levels of *ABCB1* mRNA and P-gp in peripheral mononuclear cells of human immunodeficiency virus-infected patients with the TT genotype is associated with enhanced human immunodeficiency virus protease inhibitor penetration into lymphocytes and finally with a greater rise in the CD4 cell count in comparison to the CT and CC groups (80). However, studies with other P-gp substrates did not reveal an association between the 3435TT genotype and increased drug concentrations. Fexofenadine plasma AUC values were lower in the TT group than in the CC group (144). Nelfinavir plasma concentrations were higher in patients with the 3435CC genotype than in patients with CT and TT genotypes (80), supporting findings that show increased P-gp activity in cells stably transfected with the *ABCB1*-893Ser variant, mostly linked to 3435T (144). The absence of an association with *ABCB1* SNPs could be due to differences in diet, which may contribute to a differential expression of drug transporters or to the coordinate activities of P-gp and CYP3A4 (86). The T3435C SNP of the *ABCB1* gene may be associated with tissue levels of antifungal drugs, particularly triazoles, and may explain interindividual differences in antifungal efficacies when plasma levels are similar.

Additional transporters (Table 3) localize to specific tissues that may in turn influence the extravascular levels of antifungal drugs. Most antifungal drugs are distributed throughout most tissues. Amphotericin B is predominantly distributed to the liver, spleen, bone marrow, kidney, and lung (98), while its lipid formulations are preferentially distributed to organs of the mononuclear phagocytic system, which functionally spares the kidney (117). Fluconazole distributes evenly into virtually all tissue sites and body fluids, including the CSF, brain tissue, and the eye (32). Itraconazole concentrations in nonproteinaceous body fluids are negligible, but tissue concentrations in many organs, including the brain, may exceed corresponding plasma levels by 2 to 10 times (58). Tissue and CSF levels of voriconazole exceed trough plasma levels by severalfold (98). Echinocandins distribute into all major organ sites, including the brain; however, concentrations in uninfected CSF are low (98). Terbinafine is widely distributed in tissues, accumulating in adipose tissue, sebum, skin, hair, and nail plate (60, 101).

Drug transporters show broad specificity because substrate recognition is based on physicochemical properties, such as hydrophobicity, aromaticity, hydrogen binding capacity, and an ionizable character (within a given spatial environment), rather than on defined chemical properties, such as enzyme-substrate or ligand-receptor recognition (257). Azoles are weak bases, with pK_as of 1.6 to 2.0 for fluconazole and voriconazole and 2.9 to 3.7 for itraconazole and ketoconazole (24, 57, 179) and 3.6 to 4.6 for posaconazole (45). There is little ionization at higher pH levels compared to their pK_as (i.e., in most of the body fluids except gastric juice, where due to low pH, they may have a positive charge). Terbinafine and caspofungin are bases with a predicted pK_a of 7.1 (Novartis, Inc., Dorval, Quebec, Canada, Lamisil product insert). Amphotericin B is zwitterionic, because it contains a carboxyl group that can be charged negatively and an amino group that can be charged positively.

P-gp substrates are usually hydrophobic amphipathic organic molecules ranging in mass from 0.2 to 1.9 kDa; they contain aromatic groups, although nonaromatic linear or circular molecules are also transported, and are uncharged or weakly basic, although acidic compounds can also be transported at lower rates (226). The physicochemical properties of azoles resemble the profiles of P-gp substrates. MRP1 to -3 (*ABCC1* to *-3*) substrates include organic amphipathic anions and drugs con-

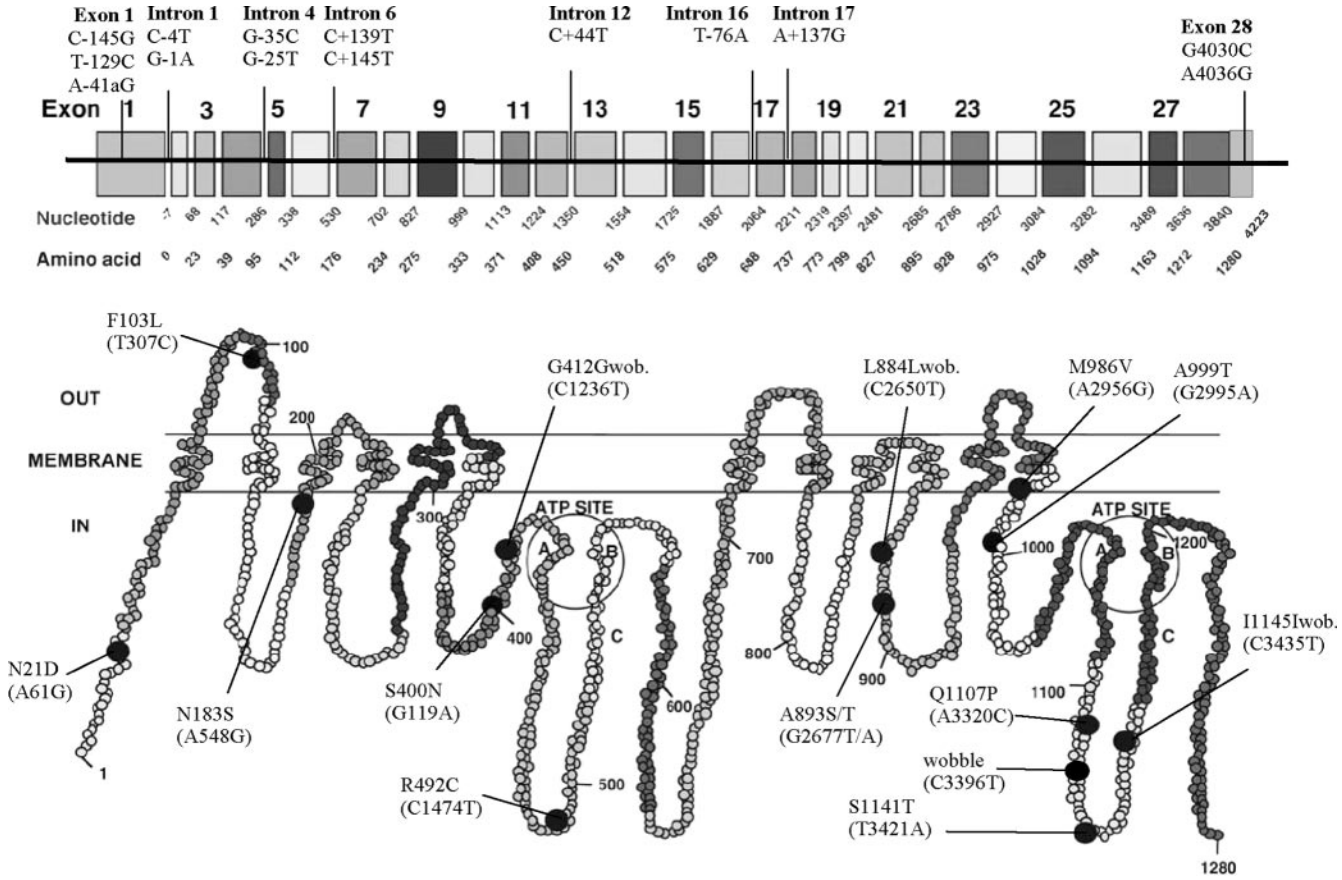

FIG. 3. Two-dimensional (2D) structure of P-gp showing the distribution of coding SNPs (black-filled circles) (229). The amino acid substitutions are presented, together with nucleotide changes (in parentheses). At the top, 28 exons of the MDR1 (*ABCB1*) gene are shown with the cDNA nucleotide and amino acid positions, together with noncoding SNPs at the promoter, introns, and untranslated regions. The region of P-gp encoded by a given exon is also highlighted in similar shading on the predicted 2D P-gp structure. The positions of the polymorphisms correspond to the positions of MDR1 (*ABCB1*) cDNA, with the first base of the ATG start codon set to 1. Mutations located in introns are given as the position downstream (−) or upstream (+) of the respective exon according to the genomic organization of MDR1 (*ABCB1*) (41). wob., wobble. (Modified from reference 3 by permission from Macmillan Publishers Ltd.)

jugated to glutathione, glucoronate, or sulfate and might be important for the transport of amphotericin B and metabolites of antifungal drugs. MRP4 (*ABCC4*) and MRP5 (*ABCC5*) may function as nucleoside analogue transporters (27, 226) and therefore may play roles in the efflux of flucytosine. OATP substrates are mainly anionic amphipathic molecules with high molecular masses (>450 kDa) that under physiological conditions are bound to proteins (mostly albumin); small hydrophilic compounds with low molecular weights and protein binding are substrates for OATs and organic cation transporters (OCTs) (107). Peptide transporter 1 (PEPT1; *SLC15A1*) and PEPT2 (*SLC15A2*) and concentrative nucleoside transporter 1 (CNT1; *SLC28A1*) and CNT2 (*SLC28A2*) mediate the uptake of peptide drugs and nucleosides, respectively, and may be important in the disposition of peptide antifungal drugs, possibly echinocandins, which are cyclic hexapeptides.

However, given the high protein binding rates of antifungal agents, the electric charge of antifungal drugs may be less important for transportation across membranes of endothelial cells. Drug uptake from endothelial cells might be associated with (i) a receptor-mediated process for the drug-protein complex, such as albumin uptake from the proximal tubular cells (33); (ii) a conformation change in albumin upon contact with cell surfaces that facilitates the release of ligands (210); or (iii) the presence within the capillary bed of a noncompetitive inhibitor of ligand binding to the plasma protein (44).

Metabolism

Most antifungal agents are metabolized primarily in the liver, although many tissues, such as the gastrointestinal tract, the lungs, the skin, and the kidneys, contribute to elimination. The hepatic biotransformation phase I and II reaction enzymes play important roles in the inactivation and subsequent elimination of drugs that are often not easily cleared through the kidney (232). Frequently, biotransformation results in the formation of a more polar metabolite that is pharmacologically inactive and is eliminated rapidly. Drug metabolism involves two classes of biochemical reactions (Fig. 2): phase I reactions (Table 4), which consist of oxidation (e.g., aromatic hydroxylation; side chain hydroxylation; N-, O-, and S-dealkylation; deamination; sulfoxidation; N-oxidation; and N-hydroxylation), reduction (e.g., azoreduction, nitroreduction, and alcohol dehydrogenase), or hydrolysis (e.g., ester and amine hy-

TABLE 3. Human transporter proteins

Transporter	Gene	Chromosome	Size (aa)[a]	Tissue distribution[b]	Membrane localization[c]
P-gp (MDR1)	*ABCB1*	7q21.1	1,280	Ubiquitous	A
MRP1	*ABCC1*	16p13.1	1,531	Ubiquitous (low in L)	BL
MRP2	*ABCC2*	10q24	1,545	L, K, I	A
MRP3	*ABCC3*	17q22	1,527	L, A, P, K, I	BL
MRP4	*ABCC4*	13q32	1,325	Pr, Lu, M, P, T, O, Bl, G	A
MRP5	*ABCC5*	3q27	1,437	Ubiquitous	BL
MRP6	*ABCC6*	16p13.1	1,503	L, K	BL?
MRP7	*ABCC10*	6p21.1	1,492	L, Lu, M	?
BCRP	*ABCG2*	4q22	655	Pl, L, I, Br	A
OATP-A	*SLCO1A2*	12	670	B, L	BL
OATP-B	*SLCO2B1*	11q13	709	K, L, B, I	BL
OATP-C	*SLCO1B1*	12p	691	L, Pl	BL
OATP-D	*SLCO3A1*	15q26	710	Ubiquitous	?
OATP-E	*SLCO4A1*	20q13.33	722	Ubiquitous	BL?
OATP-F	*SLCO1C1*	12p12.3-p14.3	712	B, T	?
OATP8	*SLCO1B3*	12p12	702	L	BL
OATPRP4	*SLCO5A1*	8q13.1	848	?	?
OCT1	*SLC22A1*	6q26	554	L, K (low), I (low)	BL
OCT2	*SLC22A2*	6q26	555	K, B, Pl, I (low), S (low)	BL
OCT3	*SLC22A3*	6q26-q27	556	L, I, H	BL
OCTN1	*SLC22A4*	5q31.1	551	K, L, Lu, I	A
OCTN2	*SLC22A5*	5q31	557	B, K, M, Pr, Pl	A, BL
OAT1	*SLC22A6*	11q13.1-q13.2	550	K	BL
OAT2	*SLC22A7*	6p21.1-p21.2	546	L, K (low)	A
OAT3	*SLC22A8*	11q11	542	K, B (low)	BL
OAT4	*SLC22A9/A11*	11q13.1	552	K, Pl	A
OAT5	*SLC22A10*	11q12.3	541	L	A
PEPT1	*SLC15A1*	13q33-q34	708	K, I, L, Pl	A, BL
PEPT2	*SLC15A2*	3q13.3-q21	729	K, B	A, BL
CNT1	*SLC28A1*	15q25-26	649	K, I, L	A
CNT2	*SLC28A2*	15q15	658	Ubiquitous	A, BL

[a] aa, amino acids.
[b] L, liver; K, kidney; B, brain; I, intestine; A, adrenals; P, pancreas; Pr, prostate; Pl, placenta; Lu, lung; M, muscle; T, testis; O, ovaries; Bl, bladder; G, gallbladder; S, spleen; H, hippocampus; Br, breast.
[c] BL, basolateral; A, apical/luminal.

drolysis), and phase II reactions, which consist of conjugation with endogenous substances, such as glucuronide, peptide, sulfate, methyl, acetyl, glycyl, or glutathione groups.

The antifungal drugs terbinafine, itraconazole, voriconazole, ketoconazole, and caspofungin are extensively metabolized (>80% of the dose) (Table 1). The primary pathways of ketoconazole metabolism are oxidative O-dealkylation and aromatic hydroxylation (60). Ketoconazole is a strong inhibitor of CYP3A4, and it has been shown to moderately inhibit CYP2E1, CYP1A2-2c, and CYP2D6 in vitro (2). Voriconazole metabolism involves primarily N-oxidation by CYP2C19, CYP2C9, and CYP3A4 (Table 4), with CYP2C19 being the major metabolic CYP450 isoenzyme (93), although glucuronide conjugates (15% of the dose) are also detected in urine (78). The main metabolic pathways of itraconazole are oxidations and N-dealkylation (116) with CYP3A4, resulting in the formation of several metabolites, including the major metabolite, hydroxyitraconazole. In addition, barbiturates, carbamazepine, phenytoin, and rifampin, known CYP3A4 inducers, accelerate the metabolism of ketoconazole, itraconazole, and miconazole, and, to a lesser extent, fluconazole (2); antiretroviral protease inhibitors, such as ritonavir, are CYP3A4 substrates and reduce the clearance of itraconazole in pediatric patients (103). Particularly for fluconazole, coadministration with rifampin decreased the AUC and half-life of the antifungal (2).

At least seven CYP enzymes (Table 4), which represent four major pathways (60), are involved in terbinafine metabolism: N-demethylation, primarily mediated by CYP2C9, CYP2C8, and CYP1A2; deamination by CYP3A4; alkyl side chain oxidation by CYP2C9, CYP2C8, CYP2C19, and CYP1A2; and dihydrodiol formation by CYP2C9 and CYP1A2 (261), resulting in 15 metabolites. Caspofungin is slowly metabolized by peptide hydrolysis and N-acetylation (16, 102). Caspofungin does not influence the plasma pharmacokinetics of indinavir, a substrate and inhibitor of CYP3A4, nor of ketoconazole, a potent CYP3A4 inhibitor (102). Posaconazole is minimally metabolized by both the CYP450 and uridine diphosphate-glucuronotransferase (UGT1A4) (94, 151). Although posaconazole is not a major substrate of CYP3A4, it is an inhibitor of this important drug-metabolizing enzyme. Finally, micafungin is metabolized by aryl sulfatases with further metabolism by catechol *O*-methyl transferases, while some products undergo hydroxylation by phase I drug-metabolizing enzymes (111).

Population differences in drug metabolism are clearly associated with phenotypic classification of patients in the categories of poor, intermediate, extensive, and ultrarapid extensive metabolizers (215). Patients who express dysfunctional or inactive drug-metabolizing enzymes are considered poor metabolizers and are at high risk for toxicity and perhaps poor treatment outcome (197). Intermediate metabolizers, with decreased drug-metabolizing enzyme activity, differ in outcomes

TABLE 4. Major human drug-metabolizing cytochrome P450 enzymes[a]

CYP	Chromosome	Expression	Relative protein abundance in liver (%)	% of drugs metabolized by enzyme (antifungal drugs)	Major variant allele(s)	Mutation	Consequence
CYP1A1	15q22-q24	Inducible	<1		CYP1A1*2A&B	3801T>C I462V	Increased inducibility Increased activity
CYP1A2	15q22qter	Inducible	8–15	11 (terbinafine)	CYP1A2*1F	−164C>A	Higher inducibility
CYP2A6	19q13.2	Constitutive	5–12	3	CYP2A6*2	L160H	Inactive enzyme
					CYP2A6*4	Gene deletion	No enzyme
					CYP2A6*9	TATA-mut	Less enzyme
CYP2B6	19q13.2	Inducible?	1–5	3	CYP2B6*5	R487C	Less enzyme
					CYP2B6*7	Q172H; K262R; R487C	Less enzyme
CYP2C8	10q24.1	Constitutive	10		CYP2C8*2	1269F	Decreased activity
					CYP2C8*3	R139K, K399R	Decreased activity
					CYP2C8*4	1264M	Decreased activity
CYP2C9	10q24	Constitutive	15–20	16 (voriconazole, terbinafine)	CYP2C9*2	R144C	Reduced affinity for P450 reductase
					CYP2C9*3	I359L	Altered substrate specificity
CYP2C19	10q24.1-q24.3	Constitutive	<5	8 (voriconazole, terbinafine)	CYP2C19*2	Altered splice site	Inactive enzyme
					CYP2C19*3	Stop codon	Inactive enzyme
CYP2D6	22q13.1	Constitutive	2	19	CYP2D6*2xn	Gene duplication	Increased activity
					CYP2D6*4	Defective splicing	Inactive enzyme
					CYP2D6*5	Gene deletion	No enzyme
					CYP2D6*6	1707T>del P34S	No enzyme
					CYP2D6*10	S486T T107I	Unstable enzyme
					CYP2D6*17	R296C S486T	Reduced affinity for substrates
CYP2E1	10q24.3-qter	Constitutive/ inducible	7–11	4	CYP2E1*2	R76H	Less enzyme expressed
					CYP2E1*3	V389I	No effects
					CYP2E1*4	V179I	No effects
CYP3A4	7q21.1	Constitutive	30–40	36 (itraconazole, ketoconazole, voriconazole, terbinafine)	CYP3A4*2	S222P	Higher K_m for substrate
					CYP3A4*3	M445T	Unknown
					CYP3A4*4	I118V	Decreased
					CYP3A4*5	P218R	Decreased
					CYP3A4*6	831 insA	Decreased
CYP3A5	7q21.1	Constitutive	<1		CYP3A5*3	Splicing defect	No enzyme
					CYP3A5*6	Splicing defect	No enzyme

[a] Modified from reference 68 with permission of the publisher and from reference 215 with permission of Elsevier; includes data from http://www.cypalleles.ki.se.

from extensive metabolizers, who have normal drug-metabolizing enzyme activity (the anticipated medication response would be seen with standard doses). Ultrarapid extensive metabolizers have increased drug-metabolizing enzyme activity, usually due to larger quantities of expressed drug-metabolizing enzymes (215). Many genetic polymorphisms in drug-metabolizing enzymes, which produce enzyme products with abolished, reduced, altered, or increased enzyme activities, have been associated with the aforementioned phenotypic polymorphisms. There are few studies in which the roles of genetic polymorphisms of drug-metabolizing enzymes in antifungal-drug metabolism have been investigated.

Phase I reactions. Both members of the CYP1A family, CYP1A1 and CYP1A2, have major roles in the biotransformation of a variety of xenobiotics, including a number that may be commonly encountered in food and environmental pollutants, such as tobacco and procarcinogens. Thus, genetic polymorphisms in these genes have been associated with susceptibility to cancer, particularly lung cancer (51). Unlike CYP1A1, which is extrahepatic, CYP1A2 is expressed in the liver and has an additional role in the metabolism of commonly prescribed drugs, including the antipsychotics clozapamine and olanzapamine, and participates in the oxidation of paracetamol and theophylline (110). Both are induced by a range of compounds via the nuclear aryl hydrocarbon receptor (51). Terbinafine is metabolized by CYP1A1, while ketoconazole is a strong inhibitor of the family. CYP2A6 has a limited range of specific xenobiotic substrates, such as nicotine, coumarin, and the drug SM-12502, but there are a number of other substrates that are also metabolized by additional CYPs, including halothane, several nitrosamines, and disulfiram (209). At least 16 distinct *CYP2A6* alleles have been described (http://www.cypalleles.ki.se), some of which are population specific. For example, the major variant *CYP2A6*4*, with a frequency of 20% in the Pacific Rim, is rare in European Caucasians (51). CYP2B6 has a role in the biotransformation of cyclophosphamide, bupropion, and various nitrosamines, although its importance in drug metabolism is recognized when its expression is induced by exposure to phenobarbital-type inducers (73). Nine common alleles have been described for *CYP2B6*; alleles *5 and *7 together have a frequency of approximately 14% in Europeans and are functionally associated with decreased enzyme activity (158).

The CYP2C family consists of four homologous genes, *CYP2C8*, *CYP2C9*, *CYP2C18*, and *CYP2C19*, on chromosome 10 but with distinctive substrate specificities. Voriconazole and terbinafine are metabolized by members of this family. Sub-

strates of CYP2C8 include paclitalex, all-trans retinoic acid, cerivastatin, rosiglitazone, and amodiaquine (96). The variant alleles, *2 (I269F), *3 (R139K, K399R), and *4 (I264M) (Table 4), are associated with decreased activity of paclitaxel in human liver microsomes (14), while in vitro the variant P404A is less effective in N-deethylation of amiodarone (238), as well as in paclitaxel metabolism (239). CYP2C9 has a major role in the metabolism of *S*-warfarin, phenytoin, tolbutamide, and nonsteroidal anti-inflammatory drugs (162). Eleven alleles have been described for *CYP2C9*, 10 of which are nonsynonymous base substitutions and base deletions (http://www.cypalleles.ki.se). The major variant alleles are *2 (R144C) and *3 (I359L), which are associated with impaired enzyme activity. Individuals expressing either of these two alleles have reduced warfarin clearance and thus altered daily dose requirements, increased phenytoin serum concentrations, increased half-life of tolbutamide, <1% conversion of a losartan dose to its pharmacologically active metabolite E3174, profound symptoms of hypoglycemia after a glipizide dose, and complications from bleeding after warfarin administration (162, 215).

CYP2C19 is responsible for the metabolism of proton pump inhibitors (e.g., omeprazole), anticonvulsants and hypnosedatives (e.g., diazepam), anti-infectives (e.g., proguanil), and antidepressants (66). Alleles *2 (splicing defect in exon 5) and *3 (stop codon in exon 4) are the most frequent (Table 4) and have been associated with better response to omeprazole treatment of peptic ulcer due to higher drug levels (88) and prolonged sedation after diazepam therapy due to increased half-life of diazepam (22). In addition, poor, intermediate, and rapid CYP2C19 metabolizers respond at rates of 100%, 60%, and 28.6%, respectively (88), while addition of clarithromycin increased *Helicobacter pylori* eradication in the last two groups but had little effect in poor metabolizers (6).

CYP2D6 metabolizes antidepressants, antipsychotics, beta-blockers, and antiarrhythmics (172). Forty-two alleles have been described as nonsynonymous SNPs, frameshifts, and splicing defects (Table 4). Intermediate metabolizers may be either heterozygous for one of the inactivating mutations or homozygous for alleles associated with impaired metabolism, while ultrarapid metabolizers may have up to 13 copies of a tandem repeat in *CYP2D6*, although the ultrarapid phenotype is more commonly associated with single-gene duplication (51). In poor metabolizers, codeine is an ineffective analgesic due to inadequate conversion to morphine by CYP2D6 (200). Poor metabolizers may experience increased adverse effects from the antiarrhythmic propafenone, because of elevated concentration (42), and from tricyclic antidepressants, while low plasma levels and rapid clearance of the latter are observed for ultrarapid metabolizers (23). Finally, ethanol-inducible CYP2E1 metabolizes low-molecular-weight compounds, such acetone, ethanol, benzene, and nitrosamines, while paracetamol, halothane, and enflurane are also substrates (51). Ketoconazole may potentially inhibit CYP2E1 and CYP2D6, resulting in dose-dependent adverse reactions. Most of the genetic polymorphisms identified lie in upstream sequences or in introns, but of the three nonsynonymous SNPs described, only one (R76H) has been associated with decreased enzyme activity (125).

CYP3A isoenzymes are the predominant subfamily of drug-metabolizing enzymes with the widest range of drug substrates; they are primarily expressed in the liver and intestine. Itraconazole, voriconazole, terbinafine, and possibly ketoconazole are metabolized by CYP3A enzymes. CYP3A activity is the sum of the activities of four CYP3A isoenzymes: CYP3A4, CYP3A5, CYP3A7, and CYP3A43 (157). Levels of CYP3A4 activity vary considerably in individuals, while CYP3A5 is expressed in 10 to 20% of adult livers and CYP3A7 is universally expressed in the fetal liver and in some adult livers (51). Eighteen alleles of *CYP3A4*, many nonsynonymous SNPs, have been identified, but some give rise to alterations in catalytic activity and most are too rare to explain the interindividual variation in CYP3A4 activity (157). Polymorphisms in one of its transcriptional regulators, pregnane X receptor, may affect levels of CYP3A4 (51). Seven alleles of *CYP3A5* have been identified (Table 4), with the majority of them resulting in absence of *CYP3A5* expression due to abnormal splicing or nonsense SNPs (157). Several genetic polymorphisms have been found in the promoter region of *CYP3A7* associated with *CYP3A7* mRNA expression in the adult liver (154), while alternative splicing events have been found in *CYP3A43*, which resulted in production of a *CYP3A4-CYP3A43* hybrid (81).

Because the CYP system is involved in biotransformation of antifungal agents, genetic polymorphisms in CYP genes may play significant roles in the pharmacokinetics of antifungal drugs. However, despite the extensive body of literature available addressing SNPs in the CYP family, only *CYP2C19* has been studied in voriconazole (128). Analysis in healthy-volunteer data has demonstrated that the *CYP2C19**2 genotype is the most important covariate determining plasma levels of voriconazole (78). The mean average plasma concentrations of voriconazole in homozygous extensive metabolizers are four times lower than in homozygous poor metabolizers, while the heterozygous individuals have intermediate levels (Fig. 4).

Phase II reactions. Glutathione conjugation is an important metabolic pathway for detoxification of hydrophobic and electrophilic drugs and is performed by the class of glutathione *S*-transferases. They are encoded by eight distinct classes of genes: alpha, kappa, mu, omega, pi, sigma, theta, and zeta. Genetic polymorphisms in *GSTM1* and *GSTT1* result in decreased catalytic activity (278), and large-scale gene deletion is associated with absent enzyme activity (230). Although genetic polymorphisms have also been described for *GSTM3*, *GSTP1*, and *GSTA1*, their roles in the pharmacogenomics of chemotherapeutic outcomes are unclear (51).

Acetylation of amino, hydroxyl, and sulfhydryl groups is performed by the enzyme *N*-acetyltransferase, of which there are two isoforms, NAT-1 and NAT-2. NAT enzymes may be involved in caspofungin metabolism. Multiple alleles have been described for *NAT1* (114) and selected variants. *NAT1**14 (R187Q), -*15 (R187Stop), -*17 (R64W), -*19 (R33Stop), and -*22 (D251V) are associated with absent or low enzyme activity (115), although interindividual variation in NAT-1 levels has been reported with 4-aminobenzoic acid (48), and low-activity alleles are probably rare (51). Nonsynonymous SNPs with functional consequences, which result in absence of catalytic activity in vitro, have been described for *NAT2* (114); three variant alleles, *NAT2**5 (I114T), *NAT2**6 (R197Q), and *NAT2**7 (G286E), account for the majority of the slow acetylators among Caucasians (51). *NAT2* polymorphisms corre-

lated with adverse effects with isoniazide, dapsone, and sulfoniazide (240). The population frequency of the slow-acetylator phenotype varies from 40 to 70% of Caucasians and African-Americans and more than 80% of Egyptians to 10 to 20% of Japanese and Canadian Eskimos (172).

Methylation reactions using *S*-adenosylmethionine for a methyl group donor are important in the metabolism of endogenous substances and xenobiotics; at least four separate enzymes can carry out S-, N-, and O-methylation reactions (274). Thiopurine *S*-methyltransferase (*TPMT*) is an enzyme that metabolizes thiopurine drugs, such as mercaptopurine, used clinically as immunosuppressants. In addition, *TPMT* deficiency is associated with increased risk for therapy-limiting toxicity and second malignancies in patients with acute lymphoblastic anemia treated with 6-mercaptopurine. The most common defective allele, *TPMT**3, is associated with two amino acid substitutions that result in complete absence of activity (182). Catechol-*O*-methyltransferase (*COMT*) is an enzyme present in mammalian cells as both membrane bound (MB) and soluble (S) cytosolic forms and plays an important role in the metabolism of catecholamine transmitters and catechol drugs used to treat hypertension, asthma, and Parkinson's disease (275). COMT enzymes may be involved in micafungin biotransformation. Family studies of red blood cell COMT activity show a bimodal frequency distribution with the trait of low-level COMT activity being associated with decreased enzyme thermal stability associated with an SNP at codon 108 in S-COMT (158 in MB-COMT) (233).

Other phase II drug-metabolizing enzymes are UDP-glucuronotransferases encoded by the *UGT* family of genes and sulfotransferases encoded by the *SULT* family of genes. A TA insertion in the TATA box and specific nonsynonymous SNPs results in decreased expression of *UGT1A1*, the gene encoding the main enzyme responsible for glucuronidation of bilirubin; these variants are associated with decreased clearance of a number of different drugs, including tolbutamide, paracetamol, and rifampin (105). SNPs in other *UGT* genes may alter the kinetics of some substrates. Genetic polymorphisms that might be functionally significant have also been described for *SULT* genes (191).

The roles of SNPs of phase II drug-metabolizing enzymes in the pharmacokinetics of antifungal drugs, and in particular for caspofungin, micafungin, and posaconazole, remain to be explored. Preliminary information points to population-based differences in the metabolism of posaconazole, perhaps by genetic variation in the family of *UGT* genes (R. Courtney, A. Sansone, B. Kantesaria, P. Soni, and M. Laughlin, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1564, 2003). The roles of SNPs in the *COMT* gene in micafungin metabolism are unknown.

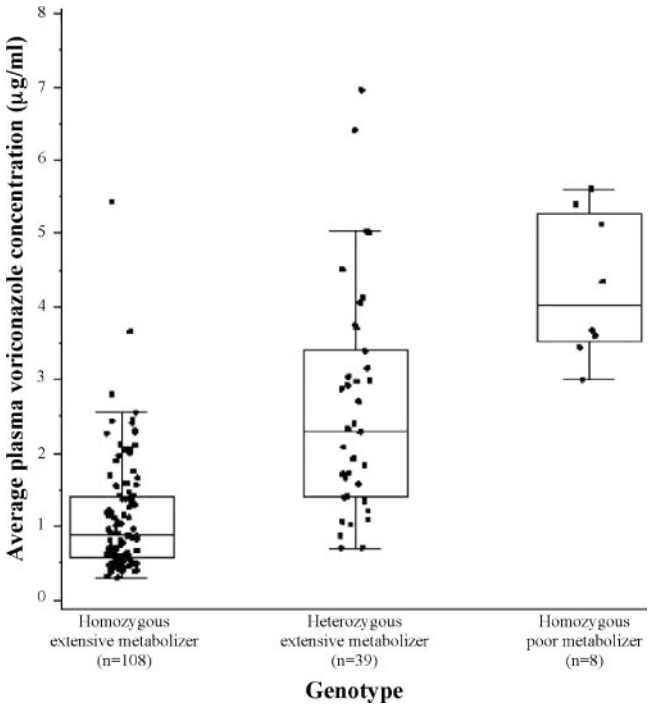

FIG. 4. Influence of the *CYP2C19* (allele *2) genotype on average steady-state plasma voriconazole concentrations as determined by a population pharmacokinetics analysis. The box-and-whisker plots display the box locations of the median, upper, and lower quartiles, with whiskers extending to the furthest data point within 1.5 times the interquartile range. The scatter of individual data is also displayed. (Reprinted from reference 78).

Excretion

Drug metabolites can be excreted by the hepatobiliary system or by the kidneys via the urine (232). Other pathways for drug excretion include the saliva, gut, milk, sweat, and tears or via the lungs into expired air. Among antifungal drugs, flucytosine (259) and fluconazole (32) are primarily (>90% of a given dose) excreted unchanged in the urine; interestingly, for fluconazole, 80% is the parent drug and 11% is in the form of known metabolites (Table 1). Fluconazole can be detected in saliva (32) and in breast milk (61) at levels comparable to those in plasma and in sweat (levels in sweat can be 2.5 times higher than those in plasma) (280) following oral administration. Amphotericin B is excreted unchanged through the kidney and bile, with 90% of the dose detected in urine (20.6%) and feces (42.5%), amounting to 75% of the total clearance (19). Unchanged itraconazole is mainly excreted from bile, since 3 to 18% of the dose is detected in the feces and no drug is detected in the urine (58); 35% of the metabolized form of itraconazole is secreted in urine and 54% in feces (60). Itraconazole is also detected in sweat at levels lower than those in plasma (38) and in saliva at levels higher than those in plasma (211) after oral administration. In the case of voriconazole, less than 5% of the drug is excreted unchanged in the urine (137), while 80% of the original dose is excreted in the urine and 20% in the feces (93). Voriconazole can be detected in saliva at levels half those detected in plasma (206). The primary excretion route of posaconazole in rats is the bile, since more 70% of the intravenous dose is detected in feces and bile while the remainder is found in the GI tract and only 7% in urine (120). Overall, biliary excretion is also the major route of elimination in humans, since the majority of the radioactivity (77%) is excreted into the feces as the parent drug while the urine contains minor amounts (14%) of posaconazole and its metabolites (151).

Caspofungin is excreted in urine and feces, accounting for 40.4% and 34.4% of the dose, respectively, with the unchanged

form comprising 9% of urinary extracts (16); these data confirm animal studies, in which <1 to 3% of the total dose was recovered in urine (108). Vechinocandin, a semisynthetic echinocandin B derivative, is detected in rabbit saliva at levels approximately 1% of those in plasma, whereas fluconazole and amphotericin B are not detectable (202). Urinary excretion of anidulafungin is negligible, while fecal excretion accounts for the entire dose as intact anidulafungin (<10%) and tertiary degradation products (>90% of the dose) (69). For micafungin, 7.4% and 43.8% are recovered in urine and feces at 168 h postdose, while the parent drug is not detectable in plasma after 72 h (87). Terbinafine is excreted at 80% in metabolized form in the urine and 20% in feces (60); 2 to 4% of ketoconazole is excreted unchanged, mainly through the bile (60), and less than 1% in the urine (171). Terbinafine is not detected in sweat (76), while ketoconazole is detected in sweat (212), in breast milk (189), and in saliva (82). There are no studies exploring the pharmacogenomic aspects of antifungal-drug excretion.

Renal excretion. Many drugs are excreted via the kidneys by one of several mechanisms, glomerular filtration, active tubular secretion, or endocytosis; however, tubular reabsorption can limit renal excretion (178). Up to 20% of the renal plasma flow is filtered through the glomerulus, where drug molecules and their metabolites are passively diffused into the glomerular filtrate due to high hydrostatic pressure within the glomerular capillaries. Drug molecules of low molecular weight and high lipophilicity diffuse more easily. The remaining 80% of the delivered drug passes through the peritubular capillaries of the tubule, where drug molecules and their metabolites can be transported to the tubular lumen and vice versa by two independent carrier systems (Fig. 2); the organic anion transport system, which is selective for acidic drugs (substrates with carbonyl and carboxyl groups) and involves, among others, the OAT1 (*SLC22A6*), OAT3 (*SLC22A8*), MRP1 (*ABCC1*), MRP3-6 (*ABCC3-6*), sodium dicarboxylate transporter 2 (SDCT2; *SLC13A3*), and sulfate anion transporter 1 (SAT1; *SLC26A1*), located in the basolateral membrane; rat Oatp1 (*slc21a1*), Oatp3 (*slco1a5*), Oatk-1, and Oatk-2 or human OAT4 (*SLC22A11*) and MRP2 (*ABCC4*), located in the luminal membrane; and the OCT system, which is selective for basic drugs (secondary and tertiary amines and quaternary ammonium salts) and involves OCT2 (*SLC22A2*), located in the basolateral membrane, and OCTN1 (*SLC22A4*), the carnitine transporter OCTN2 (*SLC22A5*), and P-gp (*ABCB1*), located in the luminal membrane (256). However, in contrast with P-gp (*ABCB1*), their specific activities in the overall handling of drugs are not yet well defined (178).

Unlike glomerular filtration, carrier-mediated transport can eliminate drugs even when they are bound to plasma proteins. Drugs with high lipid solubility may be reabsorbed mainly by passive diffusion across the renal tubule, although carrier-mediated tubular reabsorption has been reported. Reabsorption can be affected by the urine flow rate and urine pH if the drug is a weak acid or base. Finally, endocytosis has also been reported to be involved in the uptake of drugs such as aminoglycosides, because they bind to phospholipids in the brush border membrane (178).

Renal excretion is the primary excretion route for fluconazole and flucytosine (Table 1). Glomerular filtration is the mechanism of excretion for flucytosine (259) and fluconazole (32). Flucytosine is neither reabsorbed nor secreted via the tubular epithelium (259). By comparison, fluconazole is extensively reabsorbed (approximately 80%) from the tubular lumen (61, 135). Tubular reabsorption is important for amphotericin B (77), because urinary clearance is approximately 4% of the glomerular filtration rate (19). However, for both drugs, urine concentrations are much higher than those in blood (19, 32), and tubular reabsorption might occur as passive back diffusion rather than a carrier-mediated process. Nevertheless, if the main mechanism of transport of antifungal compounds through the renal membranes is passive diffusion, genetic polymorphisms in genes encoding drug transporters located in tubular cells would likely have a small impact on the renal clearance of current antifungal drugs.

Hepatobiliary excretion. Hepatobiliary excretion involves the uptake of drugs from blood into the hepatocyte through the sinusoidal (basolateral) membrane by passive diffusion or carrier-mediated transport. Transfer of drugs to the biliary canalicular membrane is mediated by intracellular transfer proteins and passive diffusion, but excretion at the canalicular membrane is mediated mainly by carrier proteins (Fig. 2) (11, 39). Members of the OATP transporters, such as OATP-A (*SLCO1A2*), -B (*SLCO2B1*), -C (*SLCO1B1*), and -8 (*SLCO1B3*), have been shown to be located on the sinusoidal membrane (Table 3) and to be responsible for the transport of many drugs, including pravastatin, benzylpenicillin, digoxin, and fexofenadine (143). It is believed that OATP-C (*SLCO1B1*) and OATP-8 (*SLCO1B3*) transport acidic compounds, whereas OATP-A (*SLCO1A2*) and -B (*SLCO2B1*) transport basic, zwitterionic, and neutral compounds. OCT1 (*SLC22A1*), -2 (*SLC22A2*), and -3 (*SLC22A3*) are also found in the sinusoidal membrane (288), although their roles in the hepatic uptake of drugs are not clear. Substrates of OCT proteins are small organic cations, such as TEA and *N*-methylnicotinamide (25). The OAT2 (*SLC22A2*) and OAT3 (*SLC22A3*) proteins are expressed in the liver, and although active renal excretion of substrates such as cimetidine, methotrexate, cidofovir, and adefovir substrates have been shown (11, 155), their roles in hepatobiliary excretion remain to be elucidated. P-gp (*ABCB1*) and MRP2 (*ABCC2*) are located in the canalicular membrane and are involved in the active secretion of drug into bile (11).

MRP1 (ABCC1) is also localized in the lateral membrane and mediates transport of anticancer drugs, as well as anionic conjugates, with glutathione, sulfate, or glucuronide (11). P-gp (*ABCB1*) is one of the major cation carriers responsible for the biliary excretion of amphiphilic drugs (186, 236, 237). MRP2 (*ABCC2*) has been shown to mediate the transport of endobiotics, such as bilirubin, as well as many anionic drugs, such as grepafloxacin, pravastatin, cefodizime, methotrexate, and irinotecan, and drug conjugates, such as glucuronide conjugates (11). In the livers of patients whose MRP2 (*ABCC2*) function is deficient, the expression of MRP3 (*ABCC3*) is localized on the sinusoidal membrane of human hepatocytes and is upregulated (147). This mechanism for protection of the hepatocytes from drug and endobiotic exposure operates by pumping the drugs out of the hepatocytes into the blood (27).

For antifungal agents, hepatobiliary excretion is the main route of elimination. In particular, amphotericin B and

posaconazole, and to lesser degrees itraconazole and ketoconazole, are excreted directly. Fluconazole is also excreted into the bile, since the drug is detected in bile at levels equal to those in the blood (29).

Very little is known about the hepatic transporters involved in biliary excretion of antifungal agents. In guinea pigs, itraconazole interacts with P-gp to reduce digoxin excretion in bile (196). In addition, the combination of itraconazole and verapamil (P-gp substrates) is reported to have caused a severe and slowly reversible cholestasis in a 74-year-old woman (250). Hepatobiliary excretion of fluconazole might not be regulated by P-gp, given that cyclosporine A, a P-gp inhibitor, did not affect the blood/bile ratio of fluconazole when coadministered in rats (161). Interaction between caspofungin and rifampin results in elevated exposure to both drugs, probably because of delayed biliary excretion (63). Posaconazole is usually (>77%) excreted via the hepatobiliary system as intact drug, but an increase in posaconazole clearance by P-gp inducers, such as phenytoin and rifabutin (5), suggests that P-gp is involved in posaconazole excretion. The liver-specific transporter OATP1B1 (SC21A6) is involved in hepatic uptake of caspofungin (222).

Genetic polymorphisms in genes encoding hepatic transporters can alter the hepatobiliary excretion of drugs. A cogent example of impaired biliary excretion due to altered function of a hepatic transporter is the Dubin-Johnson syndrome, an autosomal recessive disorder attributed to the absence of MRP2 (*ABCC2*) at the canalicular membrane; patients with this syndrome exhibit hyperbilirubinemia due to impaired biliary excretion of bilirubin conjugates (139). The absence of MRP2 (*ABCC2*) is due to the deletion of six nucleotides, encoding Arg at 1392 and Met at 1393 (141), as well as to I1173F and R1150H substitutions (188). SNP analysis of *MRP2* (*ABCC2*) in Japanese subjects identified more than 30 SNPs, including C24T (untranslated region), G1249A (exon 10) associated with Val417Ile, and C3972T (exon 28) (249). Up to a 15-fold difference in the expression level of *MRP2* (*ABCC2*) mRNA was observed in 13 patients undergoing resection of liver metastasis (289) and in 18 hepatitis patients (118). In addition to food and drugs that induce *MRP2* (*ABCC2*) expression, it has been suggested that the CAAT enhancer binding protein beta binding sequence located between −356 and −343 and hepatic nuclear factor 1 binding and upstream stimulatory factor-like elements located between +81 and +248 may also be important in the basal expression of human MRP2 (*ABCC2*) (249).

At least 14 nonsynonymous SNPs in *OATP-C* (*SLCO1B1*) have been identified (252). Overall, functional assessment of 16 *OATP-C* (*SLCO1B1*) alleles in vitro revealed that selected variants exhibited markedly reduced uptake of the OATP-C (*SLCO1B1*) substrates estrone, sulfate, and estradiol 17-β-D-glucuronide. Specifically, alterations in transport were associated with SNPs that introduced amino acid changes within the transmembrane-spanning domains (T217C [Phe73Leu], T245C [Val82Ala], T521C [Val174Ala], and T1058C [Ile353Thr]) and also with those that modified extracellular loop 5 (A1294G [Asn432Asp], A1385G [Asp462Gly], and A1463C [Gly488Ala]) (252). In the case of OAT-B, the nonsynonymous SNP S486F affects [(3)H]estrone-3-sulfate uptake from embryonic kidney cells (198). Eight nonsynonymous SNPs in OCT2 (*SLC22A2*) have been identified in ethnically diverse DNA samples, four of which (M165I, A270S, R400C, and K432Q) occurred with frequencies higher than 1% and altered transporter function in *Xenopus laevis* oocytes for metformin, phenformin, procainamide, and quinidine (160). Genetic polymorphisms in the MDR1 (*ABCB1*) gene and their roles in pharmacokinetics have been identified, although their impacts, particularly on hepatobiliary excretion, remain to be elucidated (168, 229). Whether genetic polymorphisms in hepatic drug transporters alter hepatobiliary excretion of antifungal drugs is unknown.

OTHER FACTORS THAT AFFECT PHARMACOKINETICS OF ANTIFUNGAL DRUGS

Although genetic polymorphisms may help us to partially explain interindividual variability in the pharmacokinetics of antifungal drugs and response, additional factors can influence drug levels; these include physiological, pathophysiological, and environmental changes. It is likely that genomics can provide partial predictive value, though the degree will vary according to individual circumstances; some have argued that genetics accounts for as much as 50% of response or toxicity, while estimates by other are substantially lower (132).

Age

The process of aging is particularly important in drug disposition (112, 140). For instance, drug absorption is different in children because of higher intragastric pH, the increased gastric emptying and propagating contractions, the developing intestinal surface, and the age-associated changes in splanchnic blood flow in the neonatal period. The distributions of drugs are markedly different in neonates and young infants than in adults; factors include larger extracellular and total-body water spaces; a higher water-to-lipid ratio in adipose stores; reduction in the quantity of total plasma proteins; the presence of fetal albumin, which has reduced binding affinity for weak acids; the increase in endogenous substances, e.g., bilirubin and free fatty acids, capable of displacing a drug from albumin binding sites; variability in regional splanchnic blood flow; organ perfusion; permeability of cell membranes; changes in acid-base balance; and more dynamic cardiac output (72, 234). For instance, P-gp and phase I and II drug-metabolizing enzyme expression appears to be different in neonates than in adults (140). Finally, pharmacokinetics may also be different in elderly individuals (284) due to differences in absorption (increased gastric pH and decreased absorptive surface, splanchnic blood flow, and gastrointestinal motility), distribution (decreased cardiac output, total-body water, lean body mass, and plasma albumin and increased AAG and body fat), metabolism (decreased hepatic mass, enzyme activity, and hepatic blood flow), and excretion (decreased renal blood flow, glomerular filtration rate, and tubular secretion) (112).

There are sentinel examples of the influence of age on the pharmacokinetics of antifungal drugs (60). A significant negative correlation between the mean blood concentration of ketoconazole and age has been reported (185). Terbinafine AUC values are significantly higher in children than in young adults (194), although in a separate study, higher plasma concentrations and lower half-lives of the terminal elimination phase were reported (127). For fluconazole, the volume of distribu-

tion is greater in neonates and decreases in young adults (31), the mean plasma half-life in children (22 h) is shorter than in adults (37 h) (59), and total clearance is greater in children (1.16 liters/h) than in adults (1.07 liters/h) (163). In addition, the half-life of azole is slightly prolonged in elderly people compared to the middle aged (224) and terbinafine AUC values are higher in the elderly than in young adults (193). Pharmacokinetics of itraconazole in elderly (116) and pediatric patients do not appear to be different (103); lower plasma concentrations in children and longer half times in elderly individuals have been observed in preliminary studies (58, 116). The pharmacokinetics of terbinafine are similar in elderly and young subjects (134). Neonates and children have lower C_{max} values (134), higher clearances, and longer serum half-lives of amphotericin B than older children (21, 242, 266). In neonates, the pharmacokinetics of flucytosine are as follows: slightly increased half-lives, decreased body clearance, and greater volume of distribution than in adults (17). The C_{max} and AUC of voriconazole in elderly males were 61% and 86% higher, respectively, than in young males, a difference that, interestingly, is not observed in females (78). Compared with the young control subjects, the elderly subjects had higher mean caspofungin concentrations, 26% longer mean half-lives, and 28% mean increase in AUC (244). The mean clearance and volume values of micafungin are 33% and 26%, respectively, greater in the pediatric population than in the adult population, while no significant differences in AUC, elimination half-life, distribution volume, plasma protein binding ratio, or total clearance have been found between elderly and nonelderly subjects (87).

Gender

Gender is yet another factor that could contribute to interindividual variability in drug pharmacokinetics (18). Oral absorption might be different in men and women, since women empty solids from the stomach more slowly and have higher gastric pH, and the efficacy of stomach alcohol dehydrogenase is lower in women than in men (285). In the case of drug distribution, although the concentration of albumin is largely unaffected by gender (18), the concentrations of AAG and various lipoproteins are slightly lower in women as a result of a decrease induced by endogenous estrogen (145). Although this difference may not be important for drugs that are loosely bound to plasma proteins (285), it may have a great impact on pharmacokinetics, particularly for highly protein binding drugs, such as the common antifungals. Furthermore, the activities of efflux transporters and drug-metabolizing enzymes are different in men and women. Regarding drug excretion, gender might also have some influence on tubular secretion, since the clearance of amantadine, an organic anion secreted by the kidney, is lower in women than in men and the elimination of amantadine is inhibited by quinine and quinidine in men but not in women (92).

Gender does not appear to influence fluconazole pharmacokinetics (49), and amphotericin B nephrotoxicity is not related to gender (243). Although terbinafine overall is as effective as itraconazole for treating toenail onychomycosis, stratification analysis according to age and gender reveals that terbinafine treatment is superior to itraconazole for females and patients 55 years old and older (43). Furthermore, there is no significant influence of gender on treatment results for patients with onychomycosis treated with oral itraconazole (119). The C_{max} and AUC of voriconazole in young males were 83% and 113% higher, respectively, than in young females (a difference, however, which is not observed in elderly individuals), and children have higher elimination capacity than adults on a body weight basis (78). Plasma concentrations of caspofungin are similar in men and women, but women have a mean increase in AUC of 22% over men (244). Gender has been found to influence clearance of anidulafungin (69).

Physiological Factors

Physiological factors, such as body size and composition, gastrointestinal physiology, hepatic status, and renal excretion, as well as other physiological processes involved in drug disposition, may also influence the pharmacokinetics of drugs (184). Many of the pharmacokinetic differences between men and women can be of physiological origin. For example, females generally have a lower body weight and thus smaller organ size and lower blood flow. Women also have a higher percentage of body fat (48% versus 36% in the elderly and 33% versus 18% in adults) (97), which results in a greater volume of distribution and in a decreased plasma concentration and a prolonged half-life of lipophilic drugs, such as diazepam and trazodone (285). Gastric acid secretion has been reported to be lower in women than in men, probably due to reduced gastric emptying time (203). Lastly, the glomerular filtration rate is known to be proportional to body weight, and thus, body weight might play an important role in the clearance of drugs that are eliminated from the kidneys (184).

Body weight influences the pharmacokinetics of fluconazole, since a positive correlation has been found between clearance and volume of distribution and body weight (49). Higher AUC values for voriconazole are obtained with subjects who weigh less (78). Weight has been found to be a statistically significant determinant of caspofungin pharmacokinetics, since plasma concentrations are greater in patients with lower body weights (265). Body habitus probably influences the pharmacokinetics of anidulafungin, since the clearance and volume of distribution increases with increasing body weight (69). Obesity shifts the pharmacokinetic profile of amphotericin B; in a hyperlipidemic rat model, obese animals had a twofold-increased AUC and a lower weight-corrected volume of distribution and total body clearance than lean rats (255).

Pathological Conditions

In pathological processes, such as renal or hepatic insufficiency, the pharmacokinetics of antifungal compounds can be changed, leading to toxicity or decreased efficacy. Moreover, the oral absorption of itraconazole capsules is 50% reduced as a result of hypochlorhydria; mean plasma concentrations of itraconazole and ketoconazole are lower in AIDS patients than in healthy people, though this probably reflects chronic illness (58, 224). Unbound amphotericin B levels can be higher in uremic patients than in healthy volunteers (4.15% versus 3.55%), while hepatic and renal failure does not influence blood levels, although there are reports of serum levels being

correlated with creatinine values (90). The half-life of itraconazole in patients with liver cirrhosis is prolonged to 37 h, and an average reduction of 64% in peak plasma concentrations has been detected in patients undergoing chronic ambulatory peritoneal dialysis (224). Elimination of fluconazole is delayed in patients with renal impairment, while in patients on chronic ambulatory peritoneal dialysis, peritoneal clearance of fluconazole is below the renal clearance observed in patients with normal kidney function. Terbinafine metabolism is impaired in patients with liver and renal disease (224). Impaired hepatic function decreases plasma clearance by approximately 30%, resulting in markedly increased AUC values, while impaired renal function prolongs the terminal plasma elimination half-life and doubles the AUC compared to healthy volunteers (134). The AUC of caspofungin is increased from 30% to 49% in patients with renal insufficiency and from 55% to 76% in patients with mild and moderate hepatic insufficiency, respectively (244). Although protein binding of voriconazole is not affected by impaired hepatic function, AUC after a single (but not multiple) oral dose of voriconazole is 233% higher in patients with mild and moderate hepatic cirrhosis than in subjects with normal hepatic function (78). Renal insufficiency alters flucytosine pharmacokinetics, since it slows absorption, prolongs the serum half-life, and decreases clearance (259). Neither renal impairment (D. Thye, T. Marbury, T. Kilfoil, G. Kilfoil, and T. Henkel, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1391, 2002) nor hemodialysis (D. Thye, T. Marbury, T. Kilfoil, G. Kilfoil, and T. Henkel, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1390, 2002) significantly alters the pharmacokinetics of anidulafungin and posaconazole (46), while plasma concentrations are decreased and plasma clearance is increased in patients with severe hepatic impairment (D. Thye, T. Kilfoil, G. Kilfoil, and T. Henkel, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1392, 2002).

Drug Interactions

Drug interaction is a major factor that alters the pharmacokinetics of antifungal drugs. Thus, genetic variants that alter the clearance of a competing drug can have an indirect effect on the toxicity and efficacy profile of an antifungal agent. Antacids and H2 receptor antagonists delay and reduce the absorption of flucytosine, ketoconazole, and itraconazole (2, 224). Plasma ketoconazole, itraconazole, and miconazole, and to a lesser extent fluconazole, concentrations are markedly reduced by concomitant administration of drugs that induce liver enzymes, such as phenytoin, carbamazepine, or rifampin. Voriconazole levels are also increased with coadministration of CYP450 inhibitors, such as omeprazole, phenytoin, warfarin, tacrolimus, sirolimus, and rifabutin (78). Rifabutin, phenytoin, and cimetidine decrease plasma levels and increase the clearance of posaconazole (5; R. Courtney, D. Wexler, P. Statkevich, J. Lim, V. Batra, and M. Laughlin, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1838, 2002). Terbinafine concentrations are decreased by coadministration of rifampin but, interestingly, increase after coadministration with cimetidine (224). Concomitant administration of aluminum hydroxide or magnesium hydroxide suspensions delays the absorption of flucytosine. However, this effect is minor for total bioavailability, whereas amphotericin B, which impairs glomerular filtration, could lead to an increase in the serum concentration and the half-life of flucytosine (259). Cyclosporine increases the AUC of caspofungin by 35%, while the concentration of caspofungin may be reduced by coadministration of inducers or mixed inducers/inhibitors of CYP450 isoenzymes, such as efavirenz, nelfinavir, nevirapine, phenytoin, rifampin, dexamethasone, and carbamazepine (244). However, a more complicated interaction with rifampin has been observed recently due to both inhibitory and induction effects of rifampin on caspofungin disposition, with a net effect of slight induction at steady state (245).

Environmental Factors

Environmental factors, such as pollutants or diet, can alter the pharmacokinetics of antifungal drugs. The absorption of itraconazole capsules is increased by 31% to 163% when taken with a meal, while the absorption of itraconazole solution is enhanced in the fasting state and reduced when taken with food (227). The bioavailability of ketoconazole tends to be increased by the intake of a high-fat meal but to be reduced by the intake of a high-carbohydrate meal (165). Food substantially enhanced the rate and extent of posaconazole absorption in healthy subjects (47), while the bioavailability of voriconazole is reduced by approximately 22% as measured by AUC within a dosing interval (AUC_τ) after multiple dosing when taken with food compared with fasting (207). Grapefruit juice increased plasma levels of itraconazole in guinea pigs (173) and of voriconazole in mice (247).

Chemical Properties

Stereoselectivity may also alter the pharmacokinetics of antifungal drugs, particularly those that are administered in racemic mixtures. For example, ketoconazole and itraconazole are chiral drugs, which are administered as racemic (1:1) mixtures of (+) and (−) enantiomers. Although the antifungal activities of these enantiomers are the same, the (−) enantiomers are more potent CYP3A4 inhibitors. For (−)-ketoconazole, the AUC_{0-12} is threefold higher while the half-life is shorter than for the (+)-ketoconazole (J. G. Gerber, S. Dilmaghanian, and J. Gal, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-1569, 2003). The AUC_{0-48} and C_{max} of (−)-itraconazole were three to four times higher than those of (+)-itraconazole in healthy individuals (C. Pyrgaki, J. Gal, S. Bannister,and J. G. Gerber, Abstr. 44th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A-36, 2005).

CONCLUDING REMARKS

Antifungal pharmacogenomics is an exciting area of medical mycology that may lead to individual-patient-based management of antifungal drugs by facilitating the choice of the optimal compound, dosage, and schedule. Furthermore, antifungal pharmacogenomics may be important for determining the individual risk of drug toxicity and for minimizing the risk of potential side effects. In order to achieve this goal, genomics can be applied to the study of pharmacology in directed ways, using the tools of population genetics to define interindividual

TABLE 5. Potential targets for analyzing genetic polymorphisms important for pharmacokinetics of antifungal drugs[a]

Drug	Absorption		Distribution			Metabolism		Excretion	
	GI pH (ATPase)	Efflux drug transporters (P-gp, MRP1+0 -5, BCRP)	Albumin	AAG	Lipoproteins	Phase I (CYP450)	Phase II (NAT, UGT)	Renal (OATs, MRPs, OCTs)	Hepatobiliary (P-gp, MRPs, OATPs, OCTs)
Triazoles									
Itraconazole	+	+	+	−	−	+	−	−	−
Fluconazole	−	+	−	+	−	−	−	+	−
Voriconazole	−	+	?	?	−	+	−	−	−
Posaconazole	+	+	+	?	?	+ (?)	+ (?)	−	+
Polyenes									
Amphotericin B[b]	−	+	+	+	+	−	−	+	+
Allylamines									
Terbinafine	−	+	+	+	+	+	−	−	−
Echinocandins									
Caspofungin	−	+	+	−	−	+	+	−	−
Micafungin	−	?	+	−	−	−	+	−	−
Anidulafungin	−	?	+	−	−	−	−	−	−
Pyrimidines									
Flucytosine	−	+	−	−	−	−	−	−	−

[a] +, probable; −, improbable.
[b] Few data exist for amphotericin B lipid formulations.

differences. Pharmacogenomic models can then be derived for genetic variation in absorption, distribution, metabolism, and excretion, which would be linked with antifungal pharmacokinetics.

Although the field of antifungal pharmacogenomics is in its infancy, with few genetic association studies having been conducted, there are many data indicating the importance of genetic polymorphisms in the disposition of antifungal drugs. Thus far, genetic polymorphisms in *CYP2C19* have been associated with voriconazole plasma levels and the importance of genetic polymorphisms of the *UGT* and *MDR1* genes has been shown for posaconazole pharmacokinetics in humans. These findings are of clinical importance, since subtherapeutic levels in fast metabolizers may explain clinical resistance despite microbiological susceptibility of the pathogens, whereas overexposure in slow metabolizers may be associated with toxicity. Finally, many in vitro and in vivo data have shown the roles of drug transporters and other biomolecules in antifungal-drug disposition. Whether the genetic variants of these biomolecules have different properties in transporting, binding, and metabolizing of antifungal drugs remains to be seen in order to define the real dimensions of antifungal pharmacogenomics.

Potential candidate genes for antifungal pharmacogenomic studies are summarized in Table 5. They include drug transporters involved in absorption and excretion, phase I and II enzymes involved in metabolism, albumin, AAG, and lipoproteins involved in the distribution of antifungal drugs. However, more studies are required to elucidate the contributions of allelic polymorphisms to the disposition of antifungal drugs. Appropriately designed genetic association studies in well-defined populations are important in order to characterize the outcomes with respect to variation in pathways. Finally, these models should incorporate environmental, drug interaction, pathophysiological, and other factors that could influence drug pharmacokinetics. By taking into account these variables, pharmacogenomics holds the promise of mechanistically elucidating variation in antifungal drug disposition and assessing the risk of drug response or failure. Pharmacogenomics has the potential to shift the paradigm of therapy, but the complex challenge ahead will be to address how we use information derived from population-based studies to guide the management of individual patients.

ACKNOWLEDGMENT

This research was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, NIH.

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